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Šalković-Petrišić M., Knezović 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.*** **Journal of Neural Transmission, 120 (1). pp. 233-52. ISSN 0300-9564**

http://www.springer.com/journal/702

http://link.springer.com/journal/702

http://dx.doi.org/10.1007/s00702-012-0877-9

WHAT HAVE WE LEARNED FROM THE STREPTOZOTOCIN-INDUCED ANIMAL MODEL OF SPORADIC ALZHEIMER'S DISEASE, ABOUT THE THERAPEUTIC STRATEGIES IN ALZHEIMER'S RESEARCH

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Concise title: Streptozotocin-induced rat model of sporadic Alzheimer's disease and drug testing

ABSTRACT

Experimental models that faithfully mimic the developmental pathology of sporadic Alzheimer's disease (sAD) in humans are important for testing the novel therapeutic approaches in sAD treatment. Widely used transgenic mice AD models have provided valuable insights into the molecular mechanisms underlying the memory decline but, due to the particular β-amyloid-related gene manipulation, they resemble the familial but not the sporadic AD form, and are, therefore, inappropriate for this purpose. In line with the recent findings of sAD being recognised as an insulin resistant brains state (IRBS), a new, non-transgenic, animal model has been proposed as a representative model of sAD, developed by intracerebroventricular application of the betacytotoxic drug streptozotocin (STZ-icv). The STZ-icv treated animals (mostly rats and mice) develop IRBS associated with memory impairment and progressive cholinergic deficits, glucose hypometabolism, oxidative stress and neurodegeneration that share many features in common with sAD in humans. The therapeutic strategies (acetylcholinesterase inhibitors, antioxidants and many other drugs) that have been tested until now on the STZ-icv animal model have been reviewed and the comparability of the drugs' efficacy in this non-transgenic sAD model and the results from clinical trials on sAD patients, evaluated.

Key words: intracerebroventricular streptozotocin, non-transgenic rat model, sporadic Alzheimer's disease, therapeutic strategies

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disorder clinically characterized by a progressive memory decline which becomes manifested after a long pre-symptomatic phase. In contrast to the rare, early-onset, familial form of AD caused by missens mutations of genes related to the β-amyloid (Aβ) pathological hyperproduction, the prevailing sporadic form of AD (sAD) with plaques and neurofibrillary tangles is not caused by such gene mutations. However, the exact cause of sAD is still unknown. Due to a specific nature of AD, the exploration of onset and progression of the biochemical changes in the brain is difficult, almost impossible to be performed during a life-time. Therefore, one has to rely on in vivo experimental models. Carrying the mutated Aβ-overproduction-related gene as an inevitable starting point from the very beginning makes the widely exploited transgenic mice inappropriate models for exploring the cause, onset and development of the pathological Aβ deposition in the brain in conditions which are not associated with mutations of the APP gene. Despite of that, the therapeutic potential of various drug and non-drug anti-sAD strategies has been widely tested in the transgenic mice AD models (Zahs and Ashe 2010).

In line with the hypothesis of sAD being the brain type of non-insulin dependent diabetes mellitus (DM) (Hoyer,1998), and studies which afterwards indicated the presence of insulin resistant brains state in AD patients post-mortem (Frölich et al. 1999; de la Monte et al. 2005; Steen et al. 2005; Hoyer 2004) and its progression with severity of dementia (as reviewed by Correia et al. 2011), a new, non-transgenic rat model has been proposed as a representative model of sAD (Lannert and Hoyer 1998; Salkovic-Petrisic and Hoyer 2007). The model has been developed by intracerebroventricular (icv) application of the drug streptozotocin (STZ) (Mayer et al. 1991). Following the parenteral administration of high doses, STZ selectively destroys insulin producing/secreting β cells in the pancreas, causing DM type I in adult animals (Szkudelski 2001), while multiple parenteral treatment with low to moderate STZ doses causes insulin resistance by damaging insulin receptor (IR) signalling (Blondel and Portha 1989; Kadowaki et al. 1984; Giorgino et al. 1992). Intracerebroventricular administration of low, subdiabetogenic doses of STZ has been shown to induce cognitive (Mayer et al. 1991; Lannert and Hoyer 1998) and brain cholinergic deficits (Hellweg et al. 1992; Blockland and Jolles 1993, 1994), oxidative stress (Sharma and Gupta, 2001a; Sharma and Gupta 2002; Ishrat et al. 2006; Pathan et al. 2006; Shoham et al., 2006; Kumar et al., 2010; Saxena et al., 2011) as well as decrement in brain glucose/energy metabolism (Nitsch and Hoyer 1991; Plaschke et al. 1996; Lannert and Hoyer 1998; Hoyer and Lannert 2007), and insulin resistant brain state (Salkovic-Petrisic et al. 2006; Gruenblatt et al. 2007; Steen 2006; Lester-Coll et al. 2006; Agrawal et al. 2010). These STZ-icv induced effects have been extensively reviewed elsewhere (Salkovic-Petrisic and Hoyer, 2007; Salkovic-Petrisic et al. 2012), and will not be elaborated here. Recent data on cortical distribution of glucose hypometabolism in the STZ-icv treated cynomolgus monkeys (2 mg/kg, on day 1, 7 and 14) demonstrated that the distribution pattern was similar to that at early stages of AD patients (Heo et al. 2011), providing an additional evidence that the effect of STZ-icv treatment is regionally specific and species independent. Characterization and validation of the STZ-icv treated animal as a model for

sporadic AD has been going on for more than 20 year now, and has not been finished yet. However, the important findings on sAD pathophysiology have been already provided by means of STZ-icv treated rats which revealed that development of the insulin resistant brain state induced by STZ-icv treatment precedes and eventually leads to tau and Aβ pathology, the latter manifested not earlier than 3 months following the STZ-icv treatment (Salkovic-Petrisic et al. 2006; Gruenblatt et al. 2007; Steen 2006; Lester-Coll et al. 2006; Salkovic-Petrisic et al. 2011; Shingo et al. 2012). These findings significantly contributed to the arguments against the hypothesis that β-amyloid pathology is the central, primary pathological event in sAD (Reitz 2012) which should also be reflected on the research on the novel therapies for sAD and predictive value of the animal models used for this purpose.

STZ-icv animal models have been already used to assess the therapeutic potential of various old and novel compounds and drugs, as well as other non-drug therapeutic strategies but their predictivity for efficacy in humans has never been assessed. This manuscript aims to review the therapeutic strategies that have been tested until now on STZ-icv animal model and evaluate the comparability of the drugs' efficacy in this non-transgenic sAD model in comparison with the results from clinical trials on sAD patients (Figure 1).

THERAPEUTIC STRATEGIES TESTED IN STZ-ICV ANIMAL MODELS

Acetylcholinesterase inhibitors and other cholinergic-related drugs

Evidence for a major role of acetylcholine in the pathogenesis of AD has been provided by the dramatic decrease in the hippocampus and frontal cortex of choline acetyltransferase (ChAT) (enzyme responsible for acetylcholine /ACh/ synthesis) and the marked reduction in cholinergic neuron counts in the nucleus basalis in post-mortem studies of AD brains (as reviewed by Greenwald and Davis 1983). Numerous studies that followed led to the development and, finally, marketing of the inhibitors of acetylcholinesterase (AChE) (enzyme responsible for the rapid ACh hydrolysis). It has to be emphasized that donepezil, rivastigmine, galantamine and tacrine are the only drugs (with the exception of memantine) that have been marketed today for the treatment of the Alzheimer's disease. By blocking the ACh degradation, these drugs prolong its half-live and action on the pre- and post-synaptic cholinergic receptors.

Supporting the hypothesis that the pathophysiology in the STZ-icv animal models shares huge similarities with the one in AD patients, cholinergic deficits have also been consistently found in various STZ-icv animal AD models (from newborn and adult rats to adult mice treated with STZ-icv), by demonstrating as a decrease in ChAT and an increase in AChE activity in the hippocampus, respectively (Hellweg et al. 1992; Blokland and Jolles 1993; Blokland and Jolles 1994; Prickaerts et al. 1999; Terwel et al. 1995; Sonkusare et al. 2005; Ishrat et al. 2006; (Lester-Coll et al. 2006; de la Monte et al. 2006; Kumar et al. 2010; Tota et al. 2011). Importantly, AChE inhibitors tested so far, have been consistently successful in improving/preventing memory deficits in STZ-icv sAD models.

While until now galantamine and rivastigmine have not been tested in the STZ-icv models, chronic oral administration of **donepezil** (1 and 3 mg/kg/day) to adult STZ-icv treated rats, dose-dependently inhibited AChE activity and improved STZ-icv induced cognitive deficits in memory tests at both doses (Sonkusare et al. 2005). These effects were achieved regardless of whether the treatment began 1 week prior to, in parallel, or 13 days after the STZ-icv administration. In another experiment on mice treated STZ-icv with a 1 mg/kg dose who developed severe cognitive deficits 14 days after the STZ-icv administration, oral treatment with donepezil or **tacrine** (5 mg/kg both) one hour prior to the memory testing in Passive avoidance and Morris Water Maze tests, caused a significant improvement of the memory impairment, associated with a significant decrease in AChE activity (Saxena et al. 2008). Additionally, in line with the hypothesis that oxidative stress is a major factor implicated in the degeneration of cholinergic neurons in Alzheimer's disease, both donepezil and tacrine suppressed STZ-icv-induced oxidative stress by normalizing decreased glutathione (GSH) and increased malondialdehyde (MDA) levels (Saxena et al. 2008). Mice treated with 0.1 mg/kg i.p. dose of donepezil daily for 15 days (continued during the Morris Water Maze performance days), also demonstrated significant cognitive improvement in both acquisition and probe trails, which was accompanied by restoration of AChE activity and oxidative stress in the brain (Sharma et al. 2008). This neuroprotective effect of AChE inhibitors seen in the STZ-icv animal models is in line with the neuroprotective effect of these drugs found in AD patients (Takada et al. 2003; Hashimoto et al. 2005; Akasofu et al. 2008). Literature data on cognitive evaluation of disease-modifying efficacy of AChE inhibitors in the transgenic mice AD models, which demonstrate age-dependent cognitive decline, are available only for galantamine. At age 6 weeks, heterozygous transgenic APP23 mice which were subcutaneously implanted with osmotic pumps delivering saline or galantamine (1.3 or 2.6 mg/kg/day) for 2 months, showed significantly improved spatial cognition only when treated with a low dose, and in the probe trail of Morris Water Maze test (Van Dam and De Deyn 2006). Neither of doses exerted the beneficial effects during the training trials and a higher galantamine dose was ineffective in the probe trial, suggesting that galantamine might specifically affect certain processes associated with consolidation or retrieval of spatial memory. The observed U-shaped dose-response curve is in line with the literature data for AChE inhibitors (Braida et al. 1996).

Normalization of the ChAT and AChE activity in the STZ-icv animal models has been found in the treatment with some other drugs, associated or not associated with the antioxidative effects. A decrease in hippocampal ChAT activity was completely prevented by a 2-week oral treatment of **acetyl-L-carnitine** which acts by enhancing the utilization of alternative energy sources (Prickaerts et al. 1995; Terwel et al. 1995). Changes in both ChAT and AChE in the hippocampus were prevented by chronic intraperitoneal treatment with the antioxidant **coenzyme Q10** (Ishrat et al. 2006). Pre-treatment with a hepatoprotectant **silibinin** (100 and 200 mg/kg, po) attenuated STZ-icv (1 mg/kg) induced memory impairment by reducing oxidative and nitrosative stress and synaptosomal calcium ion level, restored increased activity and mRNA expression of AChE and also significantly increased STZ-icv induced decrement in α-7-nAChR mRNA expression in addition to dose-dependent restoration of ATP levels (Tota et al. 2011). Oral treatment with **p,p'-methoxyl-diphenyl diselenide**

(/MeOPhSe-2/ 25 mg/kg) was able to reverse the learning and memory impairments in mice induced by parallel icv administration of STZ, and to protect against the increase in AChE activity, measured 9 days following the drug treatments (Pinton et al. 2010).

Beside the antioxidative effects, AChE inhibition could be successfully combined with other effects in some multifunctional compounds such as **ladostigil** (TV3326) which combines the AChE inhibitory activity of rivastigmine with the effects of selective monoamine oxidase-B inhibition from rasagiline (Weinstock et al. 2001). Chronic oral treatment with ladostigil (75 μmol/kg) almost completely prevented the STZ-icv induced memory impairment in rats and additionally reduced the STZ-icv induced neuronal damage and accompanied microgliosis in the fornix and corpus callosum. Furthermore, daily oral administration of ladostigil (1 or 17 mg/kg) for 1 week, before and after the STZ-icv treatment prevented both memory deficits and the glial and oxidative-nitrative stress changes in rats (Shoham et al. 2007). No data has been available on ladostigil testing in transgenic mice AD models.

