Journal of Steroid Biochemistry & Molecular Biology 119 (2010) 97–104

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Neuroimmunomodulatory steroids in Alzheimer dementia

Richard Hampl*, Marie Bičíková

Institute of Endocrinology, Prague, Czech Republic

ARTICLE INFO

Article history:
Received 9 November 2009
Received in revised form 3 February 2010
Accepted 4 February 2010

Keywords:
Alzheimer disease
Steroids
Glycoregulation
Autoimmunity
Apoptosis

ABSTRACT

Though pathobiochemical and neurochemical changes and accompanied morphological alterations in Alzheimer dementia are well known, the triggering mechanisms, if any, remain obscure. Important factors influencing the development and progression of Alzheimer disease include hormonal steroids and their metabolites, some of which may serve as therapeutic agents.

This review focusses on major biochemical alterations in the brain of Alzheimer patients with respect to the involvement of steroids. It includes their role in impairment of fuel supply and in brain glycoregulation, with especial emphasis on glucocorticoids and their counter-regulatory steroids as dehydroepiandrosterone and its metabolites. Further, the role of steroids in beta-amyloid pathology is reviewed including alterations in tau-protein(s) phosphorylation. The (auto)immune theory of Alzheimer dementia is briefly outlined, pointing to the possible involvement of steroids in brain ageing, immunosenescence and neuronal apoptosis. Some effects of steroids are briefly mentioned on the formation and removal of reactive oxygen species and their effect on calcium flux and cytotoxicity.

The recent biochemical research of Alzheimer disease focusses on molecular signalling at which steroids also take part. New findings may be anticipated when the mosaic describing the molecular mechanisms behind these events becomes more complete.

Contents

1. Introduction

Alzheimer dementia (AD) is one of the most severe organic psychoneurological diseases comprising as much as 60% of dementia. In spite of the fact that pathobiochemical and neurochemical changes and accompanied morphological alterations in AD are well

* Corresponding author at: Institute of Endocrinology, Narodni 8, 116 94 Prague 1, Czech Republic. Tel.: +420 224905289; fax: +420 224905325.
E-mail address: rhampl@endo.cz (R. Hampl).

0960-0760/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.jsbmb.2010.02.007

known, the triggering mechanisms, if any, remain obscure. Characteristic morphological changes visible by imaging techniques show a loss of neural tissue, especially in the hippocampus as a site of cognitive function and formation of s.c. beta-amyloid plaques.

About 10% of the causes of AD are believed to have a genetic background. However, in this text we will focus only on the (patho)biochemical mechanisms with an interest in the involvement of steroids. Hormonal steroids are potent regulators of many physiological processes and may serve as therapeutic agents (esp. glucocorticoids) or are already in use for hormone replacement therapy (estrogens, dehydroepiandrosterone, androgens). In addition, some metabolites of hormonal steroids or their precursor in the biosynthetic route appeared to possess unexpected biological activities, including those in the brain [1–3].

From a biochemical point of view the typical features of AD are general impairment of the oxidative metabolism in brain tissues resulting in insufficient fuel supply and consequent neurodegeneration. Other pathobiochemical changes in brain tissues include the aforementioned formation of beta-amyloid plaques due to impaired metabolism of beta-amyloid precursor protein, abnormal phosphorylation of tau-protein, insufficient supply of acetylcholine to neurons, imbalance in enzymes responsible for formation and removal of reactive oxygen species (ROS), increased calcium flux resulting in cytotoxic effects and lack of neurotrophic factors. Of special interest are disorders of the immune system and their relation to AD pathology.

The biochemical mechanisms behind these events are in most instances known or are being intensively studied and in general consist of an alteration of signalling cascades mediating the final biological effects. In the following text we will attempt to survey the known effects of steroids on the main biochemical features typical for AD. The main sites of steroid effects on biochemical alterations in AD are shown in Fig. 1.

2. Impairment of fuel supply and the role of steroids in brain glycoregulation

The brain is a heavy user of metabolic energy, requiring as much as 25% of the body's glucose supplies, whilst representing only 2% of the body's weight. Glucose is the main source for this metabolic energy [4]. There are two major points by which glucose utilization may be affected in diseased subjects: its transport into the cells and its mitochondrial metabolism associated with ATP formation.

One of the efficient methods for tracking glucose transport into various brain regions is the uptake of [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG), as measured by positron emission tomography (PET) [5,6]. Like glucose, 2-deoxy-D-glucose and its fluorine-labelled derivative FDG undergoes facilitated transport into the brain cells followed by phosphorylation by hexokinase, but, in contrast to glucose, metabolism does not proceed beyond phosphorylation because the hydroxyl group on C-2 is crucial in the next step catalyzed by phosphohexose isomerase. As a result, FDG is trapped in the cell providing a record of metabolism.

Concerning hormonal steroids, lower estradiol levels in cerebrospinal fluid from Alzheimer postmenopausal patients than in age-matched non-demented subjects correlated well with FDG uptake, demonstrating an association between CSF estradiol concentration and hippocampal glucose metabolism [7]. In addition, estrogens promote mitochondrial function and so sustain aerobic glycolysis and citric acid cycle-driven oxidative phosphorylation and ATP generation. These findings seemed to support the idea of the beneficial effect of estrogen therapy in AD. However, a more recent report demonstrated that the estrogen effect is valid only if neurons are healthy at the time of estrogen exposure and, in advanced states of disease, estrogens may even exacerbate neurological demise [8].

In addition to insulin and glucagon, glucocorticoids also play a pivotal role in regulation of peripheral glucose mobilization and metabolism. Their levels increase with age and they are also associated with progression of AD, due to higher activity of hypothalamo-pituitary-adrenal axis [9,10]. Although several animal studies have shown that hippocampal glucose metabolism is reduced by the action of glucocorticoids and that excess glucocorticoids are harmful to hippocampal neurons, only a few reports concern their effects on the human brain. Using the [^{18}F]FDH uptake technique, De Leon et al. [11] demonstrated a rise in plasma glucose levels, after administration of a pharmacological dose of hydrocortisone in age-matched healthy subjects, whilst the AD group did not show this effect. These data show that in normal individuals, in the presence of high doses of cortisol, glucose utilization of the hippocampus is reduced, and serum glucose levels increase. On the other hand, more recent studies based on FED-PET [6] pointed to glucose metabolic reductions as a hallmark of the early stages of AD.

