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The scientific path towards Alzheimer's disease understanding: insulin resistance as a common link between current hypotheses

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Abstract

Almost 115 years ago, Alois Alzheimer, a German psychiatrist, described Alzheimer's disease (AD) for the first time, in Tübingen, Germany. Since then, many hypotheses have been proposed. However, AD remains an enigmatic disease and a severe health public problem. The current medical approaches for AD are limited to symptomatic interventions and the complexity of this disease has led to a failure rate of approximately 99.6% in AD clinical trials. In fact, no new drug has been approved for AD treatment since 2003. These failures indicate that, because we still do not fully understand the pathophysiology of AD, we are failing in mimicking this disease in experimental models, or, at least, its sporadic form. Although most studies have focused on the amyloid cascade hypothesis of AD, the literature has made clear that AD is rather a multifactorial disorder. Therefore, the persistence in a single theory has resulted in lost opportunities, since numerous alternative hypotheses have been proposed all over the years and

did not receive equal attention, for example to those based upon the presence/detection of the triad: amyloid- β peptide, hyperphosphorylated Tau protein and neurodegeneration. In this review, we aim to present the striking points of the long scientific path followed since the description of the first AD case and the main AD hypotheses discussed over the last decades. We also highlight a rather new one, the “type 3 diabetes” hypothesis, which has presented consistent findings and proposed insulin resistance as a common link between many other hypotheses.

Running title: Alzheimer’s disease and brain insulin resistance

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INTRODUCTION

Since the first description of Alzheimer's disease (AD) in 1906 [1], researchers have coursed a long scientific path seeking for a better understanding of this neurological disorder. Many hypotheses have been proposed over the last decades [2,3], however, AD has remained an enigmatic and complex disease with etiopathogenetic mechanisms yet to be elucidated. Currently, besides neurodegeneration, AD is mainly characterized by the accumulation of the amyloid- β peptide ($A\beta$), which tends to aggregate and form $A\beta$ plaques, and by presence of tangles, caused by accumulation of hyperphosphorylated forms of Tau protein [4].

Worldwide, there are approximately 50 million people living with AD or other dementias [5]. AD is a progressive neurodegenerative condition and the most frequent type of dementia, corresponding to 60-80% of the cases [6]. In the United States, it is estimated that one in 10 people age 65 and older has AD, a total number of 5.8 million Americans [6,7]. Furthermore, epidemiological data suggests an increasing trend in prevalence with estimations being 40 million patients suffering from AD in 2016 [8] and 131 million in year 2050 [9]. Due to its complexity, AD is usually divided into familial AD (fAD) and sporadic AD (sAD). fAD accounts for approximately 1-5% of all cases and it is usually caused by autosomal mutations in the amyloid- β precursor protein ($A\beta$ PP), presenilin 1 (PS1), and/or presenilin 2 (PS2). Conversely, sAD, responsible for a majority of the cases (approximately 95-99%), does not present a well-defined etiology. It is believed that an interplay of genetic, environmental, behavioral and metabolic factors might be responsible for the development of the sporadic form of this disorder [10].

Nowadays, more than one century after the discovery of this disorder [11], AD is still a chronic condition with no cure or effective interventions to delay its progression [12]. The current medical approaches for AD are limited to symptomatic interventions and the complexity of the disease has led us to constant failures in clinical trials [13]. The pharmacology of AD is

currently limited to cholinesterase inhibitors (rivastigmine, galantamine and donepezil) and memantine, which is an N-Methyl-D-aspartate (NMDA) receptor antagonist. These treatments are not able to prevent or reverse the progression of AD and are often accompanied by many adverse effects. In fact, no new drug has been approved for AD treatment since 2003 [14].

Some authors believe that AD drugs have failed mainly because of an inadequate target, since the majority of studies have focused on the drugs targeting amyloid [15,16], however other factors such as the stage of the disease at the moment of therapy initiation and the heterogeneity of factors implicated in AD pathophysiology should also be considered [17,18]. Consequently, the multifactorial hypothesis of AD has been proposed by some to ponder divergent thinking and investigate multiple and diverse etiological factors that might be converging in a common brain pathology [19]. In this review, we aim to present the striking of the long scientific path since the first description of an AD case and the main AD hypotheses proposed over the last decades. Additionally, the “type 3 diabetes” hypothesis is discussed as accumulated evidence points towards insulin as an important factor implicated in etiopathogenesis of AD, and dysfunctional insulin signaling in the brain provides a common link between other proposed hypotheses.

THE PIONEERING DESCRIPTION OF ALZHEIMER’S DISEASE

Alois Alzheimer, a German psychiatrist, described an AD case for the first time on November 4th of 1906, at the 37th annual conference of German psychiatrists, in Tübingen, Germany [20]. In his lecture, Alzheimer reported a case study describing a “peculiar severe disease process of the cerebral cortex”. Although Alzheimer's presentation did not arouse the interest of the numerous scientists present in the audience, the case was published one year after the conference [1]. Alzheimer’s talk was based on the case of a 51-year-old woman (August D.) from Frankfurt who had presented with psychiatric symptoms of progressive cognitive impairment, aggression, and hallucinations, with subsequent autopsy revealing atherosclerotic

changes of the larger brain vessels, and specific neurofibrillary changes unknown at the time [21].

Briefly, on November 26th, 1901, a man took his wife to the Community Psychiatric Hospital at Frankfurt am Main after observing substantive changes in her personality and behavior. The first behavioral changes presented by August D. were characterized by bouts of excessive jealousy toward her husband which evolved into significant memory impairment, delusions and psychosocial incompetence [1,21]. At that time, Alzheimer was an assistant physician, and with the consent of Emil Sioli, the Director of the Frankfurt Hospital, he decided to examine and interview August D. However, in 1903, Alzheimer moved to Heidelberg to work with Emil Kraepelin, one of the main psychiatrists at that time, and shortly afterwards, they both moved to Munich, where Alzheimer supervised the completion of a new University Hospital for Psychiatry and assumed the control of a modern histopathological laboratory, where he continued his histopathological research with important scientists from all over the world, including Friedrich H. Lewy, the famous neurologist who discovered the Lewy bodies [22].

August D.'s case worsened, and she died on April 8th 1906. Following her death, Emil Sioli informed Alzheimer, who investigated the histological sections of August D.'s brain. Alzheimer analyzed the histological sections stained with Bielschowsky's silver stain and described the main hallmarks of AD for the first time: cell death, A β plaques and neurofibrillary tangles [23]. Alzheimer and Gaetano Perusini, an Italian physician specialized in dementia, kept working on other cases, and in 1909, Perusini published three more cases similar to that of Auguste D [24].

In 1910, Kraepelin included Auguste D.'s case in the 8th edition of his textbook *Psychiatrie* and proposed the term Alzheimer's disease for the first time [20]. In 1911, Alzheimer published again [25]. In this paper, he reported the case of the male patient Johann

F. who died in Munich in 1910 after being hospitalized for three years and examined by Alzheimer and Kraepelin. Johann F's case had already been mentioned by Kraepelin in his textbook, even before death, which suggest that Johann F was probably the first patient to be clinically diagnosed with AD [22]. His case presented many similarities to August D.'s case, however, Alzheimer did not identify neurofibrillary tangles in his brain slices, only A β plaques [23].

In 1998, Möller and Graeber re-examined the original histological brain slides of August D. and Johann F. with more advanced techniques [26]. They concluded that the differences observed in these two cases could be attributed to different stages of the same disease. Therefore, Alzheimer had not only reported the first case of AD, but had also described one important stage in the physiopathology of this disorder [22]. These findings laid the foundations for the most traditional and accepted theory of AD, the amyloid cascade hypothesis [27]. Nevertheless, the original debate on whether the amyloid was the cause or the consequence of the disease actually dates back to the time of Alois Alzheimer [28].

THE AMYLOID CASCADE HYPOTHESIS OF ALZHEIMER'S DISEASE

The A β , a peptide derived from a larger protein known as A β PP, was isolated in 1984, by Glenner and Wong at the University of California, in San Diego [29]. The mechanism responsible for the cleavage of A β PP and the production of A β is now well known [30]. A β PP is first cleaved off by the enzyme β -secretase (BACE 1), giving rise to two fragments: sAPP- β (N-terminal fragment), being released in the extracellular space and C-terminal fragment β (CTF β ,CT99 or CT89), which remain bound to the cell membrane. Then, the γ -secretase complex (Nicastrin, Anterior Pharynx defective 1, Presenilin enhancer 2, Presenilin 1 and or Presenilin 2) cleaves the remaining membrane-bound portion of the protein releasing the extracellular fragment A β (Fig. 1). Due to heterogeneous γ -secretase cleavage, γ -secretase can

cut A β PP at different sites, producing a 37 to 49 amino acid residue peptide. Therefore, A β can vary in length [31]. On the other hand, in the non-amyloidogenic pathway, A β PP is firstly cleaved by α -secretase within A β sequence, producing soluble α -APP fragments (sAPP α) and C-terminal fragment α (CTF α , CT83), and, posteriorly, CTF α is cut by γ -secretase, releasing non-toxic fragments [32].

In 1991, a group led by John Hardy demonstrated that mutations in the gene A β PP could cause a development of AD [33]. Subsequently, in 1996, mutations in PS1 and PS2, two genes that code for proteins from the γ -secretase complex, were found to be implicated in fAD [34]. These autosomal dominant mutations result in increased production and longer variants of A β associated with aggregation and formation of oligomers. Further agglomeration promotes the formation of insoluble fibrils, which tend to deposit in plaques. Although both types of aggregates are involved in the pathogenesis of AD [35], soluble oligomers are considered to be more toxic [36,37].

The gene encoding A β PP was found to be located on the chromosome 21 [38,39], individuals with trisomy 21 known as Down's syndrome, seem to be at an increased risk of developing AD, due to an extra copy of the gene and consequent overexpression of A β PP [40]. These factors laid the groundworks for amyloid cascade hypothesis, proposed by Hardy and Higgins in 1992 [27]. According to this theory, an acute noxious stimulus, such as head trauma, triggers the pathophysiological cascade that induces disturbances in A β PP metabolism by altering production, clearance and deposition of A β . The A β protein, in turn, leads to intracellular calcium (Ca²⁺) dysregulation, inducing neurofibrillary tangle formation and cell death [41]. Consequently, A β has been implied as a triggering factor in both forms of the disease: fAD and sAD.

On the other hand, it has already been demonstrated that A β plaques deposition can be present in elderly individuals without cognitive impairment [42–50] and it is still a matter of

debate whether or not this reflects a predisposition or a preclinical state of AD [51]. Additionally, elevated A β and the presence of plaques in individuals with Down syndrome do not always lead to the development of dementia [52]. Furthermore, the severity of dementia in humans is not proportional to quantity of A β plaques, but it is in positive correlation with the formation of neurofibrillary tangles in the neocortex, which can occur even when no plaques are present [53,54]. In fact, it has already been demonstrated that the removal of A β plaques from the brain does not prevent AD progression and the propagation of Tau pathology [55].

Another information casting doubt on the amyloid hypothesis is the fact that, although several pre-clinical studies using transgenic mice overexpressing human mutant A β PP/A β have been successful, the failure rate in AD clinical trials is approximately 99.6% [56,57]. These failures indicate that, because we still do not fully understand the pathophysiology of AD, we are failing in mimicking this disease in experimental models, or, at least, its sporadic form. Besides the fact that genetic mutations have not been sufficient to mimic sAD [58], the non-deterministic genes related to the development of the sporadic form of AD are related to lipid and glucose metabolism and not to A β production [59].

In this context, despite promising results in experimental studies with animal models, many anti-amyloid drugs have failed over the years [12,60]. In the enzyme inhibitors group, γ -secretase inhibitors, such as Semagacestat from Eli Lilly, failed mainly because of the numerous other cellular substrates of γ -secretase, which ended up worsening the cognitive impairment and increasing skin cancers and infections cases [61,62]. BACE inhibitors, such as Verubecestat (MK-8931), have also been developed and, although they seemed to be safer than γ -secretase inhibitors, these drugs were not able to promote any improvement in cognitive function [63,64].

Active and passive immunization against A β have also been tested [12,65]. In humans, active immunization against aggregated human A β ₁₋₄₂ (AN1792, Elan Pharmaceuticals) that demonstrated desirable effects on plaque burden and cognitive performance in transgenic AD

mice [66], resulted in removal of amyloid plaques in a few patients, but provoked aseptic meningoencephalitis in others [67–69]. Due to this adverse effect, the study was interrupted with drug dosing terminated in January 2002. Nevertheless, thorough clinical follow-up and monitoring of the non-affected patients continued under blinded conditions enabling retrospective analyses [67]. In one such retrospective analysis of the cohort, Nicoll and colleagues (2019) executed a 15-year post-mortem neuropathological follow-up of individuals who participated in the first trial of A β immunotherapy . The authors concluded that, although a clear evidence of plaque removal was observed, most patients progressed to severe cases of dementia, possibly due to propagation of Tau as extensive distribution of tangles (Braak V/VI) was found in a substantial number of patients [55].

Other A β -targeting antibodies (Solanezumab, Crenezumab, Gantenerumab, Bapineuzumab) were also tested, but although some positive effects have been observed, the results were not always replicable [70–74]. Defenders of the amyloid cascade hypothesis believe that the failures in these trials occurred because of difficulties in establishing adequate protocols. Problems of inappropriate dosing and administration of the drug in the late irreversible stages of the disease could explain the failure rate of clinical trials [75]. Indeed, the stage of the disease in which the drugs have been administered may have a huge impact in AD progress, since alterations in A β production, clearance and aggregation might start decades before the appearance of the first cognitive symptoms [76].

On the other hand, critics of this hypothesis argue that, besides the fact that AD is a heterogeneous disorder, the relationship between A β and AD is at least indirect. In this sense, A β might represent an end-stage of the condition rather than a cause. For them, persisting in this theory may result in loss of opportunity to consider other options, since numerous alternative hypotheses have been proposed all over the years and did not receive equal attention [15,18].

Nowadays, the two anti-A β antibodies Aducanumad and BAN2401 have shown benefits, but are still on trial [77]. Aducanumab was discontinued after a phase III futility analysis. However, after Biogen's request, the U.S. Food and Drug Administration (FDA) approved a re-dosing study [78,79]. Aducanumab has given not just support for the amyloid cascade hypothesis, but also hope to society, because, if approved, this drug will be the first medication with the ability both to remove the amyloid and slow down the cognitive decline.

ALZHEIMER'S DISEASE AS A MULTIFACTORIAL DISORDER: PROPOSAL OF OTHER HYPOTHESES

Despite all the attention the amyloid hypothesis received in the recent years, other important theories have been proposed (Table 1; Fig. 2). One example is the **cholinergic hypothesis** proposed by Davies and Maloney in 1976 [80] that provided a critical insight in the role of cholinergic transmission in the context of AD etiopathogenesis, and paved the way for development of AD drugs that are in use today [81]. The involvement of the cholinergic system in dementia was first implied by the studies which demonstrated that anticholinergic drugs could exert amnesic effect [82–84] and further corroborated with findings suggesting its reversal upon treatment with a cholinergic agonist [85]. Furthermore, the activity of the enzyme choline acetyltransferase (ChAT), responsible for the synthesis of acetylcholine (ACh), was found to be significantly decreased in postmortem samples from the amygdala, cortex and hippocampus of AD patients [80,86–88].

Shortly after, Whitehouse and colleagues observed a substantial loss of neurons in the nucleus basalis of Meynert (NbM), the source of cortical cholinergic innervation in the brain [89]. Ever since, the neurodegeneration of cholinergic projections from the NbM to the neocortex and the hippocampus has been considered as one of the main events in the pathophysiology of AD [90]. In addition, the proportion of cholinergic neurodegeneration was

found to have a positive correlation with the severity of dementia in AD [91,92]. Based on these findings, lesions in cholinergic projections from the basal forebrain to the cortex and hippocampus have been employed for induction of animal models of AD [93].

The cholinergic hypothesis was a stepping stone in the process of development of most drugs approved to treat AD - the acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine, donepezil) [94]. These drugs ameliorate cognitive symptoms, but, unfortunately, they are not able to decrease the risk, slow up the onset, or stop the progression of AD. Moreover, individual responses to these drugs may vary. Tacrine, the first drug approved by the FDA and introduced in the US marketing in 1993 [95], had quite poor adherence and presented many adverse effects, including hepatotoxicity, which led to its discontinuation in 2013 [96]. Donepezil, the second drug approved by the FDA, was marketed in 1996 for the treatment of mild and moderate AD. However, in 2010, a higher dose was approved to treat more severe cases. Donepezil is accompanied by side effects, such as nausea, diarrhea, dizziness and insomnia, and cardiac adverse effects have been reported in some rare cases [97,98].

Galantamine [99] and rivastigmine [100] were both approved in 2000 for the treatment of AD. However, rivastigmine has also been used to treat Parkinson's dementia [101]. Recently, Ray and colleagues demonstrated that rivastigmine is able to direct A β PP processing away from the amyloidogenic pathway, by promoting α -secretase activity and, therefore, it might be explored as a disease-modifying treatment [102].

The cholinergic hypothesis has given support to the amyloid cascade theory [103] since the discovery that stimulation of cholinergic receptors regulates A β PP metabolism [104] and that A β toxicity can promote cholinergic impairment [105]. Other studies have demonstrated that nicotinic cholinergic receptor stimulation can modulate phosphorylated Tau aggregation [103] also corroborating the Tau hypothesis of AD [106].

The **Tau hypothesis** claims that Tau hyperphosphorylation precedes neurodegeneration and, in association with convergent signaling mechanisms, results in AD pathophysiology [107,108]. Moreover, there is evidence that alterations in Tau phosphorylation occur before A β accumulation [109]. The microtubule-associated protein Tau is the main component of neurofibrillary tangles [107]. Tau interacts with tubulin to promote microtubule polymerization and stabilization. However, Tau functions are regulated by its phosphorylation state. In a hyperphosphorylated state, the interaction of Tau and microtubules is hindered, resulting in destabilization and loss of cytoskeletal structure [110].

The human Tau gene is localized on chromosome 17. There are six Tau isoforms expressed in the adult brain, as a result of alternative mRNA splicing [11]. In AD, all six protein isoforms may be abnormally hyperphosphorylated, resulting in the formation of neurofibrillary tangles and destabilization of the microtubule network [111]. Therefore, in AD-impaired neurons, degenerating neuronal microtubules might be gradually replaced by tangles [112].

The fact that the severity of AD cases correlates well with Tau pathology in the brain has contributed to the confirmation of Tau hypothesis [113]. Tau pathology is usually classified according to Braak and Braak [114], affecting primarily the transentorhinal region in stages I and II, the limbic system in stages III and IV, and neocortical fields, mainly temporal and parietal areas, in more advanced stages (stages V and IV) [106]. In this sense, Tau has been investigated as a potential target in AD treatment. However, similar to the anti-amyloid therapies, strategies focused on Tau have also failed in clinical trials. The Tau aggregation blocker TRx0237 [115] and the Tau-targeted passive vaccine IVIG [116], for example, have both failed in phase III trials. Other trials are in progress, yet, since we do not completely understand the pathogenesis of AD, Tau-based therapeutic approaches still remain challenging [117].

Besides microtubule dysfunction, abnormal Tau phosphorylation promotes defective axonal transport of mitochondria and other organelles [118]. In fact, mitochondrial dysfunction has been frequently reported in AD [119], and, therefore, it has given support to another theory, the so-called **mitochondrial cascade hypothesis** [120–122].

In 1989, Parker suggested that mitochondrial DNA inheritance could influence AD risk [120,123]. Other authors claimed that somatic mitochondrial DNA mutations were able to influence the aging process [124–127] and, more specifically, AD development [128–131]. Then, in 2004, Swerdlow and Khan proposed that, since the individual's baseline mitochondrial function is defined by genetic inheritance, interactions between genetic and environmental factors would define the rhythm at which mitochondrial dysfunction accumulates and, therefore, would determine the AD onset [122]. Subsequently, other studies demonstrated that a maternal family history of AD increases the risk of developing the disease, when compared to a paternal family history of this disorder, which indicates that the maternally inherited mitochondria might play an important role in mitochondrial dysfunction and mediate the risk for the development of AD [132,133].

The mitochondrial cascade hypothesis may be linked to other theories [3] especially the amyloid cascade theory as mitochondrial dysfunction affects both A β PP expression and metabolism [134–137]. Indeed, besides the fact that functional mitochondria are essential for A β neurotoxicity [134], A β PP and A β co-localize with the mitochondrial network [135]. Therefore, it has been suggested that mitochondria mediate A β toxicity [119]. Furthermore, A β PP overexpression and A β exposure alter mitochondrial function in transgenic mice, cultured cells and autopsy brains [119,136–139].

Besides A β accumulation [139], there is evidence that mitochondrial dysfunction promotes Tau hyperphosphorylation [138] inflammation [140] and oxidative stress [141]. Moreover, mitochondrial changes, such as decreased rate of metabolism [140], decreased

mitochondrial concentration in the cerebrospinal fluid [141], and mitochondrial morphological alterations [142,143] have also been described in AD [144]. For this reason, mitochondrial enzymes and energy metabolism have been investigated as potential targets of drugs for the treatment of AD [145].

Mitochondrial dysfunction has also been implicated in the pathogenesis of AD through the generation of reactive oxygen species (ROS) [146]. ROS are oxygen-containing chemicals with reactive properties that play a fundamental role in maintenance of cellular homeostasis. ROS are constantly being produced as by-products of non-enzymatic reactions in the respiratory chains, or enzymatically by macrophages upon recognition of pathogen-associated molecular patterns. Physiologically, enzymes and other compounds usually control and maintain ROS at low levels in a defined homeostatic range, as they cannot be totally eliminated because of their function as specific second messengers in signaling cascades related to cell proliferation and differentiation. However, accumulation of high levels of ROS, usually due to overproduction or inadequate clearance, disrupts cellular homeostasis by a pathophysiological process known as oxidative stress. Since oxidative stress can damage cells, proteins, lipids, Ca^{2+} homeostasis, and DNA, it is considered harmful to the human body and a strong contributor to the process of aging [147].

Central nervous system is particularly susceptible to free radical damage due to its large oxygen demand and high mitochondrial respiration rate. Besides that, the central nervous system is characterized by a high lipid content and low capacity of enzymatic and non-enzymatic antioxidant systems, which may promote cumulative oxidative damage over time and contribute to AD pathogenesis [148].