NMDA receptor antagonists

Glutamate N-methyl-d-aspartic acid (NMDA) receptor channel antagonist memantine which blocks NMDA overstimulation in excitotoxicity (Kornhuber et al. 1989) is the only drug marketed for the treatment of AD in addition to the AChE inhibitors. Few animal studies which have been focused on the glutamate neurotransmission in the STZ-icv animal models revealed, in general, changes similar to those found in AD patients. An increased expression of glutamate transporter mRNA has been found previously in the STZ-icv rats (Grünblatt E et al. 2004), and deficits in hippocampal synaptic transmission and long-term potentiation (LTP) observed in the STZ-icv treated rats were recently suggested to be mainly due to the postsynaptic mechanisms and were accompanied by changes in the expression and function of glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Shonesy et al. 2012). Furthermore, LTP deficits were found to correlate with decreased expression of NMDA receptor subunits NR2A and NR2B, which could be related to the reduction of brain derived neurotrophic factor (BDNF) in the STZ-icv rat model (Shonesy et al. 2012). Reduction in hippocampal glutamate NMDA receptor subunits NR1A and NR2B as well as down-regulation of BDNF have also been found in the brain of sAD patients post mortem (Bi and Sze 2002; Connor et al. 1997). In line with these similarities in the pathophysiological background, testing of the therapeutic potential of **memantine** in the STZ-icv rat model revealed that the memory impairment induced by 3 mg/kg STZ-icv dose in rats was successfully reversed by a 2-week memantine treatment with a 5 mg/kg i.p. dose (Ponce-Lopez et al. 2011). However, the memory functions were tested by food magazine and autoshaping training while there is no data on spatial memory in the Morris Water Maze test. Glutamate neurotransmission was not investigated in this experiment, but results showed that memantine-induced memory restoration in the STZ-icv treated rats was associated with a significant recovery of p-GSK3β levels downstream the insulin receptor signalling in the hippocampus only, indicating that the drug might have a beneficial effect on the insulin resistant brain state in this

model. Considering that decrement of the inactive p-GSK3β form turns the p-GSK3β/GSK3β ratio to increased GSK3β activity which results in tau protein hypophosphorylation, this finding in the STZ-icv rat model is in line with the finding that memantine reduces tau phosphorylation in sAD patients post mortem (Degerman Gunnarsson et al. 2007). Literature data on cognitive evaluation of disease-modifying efficacy of memantine in the transgenic mice AD models demonstrates that in heterozygous transgenic APP23 mice which were, at age 6 weeks, subcutaneously implanted with osmotic pumps delivering saline or memantine (7.2 or 14.4 mg/kg/day) for 2 months, memantine dose-dependently improved acquisition performance (path length) and spatial accuracy during probe trial of the Morris Water Maze trail (Van Dam and De Deyn 2006). Memantine treatment (30 mg/kg/day p.o.) for 2 to 3 weeks initiated at the age of 8 months also significantly improved the acquisition of the Morris Water Maze in APP/PS1 mice AD model without affecting swimming speed although it had no effects on locomotor activity or aggressive behaviour (Minkeviciene et al. 2004).

Compounds with predominant antioxidative activity, often accompanied by other neuroprotective properties

As already mentioned above, increasing evidence indicates that cholinergic deficits found in AD may interact with oxidative stress in a vicious cycle, crucial for the AD patophysiology. Oxidative stress has often been emphasized as probably the earliest feature in the AD brain with implications as an important mediator in the onset, progression and pathogenesis of the disease (Götz et al., 1994; Zhu et al. 2007). The interpretation of the results of clinical trials which tested the therapeutic activity of various antioxidants is difficult due to a lack of specificity of such drugs to neural mitochondria where ROS production is most significant, and due to the additional activities these drugs may possess such as anti-inflammatory and iron-chelating ones (Bonda et al. 2010; Wollen 2010). Many of antioxidant drugs have also been tested in the STZ-icv animal sAD models, suitable for such task due to the chemical nature of STZ which leads to generation of intracellular free radicals, nitric oxide (NO) and hydrogen peroxide, and mitochondrial damage (Szkudelski 2001). In line with that, significant and progressive elevation of MDA and decrement of GSH level, respectively, as well as oxidative-nitrative stress have been found in the rat brain 1 to 8 weeks following the STZ-icv treatment (Sharma and Gupta 2001a; Sharma and Gupta 2002; Ishrat et al 2006; Pathan et al 2006; Shoham et al. 2007; Kumar et al. 2010; Saxena et al. 2011), demonstrating resemblance to the oxidative stress condition in the human sAD patients post-mortem.

Several potential mitochondrial antioxidant therapies have been tested in the STZ-icv animal models. **Alpha-lipoic acid** (ALA) is a potent free radical scavenger, a powerful antioxidant which also chelates metals, reduces inflammation and increases ACh (as reviewed by Wollen 2010). In the rats treated chronically with alpha lipoic acid (50, 100 and 200 mg/kg) orally for 21 days starting from day 1 of STZ injection and administered before the STZ injection, a dose-dependent effect of ALA was observed (Sharma and Gupta 2003). Only the highest ALA doses significantly improved the STZ-icv induced cognitive deficits which correlated with significant reduction in MDA levels only in the high-dosed STZ-

icv treated rats. Data on ALA efficacy in AD patients suggests its beneficial effects in stopping the progressive memory decline and keeping it on the constant level but a small number of patients do not allow a firm conclusion yet (Hager et al. 2007).

Acetyl-L-carnitine (ALCAR) works synergistically with ALA to transport acetyl groups and fatty acids into the mitochondria for energy production and additionally promotes synthesis of ACh and clearing of mitochondria of toxic fatty-acid metabolites, also demonstrating various neuroprotective activities (as reviewed by Wollen 2010). Two weeks of oral pre-treatment with ALCAR (75 mg/kg) which readily passes the blood-brain barrier, prevented partly the STZ-icv induced effects in rats, as reflected by an attenuation of the STZ-icv induced decrease in hippocampal but not the cortical CAT activity, and by attenuation of cognitive deficits in the MWM probe but not in the training trials, as well as by inefficiency to restore the neuronal septal damage induced by STZ-icv (Terwel et al. 1995). The reason of this discrepancy between the low-to-moderate efficacy in STZ-icv animal models and a consistent efficacy in AD patients, in whom a meta-analysis of 21 double-blind randomized, placebo-controlled studies (3-12 months) showed either improvement or delayed progression of cognitive decline (Montgomery et al. 2003), is unclear yet, but could be related to the optimisation of the ALCAR dose and/or treatment length and initiation, in the STZ-icv rat experiments.

Coenzyme Q_{10} (CoQ_{10}) naturally resides in the inner mitochondrial membrane and acts to carry the high energy electrons in the electron transport chain from complex 1 to complex II during oxidative phosphorylation. Recent studies have shown the CoQ_{10} to be neuroprotective in various conditions but mostly in *in vitro* and *in vivo* animal models (as reviewed by Bonda et al. 2010, and Wallen 2010), as until now the only clinical trial with CoQ_{10} monotherapy was a double-blind, placebo controlled study on AD patients (N=78) treated 16 week with or with 400 mg of CoQ_{10} 3 times/d, in which no effect on cognition and cerebrospinal antioxidant biomarkers were found (Galasko et al. 2012). Additionally, a synthetic variant of CoQ_{10}, idebenone, has been tested in clinical trials in which inconsistent results were obtained; better cognitive score in with 90 -120 mg doses only (Gutzmann et al. 1998; Weyer et al. 1997) and no effect with even higher doses in another trial (Thal et al. 2003). Contrary to that, neuroprotective effect of CoQ_{10} was clearly demonstrated both at the cognitive and neurochemical level in the STZ-icv rat sAD model (Ishrat et al. 2006). Supplementation with CoQ_{10} (10 mg/kg b.w. i.p.) for 3 weeks, initiated 24 hours after the STZ-icv injection in rats significantly reversed STZ-icv induced cognitive deficits in Passive avoidance and Morris Water Maze tests as well as it reversed all changed markers of oxidative stress in the hippocampus and prefrontal cortex (MDA, GSH, glutathion peroxidase/reductase, thiobarbituric acid reactive substances), and in addition to already mentioned normalization of ChAT and AChE activity in hippocampus (Ishrat et al. 2006). The reason for such a discrepancy between the human and animal studies is unclear yet.

Some of the compounds, such as sesamol, nitric oxide synthase inhibitor or organoselenium which possess antioxidant activity alone or in combination with cholinergic or anti-inflammatory activities observed *in vitro* and in other animal models, have not been tested in AD randomized clinical trials and

in transgenic mice AD models. However, their effects on memory and neurochemical parameters in the brain have been explored in the STZ-icv animal sAD model.

Sesamol (5-hydroxy-1,3-benzodioxole or 3,4-methylenedioxyphenol), a potent anti-oxidant and anti-inflammatory molecule, markedly improved STZ-icv induced cognitive impairment in rats following 21-day oral treatment with 4 or 8 mg/kg dose (Misra et al. 2011). In addition to reducing brain AChE activity and serum tumor necrosis factor (TNF)-α levels, it also attenuated oxidative-nitrite stress in the brain of STZ-icv treated rats. Cognitive impairment and oxidative-nitrite stress in the STZ-icv treated rats were also restored by a non-specific **nitric oxide synthase** (NOS) inhibitor, L-N^G-Nitroarginine methyl ester (L-NAME) (10 mg/kg i.p.), 21-day treatment alone, while its combination with sub-effective dose of sesamol (4 mg/kg) potentiated its protective effect (Misra et al. 2011), confirming that modulation of nitrite signalling and the oxide-inflammatory cascade might provide therapeutic effects in an AD condition.

Selenium (Se), a nutritionally essential trace element with known antioxidant potential, protects the brain from oxidative damage in various models of neurodegeneration As already mentioned, neuroprotective effect of organoselenium **(MeOPhSe)(2)** administered orally (25 mg/kg) 30 min prior to STZ-icv injection in mice was manifested in cognitive improvement in the Y-maze test associated with an anticholinesterase efficacy (Pinton et al. 2010) but additional experiments demonstrated that its neuroprotection in the STZ-icv model is due to its antioxidant activity as well (Pinton et al. 2011). Pre-treatment supplementation with sodium selenite, a salt of Se (0.1 mg/kg p.o. for 7 days) significantly improved learning and memory ability in Passive avoidance and Morris Water Maze tests in the STZ-icv treated rats (Ishrat et al. 2009). This supplementation also significantly ameliorated all oxidative stress-related alterations in GSH, TBARS and glutathion peroxidase/reductase in the hippocampus and cerebral cortex, and additionally significantly restored ATP levels as well as ChAT activity in the hippocampus.

Considerable attention has been focused on increasing the internal antioxidant defences in response to AD, and in line with that, the role of **vitamin E** well known as an antioxidant drug. AD patients were found to have significantly low cerebrospinal and serum vitamin E concentrations which increased (123% and 145%, respectively) following the vitamin E supplementation (400 IU/day, 1 month) (Jimenez-Jimenez et al., 1997, Kontusch and Schekatolina, 2004). In a placebo-controlled trial, vitamin E (2000 IU/day, 2 years) alone slowed (-53%) functional deterioration in patients with moderate AD while in combination with vitamin C it reduced prevalence (-78%) and incidence (-64%) of AD (Kontusch and Schekatolina, 2004). However, recent double-blind, placebo controlled study on AD patients (N=78) treated 16 week with a combination of 800 IU/d of vitamin E plus 500 mg/d of vitamin C plus 900 mg/d of α-lipoic acid (E/C/ALA) demonstrated that E/C/ALA treatment combination accelerated the cognitive decline although the cerebrospinal fluid F-2-isoprostane levels, which represented the oxidative stress biomarker, decreased by 19% from baseline (Galasko et al. 2012).

Whether combination with ALA or some other factors have been responsible for this unfavourable effect on cognition remains to be determined.

Contrary to the conflicting results in human studies, experiments with vitamin E treatment of the STZ-icv rats give more consistent results suggesting its neuroprotective effects in the experimental sAD. Rats pre-treated with vitamin E (100 mg/kg i.p. once daily for 3 weeks) and afterwards injected icv with STZ (3 mg/kg) demonstrated significantly better cognitive performance in Passive avoidance and Morris Water Maze tests performed 2 weeks after the STZ-icv treatment (Ishrat et al. 2009). Moreover, pre-treatment with vitamin E demonstrated antioxidant activity, observed as significantly enhanced GSH level and decreased level of thiobarbituric acid reactive substances (TBARS), associated with significant restoration of CAT activity in the hippocampus. These findings have been confirmed in another experiment which explored the effect of both isoforms of vitamin E, alpha-tocopherol and tocotrienol against STZ-icv induced cognitive impairment and oxidative-nitrosative stress in rats measured 3 weeks following the STZ-icv treatments (Tiwari et al. 2009). Alpha-tocopherol as well as tocotrienol treated STZ-icv groups showed significantly less cognitive impairment in Morris Water Maze and Elevated plus maze tests but the effect was more potent with tocotrienol. In line with that, both isoforms of vitamin E effectively attenuated the reduction in GSH and catalase and reduced the MDA and nitrite levels as well as AChE activity in the brains of STZ-icv treated rats in a dose-dependent manner. These results, which provide evidence for the difference in efficacy between the different vitamin E isoforms in the STZ-icv rat sAD model, actually support the recent hypothesis that conflicting results in human AD studies might be related to the different vitamin E isoform used (Wollen 2010).