A number of studies addressed the function of enzymes involved in glucose metabolism, namely glycolysis, Kreb's cycle (tricarboxylic acid cycle, TCA) and oxidative phosphorylation of the respiratory chain in AD, as compared with age-matched non-demented subjects. The main limitation of these studies was their restriction to post-mortem samples. Using micro-array analysis and quantitative RT-PCR for screening gene expression profiles of key metabolic enzyme transcripts, Brooks et al. [4] have shown that out of 51 energy metabolism-related transcripts, 15 were significantly down-regulated in hippocampal tissues from Alzheimer patients. It included 3 of 14 glycolytic enzymes, 5 of 10 TCA enzymes, 6 of 16 enzymes of oxidative phosphorylation and one enzyme of ketone body synthesis and degradation. These data were not fully consistent with the previous measurement of enzymatic activities of selected glycolytic enzymes, which differed not only according to brain regions, but also by cell type (neurons vs. glial cells) [12]. The activity of 6-phosphofructokinase (PFK), the rate limiting enzyme in the glycolytic pathway, was significantly increased in the frontal and temporal cortex and unchanged in the other brain areas from patients with AD when compared with the brains of the controls [13], whilst its expression was insignificantly decreased [4]. Using a similar methodological approach, Gibson et al. [14] demonstrated replicable reductions in the AD brain in the pyruvate dehydrogenase complex (the link of glycolysis to the Kreb's cycle) [4], the alpha-ketoglutarate dehydrogenase complex (the link of Kreb's cycle to glutamate metabolism) and cytochrome oxidase (the link of the Kreb's cycle to oxygen utilization).

Cortisol and glucocorticoids, as commonly used therapeutic agents, and dehydroepiandrosterone, known to possess various beneficial effects on cognitive function, should be the steroids first considered due to their effects on the enzymes of glucose metabolism in AD.

Though cortisol and other glucocorticoids are tightly associated with various signs of AD, no unequivocal and specific effect of these steroids on enzymes on fuel metabolism in AD was reported. Though mostly confined to animal models, large microarray screening of thousands genes under glucocorticoid control (glucocorticoid-sensitive genes) should be mentioned here, including those of glucose metabolism [15]. These studies, however, did not confirm a hypothesis of simple positive co-operativity between brain ageing and increased glucocorticoid levels in AD.

Hormone replacement therapy with DHEA, with particular respect to AD, is a frequently discussed theme [16]. It should be emphasized that DHEA effects are very diverse and DHEA may act at various levels. Concerning AD, both beneficial but also harmful effects were described (see below). As carbohydrate metabolism

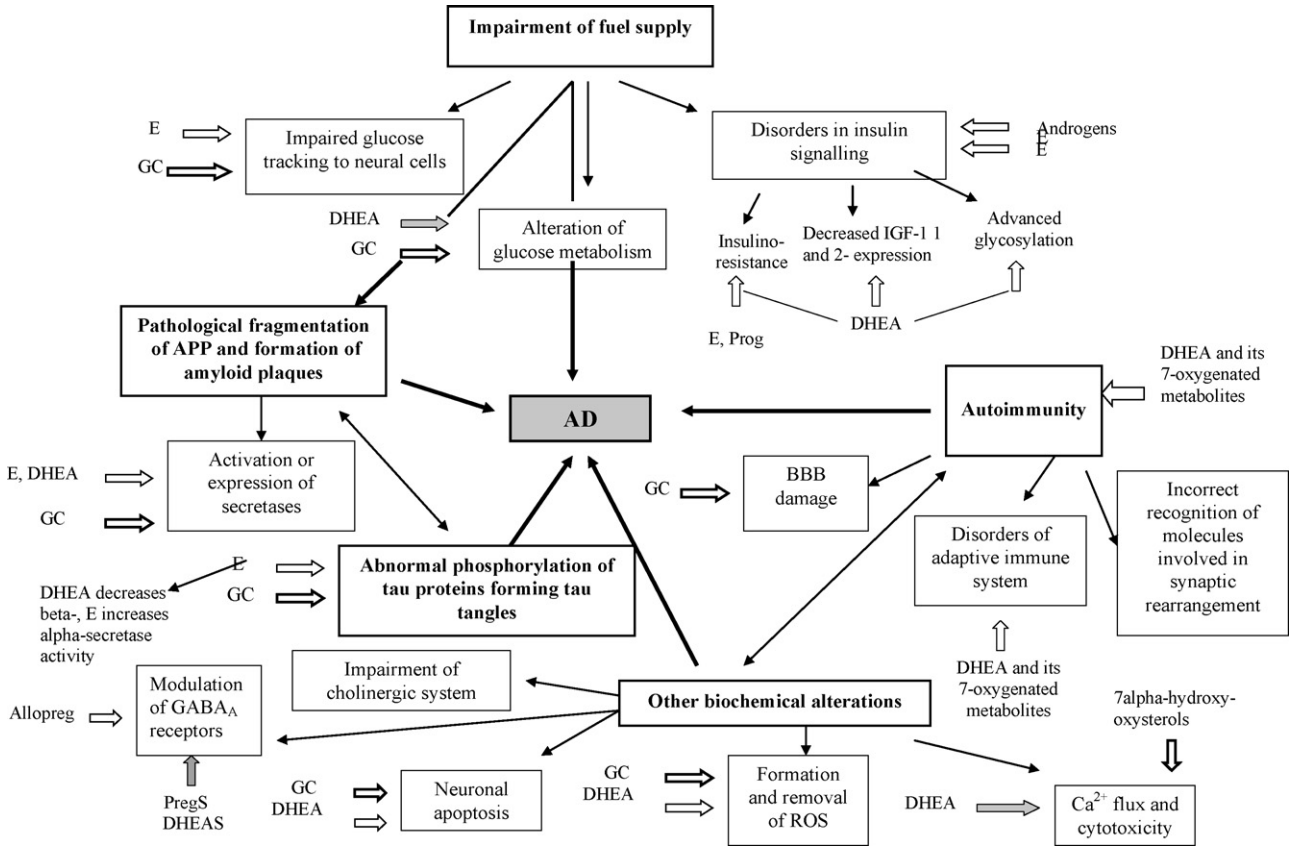

Fig. 1. Main sites of steroid effects on biochemical alterations in Alzheimer's disease. *Abbreviations*: AD: Alzheimer's disease, Allopreg: allopregnanolone, APP: amyloid precursor protein, BBB: blood–brain barrier, DHEA: dehydroepiandrosterone, DHEAS: dehydroepiandrosterone sulfate, E: estrogens, GC: glucocorticoids, IGF: insulin-like growth factor, PregS: pregnenolone sulfate, Prog: progesterone, ROS: reactive oxygen species. *Symbols*: ⇨ beneficial effects; ⇨ ambiguous effects; ⇨ adverse effects.