In AD, different biomolecules from the neuronal membrane, such as lipids, fatty acids, and proteins can undergo oxidation [149]. There is evidence showing that high ROS levels may be present in earlier stages of AD, even before the appearance of $\text{A}\beta$ accumulation or clinical

symptoms [150]. And, besides the high amount of evidence showing that A β induces oxidative stress in AD [151], regions with elevated levels of A β , such as cortex and hippocampus, present higher levels of oxidation products when compared to regions with low A β levels, such as the cerebellum [150–152]. Moreover, oxidative stress seems to be related to modifications of protein Tau conformation, which contributes to the formation of neurofibrillary tangles [153,154]. Alterations in Tau conformation, in turn, can potentiate oxidation of DNA and RNA [147,155], evolving into a pathological cycle. Biometals also play an important role in neurodegeneration [156]. In this sense, increased concentrations of redox-active transition metals such as iron and copper, and the redox-inactive metal, zinc have been observed in A β plaques and surrounding tissues [152,157].

Corroborating the **oxidative stress hypothesis**, studies have demonstrated that AD patients present depletion of plasma antioxidants when compared to controls and that a good antioxidant status may be able to protect against cognitive impairment [158]. Moreover, since oxidative stress seems to be only one of many features of AD, neuroprotective potential of antioxidant compounds has been studied as a potential treatment option, but usually in combination with other therapies [159]. In this context, the phytocannabinoid cannabidiol (CBD), a constituent of *Cannabis sativa*, has been considered as a potential compound for AD treatment [160,161]. CBD is especially attractive as, besides its antioxidative and antioxidant properties, it also presents anti-inflammatory features [162] and neuroprotective effects on memory [163–167]. In addition, CBD appears to alleviate the hyperphosphorylation of Tau protein by attenuating glycogen synthase kinase 3 beta (GSK-3 β) activity [168]. Furthermore, CBD has been shown to promote hippocampal neurogenesis [169] and prevent cortical and hippocampal neurodegeneration [170].

Another metabolic condition that has been implicated in AD along with mitochondrial dysfunction and oxidative stress is neuroinflammation [171–173]. This pathophysiological

process, characterized mainly by the accumulation of glial cells and upregulation of pro-inflammatory cytokines in the central nervous system, has been investigated as the crucial event in AD pathogenesis for more than two decades [174–177]. The peripheral immune system is linked to the brain through different mechanisms, including direct passage of cytokines from the blood through leaky regions in the blood-brain barrier (BBB), carrier-mediated transport of cytokines into the brain, and stimulation of cytokine synthesis by microglia activation after detection of a peripheral immune response via vagal afferents [178]. The immune system became particularly relevant to AD research once genome-wide association studies (GWAS) discovered that numerous immune genes are risk factors for sAD [179,180].

According to the **neuroinflammation hypothesis** of AD, an initial inflammatory stimulus, which could be a trauma, a pathogenic infection or even A β toxicity, triggers microglial activation. Microglia, in turn, secretes numerous pro-inflammatory cytokines, such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF α), and releases ROS, attracting more microglia and astrocytes towards the lesion area [181]. Physiologically, this process is critical for reparation of the damaged area. However, in pathological aging, and, more specifically, in AD, this stimulus is persistent and results in excessive activation of microglia, which initiates an auto-destructive process, culminating in neurodegeneration and AD pathogenesis [176,182].

Microglial activation is usually beneficial, as microglia participates in A β clearance and degradation [183], but its persistent activation may result in neurotoxic effects [184]. In fact, there is evidence that hyper-reactive microglia is present even in early stages of sAD [185]. In this sense, studies have demonstrated that constant microglial activation stimulated by A β , increases A β production and diminishes its clearance [186,187]. However, the inflammatory process induced by other agents is also able to increase A β production, via β -secretase cleavage [184]. Furthermore, hyperphosphorylated Tau leads to the activation of microglial cells, and

synthesis and production of pro-inflammatory cytokines [188]. Pathologically changed astrocytes have also been described in AD [189] and, although astrogliosis has been observed in regions without A β pathology, in AD brain tissue, astrogliosis is correlated with the degree of cognitive impairment [190].

In summary, the response to inflammatory stress induces hyperphosphorylation of Tau and increases A β synthesis. In addition, both A β accumulation and Tau hyperphosphorylation dysregulate the immune system and activate a constant and persistent inflammatory process, leading to a deleterious microglial and astrocytic reactivity, and, consequently, trigger a vicious circle of neurotoxic pro-inflammatory response [191].

Studies have consistently reported elevated levels of pro-inflammatory cytokines in serum and brain tissue of AD patients relative to controls, especially in severe AD [192–194]. More recently, it has been proposed that ambient air pollution might be able to trigger microglial activation and, consequently, provoke a constant inflammatory process accompanied by a permanent elevation of pro-inflammatory cytokines and ROS that could lead to AD and other neurodegenerative diseases [195,196]. Indeed, alterations in microglial morphology, increased proinflammatory cytokines and elevated oxidative stress have been observed in brains of humans and animals exposed to high levels of ambient urban air pollution [197–203].

Although the effects of the exposure to anti-inflammatory drugs in AD, specially nonsteroidal anti-inflammatory drugs (NSAIDs), are still controversial, some studies have observed benefits in the use of this type of medication before the onset of AD [204]. The early-stage responsiveness of AD to NSAIDs might be explained by the fact that, in advanced stages of the disease, the overactive microglia would go through a process of senescence and become non-functional, reaching a dystrophic status. At this stage, the senescent microglia would not be able to accomplish its physiological roles such as neuroprotection and clearance, but would maintain its ability to produce pro-inflammatory cytokines, thus accelerating the

disease progress [205,206]. Furthermore, it has been proposed that the activation of the innate immune system might act as a disease-promoting factor in which the senescent microglia is the initial trigger of AD pathogenesis [207]. In this case, AD should be considered an immune senescent disease rather than a neuroinflammatory disorder, as stated by the **innate immunity hypothesis** [208–210].

Another pathophysiological event that has been proposed as both the cause and the consequence of metabolic, oxidative, and proteotoxic stress in AD is dysregulation of Ca^{2+} homeostasis [211]. In this sense, **the calcium hypothesis**, postulated more than 30 years ago [212–214], proposes that sustained alterations in Ca^{2+} signaling in neurons might be a key event of AD pathogenesis [215]. This hypothesis has been supported by the findings suggesting that gene mutations that increase the risk for developing AD are usually related to dysfunctional Ca^{2+} signaling [211].

The Ca^{2+} ion works as an intracellular messenger in many signal-transducing pathways and as a regulator in diverse physiological functions. Because of the importance of Ca^{2+} homeostasis, a number of cellular regulatory mechanisms, such as ion channels, buffers and ATP-dependent ion pumps, are working to keep the level of Ca^{2+} at low nanomolar concentrations under resting conditions [216]. Homeostasis is particularly important as action potential-regulated influx and efflux of calcium is indispensable for proper neuronal signaling. Consequently, regulation of a complex network of calcium channels and transporters, as well as conserved activity of endoplasmic reticulum (ER) and mitochondria, two main organelles responsible for intracellular buffering, is a prerequisite for maintenance of structure and function of the central nervous system. Failures of this system results in the inability to maintain calcium homeostasis and leads to neurodegeneration [217]. Although astrocytes, the main homeostatic regulatory cells in the central nervous system, cannot generate action

potentials, they sense fluctuations in intracellular concentration of ions, especially Ca^{2+} , in order to respond to neuronal activity [218].

Corroborating the calcium hypothesis, several studies have shown a bidirectional relationship between Ca^{2+} and the $\text{A}\beta$ peptide in pathogenesis of AD [219]. In this context, it has already been demonstrated that $\text{A}\beta$ aggregates disrupt Ca^{2+} signaling in numerous ways and that Ca^{2+} dysregulation may also alter $\text{A}\beta$ PP metabolism [220–225]. This link has been confirmed by the findings of the longitudinal aging study suggesting that individuals who use calcium channel blockers (CCBs) in the antihypertensive treatment present a significantly slower rate of progression to dementia. This effect could be related to a significant CCBs-induced decrease in $\text{A}\beta_{1-42}$ levels found in neuroglioma cultures overexpressing APP [226].

Tau pathology might also be linked to disruption in Ca^{2+} signaling once microtubule dysfunction promoted by hyperphosphorylation of Tau impairs dynamics and axonal transport of organelles and vesicles, including mitochondria and ER [118]. When these components are affected, they end up directly influencing calcium signaling pathway, especially in neurons where the communication networks between ER, mitochondria and plasma membrane are fundamental for the regulation of temporal and spatial aspects of Ca^{2+} signaling [227].

Recently, Jadiya and colleagues (2019) demonstrated that impaired mitochondrial calcium efflux stimulates disease progression in AD models, by accelerating memory alterations, $\text{A}\beta$ pathology, Tau hyperphosphorylation and development of histopathological changes [228]. In fact, some authors believe that, since mitochondrial Ca^{2+} overload may appear before the typical pathological features of AD, it should be considered a priority among therapeutic targets for AD [229]. Finally, all proposed hypotheses should not be considered individually, but as pieces of the pathophysiological puzzle contributing to understanding of the etiopathogenesis of AD. Some hypotheses, such as the mitochondrial hypothesis of the disease, and oxidative stress hypothesis as well as the calcium hypotheses are more closely

related as mitochondrial dysfunction is often considered as a key contributor to cellular ROS burden, and bidirectional interaction between the ER calcium and mitochondria make it difficult to distinguish their cause-effect relationship. Nevertheless, a number of less obvious interconnections exist between all factors proposed as the main drivers of the disease, and current understanding of molecular mechanisms suggests all have the potential to trigger a pathogenic cascade of AD. Recently, accumulated evidence on the importance of metabolic factors in the context of AD provided additional information that, when considered in the context of other hypotheses, might enable deeper understanding of the pathogenesis of the disease and reveal some links that might have been overlooked. Due to numerous metabolic alterations described in AD, it was proposed that this disorder contains a significant metabolic component [230]. One of the main features of AD hypothesized as a metabolic disorder is the consistent findings suggestive of impaired insulin signaling in AD brains. In fact, the term “type 3 diabetes” has been proposed in order to englobe the cellular and molecular mechanisms by which insulin plays an important role in the pathology of AD. Interestingly, alterations in the regulation of the insulin signaling pathway, just like A β peptide accumulation, seem to be related to many aspects of AD discussed in this review.

ALZHEIMER'S DISEASE HYPOTHESIS OF A “TYPE 3” DIABETES

Although cognitive dysfunction in *Diabetes mellitus* (DM) has been frequently reported over the last decades [231–238], the first study showing worse performance in attention and memory tests in diabetic patients was made in Boston by Miles and Root, almost a century ago [239]. At that time, these findings were not well understood, however, in 1983, Bucht and colleagues found important results suggestive of decreased insulin sensitivity in AD patients [240]. These data implied for the first time that the hormone insulin could somehow be involved in the etiopathogenesis of AD. In 1998, Frölich and colleagues described alterations in the neuronal insulin signal transduction pathway in AD brains [241], which culminated in the

proposal that AD is a brain type of non-insulin dependent DM, made by Hoyer [242] in the same volume. After extensive work, in 2005, a group led by Suzanne de La Monte at the Brown Medical School proposed the term “type 3 diabetes” to refer to AD as a neuroendocrine disorder, similar, but also distinct, from DM types 1 (T1DM) and 2 (T2DM) [243].

More recently, studies have demonstrated that DM is a risk factor for developing dementia [244–247]. According to Chatterjee and colleagues, this risk is approximately 60% greater for diabetic patients compared with those without diabetes [248]. The most prominent factors that seem to be shared by T2DM and AD as common risks could be found often combined, from aging and age-related alterations like metabolic, hormonal and vascular pathology to environmental factors. Additionally, although the link between the two diseases is still not fully understood, associations have been reported also at the genetic level [249]. Caberlotto and colleagues have recently analyzed transcriptomic data of post-mortem AD and T2DM human brains and identified a central role for the autophagy pathway in both diseases. In addition, the authors used genetically modified animal AD models to confirm the role of autophagy-related genes in AD pathogenesis. These results suggest that autophagy dysregulation might be a common pathophysiological mechanism underlying AD and T2DM [250].

Considering the metabolic factors, particularly glucose metabolism in the brain, decreased glucose utilization and altered energy metabolism have been reported since early stages of AD [248], especially in regions associated with the process of learning and memory [251,252].

Evidence has gathered supporting the link between AD and T2DM based on the presence of AD biomarkers in the brain tissue of diabetic patients without clinical signs of dementia [253–256] and alterations in insulin signaling pathways found in the brain of both AD patients post mortem and AD animal models [241,243,257–259]. The insulin signal

transduction pathway is particularly important in the brain because of its functions related to neuronal survival, central regulation of body metabolism and modulation of memory and other cognitive and emotional processes [260].

The insulin signal transduction pathway in the AD brain

The presence of insulin in the central nervous system, as well as its origin and functions have been widely debated over the decades [261–265] mainly because glucose uptake by neurons is not insulin dependent. After extensive research in this field, it has become evident that both insulin and insulin receptors (IR) are distributed in a region-specific manner in the brain, with highest density in the hippocampus, cerebral cortex, olfactory bulb and hypothalamus [266–270]. Moreover, it is now known that glucose uptake in the brain can be influenced by insulin in conditions of high energy demand induced by increased neuronal activity. Increased glucose uptake upon insulin binding is mediated by the stimulation of the translocation of glucose transporters type 3 (GLUT3) and type 4 (GLUT4) to the plasma membrane in the conditions of increased energy demand, such as hippocampal-dependent tasks [271,272]. Studies have also demonstrated that systemic insulin may be actively transported through the BBB to the central nervous system [266,270,273,274], but a small portion of insulin can also be locally produced by neurons [275–279]. There is a higher density of IR in neurons as compared to glia, but astrocytes express both IR isoforms (IR-A and IR-B; IR-A, in contrast to IR-B, shows no negative cooperativity, indicating different functional regulation upon insulin binding), while neurons express exclusively the IR-A isoform [280].

IRs are composed of dimers of alpha (extracellular) and beta (intracellular) subunits joined by disulfide bonds. Insulin, or insulin-like growth factors (IGF), bind to the alpha subunits of IR inducing autophosphorylation of its beta subunit on tyrosine residues, thereby promoting the transduction of many signaling pathways [281], especially related to cell proliferation and metabolism. Then, the signal is transduced through the phosphorylation of

insulin receptor substrates (IRS), which are usually composed of six members (IRS1-6), also on tyrosine residues [282]. The IRS-1 is one of the most well described in humans and it is involved in modulation of essential functions in the cerebral cortex [260]. Phosphorylation of the IRS promotes conformational changes that enable the binding between IRS and another enzyme, phosphoinositide 3-kinases (PI3K). PI3K activation, in turn, phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP₂) at the cell membrane and results in the formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP₃). Then, PIP₃ enables protein kinase (AKT/PKB) signaling pathway [283], which regulates the activation of many intracellular proteins in pathways related to cell proliferation and survival, such as the mammalian target of rapamycin (mTOR), forkhead box (FOX) proteins and Glycogen synthase kinase-3 (GSK3), besides the facilitation of the translocation of GLUT4 to the cell membrane and glucose uptake into the cell by the metabolic pathway [284].

GSK-3 activity is extremely relevant to AD pathogenesis and has emerged as an important target for AD drug development [285–287]. There are two isoforms of GSK-3 in mammals, the isoforms α and β , encoded by two different genes [288]. While GSK-3 α regulates A β production [289], GSK-3 β modulates phosphorylation of Tau [290]. In fact, GSK-3 β is the main kinase of Tau protein, and it is able to phosphorylate at least 12 Ser/Thr of its pro-sites [291–293]. Moreover, GSK3- β activity may also be involved in A β production through the modulation of A β PP cleavage, as PS1 has been identified as a GSK-3 β substrate and GSK3- β over-activation or overexpression stimulates the cleavage of A β PP by BACE1 [288]. The activities of GSK-3 α/β are inhibited through phosphorylation of GSK-3 by AKT at serines 21 and 9, respectively [294].

GSK-3 is expressed in all tissues, but it is particularly abundant in the brain, especially in the hippocampus [295]. It can inhibit insulin signaling through serine phosphorylation of the IRS 1 and 2 [296–298]. It is also the main suppressor of Wnt signaling pathway, one of the

most important developmental pathways that regulates fundamental aspects of cell fate determination, such as cell migration and neural patterning [299], which means that GSK-3 is able to influence cell differentiation and reproduction [295,300–302]. GSK-3 is also involved in regulation of learning and memory functions, and processes of neurodegeneration, neurogenesis, inflammation and synaptic plasticity, therefore alterations in GSK-3 activity found in AD could provide a molecular background for some of the neuropathological hallmarks of the disease [295,303]. Since GSK-3 phosphorylation at serine inhibits its activity, it would be expected to observe decreased phosphorylated GSK-3 α/β levels in AD brains. Curiously, AD studies have been contradictory and, while some authors identified increased levels of GSK-3 α/β in its active form [304], others observed increased GSK-3 phosphorylation [305,306]. Elevated expression and over-activity of GSK-3 has also been reported in T2DM [307] providing further support to dysfunctional IR signaling cascade as an underlying pathology linking AD and T2DM. Furthermore, increased expression and activation of GSK-3 have also been observed in other diseases, such as bipolar disorder [308–310], Parkinson's disease [311–313], and Huntington's disease [314,315].

Therefore, inhibition of GSK-3 has been investigated as a candidate pharmacological target for the treatment of many diseases, especially AD [287]. One of the most well studied drugs in this field is lithium, a non-selective GSK-3 inhibitor. However, the obtained results are contradictory and inconclusive [316–318]. Similar results were found with a small molecule non-ATP-competitive and irreversible GSK-3 inhibitor tideglusib (NP12) [319,320]. More recently, a meta-analysis performed by Matsunagaa, Fujishirob and Takechia suggested that GSK-3 inhibitors might not be effective in AD treatment. However, the protocol established in the analyzed studies might have not been adequate, and non-selective inhibition of GSK-3 in a number of different cell types with consequent modulation of important signaling pathways

might account for both ineffectiveness and side-effects of such a treatment. Hence, further studies are needed to obtain final conclusions about GSK-3 inhibitors [287].

Besides changes in GSK-3 activity, other upstream alterations in the insulin signaling cascade have also been reported in AD pathogenesis. For example, decreased levels of insulin, IGF-1, and their receptors have already been identified in AD brains [241,243,321]. Lower levels of IRS-1 [322] and increased IRS-1 serine phosphorylation, which disable normal transmission of signal through the IR-IRS signaling pathway and may result in insulin resistance [323,324], have been described in AD [325–327], even a decade before the clinical onset of AD [328]. Serine IRS-1 phosphorylation might be associated with Tau dysfunction in AD. In Tau knockout mice, serine phosphorylation of IRS-1 is increased, and insulin-induced hippocampal tyrosine phosphorylation of IRS-1 is decreased [329]. Decreased levels of PI3K and reduced phosphorylation of Akt have also been reported in AD [273,322]. Dysfunctional PI3K/Akt pathway has important downstream signaling consequences in AD, since it has been recognized as a molecular regulator of GSK-3, mTOR, glucose transporter trafficking, and autophagy, all recognized to be altered in the process of neurodegeneration.

IR signaling pathway also leads to the activation of the mitogen-activated protein kinase (MAPK) pathway, which regulates cell differentiation, proliferation, survival, death and metabolic activity. The expression of MAPK is increased in AD brain tissue and it is found to also be involved in the process of A β plaques formation, Tau hyperphosphorylation, neuroinflammation, oxidative stress and synaptic plasticity. Furthermore, MAPK seems to be involved in the regulation of cognitive function [258,330]. Consequently, MAPK has also been proposed as a possible therapeutic target in AD [331] and some candidate molecules have been tested in this context. For example, brain-permeable orally bioavailable small molecule isoform-selective inhibitor of p38 α MAPK MW181 was reported to improve working memory,

reduce Tau phosphorylation and inflammation in Tau transgenic mouse model of tauopathy [332].

Since many studies have demonstrated that impairment in both peripheral and central metabolism is related to cognitive decline and dementia [333–335] insulin levels and sensitivity became therapeutic targets in AD treatment [336]. In line with that, both insulin secretagogues like glucagon-like peptide 1 (GLP-1) receptor agonists insulin sensitizers, such as thiazolidinediones and biguanides, have been shown to improve cognitive function in both AD patients and animal models [337–339]. Metformin, a biguanide that decreases gluconeogenesis in the liver and ameliorates insulin resistance, has been associated with a reduced risk of developing AD in older people with DM [340]. Although some results have been contradictory, studies have shown that this drug is able to interfere with the formation of A β plaques and neurofibrillary tangles and improve insulin signaling in the brain [258,341–343].

Many antidiabetic drugs have been investigated in AD treatment. These drugs may present numerous positive effects, such as improvement of insulin resistance and cell metabolism, which might result in amelioration of cognitive impairment [330]. Recently, in a literature review, Meng and colleagues summarized the available clinical and experimental studies reporting the effects and the potential mechanism of action for 14 antidiabetic drugs that have been considered for AD treatment [344]. Among them, insulin administration has led to, besides other benefits, significant improvement in cognitive function in both humans and animal models.

Effects of insulin administration on memory and Alzheimer's disease

Numerous studies have investigated the effects of insulin administration in the central nervous system in order to better understand the role of this hormone in cognition, and, more specifically, in AD [345]. Curiously, while peripheral insulin administration promotes memory deficits in rodents [346], probably through the induction of hypoglycemia [347], intranasal

insulin administration has shown positive effects in cognitive function in both clinical and experimental studies [306,348–350].

When insulin is applied to the nasal mucosa, its transport to the brain is facilitated by the axon bundles of the receptor cells in the roof of the nasal cavity that are involved in the process of olfaction. In this context olfactory bulb and hippocampus stand out as the most important brain structures involved in the process. Trigeminal pathways and rostral migratory flow also appear to be involved in this transport [351–354]. This type of administration does not alter peripheral insulin or glucose levels [355] and it usually takes 1 hour for insulin to bind to IRs in the hippocampus and frontal cortex in animals [356] and humans [351,357]. The importance of findings related to this treatment modality are further corroborated by the fact that the National Institutes of Health (NIH) appointed intranasal insulin administration as one of the most promising therapeutic strategies for the treatment and prevention of AD until the year 2025 [358].