In vitro and *in vivo* animal studies suggest potentially important role for diet in the causation and/or prevention of sAD. Causation could be related to the reduced levels of endogenous antioxidants like the above mentioned vitamin E, while prevention could refer to the antioxidant potential of polyphenolic compounds obtained from dietary sources, such as resveratrol from grapes and peanuts and curcumin from turmeric (plant of the ginger family). These compounds have been found to additionally possess anti-inflammatory as well as anti-amyloidogenic activity due to therapeutic potential of resveratrol and curcumin has been explored in AD clinical trials (Wallen 2010). **Resveratrol** is found in red wine and although several clinical studies suggested that moderate to mild red wine consumption was associated with a low risk of AD, this notion is still controversial and remains to be clearly demonstrated (as reviewed by Vingtdeux et al. 2008). Polyphenols have potent anti-amyloidogenic and anti-fibril effects *in vitro*, suggesting that resveratrol may prevent the formation of toxic Aβ oligomers and protofibrillar intermediates (Riviere et al. 2008). Moderate consumption of red wine lowered Aβ levels and the associated neuropathology in Tg2576 AD mouse model (Wang et al. 2006). Anti-amyloidogenic potential of resveratrol has not been explored in the STZ-icv rat sAD model but chronic treatment with trans resveratrol (10 and 20 mg/kg, i.p. for 21 days) starting from day 1 of STZ-icv injection significantly prevented STZ-icv induced cognitive impairment and oxidative stress manifested as increased brain GSH levels (Sharma and Gupta 2002).

Curcumin has been demonstrated to have a beneficial role in neurodegenerative disorders due to its various neuroprotective properties as in addition to antioxidant, anti-inflammatory and anti-amyloidogenic effects, curcumin possesses also copper and iron chelating activity (Baum and Ng 2004). However, clinical studies face the problem of its low bioavailability because of a hydrophobic nature and have revealed no cognitive benefit relative to placebo in AD patients (as reviewed by Wallen 2010). In spite of that, wildly used turmeric spice (curcumin) in India has been suggested to be responsible for a much lower incidence of AD in India than the United States. *In vivo* studies in AD transgenic mice models have shown that dietary curcumin can cross the blood-brain barrier and significantly decrease Aβ deposition and plaque burden as well as markedly inhibit tau phosphorylation (Wang et al. 2009; Ma et al. 2009). The effect of curcumin has been extensively investigated in the STZ-icv animal models. Administration of curcumin (200 mg/kg, po) both continuously from 1^{st} - 14^{th} day and from 14^{th} - 20^{th} post STZ-icv treatment significantly restored the memory deficit and insulin receptor protein level in the hippocampus and cerebral cortex of the STZ-icv treated rats (Agrawal et al. 2010). Curcumin pre- and post-treatment additionally normalized AChE levels in both regions and attenuated STZ-icv induced oxidative stress by restoring MDA and GSH levels. The results suggest that besides the anticholinesterase and antioxidant activity, an effect on brain IR may also be an important factor for protective effect of curcumin against STZ induced sAD model. Similar curcumin-induced (80 mg/kg for 3 weeks) antioxidant and cholinergic effect as well as prevention of the cognitive deficits in the STZ-icv rat model have been observed by others (Ishrat et al. 2009). Additionally, curcumin dose-dependently (10, 20, 50 mg/kg per os for 21 days, starting from the day of STZ-icv injection, or 20 and 50 mg/kg for 7 days initiated from 19^{th} – 25^{th} day post STZ-icv treatment) improved cerebral blood flow in STZ-icv treated mice (Awasthi et al. 2010). In another experiment, treatment with curcumin (300 mg/kg i.p. for 10 days) initiated from the 25th day after STZ-icv injection led to cognitive improvement associated with restoration of the STZ-icv induced decrement in insulin growth factor (IGF)-1 in the brain as well as to the reduced neuronal loss (Isik et al. 2009). Furthermore, the noted beneficial effect of curcumin (20 mg/kg per os for 14 days) on STZ-induced dementia in mice was significantly abolished by pre-treatment with PPAR-gamma receptor antagonist bisphenol-A-diglycidyl ether, i.e., BADGE (30 mg/kg i.p.), suggesting that its beneficial effects might be also mediated through the activation of PPAR-gamma receptors (Rinwa et al. 2010).

Daily treatment with a naturally occurring flavonoid **quercetin** (2.5, 5 and 10mg/kg, p.o. for 21 days) starting from the first icv dose of STZ to mice, prevented STZ-induced memory impairment as assessed by Morris Water Maze and passive avoidance tests and showed a dose-dependent restoration of cerebral blood flow and ATP content (Tota et al. 2010). Quercetin decreased oxidative and nitrosative stress as evidenced by a significant decrease in MDA, nitrite and increase in GSH levels, and additionally attenuated elevated AChE activity in the STZ-treated mice.

Recent evidence indicates that rutin (the glycoside between the quercetin and the disaccharide rutinose), exhibits antioxidant potential and has neuroprotective effects. **Rutin** pre-treatment (25

mg/kg, orally, once daily for 3 weeks) significantly improved impaired memory and significantly attenuated TBARS activity of poly ADP-ribosyl polymerase, and nitrite level and decreased GSH level and catalase activity in the hippocampus of STZ-icv rats, as measured two weeks following the icv treatment (Javed et al. 2012). These effects were also accompanied by anti-inflammatory activity reflected as the reduced expression of cyclooxygenase-2 (COX-2), interleukin-8 (IL-8) and inducible NOS.

Melatonin is a naturally occurring hormone which is produced in decreasing amounts with age, and is also a powerful antioxidant. Literature data suggests that melatonin provides mitochondrial support, acts anti-amyloidogenic and neuroprotective also against tau tangles, but few clinical studies have examined its effect on AD, and those that did were small and of poor quality (as reviewed by Wallen 2010). Administration of melatonin (2.5, 5.0 and 10mg/kg, i.p.), started 1h prior to 1st icv dose of STZ and continued up to 14 days, significantly attenuated the effect of STZ-induced oxidative stress (GSH and MDA levels) and histopathological changes (damaged periventricular cells and damaged cells in the hippocampal CA4 region) in STZ-icv treated mice, but cognitive deficits, measured by MWM, were attenuated only by the highest dose (Saxena et al. 2010). In line with the pathophysiological finding of mitochondrial dysfunction in AD, the effects of melatonin on brain mitochondrial function were explored in APP/PS1 transgenic mice AD model treated for 1 month with melatonin (Dragicevic et al. 2011). Subsequent in vitro analysis revealed that melatonin treatment decreased mitochondrial Aβ levels by two- to fourfold in different brain regions which was accompanied by a near complete restoration of mitochondrial respiratory rates, membrane potential, and ATP levels in isolated mitochondria from the hippocampus, cortex, or striatum.

As already mentioned, some drugs which have completely different indication have been found potentially therapeutic in dementia treatment due to the variety of their neuroprotective effects demonstrated in the non-clinical studies. **Erythropoietin,** a glycoprotein hormone that controls erythropoiesis, has been tested in the STZ-icv mice model where the post-treatment with doses of 500 and 1,000 IU/Kg i.p., significantly reversed streptozotocin-induced learning and memory deficits along with attenuation of oxidative stress (TBARS and GSH levels) and restoration of brain AChE activity in the brain (Kumar et al. 2010). Similar to that, the antioxidative effect of the HIV protease inhibitor **indinavir** (100 and 200 mg/kg p.o. for 15 days) accompanied by AChE activity restoration and cognitive improvement in the Morris Water Maze test has been observed in the STZ-icv treated mice (Sharma et al. 2008). This effect has been associated with the findings that HIV protease has structural homology to beta-secretase 1 (BACE) (Hong et al. 2000) and thus can modulate BACE activity, and consequently, possibly, the amount of amyloid-β formation (Nunan and Small 2000). Cyclic nucleotides cGMP and cAMP are known to play an important role in learning and memory processes. Enhancement of cyclic nucleotide signalling by **phosphodiesterase inhibitors** (PDE) has been reported to be beneficial in several neurodegenerative disorders associated with cognitive decline. The STZ-icv treated rats, which were administered PDE 4 inhibitor RO-20-1724 (125, 250 and 500 μg/kg i.p.) for 21 days following the first i.c.v. STZ administration, demonstrated significant, dose-

dependent attenuation of the STZ-icv induced cognitive deficits (measured by Passive avoidance and Morris Water Maze tests) and oxidative stress (measured by GSH, MDA and nitrite levels), as well as restoration of the AChE activity (Sharma et al. 2012). Chronic treatment with vinpocetine, a PDE 1 inhibitor (5, 10 and 20 mg/kg i.p.), for 21 days following first STZ-icv injection accomplished similar, dose-dependent beneficial effects on memory, oxidative stress and AChE activity in the brain of STZ-icv treated rats (Deshmukh et al. 2009). Hippocampal alterations, manifested as astroglial activation (S100B accumulation which was independent of the significant alteration in glial fibrillary acid protein), nitrative stress and glycation, found in the STZ-icv treated rats 2 weeks after the icv treatment were prevented by **aminoguanidine** (100 mg/kg i.p., given after the STZ-icv injection on days 2 and 4), as well as cognitive deficits (Rodrigeus et al. 2009).

A number of different **Chinese and Indian medicinal plants** have been demonstrated to exhibit protective effects on the STZ-icv induced memory deficits, for which various underlying mechanism, including antioxidant and anti-AChE activity, were suggested (to mention only few; Hou et al. 2012; Veerendra Kumar and Gupta 2003; Saxena et al. 2007; Diwu et al. 2011). However, the extensive review of these plants and their effects is beyond the scope of this manuscript**.**

The standardized extract EGb 761 from the dried green leaves of **Ginkgo biloba** is a complex mixture of ingredients with a uniquely broad spectrum of pharmacological activities on the central nervous system. Ginko biloba contains compounds that have antioxidant and anti-inflammatory properties. Although a quite a number of trials has been conducted with Ginkgo biloba in demented patients, a Cochrane review of 36 clinical trials concluded that the effect of Ginkgo biloba is inconsistent and that further studies are needed to elucidate its role in AD (Birks et al. 2009). STZ-icv animal models demonstrated that Ginkgo biloba is only partly effective in restoring the cognitive deficits while in transgenic mice models, Ginkgo biloba successfully normalized memory impairment. Animal studies on Ginkgo extracts showed that the ongoing deterioration in behaviour and the maintained deficit in cerebral energy metabolism occurring after a triplicate i.c.v. STZ injection were significantly slowed down by EGb761 treatment (50 mg/day/rat in food pellets for 12 weeks) (Hoyer et al. 1999). The deficits in learning, memory and cognition were partially compensated, and the disturbances in cerebral energy metabolism returned to almost completely normal values. Additional experiment on this model revealed that EGb761 treatment (25 g/day/rat in food pellets) normalized the STZ-icv induced increase in glucose transporter (GLUT) 3 expression and partially compensated the STZ-mediated enhancements in hippocampal insulin receptor binding (Löffler et al. 2001). Six-month treatment with Ginkgo biloba (70 mg/kg/day in drinking water), initiated at age of 8 month, can block an age-dependent decline in spatial cognition without altering Aβ levels and without suppressing protein oxidation in a transgenicTg2576 mouse model of AD (Stackman et al. 2003).

Considering the important role of iron as a mediator of oxidative stress in AD (Castellani et al. 2012), compounds the exhibit iron-chelating activity are of a particular interest in search for the effective AD therapy. One such compound is a multifunctional, brain permeable **iron chelating agent M30** [5-(N-

methyl-N-propargyaminomethyl)-8-hydroxyquinoline], which possesses the neuroprotective N-propargyl moiety of the anti-Parkinsonian drug, monoamine oxidase (MAO)-B inhibitor, rasagiline and the antioxidant-iron chelator moiety of an 8-hydroxyquinoline derivative of the iron chelator, VK28 (Youdim et al. 2005). Assessment of therapeutical potential of M30 is currently at the preclinical level at which it has demonstrated neuroprotective activity *in vitro* and *in vivo* in animal models of neurodegenerative disorders as well as in reversal of age-associated memory impairment (Youdim 2012; Kupershmidt et al. 2011, 2012a). Systemic treatment of APP/PS1 Tg mice with M30 for 9 months significantly attenuated cognitive impairments in a variety of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety levels, and memory for novel food and nesting behaviour (Kupershmidt et al. 2012b). These beneficial effects of M30 on cognition were associated with reduced cerebral iron accumulation and a marked decrease in cerebral Aβ levels and plaques and phospho-tau levels, and on the signalling level, with marked down-regulation of phosphorylated cyclin-dependent kinase 5 and increased protein kinase B and glycogen synthase kinase 3β phosphorylation. The latter suggests that restoration of dysfunctional brain insulin signalling might underlie neuroprotective activity of M30 in the AD condition. Therapeutical potential of M30 in the STZ-icv rat model is currently under investigation in our lab and preliminary results suggest that both M30 high-dose pre-treatment and post-treatment prevents and improves cognitive deficits, respectively (*unpublished observation*).