is concerned, DHEA is a well known strong inhibitor of glucose 6-phosphate dehydrogenase, one of the key cytosolic enzymes in the pentose phosphate pathway [17], which was significantly reduced in hippocampus of AD patients [12].Generally brain oxidative metabolism in Alzheimer disease is diminished. Since NADPH is a key cofactor in the activity of many antioxidative and reductive enzymes [18], its depletion may result in an impairment of fuel utilization and consequently to onset of the disease. As for steroid metabolism in the brain, NADPH is, among other things a cofactor for enzyme cytochrome P7B1, abundant in brain tissues, responsible for 7-hydroxylation of DHEA [19]. The expression of this enzyme in brain post-mortem tissues was decreased in AD [20]. In addition NADPH is required for reduction of cortisone to hormonally active cortisol by 11beta-hydroxysteroid dehydrogenase Type I and thus for modulation of the glucocorticoid status in tissues including brain [21,22]. Taken together, the depletion of NADPH for these enzymatic reactions to the detriment of glucose oxidative metabolism may be one of the factors contributing to the onset and progression of AD.

In conclusion, steroids may influence glucose supply and transport to the mitochondria of the brain cells, but this effect is different in healthy subjects and AD. Generally, estrogens increase whilst cortisol decreases glucose uptake. Though activity and expression of enzymes of carbohydrate metabolism in healthy and AD subjects differ considerably, the effect of hormonal and other steroids on these events is not unequivocal or even marginal and it cannot be decided whether the differences between Alzheimer patients and healthy subjects are a cause or a consequence of the disease. On the other hand, there is increasing evidence that the previously so-called "secondary factors", including a disturbed glucose metabolism, are also important for the onset and progression of AD [23].

3. AD as diabetes mellitus Type III and the role of steroids

Disorders in glucose and fuel metabolism in the brain of AD patients are intimately connected with insulin signalling. Impaired insulin sensitivity and consequent hyperinsulinemia is a common feature shared by Type II diabetes (DM 2) and AD. A number of reports, such as a large population-based study in Sweden on 2322 participants, confirmed that impaired acute insulin response at midlife was associated with an increased risk of Alzheimer disease [24].

Since circulating insulin crosses the blood–brain barrier (BBB), it can reach neurons and glial cells and so exert a region-specific effect on glucose metabolism. Elevation of peripheral insulin levels, as reflected by an increase in cerebrospinal fluid (CSF) concentration, may negatively influence neuronal function and survival as demonstrated by the abnormal removal of amyloid beta peptide, an increase of tau hyperphosphorylation and a general increase of inflammatory agents in the brain [25–27]. For a recent review of convergent mechanisms of insulin resistance occurring in DM 2 and AD see [28].

Reduced glucose utilization and deficient energy metabolism occurring even in the early stages of the disease further point to impaired insulin signalling in the pathogenesis of AD. Extensive abnormalities in insulin and insulin-like growth factor type I and II were found in AD patients due to their markedly reduced expression in the central nervous system (CNS). These abnormalities were associated with reduced levels of important molecules of

insulin signalling as insulin receptor substrate 1 (IRS 1) mRNA, IRS 1-associated phosphotidylinositol 3-kinase (PI3-K), and increased glycogen synthase kinase-3beta (GSK-3beta) activity, as well as with characteristic abnormalities typical for AD as reduced tau mRNA and amyloid precursor protein mRNA expression [29].

Physiological actions of insulin and hormonal steroids may interact in target tissues for these hormones, including those of the brain. As for the role of steroids in insulin signalling, besides the aforementioned effects of glucocorticoids, most information dealt with sex steroids as potential therapeutics in elderly subjects. Recent experiments have shown that low concentrations of estradiol induce an increase in the rate of IRS-1 phosphorylation, promote the association between IRS-1 and the subunit of PI3-K, p85alpha, cause a decrease in the rate of IRS-1 serine phosphorylation and increase the rate of Akt enzymes (serine/threonine-specific protein kinase family, also called protein kinases B, PKB). It suggests the narrow interrelation between the estrogens and insulin sensitivity, but relatively few studies have tried to resolve the molecular base of this relation in insulin-dependent tissues, particularly in the brain [30,31].

Repeated evidence has also been presented supporting the association of androgen deficiency in elderly men and its relationship to metabolic syndrome and type II diabetes [32,33] and even with AD [34,35]. The molecular mechanisms behind these finding were not investigated. Animal studies on rats showed that gonadal steroids may exert part of their neural effects through astroglia, indicating that steroids serve here for communication among cells [36]. The data concerning the association of androgen deficiency with cognitive impairment and characteristic signs of AD and the effect of androgen therapy were critically reviewed without unequivocal conclusions. Some but not all studies of androgen replacement therapy in hypogonadal younger men, older men with late onset hypogonadism and AD patients suggest a potential beneficial effect on cognition; however a recent study indicated also a negative effect [37].

Besides hormonal steroids, insulin resistance in AD patients is also often associated with vitamin D deficiency, but it is rather a common feature observed in the elder population; it is not only specific for AD [38,39].

Another characteristic feature shared by DM and AD is increased levels of advanced glycosylation end products and their receptors, often accompanied by increased lipid peroxidation, which has been detected in tissues and in the circulation [40,41]. Among steroids with beneficial effects on both of these undesired conditions, the preventive effects of dehydroepiandrosterone (DHEA) and estradiol, both candidates for steroid replacement therapy, should be mentioned here [42–44].

4. Beta-amyloid pathology and steroids

One of the typical characteristics of AD is an accumulation in the brain of amyloid beta peptides (Abeta), forming known amyloid plaques. The production of Abeta requires two sequential cleavages induced by beta- and gamma-secretases on the beta-amyloid precursor protein (APP). An alternative cleavage pathway involves alpha-secretase activity resulting in so-called non-amyloidogenic APP. Altered activity of these secretases is thus involved in the pathogenesis of AD. APP is an inherent component of cell membranes, expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been considered a regulator of synapse formation and neural plasticity [45]. The beta-secretase has been recently identified as an aspartic protease named BACE1 (beta-site APP Cleaving Enzyme 1) that initiates Abeta formation. As the rate-limiting enzyme in Abeta generation, BACE1, in principle, is a potential therapeutic target for strategies to reduce the production of Abeta in AD. Among the candidates for such therapy are also steroids [46,47]. In animal and in vitro experiments estrogen was shown to induce alpha-secretase activity via mitogen-activated protein kinases (MAP-kinase) and phosphotidylinositol 3-kinase (PI3-K) signal transduction, thus resulting in potential reduction of Abeta. These pathways may also inhibit activity of another important protein involved in cell death and tau-protein pathology, GSK3beta, mentioned previously and also in the next chapter [48].

