Persistence and Severity of Cutaneous Manifestations in IgA Vasculitis Is Associated with Development of IgA Vasculitis Nephritis in Children

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Title: Circadian changes in Alzheimer's disease: neurobiology, clinical problems and therapeutic opportunities

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Abstract:

The understanding of Alzheimer's disease (AD) pathophysiology is an active area of research, and the traditional focus on hippocampus, amyloid and tau protein, and memory impairment, has been expanded with components like neuroinflammation, insulin resistance, and circadian rhythm alterations. The bi-directional vicious cycle of neuroinflammation and neurodegeneration on a molecular level may cause functional deficits already long before the appearance of overt clinical symptoms. Located at the crossroads of metabolic, circadian and hormonal signaling, the hypothalamus has been identified as another brain region affected by AD pathophysiology.

Current findings on hypothalamic dysfunction open a broader horizon for studying AD pathogenesis and offer new opportunities for diagnosis and therapy. While treatments with cholinomimetics and memantine form a first line of pharmacological treatment, additional innovative research is pursued towards the development of anti-inflammatory, growth factor or antidiabetic types of medication. Following recent epidemiological data showing associations of AD incidence with modern societal and 'life-style' related risk factors, also non-pharmacological interventions, including sleep optimization, are being developed and some have been shown to be beneficial. Circadian aspects in AD are relevant from a pathophysiological standpoint, but they can also have an important role in pharmacologic and non-pharmacologic interventions, and appropriate timing of sleep, meals, and medication may boost therapeutic efficacy.

Keywords: Alzheimer's disease, Circadian rhythm, Hypothalamus, Neurodegeneration, Sleep.

1. Introduction

The calculated cumulative incidence of Alzheimer's disease (AD) starting at age 45 is around 20% for women and 10% for men (Chêne *et al.*, 2015). Based on anticipated increases in the absolute global population of people older than 65 years, estimates indicate that relative to 1995, the incidence of AD will have doubled by 2050, with an expected total of around 1 million cases (Hebert *et al.*, 2001). Besides memory impairment, other aspects of AD have also gained attention. Circadian changes in AD have considerable pathophysiological and clinical relevance. Neuropsychiatric symptoms in AD do not exclusively arise from hippocampal dysfunction, but other brain regions as well. Hypothalamus is one of the key regions of interest for the study of circadian changes in AD, as it contains the biological clock of the brain, i.e. the suprachiasmatic nucleus (SCN), and orchestrates crucial interactions between the nervous and endocrine system in a rhythmic pattern. With an increasing focus on hypothalamic aspects of AD, also broader implications of the disease become recognized. Focusing on those aspects may expand our pathophysiological understanding of AD symptoms and thereby help to uncover novel therapeutic targets and approaches.

2. Pathogenesis of AD: beaten tracks and novel emerging concepts

Although a vast amount of resources have been directed towards research into AD, its pathogenesis remains largely unknown. There are at least two types of AD, i.e. the familial form (fAD), accounting for 1-5% of all cases, and the sporadic form (sAD), responsible for the remaining 95-99% of the patients (Homolak *et al.*, 2018). The familial form of the disease is mainly passed down through autosomal dominant genes involved in processing amyloid β (*PSEN1*, *PSEN2* and *APP*), and the symptoms usually present around the 3rd or 4th life decade. In contrast, sAD usually starts after the 6th decade, and is therefore commonly referred to as late onset AD. Significant efforts were also put into understanding the genetic background of

the sporadic form of the disease with results suggestive of the importance of heritability (Gatz *et al*, 2006; Barber, 2012; Van Cauwenberghe *et al*., 2016). Nevertheless the pathophysiological course of the disease is defined by complex interactions of multiple genetic and environmental components that are still not well understood. In semantic terms, even though fAD and sAD are two forms of the same disease, it might be better to classify fAD as a disease, and sAD as a syndrome; "a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood" (Calvo *et al.*, 2003). This distinction is crucial in understanding AD etiopathogenesis as most of the research over the years focused on sAD and fAD interchangeably. This is probably most evident in animal research where genetic manipulation is by far the most common method for studying sAD etiopathogenesis even though it is more appropriate for understanding fAD.

Although a complex pathophysiological interplay of factors likely orchestrates the neurodegeneration in sAD, preclinical studies have so far focused on a rather narrow 'amyloidocentric' approach. We hypothesize that these conservative amyloidocentric and 'hippocampocentric' approaches have led us astray from a better understanding of the etiopathogenetic mechanisms present in AD. So far, classic models of the disease remain prevalent in preclinical literature despite the fact that novel therapeutics remain largely ineffective (Karran *et al.*, 2011).

Recent findings have proposed some overlooked molecular and anatomical patterns that appear related to hypothalamic nuclei at least in pathophysiological terms. In this chapter, we will therefore focus on the role of hypothalamus in AD and discuss alterations from a molecular and clinical perspective, and in the context of new diagnostic and therapeutic opportunities (Figure 1).

3. Hypothalamus at the crossroads of early circadian and metabolic disruptions in AD - evidence from animal models

Most of the research on AD, both in humans and animal models, is focused on understanding neuropathologic changes in two brain areas - cerebral cortex and hippocampus, the latter being an especially popular area of interest in animal models of AD due to its well established role in memory and cognition. However, studies suggests that focusing on hippocampus-driven research only may hinder the study of other etiopathogenetic aspects of AD, and changes in other brain areas may e.g. occur earlier or show a greater correlation with clinical progression (Grinberg *et al.*, 2009; Simic *et al.*, 2009). In this context, the hypothalamus is particularly interesting as both human and animal studies have reported hypothalamic areas to undergo neurodegenerative changes in AD. (Ishii and Iadecola, 2015; Zheng *et al.*, 2018).

A unique function of the hypothalamus relates to the physiological integration of metabolism, sleep, reproduction and autonomic homeostasis (Swaab, 1997). This may provide at least some of the explanations for sleep disorders, insulin resistant brain state, metabolic syndrome, and hormonal abnormalities, which are all dysfunctions reported in AD patients (Neth and Craft, 2017; Brzecka *et al.*, 2018; Zhang *et al.*, 2019). Hypothalamic atrophy was noted in early clinical stages of the disease, and pathognomonic neuropathologic changes such as plaques and tangles have been described in hypothalamic nuclei of the deceased patients (Swaab et al., 1992; Ishii and Iadecola, 2015). Interestingly, hypothalamic deposits were described even in the well-known paper on neuropathologic AD staging by Braak and Braak, with the most pronounced changes occurring in the late stages of the disease (Braak and Braak, 1991).