Drugs with predominant anti-inflammatory activity

Epidemiologic evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs) delay onset of Alzheimer's dementia (AD), but randomized trials show no benefit from NSAIDs in patients with symptomatic AD (reviewed by Wollen 2010). The results of a recent Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) which randomized 2,528 elderly persons to naproxen or celecoxib versus placebo for 2 years + 2-year extension period, suggest a revision of the original ADAPT hypothesis that NSAIDs reduce AD risk (Breitner et al. 2011). In line with these results, NSAIDs have an adverse effect in later stages of AD pathogenesis, whereas asymptomatic individuals treated with conventional NSAIDs such as naproxen experience reduced AD incidence, but only after 2 to 3 years. Thus, treatment effects seem to differ at various stages of the disease. However, based on the recent analysis of 604 potentially relevant studies carried out in AD patients population so far, the conclusion of the Cochran review is that efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven and due to these drugs cannot be recommended for the treatment of AD (Jaturapatporn et al. 2012). Considering the animal AD models, the effect of NSADIs has been investigated in genetically modified mice models and in the STZ-icv rat model, however conflicting results have been obtained. Overexpression of COX-2 in APPswe-PS1dE9 mice AD model resulted in specific deficits in spatial working memory in female but not male mice and these sex-specific deficits were abolished by pharmacological inhibition of COX-2 by **celecoxib**e, in the absence of significant changes in amyloid burden (Melnikova et al. 2006). Data indicates that COX-2 activity promotes cognitive deficits in a sex-dependent but amyloid burden-independent manner in this mice

AD model. Similar lack of amyloid burden-clearing activity of celecoxib (and ibuprofen) has been found in APP/PS1 transgenic mice AD model in which COX-1 preferring inhibitor flurbiprofen administered in a diet, dramatically reduced amyloid plaque and nonfibrillar deposit burden (Jantzen et al. 2002). In the experiment on STZ-icv rat model, selective inhibitors of COX-1 (valeryl **salicylate,** 5 and 10 mg/kg), COX-2 (**etoricoxib**, 5 and 10 mg/kg) or COX-3 (**phenacetin**, 20 and 40 mg/kg) were administered daily for 21 days, intraperitoneally (Dhull et al. 2012a). In comparison with the control animals, COX-1 and COX-2 inhibitors significantly increased the survival of hippocampus CA1 neurons in the STZ-icv treated rats in a dose dependent manner while COX-3 inhibitor had no effect, suggesting the differential role of COX isoenzymes in neuronal death in hippocampal CA1 regions in the STZ-icv rat sAD model. In the same experimental design, COX-1 and COX-2 inhibitors significantly improved STZ-induced cognitive impairment, increased the survival of pyramidal neurons, and restored oxidative stress biomarkers (GSH, MDA, nitrite levels, SOD), while COX-3 inhibitor failed to restore the cognitive performances and oxidative stress condition, and had no effect on neuronal survival (Dhull et al. 2012b. However, in the experiment of Sharma and co-workers (2008), celecoxib treatment (100 mg/kg i.p. for 5 days and continued for 5 days during the cognitive testing) was used to induce experimental dementia in rats, for which authors concluded that it might be attributed to the stimulatory effect of celecoxibe on amyloid beta-42, and on brain AChE activity, as well as on oxidative stress. In fact celecoxibe-induced dementia, oxidative stress and AChE activity were comparable to those induced by STZ-icv treatment of (Sharma et al. 2008). The reason for such a contradictory effect of celecoxibe in the two experiments of Dhull and co-workers (2012a; 2012b) and the experiment of Sharma and co-workers (2008) is unclear and should be further investigated.

NSAIDs treatment in transgenic mice AD models have generally led to a conclusion that adequate doses of traditional NSAIDs, or their nitrate esters, reduce the amyloid burden and levels of neuroinflammation, as reviewed elsewhere (McGeer et al. 2007). An acute 7 day oral treatment of 10-month-old transgenic APPV717I mice with ibuprofen resulted in decreased beta-secretase-1 (BACE1) mRNA and protein levels, and reduction in the number of activated microglia and reactive astrocytes in the hippocampus and cortex, accompanied by reduction in the expression of the proinflammatory enzymes COX2 and inducible NOS (Heneka et al. 2005). Treatment of 11-month-old Tg2576 mice with ibuprofen for 16 weeks resulted in the dramatic and selective reduction of soluble Aβ42 and 60% amyloid plaque load in the cortex (Yan et al. 2003). However, studies that tested the effects of celecoxibe in the transgenic mice AD models showed that it either failed to reduce the inflammatory burden (higher dose) or actually increased the levels of Aβ42 (lower dose) (McGeer et al. 2007).

Insulin-sensitizing and other anti-diabetic drugs

Epidemiological studies have provided direct evidence that diabetes mellitus (DM) type 2 is a strong risk factor for AD (as reviewed by Takeda et al. 2011) and insulin resistant state has been recognized to play an important role in the pathophysiology of the sporadic AD form (Bosco et al. 2011). In line with that, insulin-sensitizing agents such as peroxisome-proliferator activated receptor (**PPAR)**

agonists which also demonstrate anti-inflammatory activity, have been tested for their therapeutic potential in clinical trials and in animal experiments. Six-month **pioglitazone (**PPAR γ/α agonist) daily treatment of a small number of patients with mild AD accompanied with DM type II improved their cognition and regional cerebral blood flow in the parietal lobe in addition to decrement in fasting plasma insulin levels (Sato et al. 2011). In a small number of AD non-diabetic patients, 18-month treatment with pioglitazone (45 mg/day) as add-on therapy to the AChE inhibitors produced no significant treatment effect on cognition (Geldmacher et al. 2011). Regardless the APOE status, no evidence of statistically or clinically significant efficacy in cognition or global function was detected for 2 mg or 8 mg **rosiglitazone**-extended release formulation (PPAR γ agonist) as adjunctive therapy to ongoing AChEIs in the two clinical phase III studies on AD patients (Harrington et al. 2010; Tzimopoulou et al. 2010).

In the STZ-icv animal models, therapeutical potential of pioglitazone (but not that of rosiglitazone) has been explored. Memory impairment induced by 3 mg/kg STZ-icv dose in rats was successfully reversed by a 2-week oral **pioglitazone** treatment (30 mg/kg) in the food magazine and autoshaping training, which was accompanied by restoration of p-GSK3β levels downstream the insulin receptor signalling in the hippocampus but not in the prefrontal cortex (Ponce-Lopez et al. 2011). In another experiments, oral pioglitazone (10 and 30 mg/kg, or 20 mg/kg) administration for 14 days, starting 5 days prior to STZ-icv injection in rats improved cognitive performance in Passive avoidance and Morris Water Maze test, which was accompanied by lowered oxidative stress (GSH and MDA levels) and improved cerebral glucose utilization (Pathan et al. 2006; Kaur et al. 2009). Additionally, pioglitazone treatment of STZ-icv mice significantly attenuated higher levels of brain AChE activity, and oxidative stress levels measured by TBARS and GSH. All these beneficial effects of pioglitazone were significantly abolished by pre-treatment of nitric oxide synthase inhibitor L-NAME (3 mg/kg i.p.). Therefore, results on animal STZ-icv models suggest that pioglitazone neuroprotective effects in AD condition may involve central insulin, cholinergic, oxidative and NO pathways.

The PPAR agonist-induced effect has been explored also in the 3-day-old rat pups given STZ-icv injection (40 μg/kg) and on the same day treated with a single ip injection of saline or PPAR α/δ/γ agonists with memory evaluation and brain analysis being done 4 weeks after the drug treatment (de la Monte et al. 2006). PPAR agonist treatments showed responses in range from being inefficient to partially or completely rescuing the brains from STZ-mediated neurodegeneration. Regarding the beneficial effects, PPAR agonists increased the brain size, preserved insulin and insulin growth factor (IGF)-II receptor expressing neurons and IR signalling, also decreased phospho/total tau protein ratio and APP mRNA expression, additionally increased ChAT expression and decreased the level of oxidative stress. The effects were consistently demonstrating region- and PPAR inhibitor type-dependency, with PPAR δ agonist, generally, demonstrating the best efficacy than (de la Monte et al. 2006).

The effect of both pioglitazone and rosiglitazone has been extensively investigated in the transgenic mice AD models with results not completely comparable to those obtained in the STZ-icv models. In the experiment on APP tg mice, pioglitazone counteracted cerebral oxidative stress, glial activation, and, partly, cholinergic denervation and completely normalized the cerebral blood flow and glucose uptake responses to increased neuronal activity, but it failed to improve spatial memory (Nicolakakis et al. 2008). An acute 7 day oral pioglitazone treatment of 10-month-old APPV717I mice attenuated astrogliosis in the hippocampus and cortex and reduced the level of soluble Abeta1-42 peptide, in addition to reduction of the expression of the proinflammatory enzymes COX2 and inducible NOS, and decrement of beta-secretase-1 (BACE1) mRNA and protein levels (Heneka et al. 2005). Cognitive performance was not measured. Pioglitazone treatment of Tg2576 mice reduced Ab40 levels but the effect on memory function was not reported (Yan et al. 2003). Chronic treatment with rosiglitazone (5 mg/kg/day) facilitated Aβ clearance and reduced Aβ burden in the hippocampus and entorhinal cortex of 13-month-old transgenic (human APP-overexpressing) mice and reduced the expression of proinflammatory markers (Escribano et al. 2010). Interestingly, 4 weeks of rosiglitazone treatment in this experiment were not enough to restore the hippocampal function for an accurate performance in the Morris Water Maze test but all cognitive deficits were normalized following the 16 week-treatment. Chronic rosiglitazone treatment in transgenic APP/PS1 and Tg2576 mice also reduced Aβ aggregates and Aβ oligomers in addition to restoration of spatial memory impairment (Toledo and Inestrosa 2010; Pedersen et al. 2006). These effects were accompanied by attenuated reduction of IDE mRNA in the hippocampus (and not in the frontal cortex) of Tg2576 mice.

It is hard to explain why the results on pioglitazone are not completely comparable between the transgenic mice and STZ-icv animal AD models and why PPARγ agonists do not exert such a beneficial effect in clinical trials. Therefore, further research is needed to elucidate this inconsistency.

Fourteen days following STZ-icv injection, rats treated with twice-daily exedine-4 (Ex-4), a long-acting glucagon-like peptide-1 (**GLP-1) receptor agonist,** had better learning and memory performance in the Morris Water Maze test compared with rats treated with saline (Chen et al. 2011). Additionally, histopathological evaluation confirmed the protective effects of Ex-4 treatment on hippocampal neurons against degeneration, and its reversal effect on tau hyperphosphorylation through downregulation of GSK-3β activity. The experiment on STZ-icv treated rats indicated that treatment with (Val(8))GLP-1 (50 μM in 10 μl i.c.v.), might prevent age-related neurodegenerative changes by preventing decline of learning and memory formation, reduction of phosphorylated tau levels and protection of subcellular structures and morphology of neurons (Li et al. 2012). GLP-1 receptor agonists have not been yet studied in AD clinical trials.

GSK-3 inhibitors

GSK-3, and particularly GSK-3β isoform, is a key enzyme downstream the insulin receptor signalling, dysfunction of which has been well recognized now both in human and animal AD condition.

Dysfunction of the insulin receptor signalling cascade in the brain activates GSK-3β which consequently may lead to tau protein hyperphosphorylation, a prerequisite for neurofibrillary tangle formation. Drugs which modulate GSK-3β activity, like lithium, have been considered as a potential therapeutic strategy in AD condition (Medina and Avila, 2010). Although no benefits were obtained from short-term lithium treatment in a recent clinical study in AD patients (Hampel et al. 2009), in the long-term (12 months) trial in people with amnestic mild cognitive impairment, better performance on the cognitive ADAS subscale and in attention tasks associated with a significant decrease in cerebrospinal fluid concentrations of phospho-tau, were found in patients treated with lithium (Fortenza et al. 2011).

There is only one literature report on **lithium** treatment in the STZ-icv animal models, in which memory impairment induced by 3 mg/kg STZ-icv dose in rats was successfully reversed by a 2-week lithium treatment with a 100 mg/kg i.p. dose (Ponce-Lopez et al. 2011). However, the memory functions were tested by food magazine and autoshaping training while there is no data on spatial memory in the Morris Water Maze test. The results showed that lithium-induced memory restoration in the STZ-icv treated rats was associated with a significant recovery of p-GSK3β levels downstream the insulin receptor signalling in the hippocampus but not in the prefrontal cortex, indicating that the drug might have a beneficial effect on the insulin resistant brain state in this model. Lithium treatment in a double transgenic APP/PSEN1mouse model reduced spatial memory impairment and amyloid burden as well as astrogliosis, and additionally activated Wnt signalling by the increase in beta-catenin and by the inhibition of the GSK-3β (Toledo and Inestrosa 2010). Chronic lithium treatment in aged double transgenic mice (AβPPSwe/PS1A246E) decreased the γ-cleavage of amyloid-β protein precursor, further reduced amyloid-β production and senile plaque formation, accompanied by the improvement in spatial learning and memory abilities (Zhang et al. 2011).