Cholesterol, the precursor of hormonal steroids, was shown to be retained in the brains of AD and its impaired metabolism correlated with altered activities of beta- and gamma secretases [49]. Among the risk factors for development of AD is increased cortisol levels and general dysregulation of the hypothalamo-pituitary-adrenal axis. It was demonstrated by *in vitro* as well as *in vivo* animal experiments that stress-level glucocorticoid administration increases Abeta formation by increasing steady-state levels of amyloid precursor protein (APP) and BACE1. In addition, glucocorticoids augment tau accumulation, indicating that this hormone also accelerates the development of neurofibrillary tangles (see next Chapter). It suggests that the high levels of glucocorticoids found in AD are not merely a consequence of the disease, but rather play an important role in the development and progression of AD [50]. Dehydroepiandrosterone, believed now to counteract some excessive effects of glucocorticoids, is able to prevent the induction of beta-secretase cleavage of APP. In contrast to cortisol, this effect was confirmed on the mRNA level of BACE1 [51]. Since DHEA possess remarkable immunoprotective properties, among other things it affects favourably the apoptotic cascade (see the Chapter Autoimmune theory of AD and the role of steroids), it is among the perspective compounds in the treatment of AD. From this standpoint the recent findings that it is not DHEA itself, but its 7-oxygenated metabolites that are in some instances the locally active compounds, render them even more perspective [2,3].

Finally, as hormonal steroids concern, another risk factor in AD development is androgen deficiency in elderly men. Low free testosterone levels were demonstrated to be associated not only with impairment of fuel metabolism (see the Chapter AD as diabetes mellitus Type III and the role of steroids), but also with Abeta formation [52,53].

An interesting finding concerning Abeta pathology was the favourable role of transthyretin, a minor plasma transport protein selectively binding thyroid hormones. This protein, occurring also in cerebrospinal fluid (CSF), binds Abeta peptides and its concentration in CSF in AD patients are decreased [54]. Estrogens, at least in animal models, increased transthyretin brain expression; this is another example of the complex beneficial effects of estrogens as possible therapeutics in AD [55]. Soy phytestrogen genistein, used in hormone replacement therapy, acts similarly to estrogen [56].

5. Phoshorylation of tau-protein(s) and steroids

In addition to the formation of Abeta deposits, another characteristic feature of AD is the formation of tangles of tau proteins caused by their abnormal phosphorylation. Healthy neurons have internal support partly made up of structures called microtubules. Tau proteins are microtubule-associated proteins that are abundant in neurons in the central nervous system. One of their main functions is to modulate the stability of axonal microtubules, which act like tracks, guiding nutrients and molecules from the body of the cell down to the ends of the axon. Hyperphosphorylation or abnormal phosphorylation of tau proteins can result in the above-mentioned tangles [57,58].

Hyperphosphorylation of tau proteins correlates with the abnormal removal of the amyloid beta peptide and also with peripheral hyperinsulinemia (see the previous chapters), demonstrating the tight interrelation among characteristic biochemical

features of AD. Several kinases and their signalling cascades are involved in tau protein hyperphosphorylation. To the latter belong cyclin dependent kinases involved in driving the molecular cycle, specifically augmented cyclin dependent kinase5 (cdk5), already mentioned GSK3beta [59], PI3-K, MAP-kinase [60,61] and a broad-spectrum protein kinase A (PKA) enzyme, one of the first kinases activated by cAMP [62]. The list of these and other kinases involved in tau pathology was surveyed by Ferrer et al. [63,64] and Wang et al. [65]. Out of them, GSK3beta, is believed to play a pivotal role [59].

The therapeutic potential of steroids consists in favourably influencing the activity of these enzymes or steps in their signalling pathway at various levels. Estradiol was shown to counteract hyperphosphorylation of tau proteins [66] and recent work confirmed that this effect was based on attenuation of GSK3beta activity and later steps in its signalling [67]. Estradiol also attenuates the activity of PKA [68].

On the other hand, unfavourable effects on enzymes responsible for hyperphoshorylation of tau proteins were caused by glucocorticoids (GC). Generally, GC augment tau accumulation [50]. In cell-culture model GC treatment resulted in hyperphosphorylation of human tau proteins through the cyclin-dependent kinase 5 [69].

6. (Auto)immune theory of AD and the role of steroids

Many pathological features of AD outlined in the previous chapters are closely linked to dysfunctions of immune system. Indeed, the immune system utilizes the same or similar signalling routes as do many hormones and other ligands operating through their receptors.

Recent findings strongly support the idea that AD is an autoimmune disease, resulting from a breakdown of the BBB. From an immunological standpoint, the brain is a privileged organ and BBB protects it from an autoimmune attack. The possible mechanisms behind this were excellently reviewed by Arshavsky [70]. A brief survey of his thesis pointing out sites of possible steroid actions follows.

6.1. Blood–brain barrier damage

According to one hypothesis, BBB can be damaged by activation of the intracerebral immune system resulting in an inflammatory process. The main objection is that this concept does not explain the reason for specific degeneration of the neurons involved in memory storage, since inflammation should lead to non-specific general degeneration.

6.2. The autoimmune hypothesis of AD

The autoimmune hypothesis of AD emphasizes the key role of the adaptive immune system after BBB impairment, when blood proteins including immunoglobulins penetrate into brain parenchyma and provoke a autoimmune reaction. In this case immunoglobulins bind to antiantigens exposed on specific neurons (that is those involved in memory storage) causing degeneration and death. The autoimmune hypothesis of AD is supported by the increased migration of T lymphocytes into specific areas of the brain after BBB damage.

6.3. The synaptic plasticity hypothesis

The synaptic plasticity hypothesis of long-term memory points to the formation of new synaptic connections resulting in formation of new patterns of neural activity. In principle new proteins are synthesized and their synthesis is regulated through various pathways, primarily glutamatergic receptors and signalling. The final step is always activation of genes encoding for the synthesis of structural proteins in both modified pre-existing synapses or the formation of new ones. The autoimmune process consists in incorrect recognition of molecules involved in the synaptic rearrangement as non-self antigens. These are only those molecules that would appear after BBB formation shortly after birth and responsible for brain immune privilege. According to s.c. genomic hypothesis, the novel proteins which did not exist at the time when the immune system sorted between self and non-self (immune "learning") are products of gene recombination, similar to the building of acquired immunity.