Animal studies support hypothalamic involvement in AD pathogenesis. Some findings suggest that hypothalamic changes occur prior to the appearance of neuropathological findings and

cognitive dysfunction, both in transgenic and non-transgenic models of the disease. In the study by Zhang et al. (2018), NMR-based metabolomics was used to examine a metabolic fingerprint at different stages of cognitive decline and in different brain regions of APP/PS1 transgenic mice. Considering metabolic networks as a reflection of cellular function and cellular response to noxious signals, it has been suggested that a robust spatiotemporal metabolomics dissection might provide indispensable information to identify early drivers of AD pathophysiology (Mapstone *et al.*, 2014; Toledo *et al.*, 2017; Varma *et al.*, 2018; Low *et al.*, 2019), since recent data shows links between metabolic dysfunction and neurodegeneration (Barilar et *al.*, 2020).

While taking into account genetic background*age interaction effects, metabolomics analysis of the mouse cortex, cerebellum, hippocampus, hypothalamus, midbrain, and striatum at 1, 5, and 10 months of age, revealed that the hypothalamus is a brain region undergoing the most pronounced metabolic perturbation in the process of neurodegeneration (Zheng *et al.*, 2018). Metabolic profiling detected greatest discrepancies in the hypothalamus at 5 months of age, with metabolic changes being suggestive of hypermetabolism, while cognitive function remained unchanged until the age of 10 months, a period characterized by normalization of hypothalamic hypermetabolism. The exact molecular process responsible for the observed metabolic perturbations in hypothalamus, as well as mechanism of apparent normalization remain to be elucidated, however loss of hypothalamic functional capacity to cope with the allostatic load, and subsequent pathophysiological processes driving neurodegeneration and cognitive dysfunction, provides one compelling explanation that should be further explored. Human studies showed similar changes in nucleus basalis of Meynert (Dubelaar *et al.*, 2006) and prefrontal cortex (Bossers *et al.*, 2010), suggestive of hypermetabolism being a more general phenomenon related to AD pathogenesis.

Findings from non-transgenic animal models of AD also support an early involvement of the hypothalamus in the development of cognitive and non-cognitive pathological changes. In one of the most commonly used non-transgenic rat models of AD, that is based on the development of an insulin-resistant brain state following intracerebroventricular administration of diabetogenic toxin streptozotocin (STZ), the hypothalamus is one of the brain regions showing the most pronounced degeneration early after the induction procedure. The current concept of STZ toxicity is explained by its selective uptake by the low-affinity glucose transporter 2 (GLUT2) that is expressed abundantly in rodent insulin-producing pancreatic beta cells, liver, and kidney, and thereby enables the relatively selective damage in this rodent model of diabetes. In the brain, the GLUT2 is found to be expressed in the hypothalamus and in the circumventricular organs where the transporter is involved in the signaling mechanisms closely related to nutrient sensing (Grieb, 2016).

An early involvement of the hypothalamus in the neurodegeneration occurring after intracerebroventricular STZ (STZ-icv) administration has been reported by several groups. Oliveira Santos et al. reported pronounced hypothalamic Fluoro-Jade C signal 24 hours after STZ administration (Santos *et al.*, 2012) and Knezovic et al. (2017) have shown effects of STZ administration can be observed in the ependymal lining of the third ventricle as early as 1 hour after the administration. In the same study by Santos (Santos *et al.*, 2012), but in a separate cohort of rats used for evaluation of long term effects at the 30-day time-point, hypothalamic expression of Aβ demonstrated a 86.6% increase relative to controls, while changes in the hippocampal and cortical regions were less pronounced and failed to reach statistical significance. Interestingly, on the same time-point, one month after STZ administration, metabolic changes assessed by means of ^{18}FDG-PET suggest the hypothalamus is the most affected region of the brain and indicated the involvement of glucose hypometabolism (Knezovic *et al.*, 2018).

Others have observed pronounced changes in the hypothalamus and also in adjacent regions of the brain. For example, Shoham et al. reported an enlargement of the third ventricle by 100-150% accompanied by loss of ependymal cells and damage to hypothalamic periventricular myelin in STZ-treated rats (Shoham *et al.*, 2003), an intriguing finding considering the importance of myelinated axons adjacent to the affected region. Finally, hypothalamic involvement in the STZ-icv model, as well as in other animal models exploiting intracerebroventricular administration of different toxins (e.g. intracerebroventricular Aβ (Kim *et al.*, 2016)) should be considered in the context of methodological background, as the process of ventricular cannulation itself might contribute to the development of neuroinflammation and insults in surrounding tissue could act as a "second hit". The latter is especially interesting in the context of rapid administration procedures where significant ventricular distension is possible as rapid increment of ventricular volume has been proposed as one of the alternative etiologic models of AD mediated by axonal stretch accompanied by a separation of trans-synaptic proteins (Schiel, 2018).

4. Functional consequences of an early hypothalamic involvement in AD pathogenesis

Functional consequences of the involvement of hypothalamus in the process of neurodegeneration are well documented in the literature, however they are often described separately and are rarely reviewed in the context of the pathophysiological role of hypothalamus in AD. Among these, circadian rhythmicity and sleep, and metabolic misalignment stand out both in AD patients and animal models of the disease.

4.1 Circadian rhythmicity and sleep

Dysregulation of sleep and wakefulness patterns is present in various rodent models of AD. In Tg2576, one of the most widely used mouse models of AD with accumulation of Aβ and progressive age-dependent cognitive deterioration, a number of sleep and circadian abnormalities have been reported. The extensive study by Wisor et al. (2005) have shown that Tg2576 display altered patterns of wheel running rhythms and higher encephalographic frequencies during non-rapid eye movement (NREM) sleep. Furthermore, transgenic animals failed to show increased encephalographic delta waves (1 - 4Hz) during NREM sleep following sleep deprivation, and the wake-promoting effect of donepezil was less effective when compared to the one observed in the control group (Wisor *et al.*, 2005). Interestingly, circadian disruption was present in transgenic mice at all ages studied, with the first test trial being conducted at the age of 5 months. For contextual purposes, cognitive deficit, accumulation of amyloid plaques, and increased microglial density in Tg2576 usually occur around the age of 12 months (Alzforum research models repository: *Tg2576*). The exact cause for circadian misalignment in these transgenic animals is still speculative, however degeneration of basal forebrain cholinergic nuclei and dysfunction of suprachiasmatic nucleus, may provide possible explanations for the observed effects (Wisor *et al.*, 2005; Roy *et al.*, 2019). Circadian dysfunction has also been reported in non-transgenic models of AD. In the STZ-icv rat model of sAD, a significant increase in wakefulness, as well as decrease in both NREM and REM sleep has been reported two weeks after the induction procedure (Cui *et al.*, 2018). Further analyses revealed that the observed findings were paralleled by a reduced GABAergic tone in the ventrolateral preoptic nucleus and in the parabrachial nucleus involved in the functional maintenance of the waking state (Cui *et al.*, 2018).