Estrogens replacement therapy

Estrogens depletion in postmenopausal women is a significant risk factor for AD development and the potential of estrogen-based hormone therapy (alone or in combination with progesterone) to reduce this risk has been widely investigated with controversial results. The recently released Women's Health Initiative Memory Study has dampened any enthusiasm for the use of hormonal replacement therapy in women to prevent or delay the onset of AD, confirming the previous clinical data that estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older and additionally did not prevent mild cognitive impairment in these women (Shumaker et al. 2003; Mulnard et al. 2000). The effect of estrogens has not been extensively investigated in the STZ-icv animal AD models and insufficient data exists for a firm conclusion. Estradiol-17beta treatment (200 μg/rat sc, during cognitive testing period) slowed down the STZ-icv induced deterioration in memory functions, partially compensated the learning deficit, and improved the disturbances in cerebral energy metabolism to the extent that it was almost completely normal again (Lannert et al. 1998). Similar beneficial effect of estradiol-17beta monotreatment on cognition

has been found in transgenic mice AD model (Levin-Allerhand et al. 2002). Ovariectomy-induced depletion of sex steroid hormones in adult female 3xTg-AD mice significantly increased Aβ accumulation and worsened memory performance, and estrogen, but not progesterone (alone or combined with estrogen) treatment, prevented these effects (Carroll et al. 2007).

Antihypertensive drugs

Cardiovascular pathology appears to have a major impact in cognitive decline and antihypertensive drugs of various mechanisms of action, have potential in AD therapy (as reviewed by Wollen 2010). Aside from its vasoactive actions, brain renin-angiotensin system has also been implicated in the pathogenesis of cognitive decline, and beneficial effects of drugs affecting it are suggested in AD condition. In line with that, a recent study confirmed that angiotensin converting enzyme (ACE) inhibitors slow the progression of AD (Hajjar et al. 2008). Proposed possible mechanisms of this beneficial effect were suggested to include reduction of angiotensin II which reduces acetylcholine (leading to AChE increment) and increment in enzyme that breaks down β-amyloid (Wollen 2010). Similar beneficial effects in reducing the incidence and/or AD progression, has been found in a clinical trial with angiotensin 1 (AT-1) receptor blocker (Li et al. 2010). Although experiments in animal AD models are limited, the results support the findings from clinical trials.

When **ACE inhibitor perindopril**, was given for 21 days to STZ-icv treated rats, it dose dependently improved memory by increasing energy metabolism and cerebral blood flow, and additionally decreased oxidative and nitrosative stress, activity and mRNA expression of AChE and ACE, as well as it mitigated neurodegeneration in STZ treated rat (Tota et al. 2012). Similar effects were found in transgenic mice AD models. Perindopril, without affecting brain Aβ deposition, significantly suppressed the increase in hippocampal AChE activity and improved cognition in PS2APP-transgenic mice overexpressing Aβ in the brain, which was associated with the suppression of hippocampal astrocyte activation and attenuation of superoxide (Dong et al. 2011).

AT-1 receptor antagonist candesartan (0.05 mg/kg and 0.1 mg/kg, i.p.) given for 14 days following STZ-icv injection to mice, significantly improved latency period in passive avoidance test, and spatial memory in water maze test, but only in higher dose (Tota et al. 2009). Treatment with higher (0.1 mg/kg) dose of candesartan decreased oxidative stress (MDA and GSH) and free radicals, and restored increased AChE activity (Tota et al. 2009). Intranasal treatment of the APP/PS1 transgenic mouse AD model of AD with losartan, angiotensin II receptor antagonist (10 mg/kg every other day for 2 months), using at a dosage far below its systemic antihypertensive dose, exerted direct neuroprotective effects via its Aβ-reducing and anti-inflammatory effects in the central nervous system (Danielyan et al. 2011). Cognitive functions have not been measured.

Chronic administration of a **cardial beta blocker carvedilol** (1 and 2 mg/kg, i.p.) for a period of 25 days starting 4 days before STZ-icv administration resulted in an improvement in memory retention,

and attenuation of oxidative damage and AChE activity, suggesting carvedilol may have potential in the treatment of neurodegenerative diseases. (Prakash and Kumar 2009). Although memory function was not measured, carvedilol re-established basal synaptic transmission, enhanced neuronal plasticity and suppressed neuronal hyperexcitability in TgCRND8 mice AD model (Arrieta-Cruz et al., 2011). Beta blockers have been tested in AD clinical trials for the efficacy in reducing the disruptive behaviour, but not the cognitive improvement (Peskind et al. 2005).

Lipid-lowering drugs

High cholesterol levels have been positively correlated with a higher incidence of memory impairment and dementia. As reviewed elsewhere, epidemiology and preclinical statin research have generally supported an adverse role of high cholesterol levels regarding AD, while human studies of statins show highly variable outcomes, making it difficult to draw a firm conclusion (Hoyer and Riederer 2007; Shepardson et al. 2011a; 2011b). However, data from STZ-icv treated animal AD models, generally, demonstrate beneficial effects of lipid-lowering strategy (at least that with lipophilic characteristics) on STZ-icv induced cognitive deficits, which may be in line with the recent conclusion that differing blood-brain barrier (BBB) permeability among statins, the stage in AD at which statins were administered and variation in the functional capacity of brain capillaries in AD and respective BBB transport, as well as the drugs' pleiotropic metabolic effects, may all contribute to the substantial variability observed in statin-AD research (Shepardson et al. 2011b).

Pitavastatin and **simvastatin** (both lipophilic statins, dosed 10 mg/kg p.o. for 15 days) each significantly attenuated STZ-induced memory deficits and oxidative stress- and cholinergic deficit-related changes in mice (Dalla et al. 2010; Tramontina et al. 2011). However, **fluvastatin** (hydrophilic statin, dosed 10 mg/kg p.o. for 15 days) produced no significant effect on STZ-induced dementia or biochemical levels (Dalla et al. 2010). In a similar design, another lipid-lowering drug, **ezetimibe** (10 mg/kg, orally for 15 days) also significantly attenuated STZ-icv induced memory deficits and oxidative stress changes in mice (Dalla et al. 2009). The effect of statins on tau aggregates and neurofibrillary tangles (NFT) has been investigated in a transgenic mouse tauopathy model where it was found that statins reduced NFT burden irrespective of blood-brain barrier permeability at both early and late ages in long- and short-term treatment paradigms and under normocholesterolemic and hypercholesterolemic conditions (Boimel et al. 2009). Results suggest that the anti- NFT effect of statins may be related to their anti-inflammatory and not necessarily to their cholesterol-lowering properties.

Other therapeutic strategies

Novel strategies in AD therapy, like **inhibition of γ and β-secretases** and **passive immunization** against β-amyloid, have been tested as amyloid-reduction therapy for Alzheimer's disease and are currently under investigation (as reviewed by Wollen 2010). Amyloid-reduction strategies have been

developed on the ground of the amyloid-cascade hypothesis that Aβ pathology is the primary neuropathological core, and therefore, interventions to reduce Aβ levels in the brain have become a promising approach in the sAD therapy research. One option is to change the activity of the enzymes involved in the amyloid precursor protein (APP) processing, but the major obstacle of γ-secretase inhibitors is their toxicity, while β-secretase inhibitors seems to be less toxic and effective in reducing the Aβ levels in the brain accompanied by improvement in cognitive decline in transgenic AD mice models (as reviewed by Ghosh et al. 2012). A small number of β-secretase inhibitors have entered early phase clinical trials. On the other hand, the immunisation therapy in clinical trials has been, in general, associated with a number of issues ranging from the neurological complications to the finding that anti-Aβ vaccination–induced Aβ clearance in the brain could still result in no cognitive benefit (Holmes et al. 2008). New approaches in immunisation are being tested now, the outcome of which, however, is uncertain yet but will be hopefully beneficial in future. In general, the problem with testing of the effectiveness of the β amyloid-reduction therapy in rodents is the developmental/structural lack of production of Aβ similar to the human one and consequently lack of its pathological aggregation in the form of senile plaques, which make it difficult to explore amyloid-reduction therapy in non-transgenic rodents. This has been overcome by generating transgenic mice which overexpress the human Aβ-related genes. However, we have reported a time-dependent development of cerebral amyloid angiopathy in the STZ-icv treated rats (Salkovic-Petrisic et al. 2011), indicating that amyloid pathology should be more extensively explored and characterized in this model, which may then be hopefully exploited in the novel anti-AD drug testing. Until now, data is available from the experiments on transgenic mice AD models only (Dodart et al. 2002; Oddo et al. 2006; Tang and Ghosh 2011), while these novel strategies have not been explored in the STZ-icv animal models.

Recent clinical data suggests that **physical exercise**, brain stimulation by cognitive training and socialization have beneficial effects on cognitive decline in AD patients, as reviewed elsewhere (Wollen 2010). Experimental data in STZ-icv treated animal AD models confirms these findings only partly. Physical exercise in the form of 14 day- or 5-week treadmill training, prevented cognitive deficits, oxidative stress and astrogliosis in the brain of STZ-icv treated rats (Jee et al. 2008; Rodrigues et al. 2010). The role of brain insulin in the exercise-induced cognitive improvement has been shown to be possibly induced through the regulation of mitochondrial H2O2 production, because a prior blockade of brain insulin signalling with STZ-icv injection abolished in mice the benefits of exercise on memory performance and mitochondrial H2O2 regulation (Muller et al. 2012). Therefore, four weeks of exercise did not prevent the STZ-icv induced cognitive deficits in this experiment on mice. Data on TgCRND8 mice AD model demonstrates that whether or not access to a running wheel has beneficial effects on Alzheimer-like pathology and symptoms may strongly depend on the exact time when the wheel is provided during development of the disease, which is important for the experimental design, and suggests also the importance of early introduction of physical exercise in the AD patients (Richter et al. 2008).

CONCLUSIONS

It is difficult to establish an experimental animal model that would faithfully mimic the developmental pathology of the prevailing sporadic form of AD in humans. Widely exploited transgenic mice AD models, likeTG2576 and APP/PS1 mice models, resemble the familial form of AD, and, as suggested recently, actually simulate the asymptomatic phase of the disease and the results of interventional studies in these mice should be considered in the context of disease prevention, which is why these studies failed to predict results of human trials (Zahs and Ashe 2010).

In line with the growing body of evidence suggesting that there may be different endophenotypes of sporadic AD (e.g. APOE4-negative individuals, a pro-inflammatory phenotype or individuals with greater insulin resistance /Borroni et al. 2006/), representative animal models should mimic a specific endophenotype, such as STZ-icv treated animals which develop insulin resistant brain state. Data published until now, supports similar STZ-icv induced biochemical, structural and cognitive effects in all species investigated (rats, mice and monkeys), suggesting a kind of standardized and reproducible insulin-resistant brain state development and progression. STZ-icv animal sAD model demonstrates several advantages over the transgenic mice AD models: (i) gene manipulation is not inevitable starting point from the day of animal birth, (ii) pathological alterations in the brain can be initiated at any age of the previously intact animals, (iii) onset, development and progression of consequent cognitive deficits and associated biochemical and structural changes can be followed from the very moment of the brain damage induced by the STZ-icv injection, and (iv) this model provides the opportunity to assess the drug therapeutic potential in respect to the disease prevention, when given before or in parallel with STZ-icv injection, and the disease modification and progression, when given after the cognitive impairment has been manifested.

Therapeutic strategies tested in the STZ-icv animal model until now have been involving most frequently drugs with predominant antioxidant activity. In general, the treatments were mostly initiated after the STZ-icv-induced brain damage, and therapeutic effectiveness was most frequently demonstrated at multiple levels, as a combination of improvement in cognitive and cholinergic deficit and oxidative stress condition. Effectiveness of most of the therapeutic strategies explored in STZ-icv model has been tested also in AD patients and comparable results has been found in many of the clinical trials. Nevertheless, some therapies failed to achieve comparable results on memory deficits in the STZ-icv animal models and clinical trials with sAD patients, like those with NSAIDs and PPAR γ agonists or vitamin E and Ginkgo biloba. Several reasons could account for that: (i) STZ-icv animal model has still not been fully characterized, (ii) parameters of memory assessment in animals and humans are different, the former based mostly on the deficits in spatial and fear-conditioned memory performance and the latter on scoring of conversation with patients by different questionnaires, (iii) drugs' pleiotropic effects in addition to their antioxidant, anti-AChE and anti-inflammatory properties as well as different patient comorbidity can contribute to the substantial variability of the drug efficacy between the STZ-icv animal models and sAD patients, and (iv) different dosing regime in the human and animal studies (post STZ-icv observational period ≤3 months; drug treatment ≤1 month), sAD

endophenotype and stage of disease at which the drugs were administered in comparison with the corresponding disease stage in STZ-icv treated animals.

The last mentioned one might be of a particular importance in a view of our recent experiments of a 9-month follow up of the STZ-icv rats (*manuscript in preparation*) which have demonstrated that cognitive and neurochemical changes follow the similar time-dependent pattern (≤1 month - acute response; 1-3 months- tendency to return to normal values; 6-9 months - decompensation phase with a slow and progressive aggravation). Such pattern seems to resemble the situation in a real life where sAD might be triggered by some gene-environmental interactions (Salkovic-Petrisic et al. 2010), and yet, it does not exists in the transgenic mice AD models. Therefore, careful designing of drug interventional studies in the STZ-icv animal sAD model, in line with the STZ-icv dose- and time-dependent pattern of pathophysiology, might provide better predictive value in translating the results to humans. STZ-icv non-transgenic sAD model represents a promising experimental tool by providing new insights concerning both early and late brain alterations which can be translated in novel etiopathogenic and therapeutic approaches in this disease.