A major unanswered question remains: what is the first event, if there is one, causing the breakdown of the BBB?

Steroids are able to affect the immune or autoimmune process and neural plasticity on several, genomic as well as non-genomic, levels [71]. Glucocorticoids, on the one hand, and dehydroepiandrosterone and its metabolites, on the other, influence the cytokine environment in different ways, the alteration of which is typical for inflammation involved in the pathogenesis of AD. Since steroid 7-hydroxylation is an important enzymatic reaction occurring in primate hippocampus and reduced in Alzheimer disease, a perspective use of 7-oxygenated DHEA metabolites as immunoprotective agents should be emphasized here, too [1,72–74]. In addition, both cortisol and DHEA(S) influence cellular immunity as measured by natural killer cytotoxic activity [75,76].

In connection with 7-hydroxylation of DHEA and other C19 steroids catalyzed by cytochrome P450 enzymes, the role of 7α-hydroxylation of oxysterols should be mentioned here, too. 7α-Hydroxylation of cholesterol by the CYP71A enzyme is a rate-limiting step in bile acid biosynthesis, which may be cytotoxic when in excess. A recent report brought evidence of their surprisingly high contents in the brain [77]. The synthesis of bile acids is under various control mechanisms: there is negative feedback between their actual concentration and expression of CYP71A [78]. Another regulatory mechanism consists in the interaction of bile acids with macrophages through the expression and secretion of inflammatory cytokines as tumor necrosis factor alpha and interleukin-1beta, which also repress the CYP7A1 gene [79,80]. It may also be of interest that production of 7-hydroxylated DHEA metabolites is associated with inflammatory cytokines, as demonstrated, e.g. by recent reports on their stimulatory effect on CYP7B1 expression in synoviocytes from patients with rheumatoid arthritis [81]. Whether 7-hydroxylation represents here a protective counter-regulatory mechanism in inflammed tissues is disputed and this applies particularly for the brain.

6.4. Antiglucocorticoids and their possible use in AD treatment:

With respect to the unfavourable effect of glucocorticoid excess on cognitive disorders [82], including the development of AD, the logical question arose on the plausible effect of glucocorticoid antagonist(s). Since GCs mediate a number of initial events in AD pathogenesis, GC antagonists, e.g. mifepristone (RU 486), a potent glucocorticoid and progesterone antagonist was among the first to be considered for treatment. Indeed, administration of this drug leads to slowing of cognitive impairment typical for Alzheimer patients, though the mechanism may be more complicated [83]. The hippocampus, the brain structure most damaged in AD patients, has the highest density of GC receptors in the brain, and glucocorticoids are known to produce a variety of structural and functional changes here. Among other changes, they down regulate GC receptors, leading to disruption in the negative feedback loop [84]. Since mifepristone blocks the central actions of cortisol [85], treatment of Alzheimer patients with RU 486 resulted in a significant increase in cortisol levels [86].

7. Steroids and neuronal apoptosis

Among the principal questions posed in connection with the role of steroids in pathogenesis and treatment of AD is their effect on neuronal survival, more concretely on neuronal apoptosis. Steroids, first of all glucocorticoids and its counterpart, DHEA and some of its metabolites and precursors are involved in multiple pro- and anti-survival signalling pathways. Therefore it is not surprising that in both instances different actions have been recorded. Long-lasting exposure to glucocorticoids connected with hyperactivity of hypothalamo-pituitary-adrenal axis is known to result in cognitive impairment [87,88]. Studies with animal models revealed that glucocorticoids can prevent, but also accelerate, neurodegeneration in the adult rat hippocampus. These diverse effects were explained by adaptive mechanisms involved in various signalling pathways [89].

In most instances DHEA and probably its locally active metabolites act in brain tissues as anti-apoptocic agents taking advantage of both genomic and non-genomic pathways. The series works of Charalampopoulos (see, e.g. [89–91]) brought evidence for pro-survival effects of DHEA and also estradiol in various model systems, consisting in its influencing of phosphorylation signalling. For instance, in tissue culture DHEA induced an acute but transient sequential phosphorylation of the pro-survival kinases Src/PKC(a/b)/MEK1/2/ERK1/2 which, in turn, activate transcription factors cAMP responsive element binding protein and nuclear factor kappa B which induce the expression of the anti-apoptotic Bcl-2 genes [92]. Similar results were obtained with rat-cultured neural precursors from the embryonic forebrain where DHEA activated serine–threonine protein kinase (Akt) in neural precursor culture, in association with a decrease in apoptosis. It is of interest that the sulfated form of DHEA, DHEAS, acted in the opposite way, decreasing activated Akt levels and increasing apoptosis [93]. On the other hand, in some instances DHEA may even increase apoptosis in neuronal tissue when deprived of trophic support, as demonstrated in rat GT1-7 hypothalamic neurons following exposure to DHEA [93].

Some of the other beneficial effects that steroids exert on the genomic level include the estrogen-induced increase of the expression of the antiapoptotic protein Bcl-xL, as demonstrated in cultured hippocampal neurons [94].

8. Other effects of steroids on development and treatment of AD

8.1. Steroid and cholinergic system

With respect to the role of GC in the development of AD, one of the typical features being an impairment of cholinergic transmission, the question has been raised whether the hypothalamic–pituitary–adrenocortical axis response to cholinergic stimulus is blunted in patients with Alzheimer disease (AD). Peskind et al. [95] followed the cortisol response to the cholinesterase inhibitor physostigmine, but they did not find differences between Alzheimer patients and age-matched subjects. They concluded that the HPA axis response to physostigmine does not appear to reflect central cholinergic deficiency in the early stages of AD.

8.2. Steroid effects on the formation and removal of ROS

Oxidative stress is one of the earliest events of Alzheimer disease, characterized by mitochondrial dysfunction likely due to deficiencies in endogenous antioxidant capacity, and consequent cellular damage of susceptible neurons; for reviews see, e.g. [96,97] and the literature therein. Among the protective effects of estradiol is its antioxidant capacity consisting in activating antioxidant defense systems, scavenging reactive oxygen species and attenuation of ROS generation [98,99]. Antioxidant properties at least in human and rat cell culture models were also displayed by DHEA, another candidate for steroid replacement therapy of AD (see also previous chapters) [100]. On the other hand, glucocorticoids have pro-oxidative properties. The specificity of GC oxidative stress-induced neuronal cell death was demonstrated by its blocking by the specific GR antagonist mifepristone (RU486) [101].