Studies have demonstrated that even a single dose of intranasal insulin is sufficient to improve cognitive function in cognitively normal individuals [359–362]. In AD patients, most studies, in general, have reported positive results on cognition, [352,357,361,363–366]. Regarding the duration of treatment, literature data are inconsistent and indicate that the response might also depend on the type of insulin used for the treatment (e.g. short-acting versus long-acting) [365].

Overall, insulin treatment seems to be beneficial for the quality of life of AD patients, since studies have reported the treatment to be associated with improved functional status and daily activity [367]. Recently, the first pilot study of a single dose rapid-acting intranasal insulin in Down syndrome patients was performed by Rosenbloom and colleagues in order to verify the safety and viability of this potential treatment as this population is at high risk to develop

AD. Although the treatment was well tolerated by the subjects, the study was not powered to identify effects on cognitive function [368].

Besides the consistent reports of positive effects of insulin on memory [306,363–365,369–371], many other benefits have been observed in AD studies. Vandal and colleagues demonstrated that a single injection of insulin is able to decrease A β accumulation in a mouse model of AD [372]. In a clinical study, chronic treatment with intranasal insulin was able to modulate A β levels in early AD [366]. It has also been shown that chronic treatment with intranasal insulin decreases Tau hyperphosphorylation and improves the regulation of the insulin signaling pathway in animals [306]. Regarding neuroinflammation, one week of daily intranasal insulin treatment decreases microglial activation and increases synaptic proteins levels [373].

Although intranasal insulin administration seems to be a promising strategy in AD treatment, few studies have reported controversial results [361]. A minority of studies have observed no effect [374,375] or a reverse effect of insulin administration on memory [376]. However, some clinical studies have suggested that response to intranasal insulin may depend on other factors [367]. Four month-treatment with a short-acting insulin (20 IU or 40 IU) administered by a nasal delivery device to participants with mild cognitive impairment or AD, stratified as APOE4-carriers or -non-carriers, indicated a dose-, APOE4 status- and sex-dependent response in cognitive performance, compared to placebo [377]. The low dose group demonstrated overall treatment effect which was not seen in the high dose group where in APOE4-non-carriers cognitive improvement was observed in men and not in women while their APOE4-carrier counterparts remained cognitively stable. The results of studies with intranasal insulin treatment in cognitively impaired patients indicate that some people are better responders than the others to the treatment which targets insulin resistance in the brain, supporting thus the idea of the existence of different endophenotypes of AD and underlying the

necessity of identifying the brain insulin resistance-endophenotype features for a more successful therapy.

Some animal studies also reported conflicting results. In one study, glial overactivation has been observed following intranasal insulin treatment in F344 rats [376]. In one other study insulin treatment induced little effect on the regulation of proteins from the insulin signaling pathway [374]. Interestingly, in both studies, the treatment was tested in healthy animals, suggesting that, among other factors, the treatment effect might depend on the presence of underlying pathophysiological changes.

The link between diabetes and insulin signaling to other AD hypotheses

Evidence has gathered indicating dysfunctional insulin signaling in the brain of AD patients and animal AD models, which supports the hypothesis of AD as a "type 3 diabetes", however, alterations in the insulin signaling cascade seem to be shared by other hypotheses of AD as well. Regarding **the amyloid cascade hypothesis**, a bidirectional link between insulin and A β PP metabolism has already been identified [378]. The secretion of sAPP α , the product of normal APP processing in the non-amyloidogenic pathway related to neuronal health and brain development, is increased after insulin treatment, which indicates that insulin signaling may have functions related to the expression and activation of α -secretases that favor anti-amyloidogenic processing of A β PP and prevent A β accumulation [379,380]. Moreover, both insulin and IGFs present neuroprotective effects against A β toxicity [381–384]. These neuroprotective effects occur through the modulation of Akt and extracellular signal-regulated kinases (ERK) phosphorylation [385].

Furthermore, the insulin degrading enzyme (IDE) is one of the main factors responsible for A β degradation [386]. However, given its higher affinity, IDE binds preferentially to insulin, when compared to other substrates, including A β . Thus, insulin or pathological conditions that affect its levels, such as DM, can indirectly modulate circulating

A β levels. In this sense, conditions that decrease insulin sensitivity and increase insulin levels may result in greater accumulation of A β and, consequently, gradual deposition in senile plaques [387–389]. It has already been demonstrated that IDE's activity in the brain decreases during the process of aging and is significantly reduced in early stages of AD [390,391]. Conversely, insulin can also increase IDE protein levels via PI3K pathway and, therefore, deficient insulin signaling is correlated with decreased IDE in AD brains [392].

On the other hand, the A β peptide can form oligomers that bind to IRs, acting under certain conditions as insulin antagonists and interfering with the regulation of the insulin signaling cascade through the reduction of Akt activation and the increase of GSK-3 α/β activity [393]. A β can also induce serine phosphorylation of IRS-1, which inhibits insulin signaling and initiates a positive feedback loop, leading to an increase in A β PP processing and A β production [380]. There is also evidence that A β is able to promote the loss and redistribution of neuronal surface IRs, which might be related to the first clinical symptoms of AD [394,395].

Tau protein is related to insulin signaling in more complex ways. Marciniak and colleagues revealed this complexity when they identified brain insulin resistance in Tau knockout mice [329]. It is well known that insulin and IGF-1 modulate both Tau phosphorylation and A β production through the inhibition of GSK-3 by the PI3K-Akt signaling pathway [289,396]. However, there is also evidence that peripheral hyperinsulinemia, one of the main features T2DM, is able to alter brain insulin signaling and promote Tau hyperphosphorylation [397]. In this context, insulin resistance in T2DM is associated with elevated cerebrospinal fluid levels of Tau [398]. These findings are extremely relevant for understanding the underlying mechanism leading to an increased risk of diabetic patients to develop AD.

On the other hand, it has already been shown that intranasal insulin administration reduces Tau hyperphosphorylation in the brain of T2DM rat models induced by a high protein,

high glucose, and high fat diet followed by intraperitoneal injection of streptozotocin (STZ) [399]. STZ is a glucosamine-nitrosourea substance with alkylating properties that destroys pancreatic β -cells and leads to decreased insulin secretion and hyperglycemia, and, consequently, induces diabetes in experimental animals. Curiously, central administration of this compound produces memory deficits, impaired insulin signaling, neuroinflammation, neurodegeneration, and other molecular and pathological features that mimic those in patients with sporadic AD, and has, therefore, been considered a model of type 3 diabetes [400–403]. Chronic treatment with intranasal insulin decreases Tau hyperphosphorylation, improves cognitive function, ameliorates microglial activation and increases neurogenesis in this model [306].

Intracerebroventricular injection of STZ also generates oxidative stress and mitochondrial dysfunction, which may contribute to cognitive impairment [404,405]. Several mechanisms have been proposed to explain STZ-induced oxidative stress, and dysregulation of insulin/IGF signaling, an important regulator of redox homeostasis, provides one possible explanation [406]. Insulin resistance in T2DM is accompanied by hyperglycemia which generates the accumulation of advanced glycation end (AGE) products that promote ROS generation, and increased levels of AGE as well as overexpression of its receptor (RAGE) have also been observed in AD brains [407]. Besides oxidative stress, an imbalance between pro-oxidants and antioxidants and lipid peroxidation leading to cell damage have been identified in both AD and DM [408]. Moreover, insulin antagonizes the deleterious effects of oxidative stress in the brain. It presents neuroprotective effects against oxidative stress by restoring antioxidants and energy metabolism and modifying anti-apoptotic-associated protein synthesis through the stimulation of the PI3K/Akt pathway and inhibition of GSK-3 β [409,410]. Moreover, it has already been shown that insulin sensitizers are able to protect against mitochondrial dysfunction caused by APOE4, a genetic risk factor for AD [411].

With regards to **the cholinergic hypothesis**, Hoyer was the first researcher to associate the cholinergic system to the brain insulin signal transduction system in AD [412] based on the information that glucose and energy metabolism are fundamental to the formation of the neurotransmitter acetylcholine [406]. However, many other authors have contributed to the understanding that the memory-enhancing effects of glucose are mediated by the cholinergic system [347]. Studies with hypoglycemia due to hyperinsulinemia have demonstrated that systemic insulin administration produces memory impairments in rodents [346,347]. In addition, the authors observed that these effects were mediated by cholinergic changes, which suggested that insulin had an important role in the modulation of cholinergic influences on memory [347]. Subsequently, Rivera and colleagues demonstrated that alterations in insulin and IGF-I signaling promote brain deficiencies in acetylcholine biosynthesis [413].

Chronic **inflammation** and high levels of inflammatory markers are other two main features of DM and AD. The connection between DM and AD inflammation is corroborated by the fact that adipose-derived inflammatory mediators, usually found in T2DM, can cross the blood–brain barrier and act together with the cytokines produced by microglia, increasing brain inflammation [414]. Moreover, GSK-3 may be a key mediator between impaired insulin signaling and neuroinflammation. Increased levels of TNF α , secreted mainly by microglial cells in response to central nervous system injuries, have been identified in both DM and AD, and it has been shown that GSK-3 is able to increase its production [415]. Increased levels of TNF α have also been observed in the cerebrospinal fluid of healthy individuals after peripheral administration of a single dose of insulin [416].

In addition, it has been shown that TNF α , as well as other inflammatory cytokines and stress-sensitive kinases, can promote insulin resistance [417–419] by stimulating the serine phosphorylation of IRS via the activation of c-Jun N-terminal kinase (JNK) [257,414] and that the intracerebroventricular administration of an anti-TNF agent is able to ameliorate insulin

signaling in rats [420]. On the other hand, the anti-inflammatory cytokine IL-4 increases insulin sensitivity [418,421]. Najem and colleagues proposed that neuroinflammation, insulin resistance and A β accumulation may act together to drive the pathogenesis of AD [418]. Their proposal was based on findings that insulin signaling modulates A β -induced inflammatory response [420] and soluble oligomers of A β promote IRS-1 inhibition via TNF α activation [325]. Therefore, they suggested that AD research should focus on understanding the possible link between these three events [418].

Regarding **the calcium hypothesis**, calcium homeostasis also presents a bidirectional link with insulin signaling. Calcium flux is involved in modulation of insulin release from the pancreatic islets cells [422]. On the other hand, insulin can control calcium distribution [423]. In addition, it has already been demonstrated that PI3K-Akt signaling pathway plays important roles in the voltage-dependent calcium channel trafficking to the plasma membrane, which suggests that insulin participates in the regulation of calcium entry in excitable cells [424].

More recently, it has been shown that acute insulin treatment is able to decrease calcium transients, which may affect intracellular calcium channel functions. These results suggest that insulin-mediated changes in calcium homeostasis may contribute to the positive effects of insulin in the brain [425]. On the other hand, in the central nervous system, increased levels of intracellular calcium are related to dysfunctional glucose metabolism [426,427]. Moreover, according to De Felice, aberrant calcium influx may be related to insulin resistance in AD since neuronal response to insulin can be inhibited by the calcium chelator BAPTA-AM [428].

A possible link between AD and T2DM could also be discussed at the level of cerebrovascular pathology found in diabetic and many AD patients indicating an additive effect on dementia [429,430]. Bearing in mind the heterogeneous etiopathogenesis of vascular cognitive impairments [431] it could not be excluded that the underlying mechanisms, besides factors like hyperglycaemia, maybe also linked to insulin regulation of vascular function [336].

At normal concentrations insulin acts as vasodilator (binding to its receptors on endothelial cells stimulates release of nitric oxide via the PI3K pathway) while at high concentrations it acts as a vasoconstrictor (stimulation of endothelin-1 production via the MAPK pathway) [432]. In a T2DM condition of chronic hyperinsulinemia due to insulin resistance, the vasoconstrictory role of insulin prevails resulting in reduced cerebral perfusion which may be detected years before the cognitive impairment [336].

CONCLUSIONS

Alzheimer's disease is a severe health public problem, with no cure or interventions to delay its progression. Although numerous researchers have focused on the understanding of this disease over the last decades, AD is still a not well understood disorder, with a complex pathogenesis. A lack of perception of AD as a heterogeneous pathological condition with a multifactorial etiology might be contributing to the constant failures in AD clinical trials. After gathering all the main features and hypotheses proposed in the context of the development of AD, we can infer that a single theory that could explain all its enigmas has not yet been proposed. We believe that AD is rather a multifactorial condition that can be influenced by numerous factors and different processes and that an adequate approach of AD should englobe the multiple aspects of this disorder.

Although most studies have focused on the amyloid cascade theory of AD, the metabolic hypothesis of AD, suggesting that AD is a metabolic disorder gained a lot of attention and provided consistent basic and clinical evidence in recent years. Based on this, some authors even proposed that AD should be considered a "type 3 diabetes" to further emphasize the importance of metabolic changes in the context of etiopathogenesis of the disease. The most interesting feature of this hypothesis is the fact that it provides an integrative framework indispensable for understanding individual pathomechanisms proposed by other hypotheses and often considered individually. By adding an additional contextual layer, and providing missing

links, this integrative hypothesis of AD taking into account dysfunctional insulin signaling cascade as a missing link between many of the other proposed hypotheses, may help us deepen our understanding of the AD pathophysiology, gain different perspectives, and design better prevention and treatment strategies.

CONFLIT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

SSA conceived the original idea, participated in literature review and in writing the first draft of the manuscript. RMPSJ, GSM, JH, MSP, and NGC participated in literature review and revised the article. GSM prepared the figures for the manuscript. All authors have read and approved the final manuscript.

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REFERENCES

- [1] Alzheimer A (1907) Über eine eigenartige Erkrankung der Hirnrinde. *Zentralbl. Nervenl. Psych.* **18**, 177–179.
- [2] Magalingam KB, Radhakrishnan A, Ping NS, Haleagrahara N (2018) Current Concepts of Neurodegenerative Mechanisms in Alzheimer’s Disease. *Biomed Res. Int.* **2018**,.
- [3] Liu P-P, Xie Y, Meng X-Y, Kang J-S (2019) History and progress of hypotheses and clinical trials for Alzheimer’s disease. *Signal Transduct. Target. Ther.* **4**, 1–22.
- [4] Hanseeuw BJ, Betensky RA, Jacobs HIL, Schultz AP, Sepulcre J, Becker JA, Cosio DMO, Farrell M, Quiroz YT, Mormino EC, Buckley RF, Papp K V., Amariglio RA, Dewachter I, Ivanoiu A, Huijbers W, Hedden T, Marshall GA, Chhatwal JP, Rentz DM, Sperling RA, Johnson K (2019) Association of Amyloid and Tau with Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. *JAMA Neurol.* **76**, 915–924.
- [5] Alzheimer’s Disease International (2019) World Alzheimer Report 2019: Attitudes to dementia. *Alzheimer’s Dis. Int.*
- [6] Alzheimer’s Association (2020) 2020 Alzheimer’s Disease Facts and Figures. *Alzheimer’s Dement.* **16**,.
- [7] Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the US (2010–2015) estimated using the 2010 census. *Neurology* **80**, 1778–1783.
- [8] Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM (2016) Alzheimer’s disease. *Lancet* **388**, 505–517.

- [9] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M (2016) World Alzheimer Report 2016 Improving healthcare for people living with dementia. Coverage, Quality and costs now and in the future. *Alzheimer's Dis. Int.* 1–140.
- [10] Roher AE, Maarouf CL, Kokjohn TA (2016) Familial Presenilin Mutations and Sporadic Alzheimer's Disease Pathology: Is the Assumption of Biochemical Equivalence Justified? *J. Alzheimer's Dis.* **50**, 645–658.
- [11] Goedert M, Spillantini MG (2006) A century of Alzheimer's disease. *Science (80-.)*. **314**, 777–781.
- [12] Reynolds DS (2019) A short perspective on the long road to effective treatments for Alzheimer's disease. *Br. J. Pharmacol.* **176**, 3636–3648.
- [13] Long JM, Holtzman DM (2019) Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell* **179**, 312–339.
- [14] Cummings JL, Tong G, Ballard C (2019) Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *J. Alzheimer's Dis.* **67**, 779–794.
- [15] Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. *Nat. Neurosci.* **18**, 794–799.
- [16] Makin S (2018) The amyloid hypothesis on trial. *Nature* **559**, S4–S4.
- [17] Kepp KP (2017) Ten Challenges of the Amyloid Hypothesis of Alzheimer's Disease. *J. Alzheimer's Dis.* **55**, 447–457.
- [18] Modrego P, Lobo A (2019) A good marker does not mean a good target for clinical trials in Alzheimer's disease: the amyloid hypothesis questioned. *Neurodegener. Dis. Manag.* **9**, 119–121.

- [19] Gong CX, Liu F, Iqbal K (2018) Multifactorial Hypothesis and Multi-Targets for Alzheimer's Disease. *J. Alzheimer's Dis.* **64**, S107–S117.
- [20] G. E. BERRIOS (1990) ALZHEIMER'S DISEASE : A CONCEPTUAL HISTORY. *Int. J. Geriatr. Psychiatry* **5**, 355–365.
- [21] STRASSNIG, Martin; GANGULI M (2005) About a peculiar disease of the cerebral cortex: Alzheimer's original case revisited. *Psychiatry (Edgmont)* **2**, 30–33.
- [22] Hippus, HANNSS; NEUNDÖRFER G (2003) The discovery of Alzheimer's disease. *Clin. Res.* **5**, 101–108.
- [23] Dahm R (2006) Alzheimer ' s discovery. *Curr. Biol.* **16**, 906–910.
- [24] PERUSINI G (1909) Über klinisch und histologisch eigenartige psychische Erkrankungen des späteren Lebensalters. *Histol. und Histopathol. Arb.* **3**,
- [25] Alzheimer A (1911) Über eigenartige Krankheitsfälle des späteren Alters. *Zschr. ges. Neurol. Psychiatr.* **4**, 356–385.
- [26] Graeber H-JMMB (1998) The case described by Alois Alzheimer in 1911: Historical and conceptual perspectives based on the clinical record and neurohistological sections. *Eur. Arch. Psychiatry Clin. Neurosci.* **248**, 111–122.
- [27] Hardy JA, Higgins GA (1992) Alzheimer's Disease: The Amyloid Cascade Hypothesis. *Science (80-.)*. **256**, 184–185.
- [28] Davis JN, Chisholm JC (1999) Alois Alzheimer and the amyloid debate [3]. *Nature* **400**, 810.
- [29] Glenner GG, Wong CW (1984) ALZHEIMER'S DISEASE: INITIAL REPORT OF THE PURIFICATION AND CHARACTERIZATION OF A NOVEL

- CEREBROVASCULAR AMYLOID PROTEIN. *Biochem. Biophys. Res. Commun.* **120**, 885–890.
- [30] Nunan J, Small DH (2000) Regulation of APP cleavage by α -, β - and γ secretases. *FEBS Lett.* **483**, 6–10.
- [31] Chen G, Xu T, Yan Y, Zhou Y, Jiang Y, Melcher K, Xu HE (2017) Amyloid beta : structure , biology and structure-based therapeutic development. *Nat. Publ. Gr.* **38**, 1205–1235.
- [32] Sun X, Chen WD, Wang YD (2015) β -Amyloid: The key peptide in the pathogenesis of Alzheimer's disease. *Front. Pharmacol.* **6**, 221–215.
- [33] Goate A, Mullan M, Brown J, Crawford F, Fidani L, Giuffrat L, Haynes A, Irving N, James L, Mantl R, Newton P, Rooke K, Roques P, Talbot C, Pericak-vance M, Roses A, Williamson R, Rossor M, Owenll M, Hardy J (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**, 704–706.
- [34] Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird TD, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Viitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D YS (1996) Secreted amyloid- β protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat. Med.* **2**, 864–870.
- [35] Selkoe DJ (2011) Resolving controversies on the path to Alzheimer's therapeutics. *Nat. Med.* **17**, 1060.
- [36] Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE,

- Rozovsky I, Trommer B, Viola KL, Wals P, Zhang C, Finch CE, Krafft GA KW (1998) Diffusible, nonfibrillar ligands derived from A β 1–42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. U. S. A.* **95**, 6448–6453.
- [37] VIOLA, K. L.; KLEIN WL (2015) Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. *Acta Neuropathol.* **129**, 183–206.
- [38] Baden Rumble; Robert Retallack; Caroline Hilbich; Gail Simms; Gerd Multhaup; Ralph Martins; Athel Hockey; Philip Montgomery; Konrad Beyreuther; Colin L. Masters (1989) Amyloid A4 Protein and Its Precursor in Down's Syndrome and Alzheimer's Disease. *N. Engl. J. Med.* **320**, 1446–1452.
- [39] GLENNER, George G.; WONG CW (1984) Alzheimer's disease and Down's syndrome: Sharing of a unique cerebrovascular amyloid fibril protein. *Biochem. Biophys. Res. Commun.* **122**, 1131–1135.
- [40] Head E, Powell D, Gold BT SF (2012) Alzheimer's Disease in Down Syndrome. **1**, 353–364.
- [41] Hardy J, Selkoe DJ (2002) The Amyloid Hypothesis of Alzheimer ' s Disease : Progress and Problems on the Road to Therapeutics. *Science (80-.).* **297**, 353–356.
- [42] Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Dekosky ST, Halligan EM, Klunk WE (2008) Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly. *Arch. Neurol.* **65**, 1509–1517.
- [43] Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS (2006) Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* **66**, 1837–1844.
- [44] Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, Paykel E,

- Mukaetova-Ladinska EB, Huppert FA, O'Sullivan A, Dening T (2009) Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. *J. Alzheimer's Dis.* **18**, 645–658.
- [45] Carvalho DZ, St Louis EK, Knopman DS, Boeve BF, Lowe VJ, Roberts RO, Mielke MM, Przybelski SA, Machulda MM, Petersen RC, Jack CR, Vemuri P (2018) Association of excessive daytime sleepiness with longitudinal β -Amyloid accumulation in elderly persons without dementia. *JAMA Neurol.* **75**, 672–680.
- [46] Brayne C (2007) The elephant in the room — healthy brains in later life, epidemiology and public health. *Nat. Rev. Neurosci.* **8**, 233–239.
- [47] Dickson DW, Crystal HA, Mattiace LA, Masur DM, Blau AD, Davies P, Yen SH AM (1992) Identification of Normal and Pathological Aging in Prospectively Studied Nondemented Elderly Humans. *Neurobiol. Aging* **13**, 179–189.
- [48] Selkoe DJ (2006) Amyloid β -peptide is produced by cultured cells during normal metabolism: A reprise. *J. Alzheimer's Dis.* **9**, 163–168.
- [49] Sojkova J, Resnick SM (2011) In Vivo Human Amyloid Imaging. *Curr. Alzheimer Res.* **8**, 366–372.
- [50] Villemagne VL, Pike KE, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szoek C, Salvado O, Martins R, Keefe GO, Mathis CA, Klunk WE, Ames D, Masters CL, Rowe CC (2011) Longitudinal Assessment of A β and Cognition in Aging and Alzheimer Disease. *Ann. Neurol.* **69**, 181–192.
- [51] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavado E, Crutch S, Duyckaerts C,

- Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert M, Holtzman DM, Kivipelto M, Lista S, Bryant SEO, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR, Working I (2016) Preclinical Alzheimer ' s disease : Definition , natural history , and diagnostic criteria. *Alzheimer ' s Dement.* **12**, 292–323.
- [52] Zigman WB, Devenny DA, Krinsky-McHale SJ, Jenkins EC, Urv TK, Wegiel J, Schupf N, Silverman W (2008) *Chapter 4 Alzheimer ' s Disease in Adults with Down Syndrome*, Elsevier Inc.
- [53] Giannakopoulos P, Herrmann FR (2012) Tangle and neuron numbers , but not amyloid load , predict cognitive status in Alzheimer ' s disease. *Neurology* **60**, 1495–1500.
- [54] Arriagada P V., Growdon JH, Hedley-Whyte ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer ' s disease. *Neurology* **42**, 631–639.
- [55] Nicoll JAR, Buckland GR, Harrison CH, Page A, Harris S, Love S, Neal JW, Holmes C, Boche D (2019) Persistent neuropathological effects 14 years following amyloid- β immunization in Alzheimer ' s disease. *Brain* **142**, 2113–2126.
- [56] Banik A, Brown RE, Bamburg J, Lahiri DK, Khurana D, Friedland RP, Chen W, Ding Y, Mudher A, Padjen AL, Mukaetova-Ladinska E, Ihara M, Srivastava S, Srivastava MVP, Masters CL, Kalaria RN, Anand A (2015) Translation of pre-clinical studies into successful clinical trials for Alzheimer ' s disease: What are the roadblocks and how can they be overcome? *J. Alzheimer ' s Dis.* **47**, 815–843.
- [57] Cummings JL, Morstorf T, Zhong K (2014) Alzheimer ' s disease drug-development pipeline: Few candidates, frequent failures. *Alzheimer ' s Res. Ther.* **6**, 1–7.