Acknowledgement

Supported by the Croatian Ministry of Science, Education and Sport (project No. 108-1080003-0020), Deutscher Akademischer Austausch Dienst (project 2012) and Unity through Knowledge Fund (UKF project 10/64).

The authors declare that they have no conflict of interest.

REFERENCE LIST

Agrawal R, Mishra B, Tyagi E, Nath C, Shukla R (2010) Effect of curcumin on brain insulin receptors and memory functions in STZ (ICV) induced dementia model of rat. Pharmacol Res 61:247-252

Agrawal R, Tyagi E, Shukla R, Nath C (2011) Insulin receptor signaling in rat hippocampus: a study in STZ (ICV) induced memory deficit model. Eur Neuropsychopharmacol 21:261-273

Arrieta-Cruz I, Wang J, Pavlides C, Pasinetti GM (2010) Carvedilol reestablishes long-term potentiation in a mouse model of Alzheimer's disease. J Alzheimers Dis 21:649-654

Awasthi H, Tota S, Hanif K, Nath C, Shukla R (2010) Protective effect of curcumin against intracerebral streptozotocin induced impairment in memory and cerebral blood flow. Life Sci 86:87-94

Baum L, Ng A (2004) Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. J Alzheimers Dis 6:367-377

Birks J, Grimley Evans J (2009) Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 21:CD003120

Blokland A, Jolles J (1993) Spatial learning deficit and reduced hippocampal ChAT activity in rats after an ICV injection of streptozotocin. Pharmacol Biochem Behav 44:491-494

Blokland A, Jolles J (1994) Behavioral and biochemical effects of an ICV injection of streptozotocin in old Lewis rats. Pharmacol Biochem Behav 47:833-837

Blondel O, Portha B (1989) Early appearance of in vivo insulin resistance in adult streptozotocin-injected rats. Diabete Metab 15:382-387

Boimel M, Grigoriadis N, Lourbopoulos A, Touloumi O, Rosenmann D, Abramsky O, Rosenmann H (2009) Statins reduce the neurofibrillary tangle burden in a mouse model of tauopathy. J Neuropathol Exp Neurol 68:314-325

Bonda DJ, Wang X, Perry G, Nunomura A, Tabaton M, Zhu X, Smith MA (2010) Oxidative stress in Alzheimer disease: a possibility for prevention. Neuropharmacology 59:290-294

Borroni B, Grassi M, Agosti C, Costanzi C, Archetti S, Franzoni S, Caltagirone C, Di Luca M, Caimi L, Padovani A (2006) Genetic correlates of behavioral endophenotypes in Alzheimer disease: role of COMT, 5-HTTLPR and APOE polymorphisms. Neurobiol Aging 27:1595-1603

Bosco D, Fava A, Plastino M, Montalcini T, Pujia A (2011) Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med. 2011 15:1807-1821

Braida D, Paladini E, Griffini P, Lamperti M, Maggi A, Sala M (1996) An inverted U-shaped curve for heptylphysostigmine on radial maze performance in rats: comparison with other cholinesterase inhibitors. Eur J Pharmacol 302:13-20

Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, Brandt J, Craft S, Evans DE, Green RC, Ismail MS, Martin BK, Mullan MJ, Sabbagh M, Tariot PN (2011) ADAPT Research

Group. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimers Dement 7:402-411

Carroll JC, Rosario ER, Chang L, Stanczyk FZ, Oddo S, LaFerla FM, Pike CJ (2007) Progesterone and estrogen regulate Alzheimer-like neuropathology in female 3xTg-AD mice.J Neurosci 27:13357-133365

Castellani RJ, Moreira PI, Liu G, Dobson J, Perry G, Smith MA, Zhu X (2007) Iron: the Redox-active center of oxidative stress in Alzheimer disease. Neurochem Res 32:1640-1645

Castellani RJ, Moreira PI, Perry G, Zhu X (2012) The role of iron as a mediator of oxidative stress in Alzheimer disease. Biofactors 38:133-138

Chen S, Liu AR, An FM, Yao WB, Gao XD (2011) Amelioration of neurodegenerative changes in cellular and rat models of diabetes-related Alzheimer's disease by exendin-4. Age (Dordr) Sep 8. [Epub ahead of print] DOI: 10.1007/s11357-011-9303-8

Correia SC, Santos RX, Perry G, Zhu X, Moreira PI, Smith MA (2011) Insulin-resistant brain state: the culprit in sporadic Alzheimer's disease? Ageing Res Rev 10:264-273

Dalla Y, Singh N, Jaggi AS, Singh D (2010) Memory restorative role of statins in experimental dementia: an evidence of their cholesterol dependent and independent actions. Pharmacol Rep 62:784-796

Dalla Y, Singh N, Jaggi AS, Singh D, Ghulati P (2009) Potential of ezetimibe in memory deficits associated with dementia of Alzheimer's type in mice. Indian J Pharmacol 41:262-267

Danielyan L, Klein R, Hanson LR, Buadze M, Schwab M, Gleiter CH, Frey WH (2010) Protective effects of intranasal losartan in the APP/PS1 transgenic mouse model of Alzheimer disease. Rejuvenation Res 13:195-201

Degerman Gunnarsson M, Kilander L, Basun H, Lannfelt L (2007) Reduction of phosphorylated tau during memantine treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 24:247-252

de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR (2006) Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 10:89-109

de la Monte SM, 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 Alzheimers Dis 7:45-61

Deshmukh R, Sharma V, Mehan S, Sharma N, Bedi KL (2009) Amelioration of intracerebroventricular streptozotocin induced cognitive dysfunction and oxidative stress by vinpocetine -- a PDE1 inhibitor. Eur J Pharmacol 620:49-56

Dhull DK, Bhateja D, Dhull RK, Padi SS (2012a) Differential role of cyclooxygenase isozymes on neuronal density in hippocampus CA1 region of intracerebroventricular streptozotocin treated rat brain. J Chem Neuroanat 43:48-51

Dhull DK, Jindal A, Dhull RK, Aggarwal S, Bhateja D, Padi SS (2012b) Neuroprotective effect of cyclooxygenase inhibitors in ICV-STZ induced sporadic alzheimer's disease in rats. J Mol Neurosci 46:223-235

Diwu YC, Tian JZ, Shi J (2011) Effects of Chinese herbal medicine Yinsiwei compound on spatial learning and memory ability and the ultrastructure of hippocampal neurons in a rat model of sporadic Alzheimer disease. Zhong Xi Yi Jie He Xue Bao 9:209-215

Dodart JC, Bales KR, Gannon KS, Greene SJ, DeMattos RB, Mathis C, DeLong CA, Wu S, Wu X, Holtzman DM, Paul SM (2002) Immunization reverses memory deficits without reducing brain Abeta burden in Alzheimer's disease model. Nat Neurosci 5:452-457

Dong YF, Kataoka K, Tokutomi Y, Nako H, Nakamura T, Toyama K, Sueta D, Koibuchi N, Yamamoto E, Ogawa H, Kim-Mitsuyama S (2011) Perindopril, a centrally active angiotensin-convertingenzymeinhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. FASEB J 25:2911-2920

Dragicevic N, Copes N, O'Neal-Moffitt G, Jin J, Buzzeo R, Mamcarz M, Tan J, Cao C, Olcese JM, Arendash GW, Bradshaw PC (2011) Melatonin treatment restores mitochondrial function in Alzheimer's mice: a mitochondrial protective role of melatonin membrane receptor signaling. J Pineal Res 51:75-86

Escribano L, Simón AM, Gimeno E, Cuadrado-Tejedor M, López de Maturana R, García-Osta A, Ricobaraza A, Pérez-Mediavilla A, Del Río J, Frechilla D (2010) Rosiglitazone rescues memory impairment in Alzheimer's transgenic mice: mechanisms involving a reduced amyloid and tau pathology. Neuropsychopharmacology 35:1593-1604

Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF (2011) Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry 198:351-356

Frölich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheimer A, Turk 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

Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG, Aisen P (2012) Antioxidants for Alzheimer Disease: A Randomized Clinical Trial With Cerebrospinal Fluid Biomarker Measures. Arch Neurol 2012 Mar 19. [Epub ahead of print] DOI: 10.1001/archneurol.2012.85

Geldmacher DS, Fritsch T, McClendon MJ, Landreth G (2011) A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. Arch Neurol 68:45-50

Ghosh AK, Brindisi M, Tang J (2012) Developing β-secretase inhibitors for treatment of Alzheimer's disease. J Neurochem 120(Suppl 1):71-83

Giorgino F, Chen JH, Smith RJ (1992) Changes in tyrosine phosphorylation of insulin receptors and a 170,000 molecular weight non-receptor protein in vivo in skeletal muscle of streptozotocin-induced diabetic rats: effects of insulin and glucose. Endocrinology 130:1433-1444

Götz ME, Künig G, Riederer P, Youdim MB (1994) Oxidative stress: free radical production in neural degeneration. Pharmacol Ther 63:37-122

Greenwald BS, Davis KL (1983) Experimental pharmacology of Alzheimer disease. Adv Neurol 38:87-102

Grünblatt E, Hoyer S, Riederer P (2004) Gene expression profile in streptozotocin rat model for sporadic Alzheimer's disease. J Neural Transm 111:367-386

Grünblatt E, Salkovic-Petrisic M, Osmanovic J, Riederer P, Hoyer S (2007) Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. J Neurochem 101:757-770

Gutzmann H, Hadler D (1998) Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. J Neural Transm Suppl 54:301-310

Hager K, Kenklies M, McAfoose J, Engel J, Münch G (2007) Alpha-lipoic acid as a new treatment option for Alzheimer's disease--a 48 months follow-up analysis. J Neural Transm Suppl 72:189-193

Hajjar IM, Keown M, Lewis P, Almor A (2008) Angiotensin converting enzyme inhibitors and cognitive and functional decline in patients with Alzheimer's disease: an observational study. Am J Alzheimers Dis Other Demen 23:77-83

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

Harrington C, Sawchak S, Chiang C, Davies J, Donovan C, Saunders AM, Irizarry M, Jeter B, Zvartau-Hind M, van Dyck CH, Gold M (2011) Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. Curr Alzheimer Res 8:592-606

Hellweg R, Nitsch R, Hock C, Jaksch M, Hoyer S (1992) Nerve growth factor and choline acetyltransferase activity levels in the rat brain following experimental impairment of cerebral glucose and energy metabolism. J Neurosci Res 31:479-486.

Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, O'Banion K, Klockgether T, Van Leuven F, Landreth GE (2005) Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV717I transgenic mice. Brain 128:1442-1453

Heo JH, Lee SR, Lee ST, Lee KM, Oh JH, Jang DP, Chang KT, Cho ZH (2011) Spatial distribution of glucose hypometabolism induced by intracerebroventricular streptozotocin in monkeys. J Alzheimers Dis 25:517-523

Hong L, Koelsch G, Lin X, Wu S, Terzyan S, Ghosh AK, Zhang XC, Tang J (2000) Structure if the protease domain of memapsin 2 (beta-secretase) complexed with inhibitor. Science 290:150-153

Hou Y, Zhou L, Yang QD, Du XP, Li M, Yuan M, Zhou ZW (2012) Changes in hippocampal synapses and learning-memory abilities in a streptozotocin-treated rat model and intervention by using fasudil hydrochloride. Neuroscience 200:120-129

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

Hoyer S (2004) Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 490: 115-125

Hoyer S, Lannert H (2007) Long-term abnormalities in brain glucose/energy metabolism after inhibition of the neuronal insulin receptor: implication of tau-protein. J Neural Transm Suppl 72:195-202

Hoyer S, Lannert H, Nöldner M, Chatterjee SS (1999) Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761). J Neural Transm 106:1171-1188

Hoyer S, Riederer P (2007) Alzheimer disease--no target for statin treatment. A mini review. Neurochem Res 32:695-706

Ishrat T, Hoda MN, Khan MB, Yousuf S, Ahmad M, Khan MM, Ahmad A, Islam F (2009) Amelioration of cognitive deficits and neurodegeneration by curcumin in rat model of sporadic dementia of Alzheimer's type (SDAT). Eur Neuropsychopharmacol 19:636-647

Ishrat T, Khan MB, Hoda MN, Yousuf S, Ahmad M, Ansari MA, Ahmad AS, Islam F (2006) Coenzyme Q10 modulates cognitive impairment against intracerebroventricular injection of streptozotocin in rats. Behav Brain Res 171:9-16

Ishrat T, Parveen K, Hoda MN, Khan MB, Yousuf S, Ansari MA, Saleem S, Islam F (2009) Effects of Pycnogenol and vitamin E on cognitive deficits and oxidative damage induced by intracerebroventricular streptozotocin in rats. Behav Pharmacol 20:567-575

Ishrat T, Parveen K, Khan MM, Khuwaja G, Khan MB, Yousuf S, Ahmad A, Shrivastav P, Islam F (2009) Selenium prevents cognitive decline and oxidative damage in rat model of streptozotocin-induced experimental dementia of Alzheimer's type. Brain Res 1281:117-127