A dysfunctional circadian rhythm is a well-known feature of AD (Wu and Swaab, 2007; Ju et al., 2014;; Homolak et al., 2018). In contrast to the previous perception of sleep disturbances as consequences of the disease process, accumulating findings support an early involvement of

circadian dysfunction in AD pathogenesis (Hahn *et al.*, 2014) with a bidirectional link between circadian dysrhythmia and disease progression, and a tendency to enter a pathophysiological positive feedback loop (Ju *et al.*, 2014; Homolak *et al.*, 2018). The most common sleep problems in AD patients are frequent daytime napping, difficulty falling asleep, nocturnal sleep fragmentation, and early awakening (Musiek *et al.*, 2015), often accompanied by loss of slow-wave sleep (stage three of non-REM) and REM sleep (Homolak *et al.*, 2018). Electroencephalographic findings support the hypotheses of early non-REM involvement in AD pathogenesis as a decreased density of K-complexes is present in patients when compared to findings from patients diagnosed with MCI or healthy controls (De Gennaro *et al.*, 2017).

4.2 Metabolic dysregulation

Metabolic dysregulation has been reported in transgenic and in non-transgenic models of AD, however its involvement in pathogenesis of AD-like phenotype in transgenic models has only recently been examined more thoroughly. An impairment of glucose tolerance, such as increased fasting plasma insulin and diminished response to insulin in the intraperitoneal glucose tolerance test, has been reported in APP/PS1 transgenic mice prior to accumulation of Aβ or development of cognitive deficits, with metabolic changes being present already at the 2nd month of age (Macklin *et al.*, 2017). Furthermore, reduced glucose tolerance does not seem to be the only finding of peripheral metabolic dysfunction in transgenic models of AD as pancreatic (Liu *et al.*, 2019), kidney, and liver (González-Domínguez *et al.*, 2015) metabolic profiles of APP/PS1 differ from that of the control mice.

Metabolic dysregulation in transgenic models is also evident at the level of central regulation as rodent models of AD exhibit different patterns of feeding behavior, impaired satiation, and hypermetabolism (Adebakin *et al.*, 2012; Knight *et al.*, 2012). Altered peripheral metabolism is also evident in non-transgenic models. For example, Bloch and colleagues described a

number of peripheral metabolic changes in Lewis rats after STZ-icv (Bloch *et al.*, 2017). In the first two weeks following induction procedure, usually considered as the period of pronounced acute neuroinflammation, STZ-icv-treated rats lost weight, however, in the subsequent weeks, accelerated weight gain, liver fat accumulation, hypertrophy of pancreatic islets, and elevated blood insulin, adiponectin and leptin were reported. Interestingly, peripheral glucose levels were within normal reference range, suggesting allostatic load was still relatively compensated during the experiment (Bloch *et al.*, 2017). The pronounced metabolic changes that are not associated with a significant disruption of plasma glucose homeostasis, also suggest that peripheral metabolic changes should be more closely investigated in AD patients even when the glucose profile remains inside the reference range.

Alzheimer's disease is often accompanied by peripheral metabolic dysfunctions (Cai *et al.*, 2012). The exact role of metabolic changes in AD is still a matter of debate, however literature suggests a causative role as metabolic dysfunction, both cerebral and peripheral often precedes neurocognitive impairment. Excess body weight, obesity and metabolic syndrome during middle-age have all been described as risk factors for development of AD (Cai *et al.*, 2012). Type 2 diabetes mellitus (T2DM) is another factor associated with an increased risk for AD as shown e.g. in the Rotterdam study, where a two-fold greater risk to develop the disease was found in diabetic patients when compared to patients without T2DM, and a four-fold increase in the ones using exogenous insulin (Ott *et al.*, 1999). Differences in concentration or signaling pathways of metabolic hormones has been described in AD patients. Insulin signaling is disrupted in AD brains with molecular findings suggestive of an insulin-resistant brain state, and now considered an important early pathogenic factor and possible pharmacologic target. The importance of metabolic hypothesis of AD and the involvement of insulin in the pathophysiologic cascade is probably best reflected in the term "diabetes mellitus type 3"

proposed for AD by de la Monte, due to a number of common pathobiological mechanisms shared by AD and diabetes (Steen *et al.*, 2005). Other metabolic hormones such as leptin, adiponectin, ghrelin, and glucagon-like peptide 1 are also affected in AD, suggesting a general metabolic dysregulation to be part of the pathologic process (Cai *et al.*, 2012).

5. Clinical challenges: from bench to bedside

Basic science models provide insight into certain aspects of AD pathogenesis, but the ultimate step is translation to a clinical setting. Several challenges stand in the way of global standardization of care for the population affected by AD. Also, there is a tremendous socioeconomic burden for patient's caregivers, especially non-healthcare associated caretakers. Diagnostic methods are steadily improving as pathophysiology is more understood, but capacities are rather limited. An improved awareness combined with suitable biomarkers that would allow an earlier recognition would provide a better chance to halt or postpone a detrimental process.

5. 1 Diagnosis

Symptoms and signs of AD are underappreciated. Consequently, the AD-spectrum is underdiagnosed. Although in a sample group of individuals aged 45 years or older, many reported subjective cognitive decline, less than half sought professional assessment (Taylor, 2018). Conversely, less than half of US primary care physicians formally assess their older patients' cognitive status ('2020 Alzheimer's disease facts and figures', 2020). Due to considerable disability and morbidity associated with AD, disease burden is overwhelming and caregiver burnout is not uncommon ('2020 Alzheimer's disease facts and figures', 2020).

Developing an effective framework is work in progress as attention is also dedicated to non-cognitive symptoms, or to comorbidities commonly accompanying AD. An earlier recognition or slowing of pathophysiologic processes should improve the quality of life for patients and caregivers.

Despite the development of neuroimaging and CSF biomarkers, trained professionals are required to establish an appropriate diagnosis with careful assessment of history, risk factors, and clinical features. Diagnostic uncertainty may be resolved with CSF Aβ1-42 and tau levels, which are decreased and increased in AD, respectively (Niemantsverdriet *et al.*, 2017). Newer CSF biomarkers, such as SNAP-25 and chromogranin may even point to pre- and post- synaptic dysfunction (Moya-Alvarado *et al.*, 2016). The ultimate gold standard would be histopathological brain analysis. An exemplary finding is that brain glucose metabolism is pathologically changed for more than a decade before florid clinical symptoms appear (Mosconi *et al.*, 2009). Whereas normal aging is associated with decrease of glucose uptake mostly in medial frontal areas, individuals who develop AD already have prominently lower glucose utilization in their parietotemporal and posterior cingulate cortex initially (Mosconi, 2013).