- [58] Franco R, Martínez-Pinilla E, Navarro G (2019) Why have transgenic rodent models failed to successfully mimic Alzheimer's disease. How can we develop effective drugs without them? *Expert Opin. Drug Discov.* **14**, 327–330.
- [59] Bertram L, Lill CM, Tanzi RE (2010) The genetics of alzheimer disease: Back to the future. *Neuron* **68**, 270–281.
- [60] Karran E, De Strooper B (2016) The amyloid cascade hypothesis: are we poised for success or failure? *J. Neurochem.* **139**, 237–252.
- [61] Chévez-Gutiérrez L, Bammens L, Benilova I, Vandersteen A, Benurwar M, Borgers M, Lismont S, Zhou L, Van Cleynenbreugel S, Esselmann H, Wiltfang J, Serneels L, Karran E, Gijzen H, Schymkowitz J, Rousseau F, Broersen K, De Strooper B (2012) The mechanism of γ -Secretase dysfunction in familial Alzheimer disease. *EMBO J.* **31**, 2261–2274.
- [62] Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, Aisen PS, Siemers E, Sethuraman G, Mohs R (2013) A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N. Engl. J. Med.* **369**, 341–350.
- [63] Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B, Sur C, Mukai Y, Voss T, Furtek C, Mahoney E, Mozley LH, Vandenberghe R, Mo Y, Michelson D (2018) Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* **378**, 1691–1703.
- [64] Scott JD, Li SW, Brunskill APJ, Chen X, Cox K, Cumming JN, Forman M, Gilbert EJ, Hodgson RA, Hyde LA, Jiang Q, Iserloh U, Kazakevich I, Kuvelkar R, Mei H, Meredith J, Misiaszek J, Orth P, Rossiter LM, Slater M, Stone J, Strickland CO, Voigt JH, Wang G, Wang H, Wu Y, Greenlee WJ, Parker EM, Kennedy ME, Stamford AW (2016) Discovery of the 3-Imino-1,2,4-thiadiazinane 1,1-Dioxide Derivative

- Verubecestat (MK-8931)-A β -Site Amyloid Precursor Protein Cleaving Enzyme 1 Inhibitor for the Treatment of Alzheimer's Disease. *J. Med. Chem.* **59**, 10435–10450.
- [65] Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandeventer C, Walker S, Wogulis M, Yednock T, Games D SP (1999) Immunization with amyloid- β attenuates Alzheimer-disease-like pathology in the PDAPP mouse model. *Nature* **400**, 173–177.
- [66] Fettelschoss A, Zabel F, Bachmann MF (2014) Vaccination against Alzheimer disease: An update on future strategies. *Hum. Vaccines Immunother.* **10**, 847–851.
- [67] Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with AD after A β 42 immunization. *Neurology* **61**, 46–54.
- [68] Nicoll JAR, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO (2003) Neuropathology of human Alzheimer disease after immunization with amyloid- β peptide: A case report. *Nat. Med.* **9**, 448–452.
- [69] Check E (2002) Nerve inflammation halts trial for Alzheimer's drug Progress in human genetics hindered by reluctance to share. *Nature* 2002–2002.
- [70] Cummings JL, Cohen S, Van Dyck CH, Brody M, Curtis C, Cho W, Ward M, Friesenhahn M, Brunstein F, Quartino A, Honigberg LA, Fuji RN, Clayton D, Mortensen D, Ho C, Paul R, Rabe C (2018) A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease. *Neurology* **90**, E1889–E1897.
- [71] Doody RS, Farlow M, Aisen PS (2014) Phase 3 Trials of Solanezumab and

- Bapineuzumab for Alzheimer's Disease. *N. Engl. J. Med.* **370**, 1460.
- [72] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R (2014) Phase 3 trials of solanezumab for mild-to-moderate alzheimer's disease. *N. Engl. J. Med.* **370**, 311–321.
- [73] Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, Ashford E, Retout S, Hofmann C, Delmar P, Klein G, Andjelkovic M, Dubois B, Boada M, Blennow K, Santarelli L, Fontoura P (2017) A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimer's Res. Ther.* **9**, 1–15.
- [74] Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pontecorvo MJ, Dean RA, DeMattos R (2016) Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimer's Dement.* **12**, 110–120.
- [75] Harrison JR, Owen MJ (2016) Alzheimer's disease: The amyloid hypothesis on trial. *Br. J. Psychiatry* **208**, 1–3.
- [76] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* **12**, 207–216.
- [77] Aisen PS, Cummings J, Doody R, Kramer L, Salloway S, Selkoe DJ, Sims J, Sperling RA, Vellas B (2020) The Future of Anti-Amyloid Trials. *J. Prev. Alzheimer's Dis.* 1–6.
- [78] Howard R, Liu KY (2020) Questions EMERGE as Biogen claims aducanumab turnaround. *Nat. Rev. Neurol.* **16**, 63–64.
- [79] Schneider L (2020) A resurrection of aducanumab for Alzheimer's disease. *Lancet*

- Neurol.* **19**, 111–112.
- [80] Davies, Peter; Maloney AJF (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* **308**, 1403.
- [81] Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, Khachaturian AS, Vergallo A, Cavedo E, Snyder PJ, Khachaturian ZS (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* **141**, 1917–1933.
- [82] Bohdanecký Z, Jarvik ME, Carley JL (1967) Differential impairment of delayed matching in monkeys by scopolamine and scopolamine methylbromide. *Psychopharmacologia* **11**, 293–299.
- [83] Drachman DA, Leavitt J (1974) Human Memory and the Cholinergic System: A Relationship to Aging? *Arch. Neurol.* **30**, 113–121.
- [84] Pazzagli A, Pepeu G (1965) Amnesic properties of scopolamine and brain acetylcholine in the rat. *Neuropharmacology* **4**, 291–299.
- [85] Bartus RT (1978) Evidence for a direct cholinergic involvement in the scopolamine-induced amnesia in monkeys: Effects of concurrent administration of physostigmine and methylphenidate with scopolamine. *Pharmacol. Biochem. Behav.* **9**, 833–836.
- [86] Bowen DM, Smith CB, White P, Davison AN (1976) Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. *Brain* **99**, 459–496.
- [87] Francis PT, Palmer AM, Snape M, Wilcock GK (1999) The cholinergic hypothesis of Alzheimer's disease: A review of progress. *J. Neurol. Neurosurg. Psychiatry* **66**, 137–147.

- [88] Perry EK, Perry RH, Blessed G, Tomlinson BE (1977) Necropsy Evidence of Central Cholinergic Deficits in Senile Dementia. *Lancet* **309**, 189.
- [89] Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT DM (1982) Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* (80-.). **215**, 1237–1239.
- [90] Bierer LM, Haroutunian V, Gabriel S, Knott PJ, Carlin LS, Purohit DP, Perl DP, Schmeidler J, Kanof P, Davis KL (1995) Neurochemical Correlates of Dementia Severity in Alzheimer's Disease: Relative Importance of the Cholinergic Deficits. *J. Neurochem.* **64**, 749–760.
- [91] Francis, A M Palmer, N R Sims, D M Bowen, A N Davison, M M Esiri, D Neary, J S Snowden GKW (1985) Neurochemical studies of early-onset Alzheimer's disease: possible influence on treatment. *N. Engl. J. Med.* **313**, 7–11.
- [92] Perry EK, Tomlinson BE, Blessed G, Perry RH, Cross AJ CT (1981) Neuropathological and biochemical observations on the noradrenergic system in Alzheimer's disease. *J. Neurol. Sci.* **51**, 279–287.
- [93] Bartus RT (2000) On neurodegenerative diseases, models, and treatment strategies: Lessons learned and lessons forgotten a generation following the cholinergic hypothesis. *Exp. Neurol.* **163**, 495–529.
- [94] TERRY, Alvin V.; BUCCAFUSCO JJ (2003) The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J. Pharmacol. Exp. Ther.* **306**, 821–827.
- [95] Qizilbash N, Whitehead A, Higgins J, Wilcock G, Schneider L, Farlow M (1998) Cholinesterase inhibition for Alzheimer disease: A meta-analysis of the tacrine trials. *J.*

- Am. Med. Assoc.* **280**, 1777–1782.
- [96] Haake A, Nguyen K, Friedman L, Chakkampambil B, Grossberg GT (2020) An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer’s disease. *Expert Opin. Drug Saf.* **19**, 147–157.
- [97] BIRKS, Jacqueline S.; HARVEY RJ (2018) Donepezil for dementia due to Alzheimer’s disease. *Cochrane Database Syst. Rev.*
- [98] Lee JH, Jeong SK, Kim BC, Park KW, Dash A (2015) Donepezil across the spectrum of Alzheimer’s disease: Dose optimization and clinical relevance. *Acta Neurol. Scand.* **131**, 259–267.
- [99] Mucke HA (2015) The case of galantamine: Repurposing and late blooming of a cholinergic drug. *Futur. Sci. OA* **1**,.
- [100] BIRKS, Jacqueline S.; EVANS JG (2015) Rivastigmine for Alzheimer’s disease. *Cochrane Database Syst. Rev.*
- [101] Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S LR (2004) Rivastigmine for dementia associated with Parkinson’s disease. *N. Engl. J. Med.* **351**, 2509–2518.
- [102] Ray B, Maloney B, Sambamurti K, Karnati HK, Nelson PT, Greig NH, Lahiri DK (2020) Rivastigmine modifies the α -secretase pathway and potentially early Alzheimer’s disease. *Transl. Psychiatry* **10**, 1–17.
- [103] Pákási M, Kálmán J (2008) Interactions between the amyloid and cholinergic mechanisms in Alzheimer’s disease. *Neurochem. Int.* **53**, 103–111.
- [104] Nitsch RM, Slack BE, Wurtman RJ, Growdon JH (1992) Release of Alzheimer

- amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. *Science* (80-.). **258**, 304–307.
- [105] Roberson MR, Harrell LE (1997) Cholinergic activity and amyloid precursor protein metabolism. *Brain Res. Rev.* **25**, 50–69.
- [106] Kametani F, Hasegawa M (2018) Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. *Front. Neurosci.* **12**, 25.
- [107] Kosik KS, Joachim CL, Selkoe DJ (1986) Microtubule-associated protein tau (τ) is a major antigenic component of paired helical filaments in Alzheimer disease. *Proc. Natl. Acad. Sci. U. S. A.* **83**, 4044–4048.
- [108] Maccioni RB, Farías G, Morales I, Navarrete L (2010) The Revitalized Tau Hypothesis on Alzheimer's Disease. *Arch. Med. Res.* **41**, 226–231.
- [109] Braak H, Del Tredici K (2014) Are cases with tau pathology occurring in the absence of A β deposits part of the AD-related pathological process? *Acta Neuropathol.* **128**, 767–772.
- [110] Stoothoff WH, Johnson GW (2005) Tau phosphorylation: Physiological and pathological consequences. *Biochim. Biophys. Acta - Mol. Basis Dis.* **1739**, 280–297.
- [111] Grundke-Iqbal I, Iqbal K, Tung YC (1986) Abnormal phosphorylation of the microtubule-associated protein τ (tau) in Alzheimer cytoskeletal pathology. *Proc. Natl. Acad. Sci. U. S. A.* **83**, 44913–44917.
- [112] Mudher A, Lovestone S (2002) Alzheimer's disease - Do tauists and baptists finally shake hands? *Trends Neurosci.* **25**, 22–26.
- [113] Ghoshal N, García-Sierra F, Wu J, Leurgans S, Bennett DA, Berry RW, Binder LI (2002) Tau conformational changes correspond to impairments of episodic memory in

- mild cognitive impairment and Alzheimer's disease. *Exp. Neurol.* **177**, 475–493.
- [114] Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Tredici K (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol.* **112**, 239–259.
- [115] Gauthier S, Feldman HH, Schneider LS, Wilcock GK, Frisoni GB, Hardlund JH, Moebius HJ, Bentham P, Kook KA, Wischik DJ, Schelter BO, Davis CS, Staff RT, Bracoud L, Shamsi K, Storey JMD, Harrington CR, Wischik CM (2016) Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. *Lancet* **388**, 2873–2884.
- [116] Li C, Götz J (2017) Tau-based therapies in neurodegeneration: Opportunities and challenges. *Nat. Rev. Drug Discov.* **16**, 863–883.
- [117] Du X, Wang X, Geng M (2018) Alzheimer's disease hypothesis and related therapies. *Transl. Neurodegener.* **7**, 1–7.
- [118] Cheng Y, Bai F (2018) The association of tau with mitochondrial dysfunction in Alzheimer's disease. *Front. Neurosci.* **12**, 163.
- [119] Swerdlow RH (2018) Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. *J. Alzheimer's Dis.* **62**, 1403–1416.
- [120] Swerdlow RH, Burns JM, Khan SM (2014) The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. *Biochim. Biophys. Acta - Mol. Basis Dis.* **1842**, 1219–1231.
- [121] Swerdlow RH, Burns JM, Khan SM (2010) The Alzheimer's disease mitochondrial cascade hypothesis. *J. Alzheimer's Dis.* **20**,.

- [122] Swerdlow RH, Khan SM (2004) A “mitochondrial cascade hypothesis” for sporadic Alzheimer’s disease. *Med. Hypotheses* **63**, 8–20.
- [123] Parker WD, Boyson SJ, Parks JK (1989) Abnormalities of the electron transport chain in idiopathic parkinson’s disease. *Ann. Neurol.* **26**, 719–723.
- [124] HARMAN D (1972) The Biologic Clock: The Mitochondria? *J. Am. Geriatr. Soc.* **20**, 145–147.
- [125] Lin MT (2002) High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer’s disease brain. *Hum. Mol. Genet.* **11**, 133–145.
- [126] Linnane AW, Ozawa T, Marzuki S, Tanaka M (1989) Mitochondrial Dna Mutations As an Important Contributor To Ageing and Degenerative Diseases. *Lancet* **333**, 642–645.
- [127] Wallace DC (1992) Mitochondrial genetics: A paradigm for aging and degenerative diseases? *Science (80-.)*. **256**, 628–632.
- [128] Beal MF (1995) Aging, energy, and oxidative stress in neurodegenerative diseases. *Ann. Neurol.* **38**, 357–366.
- [129] Castellani R, Hirai K, Aliev G, Drew KL, Nunomura A, Takeda A, Cash AD, Obrenovich ME, Perry G, Smith MA (2002) Role of mitochondrial dysfunction in Alzheimer’s disease. *J. Neurosci. Res.* **70**, 357–360.
- [130] Swerdlow R, Marcus DL, Landman J, Kooby D, Frey W, Freedman ML (1994) Brain glucose metabolism in Alzheimer’s disease. *Am. J. Med. Sci.* **308**, 141–144.
- [131] Hoyer S (1993) Brain Oxidative Energy and Related Metabolism, Neuronal Stress, and Alzheimer’s Disease: A Speculative Synthesis. *J. Geriatr. Psychiatry Neurol.* **6**, 3–13.
- [132] Gómez-Tortosa E, Barquero MS, Barón M, Sainz MJ, Manzano S, Payno M, Ros R,

- Almaraz C, Gómez-Garré P, Jiménez-Escrig A (2007) Variability of age at onset in siblings with familial Alzheimer disease. *Arch. Neurol.* **64**, 1743–1748.
- [133] Xie H, Guan JS, Borrelli LA, Xu J, Serrano-Pozo A, Bacskai BJ (2013) Mitochondrial alterations near amyloid plaques in an Alzheimer's disease mouse model. *J. Neurosci.* **33**, 17042–17051.
- [134] Cardoso SM, Santos S, Swerdlow RH, Oliveira CR (2001) Functional mitochondria are required for amyloid β -mediated neurotoxicity. *FASEB J.* **15**, 1439–1441.
- [135] Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Du Yan S (2005) Mitochondrial A β : a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J.* **19**, 2040–2041.
- [136] Wang X, Su B, Fujioka H, Zhu X (2008) Dynamin-like protein 1 reduction underlies mitochondrial morphology and distribution abnormalities in fibroblasts from sporadic Alzheimer's disease patients. *Am. J. Pathol.* **173**, 470–482.
- [137] Wang X, Su B, Siedlak SL, Moreira PI, Fujioka H, Wang Y, Casadesus G, Zhu X (2008) Amyloid- β overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 19318–19323.
- [138] Manczak M, Calkins MJ, Reddy PH (2011) Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: Implications for neuronal damage. *Hum. Mol. Genet.* **20**, 2495–2509.
- [139] P. Hemachandra Reddy, Shannon McWeeney, Byung S. Park, Maria Manczak, Ramana V. Gutala, Dara Partovi, Youngsin Jung, Vincent Yau, Robert Searles,

- Motomi Mori JQ (2004) Gene expression profiles of transcripts in amyloid precursor protein transgenic mice: up-regulation of mitochondrial metabolism and apoptotic genes is an early cellular change in Alzheimer's disease. *Hum. Mol. Genet.* **13**, 1225–1240.
- [140] Santos RX, Correia SC, Wang X, Perry G, Smith MA, Moreira PI, Zhu X (2010) Alzheimer's disease: Diverse aspects of mitochondrial malfunctioning. *Int. J. Clin. Exp. Pathol.* **3**, 570–581.
- [141] Podlesniy P, Llorens F, Golanska E, Sikorska B, Liberski P, Zerr I, Trullas R (2016) Mitochondrial DNA differentiates Alzheimer's disease from Creutzfeldt-Jakob disease. *Alzheimer's Dement.* **12**, 546–555.
- [142] J. Bonda D, A. Smith M, Perry G, Lee H, Wang X, Zhu X (2011) The Mitochondrial Dynamics of Alzheimers Disease and Parkinsons Disease Offer Important Opportunities for Therapeutic Intervention. *Curr. Pharm. Des.* **17**, 3374–3380.
- [143] Trimmer PA, Swerdlow RH, Parks JK, Keeney P, Bennett JP, Miller SW, Davis RE, Parker WD (2000) Abnormal mitochondrial morphology in sporadic Parkinson's and Alzheimer's disease cybrid cell lines. *Exp. Neurol.* **162**, 37–50.
- [144] Ridge PG, Kauwe JSK (2018) Mitochondria and Alzheimer's Disease: the Role of Mitochondrial Genetic Variation. *Curr. Genet. Med. Rep.* **6**, 1–10.
- [145] Hroudová J, Singh N, Fišar Z, Ghosh KK (2016) Progress in drug development for Alzheimer's disease: An overview in relation to mitochondrial energy metabolism. *Eur. J. Med. Chem.* **121**, 774–784.
- [146] Tramutola A, Lanzillotta C, Perluigi M, Butterfield DA (2017) Oxidative stress, protein modification and Alzheimer disease. *Brain Res. Bull.* **133**, 88–96.

- [147] Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F (2018) Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol.* **14**, 450–464.
- [148] Markesbery WR (1997) Oxidative stress hypothesis in Alzheimer's disease. *Free Radic. Biol. Med.* **23**, 134–147.
- [149] Teixeira JP, de Castro AA, Soares F V., da Cunha EFF, Ramalho TC (2019) Future therapeutic perspectives into the Alzheimer's disease targeting the oxidative stress hypothesis. *Molecules* **24**, 1–17.
- [150] Tönnies E, Trushina E (2017) Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *J. Alzheimer's Dis.* **57**, 1105–1121.
- [151] Butterfield DA, Swomley AM, Sultana R (2013) Amyloid β -Peptide (1-42)-induced oxidative stress in alzheimer disease: Importance in disease pathogenesis and progression. *Antioxidants Redox Signal.* **19**, 823–835.
- [152] Butterfield DA, Halliwell B (2019) Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat. Rev. Neurosci.* **20**, 148–160.
- [153] Liu Q, Smith MA, Avilá J, DeBernardis J, Kansal M, Takeda A, Zhu X, Nunomura A, Honda K, Moreira PI, Oliveira CR, Santos MS, Shimohama S, Aliev G, De La Torre J, Ghanbari HA, Siedlak SL, Harris PLR, Sayre LM, Perry G (2005) Alzheimer-specific epitopes of tau represent lipid peroxidation-induced conformations. *Free Radic. Biol. Med.* **38**, 746–754.
- [154] Horiguchi T, Uryu K, Giasson BI, Ischiropoulos H, LightFoot R, Bellmann C, Richter-Landsberg C, Lee VMY, Trojanowski JQ (2003) Nitration of tau protein is linked to neurodegeneration in tauopathies. *Am. J. Pathol.* **163**, 1021–1031.