Isik AT, Celik T, Ulusoy G, Ongoru O, Elibol B, Doruk H, Bozoglu E, Kayir H, Mas MR, Akman S (2009) Curcumin ameliorates impaired insulin/IGF signalling and memory deficit in a streptozotocin-treated rat model. Age (Dordr) 31:39-49

Jantzen PT, Connor KE, DiCarlo G, Wenk GL, Wallace JL, Rojiani AM, Coppola D, Morgan D, Gordon MN (2002) Microglial activation and beta -amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. J Neurosci 22:2246-2254

Jaturapatporn D, Isaac MG, McCleery J, Tabet N (2012) Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. Cochrane Database Syst Rev 2:CD006378

Javed H, Khan MM, Ahmad A, Vaibhav K, Ahmad ME, Khan A, Ashafaq M, Islam F, Siddiqui MS, Safhi MM, Islam F (2012) Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type. Neuroscience Mar 6. [Epub ahead of print] DOI: 10.1016/j.neuroscience.2012.02.046

Jee YS, Ko IG, Sung YH, Lee JW, Kim YS, Kim SE, Kim BK, Seo JH, Shin MS, Lee HH, Cho HJ, Kim CJ (2008) Effects of treadmill exercise on memory and c-Fos expression in the hippocampus of the rats with intracerebroventricular injection of streptozotocin. Neurosci Lett 443:188-192

Jiménez-Jiménez FJ, de Bustos F, Molina JA, Benito-León J, Tallón-Barranco A, Gasalla T, Ortí-Pareja M, Guillamón F, Rubio JC, Arenas J, Enríquez-de-Salamanca R (1997) Cerebrospinal fluid levels of alpha-tocopherol (vitamin E) in Alzheimer's disease. J Neural Transm 104:703-710

Kadowaki T, Kasuga M, Akanuma Y, Ezaki O, Takaku F (1984) Decreased autophosphorylation of the insulin receptor-kinase in streptozotocin-diabetic rats. J Biol Chem 259:14208-142016

Kaur B, Singh N, Jaggi AS (2009) Exploring mechanism of pioglitazone-induced memory restorative effect in experimental dementia. Fundam Clin Pharmacol 23:557-566

Kontush K, Schekatolina S (2004) Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann N Y Acad Sci 1031:249-262

Kornhuber J, Bormann J, Retz W, Hübers M, Riederer P (1989) Memantine displaces [3H]MK-801 at therapeutic concentrations in postmortem human frontal cortex. Eur J Pharmacol 166:589-590

Kumar R, Jaggi AS, Singh N (2010) Effects of erythropoietin on memory deficits and brain oxidative stress in the mouse models of dementia. Korean J Physiol Pharmacol 14:345-352

Kupershmidt L, Amit T, Bar-Am O, Youdim MB, Weinreb O (2012a) The Novel Multi-Target Iron Chelating-Radical Scavenging Compound M30 Possesses Beneficial Effects on Major Hallmarks of Alzheimer's Disease. Antioxid Redox Signal Apr 17. [Epub ahead of print] DOI: 10.1089/ars.2011.4279.

Kupershmidt L, Amit T, Bar-Am O, Youdim MB, Weinreb O (2012b) Neuroprotection by the multitarget iron chelator M30 on age-related alterations in mice. Mech Ageing Dev Mar 10. [Epub ahead of print] DOI: 10.1016/j.mad.2012.03.001

Kupershmidt L, Weinreb O, Amit T, Mandel S, Bar-Am O, Youdim MB (2011) Novel molecular targets of the neuroprotective/neurorescue multimodal iron chelating drug M30 in the mouse brain. Neuroscience 189:345-358

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

Lannert H, Wirtz P, Schuhmann V, Galmbacher R (1998) Effects of Estradiol (-17beta) on learning, memory and cerebral energy metabolism in male rats after intracerebroventricular administration of streptozotocin. J Neural Transm 105:1045-1063

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 Alzheimers Dis 9:13-33

Levin-Allerhand JA, Lominska CE, Wang J, Smith JD (2002) 17Alpha-estradiol and 17beta-estradiol treatments are effective in lowering cerebral amyloid-beta levels in AbetaPPSWE transgenic mice.J Alzheimers Dis 4:449-457

Li Nc, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, Wolozin B (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 340:b5465 DOI: 10.1136/bmj.b5465

Li L, Zhang ZF, Holscher C, Gao C, Jiang YH, Liu YZ (2012) (Val□) glucagon-like peptide-1 prevents tau hyperphosphorylation, impairment of spatial learning and ultra-structural cellular damage induced by streptozotocin in rat brains. Eur J Pharmacol 674:280-286

Löffler T, Lee SK, Nöldner M, Chatterjee SS, Hoyer S, Schliebs R (2001) Effect of Ginkgo biloba extract (EGb761) on glucose metabolism-related markers in streptozotocin-damaged rat brain. J Neural Transm 108:1457-1474

Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, Chen PP, Hudspeth B, Chen C, Zhao Y, Vinters HV, Frautschy SA, Cole GM (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. J Neurosci 29:9078-9089

Mayer G, Nitsch R, Hoyer S (1990) Effects of changes in peripheral and cerebral glucose metabolism on locomotor activity, learning and memory in adult male rats. Brain Res 532:95-100

McGeer PL, McGeer EG (2007) NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging 28:639-647 .

Medina M, Avila J (2010) Glycogen synthase kinase-3 (GSK-3) inhibitors for the treatment of Alzheimer's disease. Curr Pharm Des 16:2790-2798

Melnikova T, Savonenko A, Wang Q, Liang X, Hand T, Wu L, Kaufmann WE, Vehmas A, Andreasson KI (2006) Cycloxygenase-2 activity promotes cognitive deficits but not increased amyloid burden in a model. Neuroscience 141:1149-1162

Minkeviciene R, Banerjee P, Tanila H (2004) Memantine improves spatial learning in a transgenic mouse model of Alzheimer's disease. J Pharmacol Exp Ther 311:677-682

Misra S, Tiwari V, Kuhad A, Chopra K (2011) Modulation of nitrergic pathway by sesamol prevents cognitive deficits and associated biochemical alterations in intracerebroventricular streptozotocin administered rats. Eur J Pharmacol 659:177-186

Montgomery SA, Thal LJ, Amrein R (2003) Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol 18:61-71

Muller AP, Zimmer ER, Kalinine E, Haas CB, Oses JP, Martimbianco de Assis A, Galina A, Souza DO, Portela LV (2012) Physical Exercise Exacerbates Memory Deficits Induced by Intracerebroventricular STZ but Improves Insulin Regulation of H2O2 Production in Mice Synaptosomes. J Alzheimers Dis Apr 4. [Epub ahead of print] DOI: 10.3233/JAD-2012-112066

Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Gamst A, Grundman M, Thomas R, Thal LJ (2000) Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study JAMA 283:1007-1015

Nicolakakis N, Aboulkassim T, Ongali B, Lecrux C, Fernandes P, Rosa-Neto P, Tong XK, Hamel E (2008) Complete rescue of cerebrovascular function in aged Alzheimer's disease transgenic mice by antioxidants and pioglitazone, a peroxisome proliferator-activated receptor gamma agonist. J Neurosci 28:9287-9296

Nitsch R, Hoyer S (1991) Local action of the diabetogenic drug, streptozotocin, on glucose and energy metabolism in rat brain cortex. Neurosci Lett 128:199-202

Nunan J, Small DH (2000) Regulation of APP cleavage by alpha-, beta- and gamma-secretases. FEBS Lett 483:6-10

Oddo S, Vasilevko V, Caccamo A, Kitazawa M, Cribbs DH, LaFerla FM (2006) Reduction of soluble Abeta and tau, but not soluble Abeta alone, ameliorates cognitive decline in transgenic mice with plaques and tangles. J Biol Chem 281:39413-39423

Pathan AR, Viswanad B, Sonkusare SK, Ramarao P (2006) Chronic administration of pioglitazone attenuates intracerebroventricular streptozotocin induced-memory impairment in rats. Life Sci 79:2209-2216

Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR (2006) Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp Neurol 199:265-273

Peskind ER, Tsuang DW, Bonner LT, Pascualy M, Riekse RG, Snowden MB, Thomas R, Raskind MA (2005) Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. Alzheimer Dis Assoc Disord 19:23-28

Pinton S, da Rocha JT, Gai BM, Prigol M, da Rosa LV, Nogueira CW (2011) Neuroprotector effect of p,p'-methoxyl-diphenyl diselenide in a model of sporadic dementia of Alzheimer's type in mice: contribution of antioxidant mechanism. Cell Biochem Funct 29:235-243

Pinton S, da Rocha JT, Zeni G, Nogueira CW (2010) Organoselenium improves memory decline in mice: involvement of acetylcholinesterase activity. Neurosci Lett 472:56-60

Ponce-Lopez T, Liy-Salmeron G, Hong E, Meneses A (2011) Lithium, phenserine, memantine and pioglitazone reverse memory deficit and restore phospho-GSK3β decreased in hippocampus in intracerebroventricular streptozotocin induced memory deficit model. Brain Res 1426:73-85

Prakash AK, Kumar A (2009) Effect of chronic treatment of carvedilol on oxidative stress in an intracerebroventricular streptozotocin induced model of dementia in rats. J Pharm Pharmacol 61:1665-1672

Prickaerts J, Blokland A, Honig W, Meng F, Jolles J (1995) Spatial discrimination learning and choline acetyltransferase activity in streptozotocin-treated rats: effects of chronic treatment with acetyl-L-carnitine. Brain Res 674:142-146

Prickaerts J, Fahrig T, Blokland A (1999) Cognitive performance and biochemical markers in septum, hippocampus and striatum of rats after an i.c.v. injection of streptozotocin: a correlation analysis. Behav Brain Res 102:73-88

Reitz C (2012) Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int J Alzheimers Dis 2012:369808

Richter H, Ambrée O, Lewejohann L, Herring A, Keyvani K, Paulus W, Palme R, Touma C, Schäbitz WR, Sachser N (2008) Wheel-running in a transgenic mouse model of Alzheimer's disease: protection or symptom? Behav Brain Res 190:74-84

Rinwa P, Kaur B, Jaggi AS, Singh N (2010) Involvement of PPAR-gamma in curcumin-mediated beneficial effects in experimental dementia. Naunyn Schmiedebergs Arch Pharmacol 381:529-539

Riviere C, Richard T, Vitrac X, Merillon JM, Valls J, Monti JP (2008) New polyphenols active on beta-amyloid aggregation. Bioorg Med Chem Lett 18:828–831

Rodrigues L, Dutra MF, Ilha J, Biasibetti R, Quincozes-Santos A, Leite MC, Marcuzzo S, Achaval M, Gonçalves CA (2010) Treadmill training restores spatial cognitive deficits and neurochemical alterations in the hippocampus of rats submitted to an intracerebroventricular administration of streptozotocin. J Neural Transm 117:1295-1305

Rodrigues L, Biasibetti R, Swarowsky A, Leite MC, Quincozes-Santos A, Quilfeldt JA, Achaval M, Gonçalves CA (2009) Hippocampal alterations in rats submitted to streptozotocin-induced dementia model are prevented by aminoguanidine. J Alzheimers Dis 17:193-202

Salkovic-Petrisic M, Hoyer S (2007) Central insulin resistance as a trigger for sporadic Alzheimer-like pathology: an experimental approach. J Neural Transm Suppl 72:217-233

Salkovic-Petrisic M, Hoyer S, Riederer P (2012) Experimental Approach to Alzheimer Disease. ???? in print

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

Salkovic-Petrisic M, Osmanovic J, Grünblatt E, Riederer P, Hoyer S (2009) Modeling sporadic Alzheimer's disease: the insulin resistant brain state generates multiple long-term morphobiological abnormalities including hyperphosphorylated tau protein and amyloid-beta. J Alzheimers Dis 18:729-750

Salkovic-Petrisic M, Tribl F, Schmidt M, Hoyer S, Riederer P (2006) Alzheimer-like changes in protein kinase B and glycogen synthase kinase-3 in rat frontal cortex and hippocampus after damage to the insulin signalling pathway. J Neurochem 96:1005-1015

Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T (2011) Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging 32:1626-1633

Saxena G, Bharti S, Kamat PK, Sharma S, Nath C (2010) Melatonin alleviates memory deficits and neuronal degeneration induced by intracerebroventricular administration of streptozotocin in rats. Pharmacol Biochem Behav 94:397-403

Saxena G, Singh SP, Agrawal R, Nath C (2008) Effect of donepezil and tacrine on oxidative stress in intracerebral streptozotocin-induced model of dementia in mice. Eur J Pharmacol 581:283-289

Saxena G, Singh SP, Pal R, Singh S, Pratap R, Nath C (2007) Gugulipid, an extract of Commiphora whighitii with lipid-lowering properties, has protective effects against streptozotocin-induced memory deficits in mice. Pharmacol Biochem Behav 86:797-805

Saxena G, Patro IK, Nath C (2011) ICV STZ induced impairment in memory and neuronal mitochondrial function: A protective role of nicotinic receptor. Behav Brain Res 224:50-57