Besides such central metabolic changes, peripheral metabolic dysfunction may provide valuable diagnostic information, and exclusion of metabolic factors from the current diagnostic criteria has been criticized by some. However, clear diagnostic parameters related to peripheral metabolic changes are still not reported (Cai *et al.*, 2012). Alongside metabolic parameters, recent attention is directed at other symptoms of hypothalamic dysfunction, such as compromise of circadian rhythms reflected in sleep fragmentation, alteration in daily thermodynamics, and hormonal and metabolic dysregulation (Ishii and Iadecola, 2015). An illustrative quality example is a prospective study following a cohort of 214 senior citizens without baseline dementia (Hahn *et al.*, 2014), that found sleep reduction of more than 2 hours

daily was associated with subsequent development of AD. Although symptoms of depression have been shown as a confounder, patients developing AD had a tendency for sleep disruption as a stronger associated risk-factor. Depression overlaps with dementia by symptomatology and pathophysiology, thus pointing to certain probable shared underlying pathogenetic mechanisms and clinical features, which may not be a pure confounding association, but rather a coexisting process (Herbert and Lucassen, 2016). This has been demonstrated by a meta-analysis that showed strong association between depression and subsequent risk for AD (Ownby *et al.*, 2006).

5.2 Comorbidities

As the etiopathogenesis of AD is multifactorial, implicated disease processes have usually already affected other organ systems in a related manner. Indeed, cardiovascular and metabolic diseases are common with AD, and in a larger US random sample at least a third of patients were reported to have coronary artery disease or heart failure, diabetes, or chronic kidney disease ('2020 Alzheimer's disease facts and figures', 2020). A quarter of them had five or more chronic conditions, which is six times as much as controls without AD or other forms of dementia. Anxiety, depression, and pain syndromes were also noted in almost a third of patients in a larger UK sample (Nelis *et al.*, 2019). Notably, hypertension was by far the most prevalent co-morbidity, also a known AD risk factor, and present in 40% of patients with AD (Nelis *et al.*, 2019). These facts point to an evident need to optimize the general medical condition as a prerequisite for getting most from interventions targeting AD in specific.

Regarding AD co-morbidities in relation to hypothalamic dysfunctions, also hypothyroidism (Choi *et al.*, 2017), hypogonadism (Tan and Pu, 2003; Brinton, 2004), obesity (Pegueroles *et al.*, 2018) or low weight with hypoleptinemia (Lee, 2011), and sleep fragmentation may reflect

a disturbed circadian rhythm (Lim *et al.*, 2013), and have hence been considered as both contributing factors and consequences of AD pathology.

5.3 Bi-directional vicious cycle

The urban lifestyle with prominent 'social jet-lag', random or overall extended meal timing, significant exposure to artificial light during nighttime, or shift work, leads to mistimed exposure to zeitgebers, which disrupt the physiologic regulation of the central and peripheral circadian clocks (Homolak *et al.*, 2018). Additionally, stress, which is considered to be increasingly prevalent in the modern way of life, disrupts circadian rhythm and amplifies the effects of its disruption on normal functioning of the organism (Koch *et al.*, 2017). Circadian rhythm dysfunction is associated with systemic pathophysiological alterations as reflected in its connection with metabolic syndrome features, (neuro)inflammation, and ultimately neurodegeneration - all recognized risk factors or contributors to AD pathogenesis (Rojas-Gutierrez *et al.*, 2017).

Conversely, AD affects hypothalamic nuclei, including the SCN (Ishii and Iadecola, 2015), which leads to impairments in central circadian clock regulation. A prominent clinical feature in such cases, i.e. the sleep-wake cycle alterations and sleep fragmentation, are accompanied by reduced waste-clearing via glymphatic mechanisms (Lucey *et al.*, 2018), that otherwise help to physiologically reduce the amyloid burden. Once unleashed, the bi-directional process of circadian rhythm dysfunction, neuroinflammation, and neurodegeneration may become a pathophysiologic vicious cycle (Homolak *et al.*, 2018). On top of the molecular interconnection, both processes overlap in association with clinical features. Common examples include sleep-wake cycle disruption with changes in sleep quality and quantity (Zhu

and Zee, 2012), insulin resistance (Stenvers *et al.*, 2018), obesity , hypertension (Douma and Gumz, 2018), and obstructive sleep apnea (Andrade *et al.*, 2018).

Such overlap is also present on a larger scale, and the aforementioned pathologies are major public health problems with an impact exceeding that for the individual (Roenneberg and Merrow, 2016, '2020 Alzheimer's disease facts and figures', 2020). Non-pharmacological interventions as tools to ameliorate the pathogenetic mechanisms and clinical symptoms are also a shared link. Such a complex interplay of factors necessitates a motivating clinical environment with considerable efforts in order to gain most from the therapeutic interventions. Caregiver burnout, insurance coverage, social issues, and ageism stand as possible challenges along the way ('2020 Alzheimer's disease facts and figures', 2020).

5.4 Neurodegeneration

Accumulation of amyloid and tau are neuropathologic hallmarks of AD, and *in vivo* experiments have shown that sleep is an essential process for facilitating the clearance of those substrates through glymphatic activity (Xie *et al.*, 2013). Neuroinflammation, accompanying synaptic dysfunction, and neurodegeneration are the pathogenetic drivers of neurocognitive AD features (Moya-Alvarado *et al.*, 2016). By the time the disease process has clinically manifested, alterations had been present for a considerable time.

The identification of ongoing neurogenesis in the adult hippocampus has, after extensive discussions in the field (Kempermann *et al*., 2018; Lucassen *et al.,* 2019; 2020), offered some hope that neurorestoration could a viable option (Moreno-Jiménez *et al.*, 2019; Tobin *et al*., 2019). Also, selective modification of neurogenesis was shown to interfere with, and often rescue (Richetin *et al.,* 2015), cognitive deficits in AD models (Hu *et al.*, 2010; Lazarov and

Hollands, 2016; Hollands *et al.*, 2017; Choi *et al.*, 2018). However, neurodegeneration is an irreversible process and any neural repair may result in altered plasticity.