- [155] Violet M, Delattre L, Tardivel M, Sultan A, Chauderlier A, Caillierez R, Talahari S, Nessler F, Lefebvre B, Bonnefoy E, Buée L, Galas MC (2014) A major role for Tau in neuronal DNA and RNA protection in vivo under physiological and hyperthermic conditions. *Front. Cell. Neurosci.* **8**, 1–11.
- [156] Kozłowski H, Janicka-Kłos A, Brasun J, Gaggelli E, Valensin D, Valensin G (2009) Copper, iron, and zinc ions homeostasis and their role in neurodegenerative disorders (metal uptake, transport, distribution and regulation). *Coord. Chem. Rev.* **253**, 2665–2685.
- [157] Simunkova M, Alwasel SH, Alhazza IM, Jomova K, Kollar V, Rusko M, Valko M (2019) Management of oxidative stress and other pathologies in Alzheimer’s disease. *Arch. Toxicol.* **93**, 2491–2513.
- [158] Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, Cherubini A, Catani M, Cecchetti R, Senin U, Mecocci P (2003) Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer’s disease. *Neurobiol. Aging* **24**, 915–919.
- [159] Mecocci P, Boccardi V, Cecchetti R, Bastiani P, Scamosci M, Ruggiero C, Baroni M (2018) A Long Journey into Aging, Brain Aging, and Alzheimer’s Disease Following the Oxidative Stress Tracks. *J. Alzheimer’s Dis.* **62**, 1319–1335.
- [160] Cassano T, Villani R, Pace L, Carbone A, Bukke VN, Orkisz S, Avolio C, Serviddio G (2020) From Cannabis sativa to Cannabidiol: Promising Therapeutic Candidate for the Treatment of Neurodegenerative Diseases. *Front. Pharmacol.* **11**, 1–10.
- [161] Li H, Liu Y, Tian D, Tian L, Ju X, Qi L, Wang Y, Liang C (2020) Overview of cannabidiol (CBD) and its analogues: Structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer’s disease. *Eur. J. Med. Chem.* **192**, 112163.

- [162] Atalay S, Jarocka-karpowicz I, Skrzydlewska E (2020) Antioxidative and anti-inflammatory properties of cannabidiol. *Antioxidants* **9**, 1–20.
- [163] Cheng D, Spiro AS, Jenner AM, Garner B, Karl T (2014) Long-term cannabidiol treatment prevents the development of social recognition memory deficits in alzheimer's disease transgenic mice. *J. Alzheimer's Dis.* **42**, 1383–1396.
- [164] Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D, Feilding A, Walker L, Murray RM, Kapur S (2013) Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J. Psychopharmacol.* **27**, 19–27.
- [165] Fagherazzi E V., Garcia VA, Maurmann N, Bervanger T, Halmenschlager LH, Busato SB, Hallak JE, Zuardi AW, Crippa JA, Schröder N (2012) Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders. *Psychopharmacology (Berl)*. **219**, 1133–1140.
- [166] Martín-Moreno AM, Reigada D, Ramírez BG, Mechoulam R, Innamorado N, Cuadrado A, De Ceballos ML (2011) Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: Relevance to alzheimer's disease. *Mol. Pharmacol.* **79**, 964–973.
- [167] Morgan CJA, Schafer G, Freeman TP, Curran HV (2010) Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: Naturalistic study. *Br. J. Psychiatry* **197**, 285–290.
- [168] Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T (2006) The marijuana component cannabidiol inhibits β -amyloid-induced tau protein hyperphosphorylation through Wnt/ β -catenin pathway rescue in PC12 cells. *J. Mol. Med.* **84**, 253–258.

- [169] Esposito G, Scuderi C, Valenza M, Togna GI, Latina V, de Filippis D, Cipriano M, Carratù MR, Iuvone T, Steardo L (2011) Cannabidiol reduces A β -induced neuroinflammation and promotes hippocampal neurogenesis through PPAR γ involvement. *PLoS One* **6**.
- [170] Hamelink C, Hampson A, Wink DA, Eiden LE, Eskay RL (2005) Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity. *J. Pharmacol. Exp. Ther.* **314**, 780–788.
- [171] Pimplikar SW (2014) Neuroinflammation in Alzheimer's disease: From pathogenesis to a therapeutic target. *J. Clin. Immunol.* **34**, 64–69.
- [172] Rojas-Gutierrez E, Muñoz-Arenas G, Treviño S, Espinosa B, Chavez R, Rojas K, Flores G, Díaz A, Guevara J (2017) Alzheimer's disease and metabolic syndrome: A link from oxidative stress and inflammation to neurodegeneration. *Synapse* **71**, 1–21.
- [173] Verri M, Pastoris O, Dossena M, Aquilani R, Guerriero F, Cuzzoni G, Venturini L, Ricevuti G, Bongiorno AI (2012) Mitochondrial alterations, oxidative stress and neuroinflammation in Alzheimer's disease. *Int. J. Immunopathol. Pharmacol.* **25**, 345–353.
- [174] Dansokho C, Heneka MT (2018) Neuroinflammatory responses in Alzheimer's disease. *J. Neural Transm.* **125**, 771–779.
- [175] Delanty N, Vaughan C (1998) Risk of Alzheimer's disease and duration of NSAID use. *Neurology* **51**, 652.
- [176] McGeer PL, Rogers J, McGeer EG (1994) Neuroimmune mechanisms in Alzheimer disease pathogenesis. *Alzheimer Dis. Assoc. Disord.* **8**, 149–158.
- [177] McGeer PL, Schulzer M, McGeer EG (1996) Arthritis and anti-inflammatory agents as

possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology* **47**, 425–432.

- [178] Cortese GP, Burger C (2017) Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer's disease. *Behav. Brain Res.* **322**, 269–279.
- [179] Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ERLC, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Rütther E, Schürmann B, Heun R, Kölsch H, Van Den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Gallacher J, Hüll M, Rujescu D, Giegling I, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, Van Duijn CM, Breteler MMB, Ikram MA, Destefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, Berr C, Champion D, Epelbaum J, Dartigues JF, Tzourio C, Alperovitch A, Lathrop M, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snædal J, Björnsson S, Jonsson P V., Chouraki V, Genier-Boley B, Hiltunen M, Soininen H,

Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossù P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemenschneider M, Morgan K, Younkin SG, Owen MJ, O'Donovan M, Amouyel P, Williams J (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat. Genet.* **43**, 429–436.

[180] Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buross J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford NR, De Jager PL, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JSK, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, Green RC, Rogaeva E, George-Hyslop PS, Arnold SE, Barber R, Beach T, Bigio EH, Bowen JD, Boxer A, Burke JR, Cairns NJ, Carlson CS, Carney RM, Carroll SL, Chui HC, Clark DG, Corneveaux J, Cotman CW, Cummings JL, Decarli C, Dekosky ST, Diaz-Arrastia R, Dick M, Dickson DW, Ellis WG, Faber KM, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Ganguli M, Gearing M, Geschwind DH, Ghetti B, Gilbert JR, Gilman S, Giordani B, Glass JD, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin LW, Johnson N, Karlawish J, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Lah JJ, Levey AI, Lieberman AP, Lopez OL, MacK WJ, Marson DC, Martiniuk F, Mash DC, Masliah E, McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon WW, Quinn JF, Rajbhandary RA, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN,

- Sano M, Schneider LS, Seeley W, Shelanski ML, Slifer MA, Smith CD, Sonnen JA, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Vinters H V., Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Woltjer RL, Cantwell LB, Dombroski BA, Beekly D, Lunetta KL, Martin ER, Kamboh MI, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat. Genet.* **43**, 436–443.
- [181] Minter MR, Taylor JM, Crack PJ (2016) The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *J. Neurochem.* **136**, 457–474.
- [182] Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB (2014) Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Front. Cell. Neurosci.* **8**, 1–9.
- [183] Yang CN, Shiao YJ, Shie FS, Guo BS, Chen PH, Cho CY, Chen YJ, Huang FL, Tsay HJ (2011) Mechanism mediating oligomeric A β clearance by naïve primary microglia. *Neurobiol. Dis.* **42**, 221–230.
- [184] Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann. Transl. Med.* **3**, 1–15.
- [185] Wojtera M, Sobów T, Kłoszewska I, Liberski PP, Brown DR, Sikorska B (2012) Expression of immunohistochemical markers on microglia in Creutzfeldt-Jakob disease and Alzheimer's disease: Morphometric study and review of the literature. *Folia Neuropathol.* **50**, 74–84.
- [186] Bamberger ME, Harris ME, McDonald DR, Husemann J, Landreth GE (2003) A cell

- surface receptor complex for fibrillar β -amyloid mediates microglial activation. *J. Neurosci.* **23**, 2665–2674.
- [187] Arancio O, Zhang HP, Chen X, Lin C, Trinchese F, Puzzo D, Liu S, Hegde A, Yan SF, Stern A, Luddy JS, Lue LF, Walker DG, Roher A, Buttini M, Mucke L, Li W, Schmidt AM, Kindy M, Hyslop PA, Stern DM, Yan SS Du (2004) RAGE potentiates $A\beta$ -induced perturbation of neuronal function in transgenic mice. *EMBO J.* **23**, 4096–4105.
- [188] Bellucci A, Westwood AJ, Ingram E, Casamenti F, Goedert M, Spillantini MG (2004) Induction of inflammatory mediators and microglial activation in mice transgenic for mutant human P301S tau protein. *Am. J. Pathol.* **165**, 1643–1652.
- [189] Nagele RG, D’Andrea MR, Lee H, Venkataraman V, Wang HY (2003) Astrocytes accumulate $A\beta_{42}$ and give rise to astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res.* **971**, 197–209.
- [190] Calsolaro V, Edison P (2016) Neuroinflammation in Alzheimer’s disease: Current evidence and future directions. *Alzheimer’s Dement.* **12**, 719–732.
- [191] Krstic D, Knuesel I (2013) Deciphering the mechanism underlying late-onset Alzheimer disease. *Nat. Rev. Neurol.* **9**, 25–34.
- [192] Fillit H, Ding W, Buee L, Kalman J, Altstiel L, Lawlor B, Wolf-Klein G (1991) Elevated circulating tumor necrosis factor levels in Alzheimer’s disease. *Neurosci. Lett.* **129**, 318–320.
- [193] Khemka VK, Ganguly A, Bagchi D, Ghosh A, Bir A, Biswas A, Chattopadhyay S, Chakrabarti S (2014) Raised serum proinflammatory cytokines in Alzheimer’s disease with depression. *Aging Dis.* **5**, 170–176.
- [194] Paganelli R, Di Iorio A, Patricelli L, Ripani F, Sparvieri E, Faricelli R, Iarlori C,

- Porreca E, Di Gioacchino M, Abate G (2002) Proinflammatory cytokines in sera of elderly patients with dementia: Levels in vascular injury are higher than those of mild-moderate Alzheimer's disease patients. *Exp. Gerontol.* **37**, 257–263.
- [195] Jayaraj RL, Rodriguez EA, Wang Y, Block ML (2017) Outdoor Ambient Air Pollution and Neurodegenerative Diseases: the Neuroinflammation Hypothesis. *Curr. Environ. Heal. reports* **4**, 166–179.
- [196] Kristiansson M, Sörman K, Tekwe C, Calderón-Garcidueñas L (2015) Urban air pollution, poverty, violence and health - Neurological and immunological aspects as mediating factors. *Environ. Res.* **140**, 511–513.
- [197] Bolton JL, Smith SH, Huff NC, Gilmour MI, Foster WM, Auten RL, Bilbo SD (2012) Prenatal air pollution exposure induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner. *FASEB J.* **26**, 4743–4754.
- [198] Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, Villarreal-Calderón R, Osnaya N, Stone I, García R, Brooks DM, González-Maciél A, Reynoso-Robles R, Delgado-Chávez R, Reed W (2008) Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β -42 and α -synuclein in children and young adult. *Toxicol. Pathol.* **36**, 289–310.
- [199] Calderón-Garcidueñas L, González-Maciél A, Kulesza RJ, González-González LO, Reynoso-Robles R, Mukherjee PS, Torres-Jardón R (2019) Air Pollution, Combustion and Friction Derived Nanoparticles, and Alzheimer's Disease in Urban Children and Young Adults. *J. Alzheimer's Dis.* **70**, 341–358.
- [200] Calderón-Garcidueñas L, Cross J V., Franco-Lira M, Aragón-Flores M, Kavanaugh M,

- Torres-Jardón R, Chao C kai, Thompson C, Chang J, Zhu H, D'Angiulli A (2013) Brain immune interactions and air pollution: macrophage inhibitory factor (MIF), prion cellular protein (PrPC), Interleukin-6 (IL-6), interleukin 1 receptor antagonist (IL-1Ra), and interleukin-2 (IL-2) in cerebrospinal fluid and MIF in serum differentiat. *Front. Neurosci.* **7**, 1–11.
- [201] Mumaw CL, Levesque S, McGraw C, Robertson S, Lucas S, Stafflinger JE, Campen MJ, Hall P, Norenberg JP, Anderson T, Lund AK, McDonald JD, Ottens AK, Block ML (2016) Microglial priming through the lung-brain axis: The role of air pollution-induced circulating factors. *FASEB J.* **30**, 1880–1891.
- [202] Rivas-Arancibia S, Hernandez-Zimbron LF, Rodriguez-Martinez E, Deyanira-Maldonado P, Borgonio-Pérez G, Sepulveda-Parada M (2015) Oxidative stress-dependent changes in immune responses and cell death in the substantia nigra after ozone exposure in rat. *Front. Aging Neurosci.* **7**, 1–9.
- [203] Sims P (2019) Particulate Matter (PM 2 . 5) Air Pollution and Alzheimer ' s Disease : A Systematic Literature Review Paris Sims California State University , San Marcos.
- [204] Wang J, Tan L, Wang HF, Tan CC, Meng XF, Wang C, Tang SW, Yu JT (2015) Anti-inflammatory drugs and risk of Alzheimer's Disease: An updated systematic review and meta-analysis. *J. Alzheimer's Dis.* **44**, 385–396.
- [205] Caldeira C, Oliveira AF, Cunha C, Vaz AR, Falcão AS, Fernandes A, Brites D (2014) Microglia change from a reactive to an age-like phenotype with the time in culture. *Front. Cell. Neurosci.* **8**, 1–16.
- [206] Nazem A, Sankowski R, Bacher M, Al-Abed Y (2015) Rodent models of neuroinflammation for Alzheimer's disease. *J. Neuroinflammation* **12**, 1–15.

- [207] Streit WJ, Braak H, Xue QS, Bechmann I (2009) Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathol.* **118**, 475–485.
- [208] Guillot-Sestier MV, Doty KR, Town T (2015) Innate Immunity Fights Alzheimer's Disease. *Trends Neurosci.* **38**, 674–681.
- [209] Heneka MT, Golenbock DT, Latz E (2015) Innate immunity in Alzheimer's disease. *Nat. Immunol.* **16**, 229–236.
- [210] Vijaya Kumar DK, Moir RD (2017) The Emerging Role of Innate Immunity in Alzheimer's Disease. *Neuropsychopharmacology* **42**, 362–363.
- [211] Gibson G, Cotman C, Lynch G, Blass J, Coleman P, Buell S (2017) Calcium Hypothesis of Alzheimer's disease and brain aging: A framework for integrating new evidence into a comprehensive theory of pathogenesis. *Alzheimer's Dement.* **13**, 178-182.e17.
- [212] Khachaturian ZS (1987) Hypothesis on the Regulation of Cytosol Calcium Concentration and the Aging Brain. *Neurobiol. Aging* **8**, 345–346.
- [213] LANDFIELD, Philip W.; PITLER TA (1984) Prolonged Ca²⁺-dependent afterhyperpolarizations in hippocampal neurons of aged rats. *Science (80-)*. **226**, 1089–1092.
- [214] Landfield PW (1987) "Increased calcium-current" hypothesis of brain aging. *Neurobiol. Aging* **8**, 346–347.
- [215] Popugaeva E, Pchitskaya E, Bezprozvanny I (2018) Dysregulation of Intracellular Calcium Signaling in Alzheimer's Disease. *Antioxidants Redox Signal.* **29**, 1176–1188.
- [216] Demuro A, Parker I, Stutzmann GE (2010) Calcium signaling and amyloid toxicity in

- Alzheimer disease. *J. Biol. Chem.* **285**, 12463–12468.
- [217] Magi S, Castaldo P, MacRi ML, Maiolino M, Matteucci A, Bastioli G, Gratteri S, Amoroso S, Lariccia V (2016) Intracellular Calcium Dysregulation: Implications for Alzheimer's Disease. *Biomed Res. Int.* **2016**,.
- [218] Verkhratsky A (2019) Astroglial calcium signaling in aging and alzheimer's disease. *Cold Spring Harb. Perspect. Biol.* **11**,.
- [219] Tong BCK, Wu AJ, Li M, Cheung KH (2018) Calcium signaling in Alzheimer's disease & therapies. *Biochim. Biophys. Acta - Mol. Cell Res.* **1865**, 1745–1760.
- [220] Arispe N, Rojas E, Pollard HB (1993) Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: blockade by tromethamine and aluminum. *Sci. York* **90**, 567–571.
- [221] Ferreiro E, Oliveira CR, Pereira CMF (2004) Involvement of endoplasmic reticulum Ca²⁺ release through ryanodine and inositol 1,4,5-triphosphate receptors in the neurotoxic effects induced by the amyloid- β peptide. *J. Neurosci. Res.* **76**, 872–880.
- [222] Petryniak MA, Wurtman RJ, Slack BE (1996) Elevated intracellular calcium concentration increases secretory processing of the amyloid precursor protein by a tyrosine phosphorylation-dependent mechanism. *Biochem. J.* **320**, 957–963.
- [223] Pierrot N, Ghisdal P, Caumont AS, Octave JN (2004) Intraneuronal amyloid- β 1-42 production triggered by sustained increase of cytosolic calcium concentration induces neuronal death. *J. Neurochem.* **88**, 1140–1150.
- [224] Rice RA, Berchtold NC, Cotman CW, Green KN (2014) Age-related downregulation of the CaV3.1 T-type calcium channel as a mediator of amyloid beta production. *Neurobiol. Aging* **35**, 1002–1011.

- [225] Supnet C, Grant J, Kong H, Westaway D, Mayne M (2006) Amyloid- β -(1-42) increases ryanodine receptor-3 expression and function in neurons of TgCRND8 mice. *J. Biol. Chem.* **281**, 38440–38447.
- [226] Lovell MA, Abner E, Kryscio R, Xu L, Fister SX, Lynn BC (2015) Calcium Channel Blockers, Progression to Dementia, and Effects on Amyloid Beta Peptide Production. *Oxid. Med. Cell. Longev.* **2015**,.
- [227] Mattson MP, LaFerla FM, Chan SL, Leissring MA, Shepel PN, Geiger JD (2000) Calcium signaling in the ER: Its role in neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.* **23**, 222–229.
- [228] Jadiya P, Kolmetzky DW, Tomar D, Di Meco A, Lombardi AA, Lambert JP, Luongo TS, Ludtmann MH, Praticò D, Elrod JW (2019) Impaired mitochondrial calcium efflux contributes to disease progression in models of Alzheimer’s disease. *Nat. Commun.* **10**, 1–14.
- [229] Aston Jiayi Wu, Benjamin Chun-Kit Tong, Alexis Shiyang Huang, Min Li K-HC (2019) Mitochondrial calcium signaling as a therapeutic target for Alzheimer’s disease. *Curr. Alzheimer Res.*
- [230] Bloom GS, Norambuena A (2018) State and trends of oil crops production in China; State and trends of oil crops production in China. *Ocl* **25**, D403.
- [231] Biessels GJ, Whitmer RA (2020) Cognitive dysfunction in diabetes: how to implement emerging guidelines. *Diabetologia* **63**, 3–9.
- [232] Crosson SCM, Jagger C (1995) Diabetes and cognitive impairment: A community-based study of elderly subjects. *Age Ageing* **24**, 421–424.
- [233] Cuevas HE (2019) Type 2 diabetes and cognitive dysfunction in minorities: a review of

- the literature. *Ethn. Heal.* **24**, 512–526.
- [234] Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KMV, Cummings SR (2000) Is diabetes associated with cognitive impairment and cognitive decline among older women? *Arch. Intern. Med.* **160**, 174–180.
- [235] Kawamura T, Umemura T, Hotta N (2012) Cognitive impairment in diabetic patients: Can diabetic control prevent cognitive decline? *J. Diabetes Investig.* **3**, 413–423.
- [236] Perlmutter LC, Hakami MK, Hodgson-Harrington C, Ginsberg J, Katz J, Singer DE, Nathan DM (1984) Decreased cognitive function in aging non-insulin-dependent diabetic patients. *Am. J. Med.* **77**, 1043–1048.
- [237] Shalimova A, Graff B, Gasecki D, Wolf J, Sabisz A, Szurowska E, Jodzio K, Narkiewicz K (2019) Cognitive dysfunction in type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **104**, 2239–2249.
- [238] Teixeira MM, Passos VMA, Barreto SM, Schmidt MI, Duncan BB, Beleigoli AMR, Fonseca MJM, Vidigal PG, Araújo LF, Diniz M de FHS (2020) Association between diabetes and cognitive function at baseline in the Brazilian Longitudinal Study of Adult Health (ELSA- Brasil). *Sci. Rep.* **10**, 1596.
- [239] Miles WR, Root HF (1922) Psychologic tests applied to diabetic patients. *Arch. Intern. Med.* **30**, 767–777.
- [240] Bucht G, Adolfsson R, Lithner F, Winblad B (1983) Changes in Blood Glucose and Insulin Secretion in Patients with Senile Dementia of Alzheimer Type. *Acta Med. Scand.* **213**, 387–392.
- [241] Frölich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheimer A, Türk A, Hoyer S, Zöchling R, Boissl KW, Jellinger K,

- Riederer P (1998) Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *J. Neural Transm.* **105**, 423–438.
- [242] Hoyer S (1998) Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. *J. Neural Transm.* **105**, 415–422.
- [243] Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, De La Monte SM (2005) Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease - Is this type 3 diabetes? *J. Alzheimer's Dis.* **7**, 63–80.
- [244] Ciudin A, Espinosa A, Simó-Servat O, Ruiz A, Alegret M, Hernández C, Boada M, Simó R (2017) Type 2 diabetes is an independent risk factor for dementia conversion in patients with mild cognitive impairment. *J. Diabetes Complications* **31**, 1272–1274.
- [245] Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, Chiang CH, Huang PH, Chen TJ, Lin SJ, Chen JW, Chan WL (2014) Diabetes mellitus and the risk of Alzheimer's disease: A nationwide population-based study. *PLoS One* **9**,.
- [246] Li W, Huang E (2016) An Update on Type 2 Diabetes Mellitus as a Risk Factor for Dementia. *J. Alzheimer's Dis.* **53**, 393–402.
- [247] Li W, Wang T, Xiao S (2016) Type 2 diabetes mellitus might be a risk factor for mild cognitive impairment progressing to Alzheimer's disease. *Neuropsychiatr. Dis. Treat.* **12**, 2489–2495.
- [248] Chatterjee S, Peters SAE, Woodward M, Arango SM, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M, Hassing LB, Hayden KM, Kiyohara Y, Larson EB, Li CY, Ninomiya T, Ohara T, Peters R, Russ TC, Seshadri S, Strand BH, Walker R, Xu W, Huxley RR (2016) Type 2 diabetes as a risk factor for dementia in women compared

with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* **39**, 300–307.