8.3. Effect of steroids on calcium flux and its cytotoxic effects:

Disruption of cellular Ca^{2+} homeostasis in neurons of AD patients leads to excitotoxicity, apoptosis and the appearance of neurotoxic factors including reactive oxygen species (ROS), nitric oxide (NO), and cytokines [102]. Among the underlying mechanisms leading to neurodegeneration is excessive activation of glutamate receptors by excitatory amino acids including N-methyl-D-aspartate receptors (NMDA) [103].

Both female and male sex hormones can modulate glutamate receptors and influence calcium homeostasis at a genomic as well as nongenomic level, see for instance [104,105].

Several steroids called neurosteroids or neuroactive steroids are well known allosteric modulators of the $GABA_A$ receptor. Since this receptor functions as a chloride channel, these steroids can influence Cl^- influx and consequently the polarization/depolarization of neuronal membrane. Neurosteroids are formed *de novo* in the brain and they persist there after the removal of endogenous sources (castration and adrenalectomy), whilst neuroactive steroids include all natural or synthetic steroids with biological activity in the nervous system [106].

Neurosteroids include the precursors in the biosynthetic pathway to androgens, pregnenolone and DHEA, their sulfates and 5α-saturated metabolites of progesterone, especially 3α-hydroxy-5α-pregnan-20-one (allopregnanolone) [107,108]. Whilst DHEA, its sulfate and pregnenolone sulfate act as negative modulators of ionotropic $GABA_A$ receptors, resulting in depolarization of neuronal membrane and finally in an increase of its excitability, allopregnanolone acts in the opposite way leading to a decrease of neuronal excitability [108].

In addition, DHEA (but not its sulate) is a potent positive modulator of NMDA receptors, causing an increase in Ca^{2+} flux [108]. In the absence of counter-regulatory mechanisms, it may even lead to neurotoxicity. This is apparently in discrepancy with the pleiotropic, mostly neuroprotective effects of DHEA (see previous chapters), such as its action as an agonist of sigma receptors [109]. In our work we measured DHEA, its sulfate and also its 7-hydroxylated metabolites in the CSF of patients with AD and vascular dementia. The concentrations of DHEA, in contrast to its sulate and 7-hydroxylated metabolites, were significantly higher in AD, demonstrating the accummulation of DHEA to the detriment of the latter metabolites [110], believed now to be the local neuroprotective agents [1,108].

9. Conclusion

As demonstrated, steroids, especially glucocorticoids and DHEA(S) and its metabolites are among the important factors which are involved in the pathogenesis of AD. With regard to the autoimmune theory of AD the steroids affecting the immune system and their potential use in therapeutics are of particular importance. The recent research of AD biochemistry focusses on molecular signalling and the role of steroids in it. New findings may be anticipated as the mosaic covering the molecular mechanisms behind it becomes more complete.

Acknowledgement

The work was supported by Grant No. 9835-4 from the Internal Grant Agency of the Czech Ministry of Health.