The complex ontogenesis of cerebral cortex and neural networks remains a challenge when considering full reversal of AD pathology (Reisberg *et al.*, 1999). Although neuroplasticity offers many theoretical possibilities for neurorehabilitation, involved neurons are highly dependent on metabolic milieu governed by glial cells. As the understanding of the salience of central nervous system (CNS) insulin signaling and peripheral-to-central immune cell trafficking for AD pathogenesis is expanded, it is clear that the CNS immunometabolic environment is intertwined with the systemic or 'peripheral' one.

As long as pharmacotherapy for dementia remains symptomatic, without causal targets, addressing medical comorbidities remains a great priority in order to minimize contribution to disease burden. Beyond the common focus on hippocampal and cortical involvement in AD, there are substantial reports of hypothalamus being affected by AD-related neurodegeneration, including consequential functional compromise, notably of SCN as the important circadian rhythm hub (Ishii and Iadecola, 2015). Current understanding implies that pharmacologic and non-pharmacologic modalities addressing circadian disruption ought to ameliorate AD-related features. Ideally, such well-timed interventions could slow-down AD progression even in a pre-clinical phase.

6. Therapeutic opportunities

Currently established and specific pharmacotherapy for AD consists of cholinomimetics rivastigmine, galantamine, donepezil and an NMDA-antagonist, memantine ('2020 Alzheimer's disease facts and figures', 2020). The rationale behind these medications is to bolster cholinergic neurotransmission and enhance neuroplasticity in a favorable direction, as

both processes are severely impaired in AD. Antidepressants and antipsychotics are used to manage dementia-associated symptoms such as mood changes and agitation. Melatonin as a pharmacologic treatment or in combination with bright light (Riemersma-van der Lek *et al.* 2008) is an attempt to replace the deficiency of this endogenous hormone, a noted feature of hypothalamic dysfunction associated with AD (Wu and Swaab, 2007), with an aim to hopefully relieve some of the circadian abnormalities which is clinically reflected as evening agitation ('sundowning') and sleep fragmentation. Non-pharmacologic modalities such as cognitive stimulation training and supportive psychosocial interventions improve cognitive and behavioral performance, and quality of life, though a substantial support system is a prerequisite (Berg-Weger and Stewart, 2017)(Figure 2).

Multiple therapies aimed at AD pathologic substrates, namely Aβ and tau protein, have so far failed to reach the necessary clinical trial goals. Considering the AD pathophysiology on a molecular level, ongoing neurodegenerative and neuroinflammatory mechanisms are highly interconnected in an overlapping signaling network. Clinically, this means addressing multiple pathogenetic factors with a single intervention is more likely with a less target-specific treatment than with a highly selective antibody. The underlying pathophysiological and clinical complexity, with multiple co-occurring pathologies, warrants a multimodal approach.

6.1 Restoring circadian rhythmicity

Targets for restoring circadian rhythmicity may be central or peripheral cellular clocks. For the former, appropriate exposure to light and dark is the key. Daytime should be associated with adequate exposure to properly timed (sun)light, whereas chronological nighttime should be associated with darkness. Environmental disruptors during those phases, such as artificial light

and noise, and behavioral habits such as frequent or prolonged daytime napping and late bedtime, should be minimized. Also, pharmacological agents that alter sleep architecture such as benzodiazepines, other sedative-hypnotics, or alcohol, should not be used. These steps should aid in keeping a proper sleep hygiene. Physiologically, due to aging-associated homeostatic changes, some central rhythmicity is lost, which is evident as loss of nighttime sleep duration, and a greater propensity for afternoon daytime naps (Schmidt, Peigneux and Cajochen, 2012). Additionally, the urge for nighttime sleep occurs earlier, the diurnal temperature oscillations are less pronounced, cortisol secretion shows a phase advance and lower amplitude, and melatonin synthesis is decreased (Hood and Amir, 2017). The latter may also be compromised by exposure to (artificial) blue light.

Longitudinal research over a period of 10 years has shown a preserved melatonin secretion pattern in middle aged or older men, but not women (Kin *et al.*, 2004). However, an underlying neurodegenerative process is often linked with reductions in melatonin secretion. Since AD pathology is definitely associated with the SCN degeneration (Swaab *et al*, 1985, Wu and Swaab 2007), interventions that represent otherwise healthy circadian patterns may improve behavioral symptoms. Light therapy and melatonin supplementation, one timed during daytime, the other during evening, helps prevent sundowning and improves quality of sleep. Exposure to light with an intensity of at least 1000 lux for a few hours in the morning, or during chronological day, and dimmer lights in the evening (200-300 lux) increases daytime wakefulness, and reduces daytime napping (Hanford and Figueiro, 2013).

In smaller trials with less than 100 participants at a time, melatonin in a 3-10 mg oral dose at bedtime was shown to be effective for increasing sleep duration or even improving scores on cognitive tests, but larger randomized trials have failed to replicate such findings to confirm robust effects (Cardinali *et al.*, 2010). Nevertheless, melatonin should primarily be considered a chronobiotic instead of a hypnotic, and supplementation in AD is reasonable given

neurodegenerative changes of SCN and reduced melatonin production in such pathology. Higher therapeutic doses may be needed given the number of SCN neurons expressing MT1 melatonin receptors is reduced in aging and AD (Wu and Swaab, 2007). Entrainers of peripheral clocks, which ultimately affect the central one, are physical activity and meal timing. Morning seems to be the optimal time for exercise in case of AD, and aside from aiding in circadian resynchronization with improvement in sleep quality, it also showed benefits for cognitive performance (Baldacchino *et al.*, 2018). Timing meals less frequently, yet at a similar schedule, can induce food anticipatory behavior with promoted activity, but which then also ultimately presents as a zeitgeber for the central clock (Kent, 2014). These features could be clinically used to enhance daytime activity and provide physiologic entrainment signals when circadian asynchrony is present, with AD being one of those conditions.

Standard pharmacologic agents and treatment strategies should also be re-examined in the context of circadian rhythmicity. For example, a positive effect of donepezil seems to be pronounced during the diurnal period, however prolonged (>24h) increment of ACh disrupts physiological dip of ACh during the slow wave sleep, the deepest stage of NREM sleep thought to be important for consolidation of memory traces into neocortical networks. In order to prevent potential potentiation of sleep disorders through ACh modulation pharmacokinetics, type of drug and treatment timing should be carefully considered and optimized individually (Van Erum *et al.*, 2019).

Novel pharmacologic agents, e.g. acting as orexin receptor antagonists, are being investigated as effective sleeping aids with less unwanted side effects for which sedative hypnotics are known (Janto *et al.,* 2018). In a randomized trial involving 285 patients with mild-to-moderate AD, the orexin antagonist suvorexant enabled half an hour of extra sleep time as compared to placebo (Herring *et al.*, 2020).