- [249] Hao K, Di Narzo AF, Ho L, Luo W, Li S, Chen R, Li T, Dubner L, Pasinetti GM (2015) Shared genetic etiology underlying Alzheimer's disease and type 2 diab[1] Hao K, Di Narzo AF, Ho L, Luo W, Li S, Chen R, Li T, Dubner L, Pasinetti GM (2015) Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes. *Mol. Aspects Med.* 43–4. *Mol. Aspects Med.* **43–44**, 66–76.
- [250] Caberlotto L, Nguyen TP, Lauria M, Priami C, Rimondini R, Maioli S, Cedazo-Minguez A, Sita G, Morroni F, Corsi M, Carboni L (2019) Cross-disease analysis of Alzheimer's disease and type-2 Diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases. *Sci. Rep.* **9**, 1–13.
- [251] MOSCONI, Lisa; PUPI, Alberto; DE LEON MJ (2008) Brain Glucose Hypometabolism and Oxidative Stress in Preclinical Alzheimer's Disease. *Ann. N. Y. Acad. Sci.* **1147**, 180.
- [252] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J (2004) Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 284–289.
- [253] Chris Moran, Richard Beare, Thanh G. Phan, David G. Bruce, Michele L. Callisaya VS (2015) Type 2 diabetes mellitus and biomarkers of neurodegeneration. *Neurology* **85**, 1123–1130.
- [254] Li W, Risacher SL, Gao S, Boehm SL, Elmendorf JS, Saykin AJ (2018) Type 2 diabetes mellitus and cerebrospinal fluid Alzheimer's disease biomarker amyloid β 1-42 in Alzheimer's Disease Neuroimaging Initiative participants. *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.* **10**, 94–98.

- [255] Moran C, Beare R, Phan T, Starkstein S, Bruce D, Romina M, Srikanth V (2017) Neuroimaging and its Relevance to Understanding Pathways Linking Diabetes and Cognitive Dysfunction. *J. Alzheimer's Dis.* **59**, 405–419.
- [256] Tessier MD; Meneilly GS (2015) Diabetes in an older woman living in a long-term care residence. *Can. Med. Assoc. J.* **187**, 269–271.
- [257] Gabbouj S, Ryhänen S, Marttinen M, Wittrahm R, Takalo M, Kemppainen S, Martiskaine H, Tanila H, Haapasalo A, Hiltunen M, Natunen T (2019) Altered insulin signaling in Alzheimer's disease brain-special emphasis on pi3k-akt pathway. *Front. Neurosci.* **13**, 1–8.
- [258] Griffith CM, Eid T, Rose GM, Patrylo PR (2018) Evidence for altered insulin receptor signaling in Alzheimer's disease. *Neuropharmacology* **136**, 202–215.
- [259] Yang Y, Song W (2013) Molecular links between Alzheimer's disease and diabetes mellitus. *Neuroscience* **250**, 140–150.
- [260] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM, Nathan DM (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. *Nat. Rev. Neurol.* **14**, 168–181.
- [261] Kullmann S, Kleinridders A, Small DM, Fritsche A, Häring HU, Preissl H, Heni M (2020) Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol.* **8**, 524–534.
- [262] Lee SH, Zabolotny JM, Huang H, Lee H, Kim YB (2016) Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood. *Mol. Metab.* **5**, 589–601.
- [263] Pliquet RU, Führer D, Falk S, Zysset S, Von Cramon DY, Stumvoll M (2006) The

- effects of insulin on the central nervous system - Focus on appetite regulation. *Horm. Metab. Res.* **38**, 442–446.
- [264] Rhea EM, Salameh TS, Banks WA (2019) Routes for the delivery of insulin to the central nervous system: A comparative review. *Exp. Neurol.* **313**, 10–15.
- [265] Wozniak M, Rydzewski B, Baker SP, Raizada MK (1993) The cellular and physiological actions of insulin in the central nervous system. *Neurochem. Int.* **22**, 1–10.
- [266] Banks WA, Jaspan JB, Huang W, Kastin AJ (1997) Transport of insulin across the blood-brain barrier: Saturability at euglycemic doses of insulin. *Peptides* **18**, 1423–1429.
- [267] Devaskar SU, Giddings SJ, Rajakumar P a, Carnaghi LR, Menon RK, Zahm DS (1994) Insulin gene expression and insulin synthesis in mammalian neuronal cells. *J. Biol. Chem.* **269**, 8445–8454.
- [268] Havrankova J, Schmechel D, Roth J, Brownstein M (1978) Identification of insulin in rat brain. *Proc. Natl. Acad. Sci. U. S. A.* **75**, 5737–5741.
- [269] Havrankova J, Roth J, Brownstein M (1978) Insulin receptors are widely distributed in the central nervous system of the rat. *Nature* **272**, 827–829.
- [270] Schwartz MW, Bergman RN, Kahn SE, Taborsky GJ, Fisher LD, Sipols AJ, Woods SC, Steil GM, Porte D (1991) Evidence for entry of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs. Quantitative aspects and implications for transport. *J. Clin. Invest.* **88**, 1272–1281.
- [271] Pearson-Leary J, Jahagirdar V, Sage J, McNay EC (2018) Insulin modulates hippocampally-mediated spatial working memory via glucose transporter-4. *Behav.*

Brain Res. **338**, 32–39.

- [272] Uemura E, Greenlee HW (2006) Insulin regulates neuronal glucose uptake by promoting translocation of glucose transporter GLUT3. *Exp. Neurol.* **198**, 48–53.
- [273] Baura GD, Foster DM, Porte D, Kahn SE, Bergman RN, Cobelli C, Schwartz MW (1993) Saturable transport of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *J. Clin. Invest.* **92**, 1824–1830.
- [274] Pardridge WM, Eisenberg J, Yang J (1985) Human Blood—Brain Barrier Insulin Receptor. *J. Neurochem.* **44**, 1771–1778.
- [275] Clarke DW, Mudd L, Boyd FT, Fields M, Raizada MK (1986) Insulin Is Released from Rat Brain Neuronal Cells in Culture. *J. Neurochem.* **47**, 831–836.
- [276] Devaskar SU, Giddings SJ, Rajakumar PA, Carnaghi LR, Menon RK, Zahm DS (1994) Insulin gene expression and insulin synthesis in mammalian neuronal cells. *J. Biol. Chem.* **269**, 8445–8454.
- [277] Giddings SJ, Chirgwin J, Permutt MA (1985) Evaluation of rat insulin messenger RNA in pancreatic and extrapancreatic tissues. *Diabetologia* **28**, 343–347.
- [278] Schechter R, Holtzclaw L, Sadiq F, Kahn A, Devaskar S (1988) Insulin synthesis by isolated rabbit neurons. *Endocrinology* **123**, 505–513.
- [279] YOUNG III WS (1986) Periventricular hypothalamic cells in the rat brain contain insulin mRNA. *Neuropeptides* **8**, 93–97.
- [280] Pomytkin I, Costa-Nunes JP, Kasatkin V, Veniaminova E, Demchenko A, Lyundup A, Lesch KP, Ponomarev ED, Strekalova T (2018) Insulin receptor in the brain: Mechanisms of activation and the role in the CNS pathology and treatment. *CNS*

Neurosci. Ther. **24**, 763–774.

- [281] Wilden PA, Siddle K, Haring E, Backer JM, White MF, Kahn CR (1992) The role of insulin receptor kinase domain autophosphorylation in receptor-mediated activities. Analysis with insulin and anti-receptor antibodies. *J. Biol. Chem.* **267**, 13719–13727.
- [282] Plum L, Schubert M, Brüning JC (2005) The role of insulin receptor signaling in the brain. *Trends Endocrinol. Metab.* **16**, 59–65.
- [283] O’Neill C (2013) PI3-kinase/Akt/mTOR signaling: Impaired on/off switches in aging, cognitive decline and Alzheimer’s disease. *Exp. Gerontol.* **48**, 647–653.
- [284] Aljanabi NM, Mamtani S, Al-Ghuraibawi MMH, Yadav S, Nasr L (2020) Alzheimer’s and Hyperglycemia: Role of the Insulin Signaling Pathway and GSK-3 Inhibition in Paving a Path to Dementia. *Cureus* **12**,.
- [285] Laurettil E, Dincer O, Praticò D (2020) Glycogen synthase kinase-3 signaling in Alzheimer’s disease. *Biochim. Biophys. Acta - Mol. Cell Res.* **1867**, 118664.
- [286] Maqbool M, Mobashir M, Hoda N (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer’s disease. *Eur. J. Med. Chem.* **107**, 63–81.
- [287] Matsunaga S, Fujishiro H, Takechi H (2019) Efficacy and safety of glycogen synthase kinase 3 inhibitors for Alzheimer’s disease: A systematic review and meta-analysis. *J. Alzheimer’s Dis.* **69**, 1031–1039.
- [288] Woodgett JR (1990) Molecular cloning and expression of glycogen synthase kinase-3/factor A. *EMBO J.* **9**, 2431–2438.
- [289] Christopher J. Phiel*†, Christina A. Wilson†‡ VM-YL& PSK (2003) GSK-3 α regulates production of Alzheimer’s disease amyloid- β peptides. *Nature* **3**, 435–439.

- [290] Hanger DP, Hughes K, Woodgett JR, Brion JP, Anderton BH (1992) Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: Generation of paired helical filament epitopes and neuronal localisation of the kinase. *Neurosci. Lett.* **147**, 58–62.
- [291] Lovestone S, Reynolds CH, Latimer D, Davis DR, Anderton BH, Gallo JM, Hanger D, Mulot S, Marquardt B, Stabel S, Woodgett JR, Miller CCJ (1994) Alzheimer's disease-like phosphorylation of the microtubule-associated protein tau by glycogen synthase kinase-3 in transfected mammalian cells. *Curr. Biol.* **4**, 1077–1086.
- [292] Mandelkow EM, Drewes G, Biernat J, Gustke N, Van Lint J, Vandenheede JR, Mandelkow E (1992) Glycogen synthase kinase-3 and the Alzheimer-like state of microtubule-associated protein tau. *FEBS Lett.* **314**, 315–321.
- [293] Sperbera BR, Leight S, Goedert M, Lee VMY (1995) Glycogen synthase kinase-3 β phosphorylates tau protein at multiple sites in intact cells. *Neurosci. Lett.* **197**, 149–153.
- [294] D.A. Cross, D.R. Alessi, P. Cohen, M. Andjelkovich BH (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature* **378**, 785–788.
- [295] Maqbool M, Mobashir M, Hoda N (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur. J. Med. Chem.* **107**, 63–81.
- [296] Eldar-Finkelman H, Krebs EG (1997) Phosphorylation of insulin receptor substrate 1 by glycogen synthase kinase 3 impairs insulin action. *Proc. Natl. Acad. Sci. U. S. A.* **94**, 9660–9664.
- [297] Liberman Z, Eldar-Finkelman H (2005) Serine 332 phosphorylation of insulin receptor substrate-1 by glycogen synthase kinase-3 attenuates insulin signaling. *J. Biol. Chem.*

280, 4422–4428.

- [298] Sharfi H, Eldar-Finkelman H (2008) Sequential phosphorylation of insulin receptor substrate-2 by glycogen synthase kinase-3 and c-Jun NH2-terminal kinase plays a role in hepatic insulin signaling. *Am. J. Physiol. - Endocrinol. Metab.* **294**, 307–315.
- [299] Komiya Y, Habas R (2008) Wnt signal transduction pathways. *Organogenesis* **4**, 68–75.
- [300] Angers S, Moon RT (2009) Proximal events in Wnt signal transduction. *Nat. Rev. Mol. Cell Biol.* **10**, 468–477.
- [301] Cohen ED, Tian Y, Morrisey EE (2008) Wnt signaling: An essential regulator of cardiovascular differentiation, morphogenesis and progenitor self-renewal. *Development* **135**, 789–798.
- [302] Liu C, Li Y, Semenov M, Han C, Baeg G, Tan Y, Zhang Z, Lin X, He X, Signaling C (2002) Control of β -Catenin Phosphorylation/Degradation by a Dual-Kinase Mechanism. *Cell Press* **108**, 837–847.
- [303] Drulis-Fajdasz D, Rakus D, Wiśniewski JR, McCubrey JA, Gizak A (2018) Systematic analysis of GSK-3 signaling pathways in aging of cerebral tissue. *Adv. Biol. Regul.* **69**, 35–42.
- [304] Takashima A (2006) GSK-3 is essential in the pathogenesis of Alzheimer's disease. *J. Alzheimer's Dis.* **9**, 309–317.
- [305] Griffin RJ, Moloney A, Kelliher M, Johnston JA, Ravid R, Dockery P, O'Connor R, O'Neill C (2005) Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. *J. Neurochem.* **93**, 105–117.

- [306] Guo Z, Chen Y, Mao YF, Zheng T, Jiang Y, Yan Y, Yin X, Zhang B (2017) Long-term treatment with intranasal insulin ameliorates cognitive impairment, tau hyperphosphorylation, and microglial activation in a streptozotocin-induced Alzheimer's rat model. *Sci. Rep.* **7**, 1–12.
- [307] Nikoulina SE, Ciaraldi TP, Mudaliar S, Mohideen P, Carter L, Henry RR (2000) Potential role of glycogen synthase kinase-3 in skeletal muscle insulin resistance of type 2 diabetes. *Diabetes* **49**, 263–271.
- [308] Li X, Liu M, Cai Z, Wang G, Li X (2010) Regulation of glycogen synthase kinase-3 during bipolar mania treatment. *Bipolar Disord.* **12**, 741–752.
- [309] Munkholm K, Miskowiak KW, Jacoby AS, Vinberg M, Leme Talib L, Gattaz WF, Kessing LV (2018) Glycogen synthase kinase-3 β activity and cognitive functioning in patients with bipolar I disorder. *Eur. Neuropsychopharmacol.* **28**, 361–368.
- [310] Valvezan AJ, Klein PS (2012) GSK-3 and Wnt signaling in neurogenesis and bipolar disorder. *Front. Mol. Neurosci.* **5**, 1–13.
- [311] Albeely AM, Ryan SD, Perreault ML (2018) Pathogenic Feed-Forward Mechanisms in Alzheimer's and Parkinson's Disease Converge on GSK-3. *Brain Plast.* **4**, 151–167.
- [312] Choi H, Koh SH (2018) Understanding the role of glycogen synthase kinase-3 in L-DOPA-induced dyskinesia in Parkinson's disease. *Expert Opin. Drug Metab. Toxicol.* **14**, 83–90.
- [313] Golpich M, Amini E, Hemmati F, Ibrahim NM, Rahmani B, Mohamed Z, Raymond AA, Dargahi L, Ghasemi R, Ahmadiani A (2015) Glycogen synthase kinase-3 beta (GSK-3 β) signaling: Implications for Parkinson's disease. *Pharmacol. Res.* **97**, 16–26.
- [314] Lim NKH, Hung LW, Pang TY, Mclean CA, Liddell JR, Hilton JB, Li QX, White AR,

- Hannan AJ, Crouch PJ (2014) Localized changes to glycogen synthase kinase-3 and collapsin response mediator protein-2 in the Huntington's disease affected brain. *Hum. Mol. Genet.* **23**, 4051–4063.
- [315] L'Episcopo F, Drouin-Ouellet J, Tirolo C, Pulvirenti A, Giugno R, Testa N, Caniglia S, Serapide MF, Cisbani G, Barker RA, Cicchetti F, Marchetti B (2016) GSK-3 β -induced Tau pathology drives hippocampal neuronal cell death in Huntington's disease: Involvement of astrocyte-neuron interactions. *Cell Death Dis.* **7**, 1–14.
- [316] Andrade Nunes M, Araujo Viel T, Sousa Buck H (2013) Microdose Lithium Treatment Stabilized Cognitive Impairment in Patients with Alzheimer's Disease. *Curr. Alzheimer Res.* **10**, 104–107.
- [317] Hampel H, Ewers M, Bürger K, Annas P, Mörtberg A, Bogstedt A, Frölich L, Schröder J, Schönknecht P, Riepe MW, Kraft I, Gasser T, Leyhe T, Möller HJ, Kurz A, Basun H (2009) Lithium trial in Alzheimer's disease: A randomized, single-blind, placebo-controlled, multicenter 10-week study. *J. Clin. Psychiatry* **70**, 922–931.
- [318] Matsunaga S, Kishi T, Annas P, Basun H, Hampel H, Iwata N (2015) Lithium as a Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J. Alzheimer's Dis.* **48**, 403–410.
- [319] Lovestone S, Boada M, Dubois B, Hüll M, Rinne JO, Huppertz HJ, Calero M, Andrés M V., Gómez-Carrillo B, León T, Del Ser T (2015) A phase II trial of tideglusib in alzheimer's disease. *J. Alzheimer's Dis.* **45**, 75–88.
- [320] Del Ser T, Steinwachs KC, Gertz HJ, Andrés M V., Gómez-Carrillo B, Medina M, Vericat JA, Redondo P, Fleet D, León T (2013) Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: A pilot study. *J. Alzheimer's Dis.* **33**, 205–215.

- [321] Liu Y, Liu F, Grundke-iqbal I, Iqbal K, Gong C (2011) Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *J. Pathol.* **225**, 54–62.
- [322] Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C (2010) Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol. Aging* **31**, 224–243.
- [323] Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS (2002) A central, role for JNK in obesity and insulin resistance. *Nature* **420**, 333–336.
- [324] Qiao LY, Goldberg JL, Russell JC, Xiao Jian S (1999) Identification of enhanced serine kinase activity in insulin resistance. *J. Biol. Chem.* **274**, 10625–10632.
- [325] Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, Silverman MA, Kazi H, Melo HM, McClean PL, Holscher C, Arnold SE, Talbot K, Klein WL, Munoz DP, Ferreira ST, De Felice FG (2012) An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated A β oligomers. *J. Clin. Invest.* **122**, 1339–1353.
- [326] Talbot K, Wang H, Kazi H, Han L, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider J a, Wolf B a, Bennett D a, Trojanowski JQ, Arnold SE (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J. Clin. Invest.* **122**,.
- [327] Yarchoan M, Toledo JB, Lee EB, Arvanitakis Z, Kazi H, Han LY, Louneva N, Lee VMY, Kim SF, Trojanowski JQ, Arnold SE (2014) Abnormal serine phosphorylation of insulin receptor substrate 1 is associated with tau pathology in Alzheimer's disease and tauopathies. *Acta Neuropathol.* **128**, 679–689.

- [328] Kapogiannis D, Boxer A, Schwartz JB, Abner EL, Biragyn A, Masharani U, Frassetto L, Petersen RC, Miller BL, Goetzl EJ (2015) Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease. *FASEB J.* **29**, 589–596.
- [329] Marciniak E, Leboucher A, Caron E, Ahmed T, Tailleux A, Dumont J, Issad T, Gerhardt E, Pagesy P, Vileno M, Bournonville C, Hamdane M, Bantubungi K, Lancel S, Demeyer D, Eddarkaoui S, Vallez E, Vieau D, Humez S, Faivre E, Grenier-Boley B, Outeiro TF, Staels B, Amouyel P, Balschun D, Buee L, Blum D (2017) Tau deletion promotes brain insulin resistance. *J. Exp. Med.* **214**, 2257–2269.
- [330] Boccardi V, Murasecco I, Mecocci P (2019) Diabetes drugs in the fight against Alzheimer's disease. *Ageing Res. Rev.* **54**, 100936.
- [331] Munoz L, Ammit AJ (2010) Targeting p38 MAPK pathway for the treatment of Alzheimer's disease. *Neuropharmacology* **58**, 561–568.
- [332] Maphis N, Jiang S, Xu G, Kokiko-Cochran ON, Roy SM, Van Eldik LJ, Watterson DM, Lamb BT, Bhaskar K (2016) Selective suppression of the α isoform of p38 MAPK rescues late-stage tau pathology. *Alzheimer's Res. Ther.* **8**, 1–15.
- [333] Biessels GJ, Despa F (2018) Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat. Rev. Endocrinol.* **14**, 591–604.
- [334] Kothari V, Luo Y, Tornabene T, O'Neill AM, Greene MW, Geetha T, Babu JR (2017) High fat diet induces brain insulin resistance and cognitive impairment in mice. *Biochim. Biophys. Acta - Mol. Basis Dis.* **1863**, 499–508.
- [335] Spinelli M, Fusco S, Grassi C (2019) Brain insulin resistance and hippocampal plasticity: Mechanisms and biomarkers of cognitive decline. *Front. Neurosci.* **10**, 1–13.