References

[1] R. Morfin, L. Stárka, Neurosteroid 7-hydroxylation products in the brain, Int. Rev. Neurobiol. 46 (2001) 79–95.
[2] R. Morfin, P. Lafaye, A.C. Cotillon, F. Nato, V. Chmielewski, D. Pompon, 7-Alpha-hydroxy-dehydroepiandrosterone and immune response, Ann. N. Y. Acad. Sci. 917 (2000) 971–982.
[3] C. Muller, O. Hennebert, R. Morfin, The native anti-glucocorticoid paradigm, J. Steroid Biochem. Mol. Biol. 100 (2006) 95–105.
[4] W.M. Brooks, P.J. Lynch, C.C. Ingle, A. Hatton, P.C. Emson, R.L.M. Faull, M.P. Starkey, Gene expression profiles of metabolic enzyme transcripts in Alzheimer disease, Brain Res. 1127 (2007) 127–135.
[5] J.S. Fowler, T. Ido, Initial and subsequent approach for the synthesis of 18FDG, Semin. Nucl. Med. 32 (2002) 6–12.
[6] L. Mosconi, Brain glucose metabolism in the early and specific diagnosis of Alzheimer disease. FDG-PET studies in MCI and AD, Eur. J. Nucl. Med. Mol. Imageing 32 (2005) 486–510.
[7] P. Schönknecht, M. Henze, A. Hunt, K. Klinga, U. Haberkorn, J. Schröder, Hippocampal glucose metabolism is associated with cerebrospinal fluid estrogen levels in postmenopausal women with Alzheimer disease, Psychiatry Res. 124 (2003) 125–127.
[8] R.D. Brinton, estrogen regulation of glucose metabolism and mitochondrial function: therapeutic implications for prevention of Alzheimer disease, Adv. Drug. Deliv. Rev. 60 (2008) 1504–1511.
[9] J.G. Csernansky, H. Dong, A.M. Fagan, L. Wang, G. Xiong, D.M. Holtzman, J.C. Morris, Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia, Am. J. Psychiatry 163 (2006) 2164–2169.
[10] F. Magri, L. Cravello, L. Barili, S. Sarra, W. Cinchetti, F. Salmoiraghi, G. Micale, E. Ferrari, Stress and dementia: the role of the hypothalamic–pituitary–adrenal axis, Ageing Clin. Exp. Res. 18 (2006) 167–170.
[11] M.J. De Leon, T. McRae, H. Rusinek, A. Convit, S. De Santi, C. Tarshish, J. Golomb, N. Volkow, K. Daisley, N. Orentreich, B. McEwen, Cortisol reduces hippocampal glucose metabolism in the normal elderly, but not in Alzheimer disease, J. Clin. Endocrinol. Metab. 82 (1997) 3251–3259.
[12] M. Bigl, M.K. Brückner, T. Arendt, V. Bigl, K. Eschrich, Activities of key glycolytic enzymes in the brains of patients with Alzheimer disease, J. Neural Transm. 106 (1999) 499–511.
[13] M. Bigl, A.D. Bleyl, D. Zedlick, T. Arendt, V. Bigl, K. Eschrich, Changes of activity and isozyme pattern of phosphofructokinase in the brains of patients with Alzheimer disease, J. Neurochem. 67 (1996) 1164–1171.
[14] G.E. Gibson, K.F. Sheu, J.P. Blass, Abnormalities of mitochondrial enzymes in Alzheimer disease, J. Neural Transm. 105 (1998) 855–870.
[15] P.W. Landfield, E.M. Blalock, K.C. Chen, N.M. Porter, A new glucocorticoid hypothesis of brain ageing: implication for Alzheimer's disease, Curr. Alzheimer Res. 4 (2007) 205–212.
[16] Cochrane Database Syst. Rev. 18 (2007) CD000304.
[17] A.G. Schwartz, L.L. Pashko, Dehydroepiandrosterone, glucose-6-phosphate dehydrogenase, and longevity, Ageing Res. Rev. 3 (2004) 171–187.
[18] M. Mamelak, Alzheimer' s disease, oxidative stress and gammahydroxybutyrate, Neurobiol. Aging 28 (2007) 1340–1360.
[19] S. Chalbot, R. Morfin, Dehydroepiandrosterone metabolites and their interactions in humans, Drug Metabol. Drug Interact. 22 (2006) 1–23.
[20] J.L. Yau, S. Rasmuson, R. Andrew, M. Graham, J. Noble, T. Olsson, E. Fuchs, R. Lathe, J.R. Seckl, Dehydroepiandrosterone 7-hydroxylase CYP7B: predominant expression in primate hippocampus and reduced expression in Alzheimer disease, Neuroscience 121 (2003) 307–314.
[21] C. Muller, D. Pompon, P. Urban, R. Morfin, Inter-conversion of 7alpha- and 7beta-hydroxy-dehydroepiandrosterone by the human 11beta-hydroxysteroid dehydrogenase type I, J. Steroid Biochem. Mol. Biol. 99 (2006) 215–222.
[22] O. Hennebert, C. Pernelle, C. Ferroud, R. Morfin, 7Alpha- and 7beta-hydroxy-epiandrosterone as substrates and inhibitors for the human 11beta-hydroxysteroid dehydrogenase type 1, J. Steroid Biochem. Mol. Biol. 105 (2007) 159–165.
[23] G. Münch, R. Schinzel, C. Loske, A. Wong, N. Durany, J.J. Li, H. Vlassara, M.A. Smith, G. Perry, P. Riederer, Alzheimer's disease-synergistic effects of glucose deficit, oxidative stress and advanced glycation end products, J. Neural Transm. 105 (1998) 439–461.
[24] E. Rönnemaa, B. Zethelius, J. Sundelöf, J. Sundström, M. Degerman-Gunnarsson, C. Berne, L. Lannfelt, L. Kilander, Impaired insulin secretion increases the risk of Alzheimer disease, Neurology 71 (2008) 1065–1071.
[25] M.K. Sun, D.L. Alkon, Links between Alzheimer disease and diabetes, Drugs Today (Barc.) 42 (2006) 481–489.
[26] K.F. Neumann, L. Rojo, L.P. Navarrete, G. Farías, P. Reyes, R.B. Maccioni, Insulin resistance and Alzheimer disease: molecular links & clinical implications, Curr. Alzheimer Res. 5 (2008) 438–447.
[27] S. Craft, Insulin resistance and Alzheimer disease pathogenesis: potential mechanisms and implications for treatment, Curr. Alzheimer Res. 4 (2007) 147–152.
[28] S. Craft, The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged, Arch. Neurol. 66 (2009) 300–305.
[29] E. Steen, B.M. Terry, E.J. Rivera, J.L. Cannon, T.R. Neely, R. Tavares, X.J. Xu, J.R. Wands, S.M. de la Monte, Impaired insulin and insulin-like growth factor expression and signalling mechanisms in Alzheimer disease—is this type 3 diabetes? J. Alzheimers Dis. 7 (2005) 63–80.
[30] A. Alonso, C. González, Relationship between non-genomic actions of estrogens and insulin resistace, Infect. Disord. Drug Targets 8 (2008) 48–51.
[31] P. Ordóñez, M. Moreno, A. Alonso, P. Llaneza, F. Díaz, C. González, 17beta-Estradiol and/or progesterone protect from insulin resistance in STZ-induced diabetic rats, J. Steroid Biochem. Mol. Biol. 111 (2008) 287–294.
[32] J.B. Farrell, A. Deshmukh, A.A. Baghaie, Low testosterone and the association with type 2 diabetes, Diabetes Educ. 34 (2008) 799–806.
[33] A.M. Traish, F. Saad, A. Guay, The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance, J. Androl. 30 (2009) 23–32.
[34] M.J. Gillett, R.N. Martins, R.M. Clarnette, S.A. Chubb, D.G. Bruce, B.B. Yeap, Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia, J, Alzheimers Dis. 5 (2003) 267–269.
[35] M.S. Okun, M.R. DeLong, J. Hanfelt, M. Gearing, A. Levey, Plasma testosterone levels in Alzheimer and Parkinson diseases, Neurology 62 (2004) 411–413.
[36] L.M. Garcia-Segura, M. Dueñas, S. Busiguina, F. Naftolin, J.A. Chowen, Gonadal hormone regulation of neuronal-glial interactions in the developing neuroendocrine hypothalamus, J. Steroid Biochem. Mol. Biol. 53 (1995) 293–298.
[37] M.M. Cherrier, Testosterone effects on cognition in health and disease, Front. Horm. Res. 37 (2009) 150–162.
[38] C.H. Wilkins, Y.I. Sheline, C.M. Roe, S.J. Birge, J.C. Morris, Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults, Am. J. Geriatr. Psychiatry 14 (2006) 1032–1040.
[39] M.L. Evatt, M.R. Delong, N. Khazai, A. Rosen, S. Triche, V. Tangpricha, Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease, Arch. Neurol. 65 (2008) 1348–1352.
[40] S. Mruthinti, R.F. Schade, D.U. Harrell, N.K. Gulati, S. Swamy-Mruthinti, G.P. Lee, J.J. Buccafusco, Autoimmunity in Alzheimer disease as evidenced by plasma immunoreactivity against RAGE and Abeta42: complication of diabetes, Curr. Alzheimer Res. 3 (2006) 229–235.
[41] T. Sato, N. Shimogaito, X. Wu, S. Kikuchi, S. Yamagishi, M. Takeuchi, Toxic advanced glycation end products (TAGE) theory in Alzheimer disease, Am. J. Alzheimers Dis. Other Demen. 21 (2006) 197–208.
[42] E. Brignardello, C. Runzo, M. Aragno, M.G. Catalano, M. Cassader, P.C. Perin, G. Boccuzzi, Dehydroepiandrosterone administration counteracts oxidative imbalance and advanced glycation end product formation in type 2 diabetic patients, Diabetes Care 30 (2007) 2922–2927.
[43] L. Chen, Y. Liu, B. Cui, Q. Mi, Y. Huang, L. Fan, Q. Chen, J. Tang, A. Ferro, Y. Ji, 17Beta-oestradiol partially attenuates the inhibition of nitric oxide synthase-3 by advanced glycation end-products in human platelets, Clin. Exp. Pharmacol. Physiol. 34 (2007) 972–978.
[44] J. Gasic-Milenkovic, C. Loske, G. Münch, Advanced glycation end products cause lipid peroxidation in the human neuronal cell line SH-SY5Y, J. Alzheimers Dis. 5 (2003) 25–30.
[45] M. Tabaton, E. Tamagno, The molecular link between beta- and gamma-secretase activity on the amyloid beta precursor protein, Cell. Mol. Life Sci. 64 (2007) 2211–2218.
[46] R. Vassar, Beta-secretase (BACE) as a drug target for Alzheimer disease, Adv. Drug Deliv. Rev. 54 (2002) 1589–1602.
[47] S.L. Cole, R. Vassar, BACE1 structure and function in health and Alzheimer disease, Curr. Alzheimer Res. 5 (2008) 100–120.
[48] S. Goodenough, M. Schäfer, C. Behl, Estrogen-induced cell signalling in a cellular model of Alzheimer disease, J. Steroid Biochem. Mol Biol. 84 (2003) 301–305.
[49] H. Xiong, D. Callaghan, A. Jones, D.G. Walker, L.F. Lue, T.G. Beach, L.I. Sue, J. Woulfe, H. Xu, D.B. Stanimirovic, W. Zhang, Cholesterol retention in Alzheimer's brain is responsible for high beta- and gamma-secretase activities and Abeta production, Neurobiol. Dis. 29 (2008) 422–437.
[50] K.N. Green, L.M. Billings, B. Roozendaal, J.L. McGaugh, F.M. LaFerla, Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer disease, J. Neurosci. 26 (2006) 9047–9056.
[51] E. Tamagno, M. Guglielmotto, P. Bardini, G. Santoro, A. Davit, D. Di Simone, O. Danni, M. Tabaton, Dehydroepiandrosterone reduces expression and activity of BACE in NT2 neurons exposed to oxidative stress, Neurobiol. Dis. 14 (2003) 291–301.
[52] E.R. Rosario, C.J. Pike, Androgen regulation of beta-amyloid protein and the risk of Alzheimer disease, Brain Res. Rev. 57 (2008) 444–453.
[53] C.J. Pike, T.V. Nguyen, M. Ramsden, M. Yao, M.P. Murphy, E.R. Rosario, Androgen cell signalling pathways involved in neuroprotective actions, Horm. Behav. 53 (2008) 693–705.
[54] J.C. Sousa, I. Cardoso, F. Marques, M.J. Saraiva, J.A. Palha, Transthyretin and Alzheimer disease: where in the brain? Neurobiol. Ageing 28 (2007) 713–718.
[55] Y.P. Tang, S.Z. Haslam, S.E. Conrad, C.L. Sisk, Estrogen increases brain expression of the mRNA encoding transthyretin, an amyloid beta scavenger protein, J. Alzheimers Dis. 6 (2004) 413–420.
[56] N.S. Green, T.R. Foss, J.W. Kelly, Genistein, a natural product from soy, is a potent inhibitor of transthyretin amyloidosis, Proc. Natl. Acad. Sci. U.S.A. 102 (2005) 14545–14550.