6.2 Reducing inflammation and neuroinflammation

Chronic low-grade inflammation is a reflection of (immuno)metabolic changes present in chronic conditions and AD is not an exception. Besides being associated with metabolic syndrome and related pathophysiology, neuroinflammation is parallelly ongoing in the AD-affected CNS. Glia is key to this process, since glial cells determine the metabolic and immune environment for the neurons, as well as govern the glymphatic clearance. Therefore, therapeutic targets can be broader, in terms of reducing overall systemic inflammatory processes, or narrower in targeting the CNS itself. This division still implies mutual dependence as there is direct and indirect communication between the CNS and the peripheral tissues. Given the available anti-inflammatories, NSAIDs and steroids were studied for AD prevention or treatment, without encouraging end results (Aisen *et al.*, 2000; Ali *et al.*, 2019). One of the larger interventions with NSAIDs was the ADAPT trial with more than 2000 participants older than 70 years. After a 10 year follow-up from initial intervention (1-3 years of NSAID use), there were no significant benefits for cognitive health as compared to placebo (ADAPT-FS research group, 2015).

While dietary interventions have to some extent been effective in adult rodent models in rescuing cognitive deficits induced by early life stress (Naninck *et al.*, 2017; Yam *et al.*, 2019; Wang *et al.*, 2019; Liu *et al.*, 2019; Wang *et al.*, 2020), lifestyle interventions combined with polyunsaturated omega-3 acids or vitamin supplements have been studied in smaller human trials, with disappointing results, but warranting firmer conclusions with higher power (Kivipelto *et al.*, 2018).

Microglia and astrocytes have both protective and detrimental roles for AD pathogenesis, depending on the level of neuroinflammation present. With advanced vicious cycles, glia contributes to further neurodegeneration as its protective mechanisms have been exhausted

(Fakhoury, 2018). In vitro experiments have shown benefits of NSAIDs targeting glial cells in AD models, but clinical trials failed to support their use (Ali *et al.*, 2019). An active area of basic and clinical research are glial modulators such as minocycline (Metz *et al.*, 2017) (Plane *et al.*, 2010), ibudilast (Fox *et al.*, 2018), and naltrexone (Toljan and Vrooman, 2018). They are clinically studied in neurologic conditions such as multiple sclerosis and Parkinson's disease as neuroinflammation attenuators, however still not clinically for AD-spectrum. *In vitro* and animal studies provide a mechanistic rationale for benefits in a clinical scenario, and it was demonstrated that those compounds act as Toll-like receptor-4 antagonists, a receptor upregulated following microglial activation (Fiebich *et al.*, 2018). Their efficacy varies in regards to clinical metrics or symptoms, but their safety profile is excellent with adverse effects comparable to placebo. The latter feature should make them attractive for future investigations. Other emerging fundamental understanding of CNS (patho)physiology implies that waste clearing via the glymphatic system could be enhanced with adequate sleep, as animal experiment showed that the interstitial glymphatic space and bulk flow increases during sleep and low arousal (Hauglung *et al.*, 2020). Interventions that improve circadian rhythmicity would cover this aspect as well. Finally, there is great interest in modulating the autonomic nervous system, which is the direct channel between the viscera and the brain, to enhance the anti-inflammatory signaling and decrease the pro-inflammatory, primarily by targeting the vagal nerve transmission (NCT03359902). In an extended scope, microbiota is also a factor that could be utilized for optimizing autonomic nervous system activation and ultimately decreasing neuroinflammatory cascades (Angelucci *et al.*, 2019). Treatments with antibiotics such as doxycycline, rifampin, and D-cycloserine, showed initial positive results, but repeated studies did not redemonstrate the benefits. Ongoing clinical trials are investigating the potential of probiotics as an intervention (NCT03847714).

6.3 Increasing neuronal resilience

Decreasing or halting neurodegeneration is a daunting task, especially with advanced disease stages on a cellular level. Addressing the underlying risk factors, comorbidities, and lifestyle modifications remains the cornerstone of enabling a more favorable environment for neurorestoration. As such, the substrate underlying neuronal resilience remains poorly understood (Lesuis *et al*., 2018). Specific neurorepair therapies focus, for example, on stem cells (Wang *et al.*, 2019), neural growth factors (Mitra *et al.*, 2019) and autophagy enhancers (Liu and Li, 2019). The outcomes of currently ongoing clinical trials on the use of stem cells for AD are still awaited. Devices for reliable biodelivery of neural growth factors are tested (Mitra *et al.*, 2019), but some encouraging results are reported with use of peptide preparation Cerebrolysin as an adjuvant to standard treatment (Allegri and Guekht, 2012). Importantly, the pleiotropic effects of physical activity on cognition, so far mainly in elderly (Castells-Sanchez *et al*., 2019; Stillman *et al.*, 2020;), include associated increase in levels of BDNF, and possibly increased hippocampal blood flow and neurogenesis, the latter two shown in animal experiments for now only (Marlatt *et al.*, 2012; Marlatt *et al.*, 2013; Liu and Nusslock, 2018). Autophagy enhancement is seen as a key therapeutic approach to age-associated degeneration or cellular malfunction, including for CNS related tissues. Non-human experimental findings point to possible use of autophagy boosters based on trehalose, lithium, and rapamycin, as options for future clinical studies of a wide spectrum of neurodegenerative conditions (Liu and Nusslock, 2018).

6.4 Optimizing vascular health

The overlap between traditional cerebrovascular and AD risk factors, namely hypertension, type 2 diabetes mellitus, dyslipidemia, atherosclerosis, and atrial fibrillation, indicates that appropriate management of those stands as a salient preventative and therapeutic task (Cechetto *et al.*, 2008). Worse vascular health is associated with neurodegeneration, but not increased amyloid deposition per se (Vemuri *et al.*, 2017). Application of non-pharmacologic lifestyle interventions that have shown benefits for cerebrovascular health is recommended in regards to AD as well. Furthermore, medications such as statins and ACE inhibitors may bring additional benefits. Lipophilic statins such as lovastatin and atorvastatin were possibly associated with worsening of cognitive health, but other analysis actually showed benefits with statin use. Ultimate analysis points to a more favorable effect of statins for cognitive health, though for a smaller group of especially vulnerable patients, those medications could be associated with cognitive decline (Schultz *et al.*, 2018). ACE inhibitors may exert their observed positive clinical effects indirectly by controlling hypertension, and directly by acting on CNS angiotensin metabolism which reduces neuroinflammatory cascades (Rygiel, 2016). Compromised cerebral perfusion is associated with increased risk for cognitive decline (Wolters *et al.*, 2017), and the vast majority of AD co-exists with cerebrovascular disease (Attems and Jellinger, 2014). With regards to commonly used heart failure medications, beta blockers are known to delay the functional decline in AD, whereas diuretics were associated with the opposite trend (Rosenberg *et al.*, 2008). Additionally, insulin resistance or hyperglycemia are key detrimental factors for endothelial health, and the use of anti-diabetic drugs provides indirect benefits in regards to AD (Rizvi *et al.*, 2015).