- [336] Kellar D, Craft S (2020) Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol.* **19**, 758–766.
- [337] Searcy JL, Phelps JT, Pancani T, Kadish I, Popovic J, Anderson KL, Beckett TL, Murphy MP, Chen KC, Blalock EM, Landfield PW, Porter NM, Thibault O (2012) Long-term pioglitazone treatment improves learning and attenuates pathological markers in a mouse model of alzheimer's disease. *J. Alzheimer's Dis.* **30**, 943–961.
- [338] Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML, Craft S (2005) Preserved Cognition in Patients With Early Alzheimer Disease and Amnesic Mild Cognitive Impairment During Treatment With Rosiglitazone. *Am. J. Geriatr. Psychiatry* **13**, 950–958.
- [339] Yu Y, Li X, Blanchard J, Li Y, Iqbal K, Liu F, Gong CX (2015) Insulin sensitizers improve learning and attenuate tau hyperphosphorylation and neuroinflammation in 3xTg-AD mice. *J. Neural Transm.* **122**, 593–606.
- [340] Slugggett JK, Koponen M, Bell JS, Taipale H, Tanskanen A, Tiihonen J, Uusitupa M, Tolppanen AM, Hartikainen S (2020) Metformin and Risk of Alzheimer's Disease Among Community-Dwelling People With Diabetes: A National Case-Control Study. *J. Clin. Endocrinol. Metab.* **105**,.
- [341] Ahmad W, Ebert PR (2017) Metformin Attenuates A β Pathology Mediated Through Levamisole Sensitive Nicotinic Acetylcholine Receptors in a *C. elegans* Model of Alzheimer's Disease. *Mol. Neurobiol.* **54**, 5427–5439.
- [342] Farr SA, Roesler E, Niehoff ML, Roby DA, McKee A, Morley JE (2019) Metformin improves learning and memory in the samp8 mouse model of Alzheimer's disease. *J. Alzheimer's Dis.* **68**, 1699–1710.

- [343] Markowicz-Piasecka M, Sikora J, Szydłowska A, Skupień A, Mikiciuk-Olasik E, Huttunen KM (2017) Metformin – a Future Therapy for Neurodegenerative Diseases: Theme: Drug Discovery, Development and Delivery in Alzheimer’s Disease Guest Editor: Davide Brambilla. *Pharm. Res.* **34**, 2614–2627.
- [344] Meng L, Li XY, Shen L, Ji HF (2020) Type 2 Diabetes Mellitus Drugs for Alzheimer’s Disease: Current Evidence and Therapeutic Opportunities. *Trends Mol. Med.* **26**, 597–614.
- [345] Lu J, Xu Z (2018) Efficacy of Intranasal Insulin in Improving Cognition in Mild Cognitive Impairment and Alzheimer Disease: A Systematic Review and Meta-analysis. *Am. J. Ther.* **26**, e756–e762.
- [346] Santucci AC, Schroeder H, Riccio DC (1990) Homeostatic disruption and memory: effect of insulin administration in rats. *Behav. Neural Biol.* **53**, 321–333.
- [347] Watson GS, Craft S (2004) Modulation of memory by insulin and glucose: Neuropsychological observations in Alzheimer’s disease. *Eur. J. Pharmacol.* **490**, 97–113.
- [348] Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, Kern W (2004) Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* **29**, 1326–1334.
- [349] Hamidovic A, Candelaria L, Rodriguez I, Yamada M, Nawarskas J, Burge MR (2018) Learning and memory performance following acute intranasal insulin administration in abstinent smokers. *Hum. Psychopharmacol.* **33**, 1–7.
- [350] Park C. (2001) Cognitive effects of insulin in the central nervous system. *Neurosci. Biobehav. Rev.* **25**, 311–323.

- [351] Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL (2002) Sniffing neuropeptides: a transnasal approach to the human brain. *Nat. Neurosci.* **5**, 514–516.
- [352] Chapman CD, Frey WH, Craft S, Danielyan L, Hallschmid M, Schiöth HB, Benedict C (2013) Intranasal treatment of central nervous system dysfunction in humans. *Pharm. Res.* **30**, 2475–2484.
- [353] Thorne RG, Pronk GJ, Padmanabhan V, Frey WH (2004) Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience* **127**, 481–496.
- [354] Thorne RG, Emory CR, Ala TA, Frey WH (1995) Quantitative analysis of the olfactory pathway for drug delivery to the brain. *Brain Res.* **692**, 278–282.
- [355] Renner DB, Svitak AL, Gallus NJ, Ericson ME, Frey WH, Hanson LR (2012) Intranasal delivery of insulin via the olfactory nerve pathway. *J. Pharm. Pharmacol.* **64**, 1709–1714.
- [356] Francis GJ, Martinez JA, Liu WQ, Xu K, Ayer A, Fine J, Tuor UI, Glazner G, Hanson LR, Frey WH, Toth C (2008) Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. *Brain* **131**, 3311–3334.
- [357] Reger MA, Watson GS, Frey WH, Baker LD, Cholerton B, Keeling ML, Belongia DA, Fishel MA, Plymate SR, Schellenberg GD, Cherrier MM, Craft S (2006) Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype. *Neurobiol. Aging* **27**, 451–458.
- [358] Wadman M (2012) US government sets out Alzheimer’s plan. *Nature* **485**, 426–427.
- [359] Benedict C, Kern W, Schultes B, Born J, Hallschmid M (2008) Differential sensitivity

- of men and women to anorexigenic and memory-improving effects of intranasal insulin. *J. Clin. Endocrinol. Metab.* **93**, 1339–1344.
- [360] Brüner YF, Kofoet A, Benedict C, Freiherr J (2015) Central insulin administration improves odor cued reactivation of spatial memory in young men. *J. Clin. Endocrinol. Metab.* **100**, 212–219.
- [361] Chapman CD, Schiöth HB, Grillo CA, Benedict C (2018) Intranasal insulin in Alzheimer's disease: Food for thought. *Neuropharmacology* **136**, 196–201.
- [362] Novak V, Milberg W, Hao Y, Munshi M, Novak P, Galica A, Manor B, Roberson P, Craft S, Abduljalil A (2014) Enhancement of vasoreactivity and cognition by intranasal insulin in Type 2 diabetes. *Diabetes Care* **37**, 751–759.
- [363] Claxton A, Baker LD, Hanson A, Trittschuh EH, Cholerton B, Morgan A, Callaghan M, Arbuckle M, Behl C, Craft S (2015) Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's Disease dementia. *J. Alzheimer's Dis.* **44**, 897–906.
- [364] Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS, Leverenz J, Cross D, Gerton B (2012) Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: A pilot clinical trial. *Arch. Neurol.* **69**, 29–38.
- [365] Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, Trittschuh EH, Dahl D, Caulder E, Neth B, Montine TJ, Jung Y, Maldjian J, Whitlow C, Friedman S, De La Monte S (2017) Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. *J. Alzheimer's Dis.* **57**, 1325–1334.

- [366] Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, Fishel MA, Plymate SR, Cherrier MM, Schellenberg GD, Frey WH, Craft S (2008) Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid- β in memory-impaired older adults. *J. Alzheimer's Dis.* **13**, 323–331.
- [367] Avgerinos KI, Kalaitzidis G, Malli A, Kalaitzoglou D, Myserlis PG, Lioutas VA (2018) Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: a systematic review. *J. Neurol.* **265**, 1497–1510.
- [368] Rosenbloom M, Barclay T, Johnsen J, Erickson L, Svitak A, Pyle M, Frey W, Hanson LR (2020) Double-Blind Placebo-Controlled Pilot Investigation of the Safety of a Single Dose of Rapid-Acting Intranasal Insulin in Down Syndrome. *Drugs R D* **20**, 11–15.
- [369] Beirami E, Oryan S, Seyedhosseini Tamijani SM, Ahmadiani A, Dargahi L (2018) Intranasal insulin treatment restores cognitive deficits and insulin signaling impairment induced by repeated methamphetamine exposure. *J. Cell. Biochem.* **119**, 2345–2355.
- [370] Farzampour S, Majdi A, Sadigh-Eteghad S (2016) Intranasal insulin treatment improves memory and learning in a rat amyloid-beta model of Alzheimer's disease. *Acta Physiol. Hung.* **103**, 344–353.
- [371] Rajasekar N, Nath C, Hanif K, Shukla R (2017) Intranasal Insulin Administration Ameliorates Streptozotocin (ICV)-Induced Insulin Receptor Dysfunction, Neuroinflammation, Amyloidogenesis, and Memory Impairment in Rats. *Mol. Neurobiol.* **54**, 6507–6522.
- [372] Vandal M, White PJ, Tremblay C, St-Amour I, Chevrier G, Emond V, Lefrançois D, Virgili J, Planel E, Giguere Y, Marette A, Calon F (2014) Insulin reverses the high-fat diet-induced increase in brain A β and improves memory in an animal model of

- Alzheimer disease. *Diabetes* **63**, 4291–4301.
- [373] Chen Y, Zhao Y, Dai C ling, Liang Z, Run X, Iqbal K, Liu F, Gong CX (2014) Intranasal insulin restores insulin signaling, increases synaptic proteins, and reduces A β level and microglia activation in the brains of 3xTg-AD mice. *Exp. Neurol.* **261**, 610–619.
- [374] Bell GA, Fadool DA (2017) Awake, long-term intranasal insulin treatment does not affect object memory, odor discrimination, or reversal learning in mice. *Physiol. Behav.* **174**, 104–113.
- [375] Rosenbloom MH, Barclay TR, Pyle M, Owens BL, Cagan AB, Anderson CP, Frey WH, Hanson LR (2014) A single-dose pilot trial of intranasal rapid-acting insulin in apolipoprotein E4 carriers with mild-moderate Alzheimer’s disease. *CNS Drugs* **28**, 1185–1189.
- [376] Anderson KL, Frazier HN, Maimaiti S, Bakshi V V., Majeed ZR, Brewer LD, Porter NM, Lin AL, Thibault O (2017) Impact of Single or Repeated Dose Intranasal Zinc-free Insulin in Young and Aged F344 Rats on Cognition, Signaling, and Brain Metabolism. *J. Gerontol. A. Biol. Sci. Med. Sci.* **72**, 189–197.
- [377] Claxton A, Baker LD, Wilkinson CW, Trittschuh EH, Chapman D, Watson GS, Cholerton B, Plymate SR, Arbuckle M, Craft S (2013) Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or alzheimer’s disease. *J. Alzheimer’s Dis.* **35**, 789–797.
- [378] Bedse G, Di Domenico F, Serviddio G, Cassano T (2015) Aberrant insulin signaling in Alzheimer’s disease: Current knowledge. *Front. Neurosci.* **9**, 1–13.
- [379] Najem D, Bamji-Mirza M, Yang Z, Zhang W (2016) A β -Induced Insulin Resistance

- and the Effects of Insulin on the Cholesterol Synthesis Pathway and A β Secretion in Neural Cells. *Neurosci. Bull.* **32**, 227–238.
- [380] Shieh JCC, Huang PT, Lin YF (2020) Alzheimer's Disease and Diabetes: Insulin Signaling as the Bridge Linking Two Pathologies. *Mol. Neurobiol.* **57**, 1966–1977.
- [381] Doré S, Bastianetto S, Kar S, Quirion R (1999) Protective and rescuing abilities of IGF-I and some putative free radical scavengers against β -amyloid-inducing toxicity in neurons. *Ann. N. Y. Acad. Sci.* **890**, 356–364.
- [382] Ghasemi R, Zarifkar A, Rastegar K, Maghsoudi N, Moosavi M (2014) Insulin protects against A β -induced spatial memory impairment, hippocampal apoptosis and MAPKs signaling disruption. *Neuropharmacology* **85**, 113–120.
- [383] Mattson MP (1997) Cellular actions of β -amyloid precursor protein and its soluble and fibrillogenic derivatives. *Physiol. Rev.* **77**, 1081–1132.
- [384] Moreira PI, Santos MS, Sena C, Seiça R, Oliveira CR (2005) Insulin protects against amyloid β -peptide toxicity in brain mitochondria of diabetic rats. *Neurobiol. Dis.* **18**, 628–637.
- [385] Ghasemi R, & & MM& AZ& KR, Maghsoudi N (2015) The Interplay of Akt and ERK in A β Toxicity and Insulin- Mediated Protection in Primary Hippocampal Cell Culture. *J. Mol. Neurosci.* **57**, 325–334.
- [386] Qiu WQ, Walsh DM, Ye Z, Vekrellis K, Zhang J, Podlisny MB, Rosner MR, Safavi A, Hersh LB, Selkoe DJ (1998) Insulin-degrading enzyme regulates extracellular levels of amyloid β - protein by degradation. *J. Biol. Chem.* **273**, 32730–32738.
- [387] Qiu WQ, Folstein MF (2006) Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: Review and hypothesis. *Neurobiol. Aging* **27**, 190–198.

- [388] Pivovarova O, Höhn A, Grune T, Pfeiffer AFH, Rudovich N (2016) Insulin-degrading enzyme: new therapeutic target for diabetes and Alzheimer's disease? *Ann. Med.* **48**, 614–624.
- [389] Townsend MK, Okereke OI, Xia W, Yang T, Selkoe DJ, Grodstein F (2012) Relation between insulin, insulin-related factors, and plasma amyloid beta peptide levels at midlife in a population-based study. *Alzheimer Dis. Assoc. Disord.* **26**, 50–54.
- [390] Kurochkin I V., Guarnera E, Berezovsky IN (2018) Insulin-Degrading Enzyme in the Fight against Alzheimer's Disease. *Trends Pharmacol. Sci.* **39**, 49–58.
- [391] Stargardt A, Gillis J, Kamphuis W, Wiemhoefer A, Kooijman L, Raspe M, Benckhuijsen W, Drijfhout JW, M. Hol E, Reits E (2013) Reduced amyloid- β degradation in early Alzheimer's disease but not in the APP^{swe}PS1^{dE9} and 3xTg-AD mouse models. *Aging Cell* **12**, 499–507.
- [392] Zhao L, Teter B, Morihara T, Lim GP, Ambegaokar SS, Ubeda OJ, Frautschy SA, Cole GM (2004) Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: Implications for Alzheimer's disease intervention. *J. Neurosci.* **24**, 11120–11126.
- [393] Hernández F, Gómez de Barreda E, Fuster-Matanzo A, Lucas JJ, Avila J (2010) GSK3: A possible link between beta amyloid peptide and tau protein. *Exp. Neurol.* **223**, 322–325.
- [394] De Felice FG, Vieira MNN, Bomfim TR, Decker H, Velasco PT, Lambert MP, Viola KL, Zhao WQ, Ferreira ST, Klein WL (2009) Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of A β oligomers. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 1971–1976.

- [395] Zhao W, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, Krafft GA, Klein WL (2008) Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J.* **22**, 246–260.
- [396] Hong M, Lee VMY (1997) Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J. Biol. Chem.* **272**, 19547–19553.
- [397] Freude S, Plum L, Schnitker J, Leeser U, Udelhoven M, Krone W, Bruning JC, Schubert M (2005) Peripheral Hyperinsulinemia Promotes Tau Phosphorylation In Vivo. *Diabetes* **54**, 3343–3348.
- [398] Laws SM, Gaskin S, Woodfield A, Srikanth V, Bruce D, Fraser PE, Porter T, Newsholme P, Wijesekara N, Burnham S, Doré V, Li QX, Maruff P, Masters CL, Rainey-Smith S, Rowe CC, Salvado O, Villemagne VL, Martins RN, Verdile G (2017) Insulin resistance is associated with reductions in specific cognitive domains and increases in CSF tau in cognitively normal adults. *Sci. Rep.* **7**, 1–11.
- [399] Yang Y, Ma D, Wang Y, Jiang T, Hu S, Zhang M, Yu X, Gong CX (2013) Intranasal insulin ameliorates tau hyperphosphorylation in a rat model of type 2 diabetes. *J. Alzheimer's Dis.* **33**, 329–338.
- [400] Lannert H, Hoyer S (1998) Intracerebroventricular administration of streptozotocin causes long- term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav. Neurosci.* **112**, 1199–1208.
- [401] Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, De La Monte SM (2006) Intracerebral streptozotocin model of type 3 diabetes: Relevance to sporadic Alzheimer's disease. *J. Alzheimer's Dis.* **9**, 13–33.
- [402] Salkovic-Petrisic M, Knezovic A, Hoyer S, Riederer P (2013) What have we learned

- from the streptozotocin-induced animal model of sporadic Alzheimer's disease, about the therapeutic strategies in Alzheimer's research. *J. Neural Transm.* **120**, 233–252.
- [403] Salkovic-Petrisic M, Osmanovic-Barilar J, Brückner MK, Hoyer S, Arendt T, Riederer P (2011) Cerebral amyloid angiopathy in streptozotocin rat model of sporadic Alzheimer's disease: A long-term follow up study. *J. Neural Transm.* **118**, 765–772.
- [404] C. Correia S, X. Santos R, S. Santos M, Casadesus G, C. LaManna J, Perry G, A. Smith M, I. Moreira P (2013) Mitochondrial Abnormalities in a Streptozotocin-Induced Rat Model of Sporadic Alzheimer's Disease. *Curr. Alzheimer Res.* **10**, 406–419.
- [405] Hoyer S, Lannert H (1999) Inhibition of the neuronal insulin receptor causes Alzheimer-like disturbances in oxidative/energy brain metabolism and in behavior in adult rats. *Ann. N. Y. Acad. Sci.* **893**, 301–303.
- [406] Monte SM De, Wands JR (2005) Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J. Alzheimer's Dis.* **7**, 45–61.
- [407] Prasad K (2019) AGE–RAGE stress: a changing landscape in pathology and treatment of Alzheimer's disease. *Mol. Cell. Biochem.* **459**, 95–112.
- [408] Kandimalla R, Thirumala V, Reddy PH (2016) Is Alzheimer's disease a Type 3 Diabetes? A Critical Appraisal. *Biochim. Biophys. Acta - Mol. Basis Dis.*
- [409] Duarte AI, Proença T, Oliveira CR, Santos MS, Rego AC (2006) Insulin restores metabolic function in cultured cortical neurons subjected to oxidative stress. *Diabetes* **55**, 2863–2870.
- [410] Duarte AI, Santos P, Oliveira CR, Santos MS, Rego AC (2008) Insulin neuroprotection against oxidative stress is mediated by Akt and GSK-3 β signaling pathways and

- changes in protein expression. *Biochim. Biophys. Acta - Mol. Cell Res.* **1783**, 994–1002.
- [411] Biessels GJ, Reagan LP (2015) Hippocampal insulin resistance and cognitive dysfunction. *Nat. Rev. Neurosci.* **16**, 660–671.
- [412] Hoyer S (2002) The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: An update. *J. Neural Transm.* **109**, 341–360.
- [413] Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, De La Monte SM (2005) Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: Link to brain reductions in acetylcholine. *J. Alzheimer's Dis.* **8**, 247–268.
- [414] Ferreira ST, Clarke JR, Bomfim TR, De Felice FG (2014) Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. *Alzheimer's Dement.* **10**, 76–83.
- [415] Mei-Jen Wang, Hsin-Yi Huang, Wu-Fu Chen H-FC& J-SK (2010) Glycogen synthase kinase-3 β inactivation inhibits tumor necrosis factor- α production in microglia by modulating nuclear factor κ B and MLK3/JNK signaling cascades. *J. Neuroinflammation* **7**, 99.
- [416] Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, Cook DG, Peskind ER, Baker LD, Goldgaber D, Nie W, Asthana S, Plymate SR, Schwartz MW, Craft S (2005) Hyperinsulinemia provokes synchronous increases in central inflammation and β -amyloid in normal adults. *Arch. Neurol.* **62**, 1539–1544.
- [417] Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G (2001) Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance.

Am. J. Physiol. - Endocrinol. Metab. **280**, 745–751.