Sharma V, Bala A, Deshmukh R, Bedi KL, Sharma PL (2012) Neuroprotective effect of RO-20-1724-a phosphodiesterase4 inhibitor against intracerebroventricular streptozotocin induced cognitive deficit and oxidative stress in rats. Pharmacol Biochem Behav 101:239-245

Sharma M, Gupta YK (2001) Intracerebroventricular injection of streptozotocin in rats produces both oxidative stress in the brain and cognitive impairment. Life Sci 68:1021-1029

Sharma M, Gupta YK (2002) Chronic treatment with trans resveratrol prevents intracerebroventricular streptozotocin induced cognitive impairment and oxidative stress in rats. Life Sci 71:2489-2498

Sharma M, Gupta YK (2003) Effect of alpha lipoic acid on intracerebroventricular streptozotocin model of cognitive impairment in rats. Eur Neuropsychopharmacol 13:241-247

Sharma B, Singh N, Singh M (2008a) Modulation of celecoxib- and streptozotocin-induced experimental dementia of Alzheimer's disease by pitavastatin and donepezil. J Psychopharmacol 22:162-171

Sharma B, Singh N, Singh M, Jaggi AS (2008b) Exploitation of HIV protease inhibitor Indinavir as a memory restorative agent in experimental dementia. Pharmacol Biochem Behav 89:535-545

Shepardson NE, Shankar GM, Selkoe DJ (2011a) Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. Arch Neurol 68:1239-1244

Shepardson NE, Shankar GM, Selkoe DJ (2011b) Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations. Arch Neurol 68:1385-1392

Shingo AS, Kanabayashi T, Murase T, Kito S (2012) Cognitive decline in STZ-3V rats is largely due to dysfunctional insulin signalling through the dentate gyrus. Behav Brain Res 229:378-383

Shoham S, Bejar C, Kovalev E, Schorer-Apelbaum D, Weinstock M (2007) Ladostigil prevents gliosis, oxidative-nitrative stress and memory deficits induced by intracerebroventricular injection of streptozotocin in rats. Neuropharmacology 52:836-843

Shonesy BC, Thiruchelvam K, Parameshwaran K, Rahman EA, Karuppagounder SS, Huggins KW, Pinkert CA, Amin R, Dhanasekaran M, Suppiramaniam V (2012) Central insulin resistance and synaptic dysfunction in intracerebroventricular-streptozotocin injected rodents. Neurobiol Aging 33:430.e5-18

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN 3rd, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J; WHIMS Investigators (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289:2651-2662

Sonkusare S, Srinivasan K, Kaul C, Ramarao P (2005) Effect of donepezil and lercanidipine on memory impairment induced by intracerebroventricular streptozotocin in rats. Life Sci 77:1-14

Stackman RW, Eckenstein F, Frei B, Kulhanek D, Nowlin J, Quinn JF (2003) Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. Exp Neurol 184:510-520

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

Szkudelski T (2001) The mechanism of alloxan and streptozotocin action in B cell of the rat pancreas. Physiol Res 50: 537-546

Takeda S, Sato N, Rakugi H, Morishita R (2011) Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. Mol Biosyst 7:1822-1827

Tang J, Ghosh A (2011) Treating transgenic Alzheimer mice with a β-secretase inhibitor, what have we learned? Aging (Albany NY) 3:14-16

Terwel D, Prickaerts J, Meng F, Jolles J (1995) Brain enzyme activities after intracerebroventricular injection of streptozotocin in rats receiving acetyl-L-carnitine. Eur J Pharmacol 287:65-71

Thal LJ, Grundman M, Berg J, Ernstrom K, Margolin R, Pfeiffer E, Weiner MF, Zamrini E, Thomas RG (2003) Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. Neurology 61:1498-1502

Tiwari V, Kuhad A, Bishnoi M, Chopra K (2009) Chronic treatment with tocotrienol, an isoform of vitamin E, prevents intracerebroventricular streptozotocin-induced cognitive impairment and oxidative-nitrosative stress in rats. Pharmacol Biochem Behav 93:183-189

Toledo EM, Inestrosa NC (2010) Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. Mol Psychiatry 15:272-285

Tota S, Awasthi H, Kamat PK, Nath C, Hanif K (2010) Protective effect of quercetin against intracerebral streptozotocin induced reduction in cerebral blood flow and impairment of memory in mice. Behav Brain Res 209:73-79

Tota S, Kamat PK, Awasthi H, Singh N, Raghubir R, Nath C, Hanif K (2009) Candesartan improves memory decline in mice: involvement of AT1 receptors in memory deficit induced by intracerebral streptozotocin. Behav Brain Res 199:235-240

Tota S, Kamat PK, Saxena G, Hanif K, Najmi AK, Nath C (2012) Central angiotensin converting enzyme facilitates memory impairment in intracerebroventricular streptozotocin treated rats. BehavBrain Res 226:317-330

Tota S, Kamat PK, Shukla R, Nath C (2011) Improvement of brain energy metabolism and cholinergic functions contributes to the beneficial effects of silibinin against streptozotocin induced memory impairment. Behav Brain Res 221:207-215

Tramontina AC, Wartchow KM, Rodrigues L, Biasibetti R, Quincozes-Santos A, Bobermin L, Tramontina F, Gonçalves CA (2011) The neuroprotective effect of two statins: simvastatin and pravastatin on a streptozotocin-induced model of Alzheimer's disease in rats. J Neural Transm 118:1641-1649

Tzimopoulou S, Cunningham VJ, Nichols TE, Searle G, Bird NP, Mistry P, Dixon IJ, Hallett WA, Whitcher B, Brown AP, Zvartau-Hind M, Lotay N, Lai RY, Castiglia M, Jeter B, Matthews JC, Chen K, Bandy D, Reiman EM, Gold M, Rabiner EA, Matthews PM (2010) A multi-center

randomized proof-of-concept clinical trial applying [¹□F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. J Alzheimers Dis 22:1241-1256

Van Dam D, De Deyn PP (2006) Cognitive evaluation of disease-modifying efficacy of galantamine and memantine in the APP23 model. Eur Neuropsychopharmacol 16:59-69

Veerendra Kumar MH, Gupta YK (2003) Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol 30:336-342

Vingtdeux V, Dreses-Werringloer U, Zhao H, Davies P, Marambaud P (2008) Therapeutic potential of resveratrol in Alzheimer's disease. BMC Neurosci 9:S6

Wang J, Ho L, Zhao Z, Seror I, Humala N, Dickstein DL, Thiyagarajan M, Percival SS, Talcott ST, Pasinetti GM (2006) Moderate consumption of Cabernet Sauvignon attenuates Abeta neuropathology in a mouse model of Alzheimer's disease. FASEB J 20:2313–2320

Wang YJ, Thomas P, Zhong JH, Bi FF, Kosaraju S, Pollard A, Fenech M, Zhou XF (2009) Consumption of grape seed extract prevents amyloid-beta deposition and attenuates inflammation in brain of an Alzheimer's disease mouse. Neurotox Res 15:3-14

Weinstock M, Kirschbaum-Slager N, Lazarovici P, Bejar C, Youdim MB, Shoham S (2001) Neuroprotective effects of novel cholinesterase inhibitors derived from rasagiline as potential anti-Alzheimer drugs. Ann N Y Acad Sci 939:148-161

Weyer G, Babej-Dölle RM, Hadler D, Hofmann S, Herrmann WM (1997) A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. Neuropsychobiology 36:73-82

Wollen KA (2010) Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev 15:223-244

Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, Citron M, Landreth G (2003) Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. J Neurosci 23:7504-7509

Youdim MB, Fridkin M, Zheng H (2005) Bifunctional drug derivatives of MAO-B inhibitor rasagiline and iron chelator VK-28 as a more effective approach to treatment of brain ageing and ageing neurodegenerative diseases.Mech Ageing Dev 126:317-326

Youdim MB (2012) M30, a brain permeable multi target neurorestorative drug in post nigrostriatal dopamine neuron lesion of parkinsonism animal models. Parkinsonism Relat Disord 18:S151-154

Zahs KR, Ashe KH (2010) Too much good news' - are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease? Trends Neurosci 33:381-389

Zhang X, Heng X, Li T, Li L, Yang D, Zhang X, Du Y, Doody RS, Le W (2011) Long-term treatment with lithium alleviates memory deficits and reduces amyloid-β production in an aged Alzheimer's disease transgenic mouse model. J Alzheimers Dis 24:739-749

Zhu X, Su B, Wang X, Smith MA, Perry G (2007) Causes of oxidative stress in Alzheimer disease. Cell Mol Life Sci 64:2202-2210

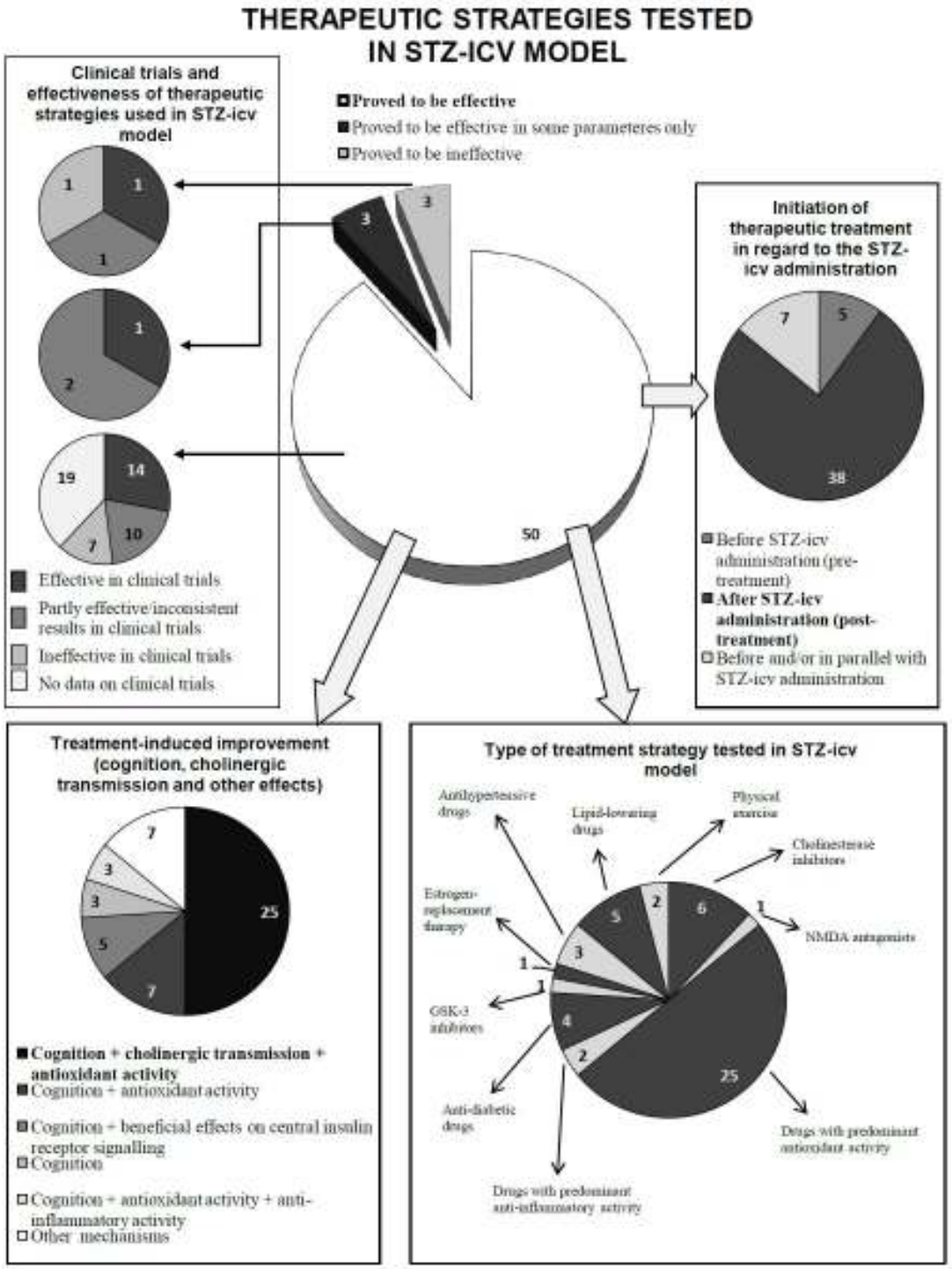

Figure 1. Therapeutic strategies tested in streptozotocin-intracerebroventricularly-treated (STZ-icv) animal model of sporadic Alzheimer's disease (sAD). Interventional drug treatments in the STZ-icv animal model of sAD have been presented in regard to the effectiveness in the STZ-icv model in relation to the investigated parameters of cognition and/or brain neurochemistry and initiation of the drug treatment in relation to the STZ-icv administration (pre- or post-treatment). Furthermore, results are expressed in relation to the type of the treatment strategy/mechanism of drug action tested in STZ-icv animal model and treatment-induced improvement in various parameters. Finally, comparison to the effectiveness of the same therapeutic strategies in clinical trials has been presented. Except for the last one where effectiveness in clinical trials is expressed by number of therapeutic approaches performed in STZ-icv model (one approach may cover more than one exact experiment), all other results are expressed as number of exact experiments performed in STZ-icv model until April 2012. Experiments with Indian and Chinese herbal drugs have been excluded.