6.5 Increasing insulin sensitivity

Insulin sensitivity and peripheral metabolic homeostasis are closely related to processes driving neurodegeneration and a number of indicators of metabolic health such as glucostasis, BMI, and obesity have been recognized as important risk factors for AD (Cai *et al.*, 2012). Consequently, both pharmacological and non-pharmacological interventions targeting metabolism and insulin signaling have been proposed in the context of prevention and treatment of AD. A number of modulators of insulin signaling are being tested as a potential therapy for AD both in the preclinical and clinical setting (Ohyagi and Takei, 2020). A group led by Suzzane Craft has shown that intranasal insulin is able to improve memory in AD/MCI with regular insulin being superior to long acting insulin detemir (Craft *et al.*, 2012, 2017) and that insulin treatment might be more effective in males and carriers of APO-ε4 (Claxton *et al.*, 2013, Claxton *et al.* 2015). Other antidiabetics have also shown some promising effects in clinical trials. Pioglitazone and rosiglitazone, agonists of peroxisome proliferator-activated receptors γ that are currently used in therapy of T2DM have been investigated as a possible therapy for AD due to their dual anti-inflammatory and insulin sensitizing effect (Cai *et al.*, 2012).

A clinical trial suggested that rosiglitazone might be able to decrease the progression of cognitive dysfunction in AD/MCI (Watson *et al.*, 2005), and pioglitazone has been shown to improve cognitive function in healthy individuals (Knodt *et al.*, 2019), as well as in patients with mild AD accompanied with DM, in whom pioglitazone also increased parietal lobe blood flow and insulin sensitivity (Sato *et al.*, 2011). Sitagliptin, an inhibitor of dipeptidyl peptidase-4 has shown some promising effects since a 6 month treatment was able to increase MMSE scores both in elderly with T2DM, and T2DM and AD, in comparison to metformin (Isik *et al.*, 2017). Agonists of GLP-1 receptor are also potential candidate drugs for AD as Gejl et al. demonstrated 6 month treatment with liraglutide was able to recover glucose transport across the blood-brain barrier (Gejl *et al.*, 2017).

Non-pharmacologic efforts to increase insulin sensitivity have been explored in the context of protective effects on cognition. Aerobic exercise and physical activity are well-known for their protective effects on cognitive performance and metabolic health, and there is evidence that implementation of physical activity might be a good strategy to postpone cognitive decline and reduce the effect of AD risk factors such as glucose intolerance (Baker *et al.*, 2010; Castells-Sanchez et al., 2019; Stillman *et al.*, 2020). Exercise affects both central and peripheral circadian clocks, and correct implementation of physical activity might help reduce harmful consequences of circadian dysrhythmia (Tahara *et al.*, 2017). Another important non-pharmacological treatment modality targeting metabolism in AD is optimization of nutrient intake. Numerous nutritional deficiencies were reported in the elderly and multi-nutritional correction of deficient polyunsaturated fatty acids, B-vitamins, and antioxidants was proposed both for preventive and therapeutic purposes (Kamphuis and Scheltens, 2010). Furthermore, meal timing should be optimized in AD as it might help restore circadian rhythmicity and enable proper nutrient extraction (Homolak *et al.*, 2018).

7. Conclusion/summary

Alzheimer's disease is a clinical dementia syndrome with increasing epidemiologic importance as the general population ages. Traditional focus on memory problems as the hallmark has been expanded with the recognition of accompanying symptoms and common comorbidities that also point to hypothalamic, neuroendocrine, and neurovascular dysregulation, such as decreased sleep quality and quantity, and features of metabolic syndrome.

Disrupted circadian rhythms, notably by environmental factors or behavior, and impaired brain glucose metabolism, were found to be associated with later development of AD. On a molecular level, a wide-spread vicious cycle between neurodegeneration and

neuroinflammation in the CNS is evident in AD, and hypothalamus, including the SCN, is also affected by these destructive processes. Complex multi-directional pathophysiologic interactions ensue as circadian rhythm disruption and inflammatory processes related to metabolic changes promote further neurodegeneration and neuroinflammation. Ultimately, it leads to a common pathway characterized by CNS amyloid and tau protein buildup. With still evolving understanding of the full AD pathophysiology, therapeutic arsenal remains limited. Cholinomimetics and memantine as approved treatment yield humble benefits and cause clinically relevant side effects (Leonard, 2004), whereas recent attempts with monoclonal antibodies targeting the pathologic substrates seen in AD have not lived up to their expectations. By deeper understanding of the underlying disease processes, attention is slowly being directed at addressing the neuroinflammation and brain metabolic alterations, as these steps precede the generation of microscopically visible pathologic end-products associated with AD. Compounds with potential to promote lowering of brain insulin resistance (insulin-based and other antidiabetic drugs), decrease neuronal and glial inflammation (traditional anti-inflammatories and glial modulators), and promote neuronal resilience (various growth factors), are being investigated as possible pharmacologic treatments effective for AD. Non-pharmacologic interventions that improve sleep and circadian rhythmicity, decrease cerebrovascular risk factors, and improve overall metabolic aspects of health, have been shown to be beneficial for AD, and represent readily available therapeutic modalities. However, the epidemiologic context is broadened with the impact of caregiver burnout and indirect disease burden for the society. Ideally, by detecting subclinical changes that are associated with greater risk for developing AD, timely interventions may slow the disease progression and impact the quality and quantity of life for the patients and their caregivers. A greater understanding of AD etiopathogenesis should yield more effective or new therapies. Considering AD beyond

hippocampus and memory problems, one possible route to achieve the aforementioned is by expanding it with the hypothalamic perspective.