- [418] Najem D, Bamji-Mirza M, Chang N, Liu QY, Zhang W (2014) Insulin resistance, neuroinflammation, and Alzheimer's disease. *Rev. Neurosci.* **25**, 509–525.
- [419] Zúñiga LA, Shen W-J, Joyce-Shaikh B, Pyatnova EA, Richards AG, Thom C, Andrade SM, Cua DJ, Kraemer FB, Butcher EC (2010) IL-17 Regulates Adipogenesis, Glucose Homeostasis, and Obesity. *J. Immunol.* **185**, 6947–6959.
- [420] Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, Carvalheira JB, Velloso LA (2011) Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology* **152**, 1314–1326.
- [421] Chang YH, Ho KT, Lu SH, Huang CN, Shiau MY (2012) Regulation of glucose/lipid metabolism and insulin sensitivity by interleukin-4. *Int. J. Obes.* **36**, 993–998.
- [422] Wollheim CB, Sharp GW (1981) Regulation of insulin release by calcium. *Physiol. Rev.* **61**, 914–973.
- [423] Clausen, T.; Elbrink, J.; Martin BR (1974) Insulin controlling calcium distribution in muscle and fat cells. *Eur. J. Endocrinol.* **77**, S137–S143.
- [424] Viard P, Butcher AJ, Halet G, Davies A, Nürnberg B, Hebllich F, Dolphin AC (2004) PI3K promotes voltage-dependent calcium channel trafficking to the plasma membrane. *Nat. Neurosci.* **7**, 939–946.
- [425] Maimaiti S, Frazier HN, Anderson KL, Ghoweri AO, Brewer LD, Porter NM, Thibault O (2017) Novel calcium-related targets of insulin in hippocampal neurons. *Neuroscience* **364**, 130–142.
- [426] Neth BJ, Craft S (2017) Insulin resistance and Alzheimer's disease: Bioenergetic

- linkages. *Front. Aging Neurosci.* **9**, 1–20.
- [427] Pancani T, Anderson KL, Porter NM, Thibault O (2011) Imaging of a glucose analog, calcium and NADH in neurons and astrocytes: Dynamic responses to depolarization and sensitivity to pioglitazone. *Cell Calcium* **50**, 548–558.
- [428] De Felice FG, Felice FG De (2013) Alzheimer ' s disease and insulin resistance : translating basic science into clinical applications Find the latest version : Science in medicine Alzheimer ' s disease and insulin resistance : translating basic science into clinical applications. *J. Clin. Invest.* **123**, 531–539.
- [429] Jellinger KA (2013) Pathology and pathogenesis of vascular cognitive impairment-a critical update. *Front. Aging Neurosci.* **5**, 1–19.
- [430] Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, Monsell SE, Kukull WA, Trojanowski JQ (2013) Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* **136**, 2697–2706.
- [431] Kalaria RN (2018) The pathology and pathophysiology of vascular dementia. *Neuropharmacology* **134**, 226–239.
- [432] Muniyappa R, Yavuz S (2013) Metabolic actions of angiotensin II and insulin: A microvascular endothelial balancing act. *Mol. Cell. Endocrinol.* **378**, 59–69.
- [433] Castellani RJ, Plascencia-Villa G, Perry G (2019) The amyloid cascade and Alzheimer's disease therapeutics: theory versus observation. *Lab. Investig.* **99**, 958–970.
- [434] Almansoub HAMM, Tang H, Wu Y, Wang DQ, Mahaman YAR, Wei N, Almansob YAM, He W, Liu D (2019) Tau Abnormalities and the Potential Therapy in

- Alzheimer's Disease. *J. Alzheimer's Dis.* **67**, 13–33.
- [435] Cenini G, Voos W (2019) Mitochondria as potential targets in Alzheimer disease therapy: An update. *Front. Pharmacol.* **10**, 1–20.
- [436] Perez Ortiz JM, Swerdlow RH (2019) Mitochondrial dysfunction in Alzheimer's disease: Role in pathogenesis and novel therapeutic opportunities. *Br. J. Pharmacol.* **176**, 3489–3507.
- [437] Cassidy L, Fernandez F, Johnson JB, Naiker M, Owoola AG, Broszczak DA (2020) Oxidative stress in alzheimer's disease: A review on emergent natural polyphenolic therapeutics. *Complement. Ther. Med.* **49**, 102294.
- [438] Cerovic M, Forloni G, Balducci C (2019) Neuroinflammation and the Gut Microbiota: Possible Alternative Therapeutic Targets to Counteract Alzheimer's Disease? *Front. Aging Neurosci.* **11**, 1–9.
- [439] Dong Y, Li X, Cheng J, Hou L (2019) Drug development for alzheimer's disease: Microglia induced neuroinflammation as a target? *Int. J. Mol. Sci.* **20**,.
- [440] Shal B, Ding W, Ali H, Kim YS, Khan S (2018) Anti-neuroinflammatory potential of natural products in attenuation of Alzheimer's disease. *Front. Pharmacol.* **9**,.
- [441] Fu AKY, Hung KW, Yuen MYF, Zhou X, Mak DSY, Chan ICW, Cheung TH, Zhang B, Fu WY, Liew FY, Ip NY (2016) IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. *Proc. Natl. Acad. Sci. U. S. A.* **113**, E2705–E2713.
- [442] Bezprozvanny I (2009) Calcium signaling and neurodegenerative diseases. *Trends Mol. Med.* **15**, 89–100.
- [443] Feldman L, Vinker S, Efrati S, Beberashvili I, Gorelik O, Wasser W, Shani M (2016) Amlodipine treatment of hypertension associates with a decreased dementia risk. *Clin.*

Exp. Hypertens. **38**, 545–549.

- [444] Gibson G, Cotman C, Lynch G, Blass J (2017) Calcium Hypothesis of Alzheimer’s disease and brain aging: A framework for integrating new evidence into a comprehensive theory of pathogenesis. *Alzheimer’s Dement.* **13**, 178-182.e17.
- [445] Lawlor B, Segurado R, Kennelly S, Olde Rikkert MGM, Howard R, Pasquier F, Börjesson-Hanson A, Tsolaki M, Lucca U, Molloy DW, Coen R, Riepe MW, Kálmán J, Kenny RA, Cregg F, O’Dwyer S, Walsh C, Adams J, Banzi R, Breuilh L, Daly L, Hendrix S, Aisen P, Gaynor S, Sheikhi A, Taekema DG, Verhey FR, Nemni R, Nobili F, Franceschi M, Frisoni G, Zanetti O, Konsta A, Anastasios O, Nenopoulou S, Tsolaki-Tagaraki F, Pakaski M, Dereeper O, de la Sayette V, Sénéchal O, Lavenu I, Devendeville A, Calais G, Crawford F, Mullan M (2018) Nilvadipine in mild to moderate Alzheimer disease: A randomised controlled trial. *PLoS Med.* **15**, 1–20.
- [446] Mcshane R, Westby M, Roberts E, Minakaran N, Schneider L, Farrimond L, Maayan N, Ware J, Debarros J (2019) Memantine for dementia [Systematic Review]. *Cochrane Database Syst. Rev.*
- [447] De La Monte SM, Tong M, Wands JR (2018) The 20-Year Voyage Aboard the Journal of Alzheimer’s Disease: Docking at “Type 3 Diabetes”, Environmental/Exposure Factors, Pathogenic Mechanisms, and Potential Treatments. *J. Alzheimer’s Dis.* **62**, 1381–1390.

FIGURES

Figure 1

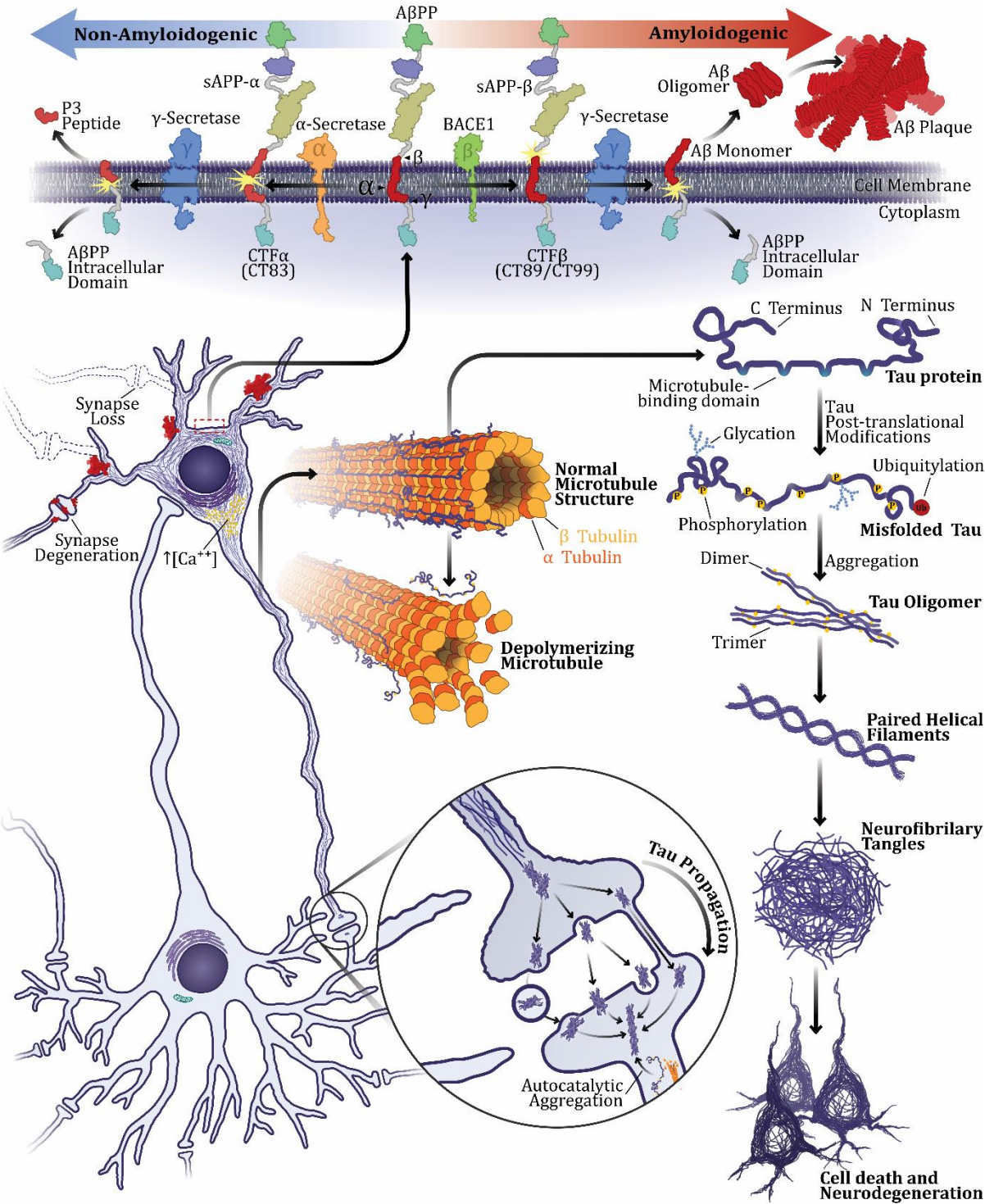


Figure 2

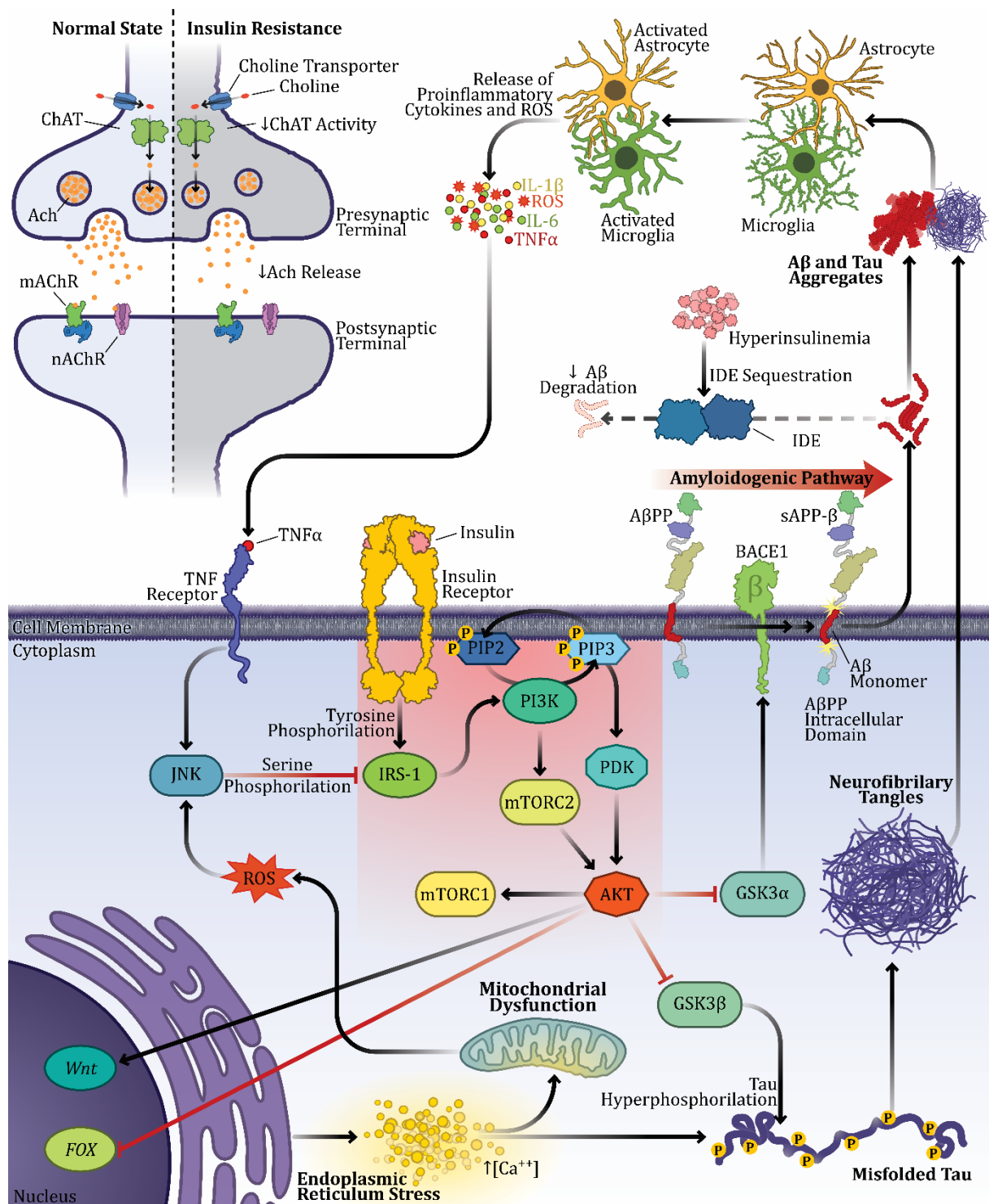


FIGURE LEGENDS

Fig. 1. The traditional triad in Alzheimer's disease pathogenesis: amyloid- β peptide, hyperphosphorylated Tau protein and neurodegeneration. A β plaques, neurofibrillary tangles, and cell death had been seen the main neuropathological hallmarks and major factors in AD pathogenesis for more than a century. According to the amyloid cascade hypothesis, the most traditional hypothesis of AD, disturbances in A β PP metabolism are the triggering event in AD. In the amyloidogenic pathway, A β PP is first cleaved off by the enzyme β -secretase (BACE 1), giving rise to two fragments: sAPP- β (N-terminal fragment) and CT99 or CT89. Then, the γ -secretase complex cleaves the remaining membrane-bound portion of the protein releasing the extracellular fragment A β . On the other hand, in the non-amyloidogenic pathway, A β PP is firstly cleaved by α -secretase within A β sequence, producing soluble α -APP fragments (sAPP α) and C-terminal fragment α (CTF α , C83), posteriorly, CTF α is cut by γ -secretase, releasing non-toxic fragments (P3 peptide and A β PP intracellular domain). Alterations in A β PP processing usually result in increased A β production in the amyloidogenic pathway. Excessive A β production, aggregation and deposition into plaques, in turn, lead to intracellular Ca²⁺ dysregulation and induce Tau protein hyperphosphorylation and cell death. Tau is highly abundant in neurons and interacts with tubulin to promote microtubule polymerization and stabilization. However, when hyperphosphorylated, the ability of Tau to interact with microtubules is impaired. Hyperphosphorylated Tau undergoes conformational changes and self-aggregates into oligomers. Elongated oligomers usually form paired helical filaments, which culminate in neurofibrillary tangles formation, inducing neurodegeneration. Moreover, hyperphosphorylated Tau can sequester normal tau into filamentous tau aggregates.

Fig.2. Alzheimer's disease as a multifactorial disorder: multiple factors converging into a single disease. Interactions between different events proposed in AD pathogenesis over the last decades: A β overproduction, tau hyperphosphorylation, neuroinflammation, alterations in the

cholinergic system, mitochondrial dysfunction, oxidative stress, calcium imbalance, and insulin resistance as the main link connecting different factors. The PI3K-Akt signaling pathway is particularly important in AD pathogenesis due to its numerous interactions with AD events, but mainly because of its modulation of A β production and Tau protein hyperphosphorylation through GSK-3 activity. Insulin binds to the alpha subunits of the insulin receptor (IR) by inducing autophosphorylation of its beta subunit on tyrosine residues. Then, the signal is transduced through the phosphorylation of insulin receptor substrates (IRS), also on tyrosine residues. Phosphorylation of the IRS promotes conformational changes that enable the binding between IRS and another enzyme known as phosphoinositide 3-kinases (PI3K). PI3K activation, in turn, phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP₂) in the cell membrane and results in phosphatidylinositol (3,4,5)-trisphosphate (PIP₃) formation. Then, PIP₃ enables protein kinase (AKT/PKB) signaling pathway, which regulates the activation of many intracellular proteins in pathways related to cell proliferation and survival, such as the mammalian target of rapamycin (mTOR), forkhead box (FOX) proteins and Glycogen synthase kinase-3 (GSK3). There are two isoforms of GSK-3 in mammals, the isoforms α and β . While GSK-3 α regulates A β production, GSK-3 β modulates Tau phosphorylation. Besides GSK-3 activity, alterations of many other proteins in the insulin signaling cascade have also been reported in AD.

TABLE

Table 1. Main hypotheses on the pathogenesis of sporadic Alzheimer’s disease and associated therapies

Hypothesis	Main concept	Related therapies	References
Amyloid cascade hypothesis	The A β peptide is the triggering factor of AD. Acute effects, such as head trauma, promote disturbances in A β PP metabolism, altering A β production, clearance and deposition. The A β protein, in turn, promotes intracellular calcium dysregulation, inducing neurofibrillary tangle formation and cell death.	Vaccines, antibodies and molecules targeting monomeric, oligomeric and fibrillar A β species, soluble and insoluble A β , A β protofibrils, A β oligomer receptor, A β synthesis, A β aggregation, A β -glycosaminoglycan binding, and pyroglutamate-A β (ABvac40, Adubanutab, Bapineuzumab, Solanezumab BAN2401, acitretin,	[27,433]

		<p>atabacestat, semagacestat, elenbecestat bexarotene, Alzhemed, PQ912, etc.)</p>	
<p>Cholinergic hypothesis</p>	<p>AD is a brain cholinergic system failure and the cognitive symptoms observed in this disorder are caused mainly by degeneration of cholinergic neurons in the basal forebrain and by cholinergic synaptic loss in the cerebral cortex.</p>	<p>Cholinesterase inhibitors (tacrine, donezepil, rivastigmine, galantamine).</p>	<p>[80,96]</p>
<p>Tau hypothesis</p>	<p>Tau hyperphosphorylati on precedes neurodegeneration</p>	<p>Modulators of tau posttranslational modifications, Tau aggregation</p>	<p>[107,108,117,434]</p>

	<p>and Aβ accumulation, and in association with convergent signaling mechanisms, result in AD pathogenesis.</p>	<p>inhibitors, tau disaggregating agents, stabilizing microtubules (ACI35, AADvac-1, RG6100, ABBv-8E12, lithium, tideglusib, saracatinib, salsalate, ASN120290, epothilone D, methylene blue, nilotinib, TRx0237, etc.).</p>	
<p>Mitochondrial cascade hypothesis</p>	<p>The individual's baseline mitochondrial function is defined by genetic inheritance, and interactions between genetic and environmental factors define the</p>	<p>Antioxidants, bioenergetic medicine, vitamins, cofactors, electron acceptors, redox molecule precursors, intermediate compounds of the Krebs cycle and</p>	<p>[122,435,436]</p>

<p>rhythm at which mitochondrial dysfunction accumulates and, therefore, determine the AD onset.</p>	<p>gluconeogenesis, intermediate compounds of mitochondrial metabolic pathways, peroxisome proliferator- activated receptor gamma Phenylpropanoids, antihistaminic drug, actions on the lifestyle (vitamin E and C, coenzyme Q10, selenium, mitoquinone mesylate, melatonin, α-lipoic acid, catalase, resveratrol, curcumin rapamycin, Dimebon, nicotinamide</p>	
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		adenine dinucleotide, physical exercise, calories restriction, , etc.).	
Oxidative stress hypothesis	The CNS presents a high lipid content and decreased amount of antioxidant enzymes relative to other systems, which may promote cumulative oxidative damage over time and result in AD pathogenesis. Different biomolecules from the neuronal membrane, such as lipids, fatty acids, and proteins undergo oxidation,	Antioxidant, vitamins, supplementary diets, polyphenolic compounds, Flavonoids, medicinal plants (rosmarinic acid, quercetin, epicatechin, cannabidiol, melatonin, vitamins A, C, and E, β -carotene, B-complex vitamins, proanthocyanidin, <i>Centella asiatica</i> , <i>Aloe arborescens</i> , <i>Capparis spinosa</i> L., Alpinia	[148,149,162,437]

	even in earlier stages of AD.	galanga L., <i>Abelmoschus esculentus</i> , <i>Curcuma longa</i> , etc.).	
Neuroinflammation hypothesis	A persistent inflammatory stimulus, (trauma, pathogenic infection, A β toxicity) triggers microglia activation. Microglia, in turn, secrete numerous pro-inflammatory cytokines and release ROS, attracting more microglia and astrocytes migrating towards the lesion area. Microglia become	Non-steroidal anti-inflammatory drugs, antioxidants, probiotics, steroid and phenolic phytochemicals, Terpenoid-Derived phytochemicals, alkaloidal phytochemicals, Tumor necrosis factor-alpha inhibitor, 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitor, p38 mitogen-activated	[176,177,438–440]

<p>overactive, which initiates an auto-destructive process, culminating in neurodegeneration and AD pathogenesis.</p>	<p>serine/threonine protein kinase p38 MAPK (p38 MAPKα) selective inhibitor, receptor for advanced glycation endproducts (RAGE) inhibitor, peroxisome-proliferator activated receptor γ (PPARγ) agonists (ibuprofen, tarenflurbil, salsalate, celecoxib, resveratrol, etanercept, simvastatin, neflamapimod, azeliragon,</p>	
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		Diosgenin, Prosapogenin III, quercetin, Ginkgolide, berberine, etc.).	
Innate immunity hypothesis	The activation of the innate immune system is the disease-promoting factor and the activation of a senescent and non-functional microglia is the initial trigger of AD pathogenesis.	Pharmacological and genetic therapies targeting impaired microglial clearance, nonsteroidal anti-inflammatory drugs, actions in lifestyle (galantamine, thiazolidinedione, interleukin 33, etc.).	[208–210,441]
Calcium hypothesis	Sustained alterations in Ca ²⁺ signaling in neurons is a key event of AD pathogenesis.	Modulation of Ca ²⁺ related proteins and pathways, therapeutic strategies to balance calcium	[212,442–446]

		homeostasis, and actions in lifestyle. (nilvadipine, memantine, amlodipine, MEM-1003, EVT-101, physical exercise, etc.).	
Type 3 diabetes hypothesis	AD is a neuroendocrine disorder, similar, but also distinct, from DM types 1 and 2. Insulin deficiency and alterations in the insulin signaling pathway play major roles in AD pathogenesis.	Agents that treat hyperglycemia and ameliorates insulin sensitivity and the regulation of insulin signaling pathway, antidiabetic drugs, amylin analog drugs, insulin, glucagon-like peptide-1 receptor agonists, thiazolidinediones, sulfonylurea, inhibitors of dipeptidyl	[243,344,447]

		peptidase 4, biguanides and gliflozin class drugs, glucosidase inhibitors, and meglitinides (liraglutide, pioglitazone, sitagliptin, pramlintide, glimepiride, metformin, canagliflozin, acarbose, repaglinide, etc.).	
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