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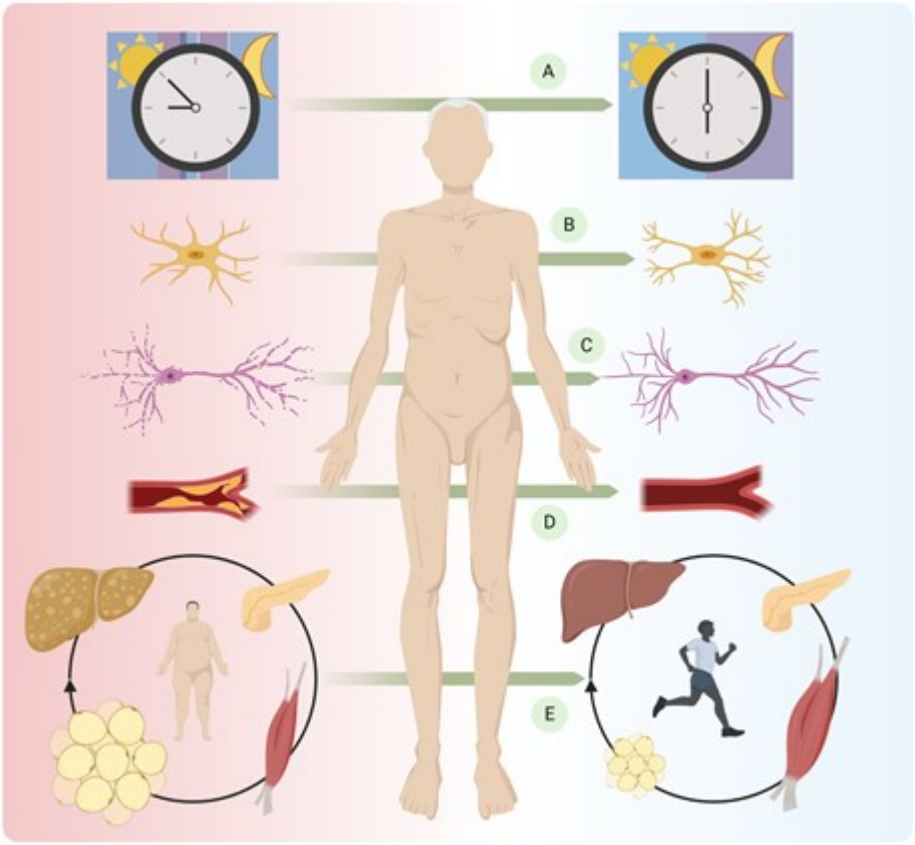
Figure Legends:

Figure 1. A bidirectional association between neurodegeneration and functional hypothalamic dysfunction reflected by circadian and peripheral metabolic dyshomeostasis. A) Neurodegeneration of hypothalamic nuclei, especially suprachiasmatic nucleus (SCN), induces circadian dysrhythmia. B) Circadian misalignment and dysrhythmia disrupts peripheral metabolic homeostasis. C) Dysfunctional peripheral metabolism potentiates neurodegeneration through disruption of cerebral energy homeostasis, vascular health, and (neuro)inflammation. D) Circadian dysrhythmia affects cerebral homeostasis by affecting amyloid clearance and tau

homeostasis, and by potentiating inflammation and oxidative stress. E) Metabolic dysregulation affects circadian rhythmicity and sleep through direct hormonal regulation, nutrient availability, autonomic activation, and inflammation. F) Neurodegeneration of associated or regulatory hypothalamic nuclei affects behavioral activity patterns, autonomic system function and satiety, and affects peripheral metabolism directly through neurovisceral and hormonal homeostatic modulation.

Figure 2. A schematic representation of therapeutic opportunities targeting hypothalamic dysfunction in Alzheimer's disease. A) Restoring circadian rhythmicity by reducing the burden of environmental circadian disruptors, improving sleep hygiene and optimizing endogenous rhythms by melatonin and modulation of pharmacotherapy. B) Reducing systemic and neuroinflammation by targeting etiologic factors driving systemic low-grade inflammation. C) Increasing neuronal resilience by stimulation of neuronal growth factor signaling. D) Improving vascular health by behavioral and pharmacological targeting of hypertension, dyslipidemia, and insulin resistance. E) Improving metabolic homeostasis in the brain and in peripheral organs by pharmacological and non-pharmacological interventions.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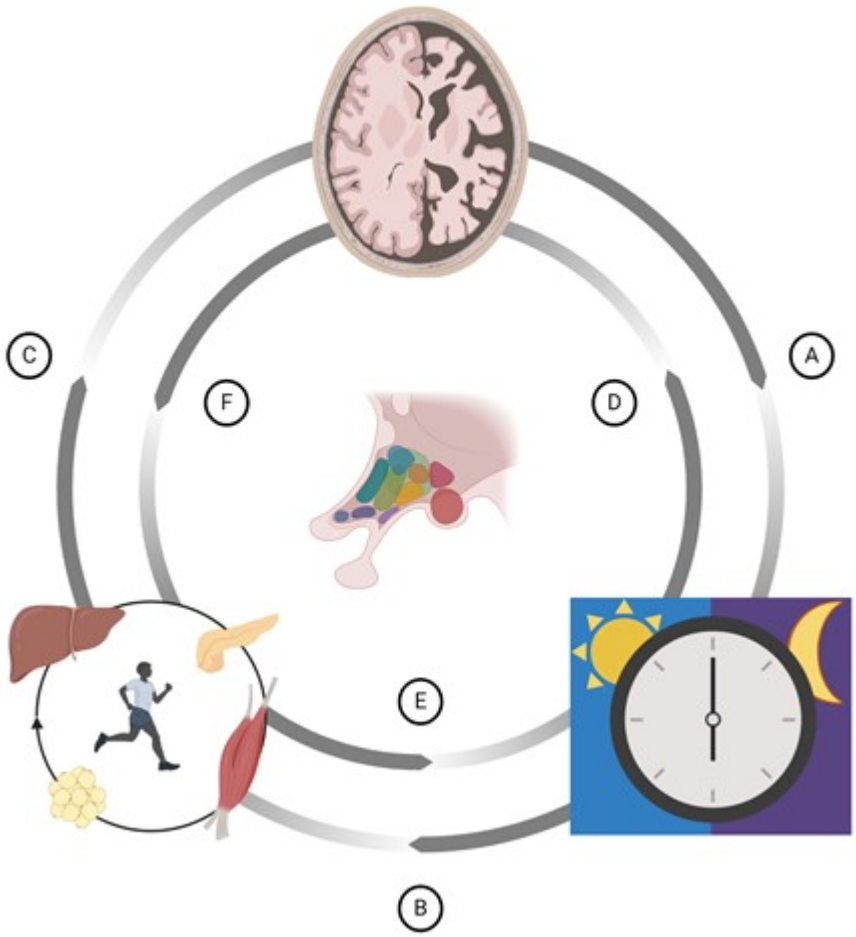
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