[57] W.H. Stoothoff, G.V. Johnson, Tau phosphorylation: physiological and pathological consequences, Biochim. Biophys. Acta 1739 (2005) 280–297.
[58] K. Mi, G.V. Johnson, The role of tau phosphorylation in the pathogenesis of Alzheimer disease, Curr. Alzheimer Res. 3 (2006) 449–463.
[59] A. Takashima, GSK-3 is essential in the pathogenesis of Alzheimer disease, J. Alzheimers Dis. 9 (Suppl. 3) (2006) 309–317.
[60] M.S. Perkinton, J.K. Ip, G.L. Wood, A.J. Crossthwaite, R.J. Williams, Phosphatidylinositol 3-kinase is a central mediator of NMDA receptor signalling to MAP kinase (Erk1/2), Akt/PKB and CREB in striatal neurones, J. Neurochem. 80 (2002) 239–254.
[61] W.G. Zhao, L. Ravindranath, A.S. Mohamed, O. Zohar, G.H. Chen, C.G. Lyketsos, R. Etcheberrigaray, D.L. Alkon, MAP kinase signalling cascade dysfunction specific to Alzheimer disease in fibroblasts, Neurobiol. Dis. 11 (2002) 166–183.
[62] G. Sadik, T. Tanaka, K. Kato, H. Yamamori, B.N. Nessa, T. Morihara, M. Takeda, Phosphorylation of tau at Ser214 mediates its interaction with 14-3-3 protein: implications for the mechanism of tau aggregation, J. Neurochem. 108 (2009) 33–43.
[63] I. Ferrer, M. Barrachina, M. Tolnay, M.J. Rey, N. Vidal, M. Carmona, R. Blanco, B. Puig, Phosphorylated protein kinases associated with neuronal and glial tau deposits in argyrophilic grain disease, Brain Pathol. 13 (2003) 62–78.
[64] I. Ferrer, T. Gomez-Isla, B. Puig, M. Freixes, E. Ribé, E. Dalfó, J. Avila, Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer disease and tauopathies, Curr. Alzheimer Res. 2 (2005) 3–18.
[65] J.Z. Wang, I. Grundke-Iqbal, K. Iqbal, Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration, Eur. J. Neurosci. 25 (2007) 59–68.
[66] M. Alvarez-de-la-Rosa, I. Silva, J. Nilsen, M.M. Pérez, L.M. García-Segura, J. Avila, F. Naftolin, Estradiol prevents neural tau hyperphosphorylation characteristic of Alzheimer disease, Ann. N. Y. Acad. Sci. 1052 (2005) 210–224.
[67] H.R. Shi, L.Q. Zhu, S.H. Wang, X.A. Liu, Q. Tian, Q. Zhang, Q. Wang, J.Z. Wang, 17Beta-estradiol attenuates glycogen synthase kinase-3beta activation and tau hyperphosphorylation in Akt-independent manner, J. Neural Transm. 115 (2008) 879–888.
[68] X.A. Liu, L.Q. Zhu, Q. Zhang, H.R. Shi, S.H. Wang, Q. Wang, J.Z. Wang, Estradiol attenuates tau hyperphosphorylation induced by upregulation of protein kinase-A, Neurochem. Res. 33 (2008) 1811–1820.
[69] I. Sotiropoulos, C. Catania, T. Riedemann, J.P. Fry, K.C. Breen, T.M. Michaelidis, O.F. Almeida, Glucocorticoids trigger Alzheimer disease-like pathobiochemistry in rat neuronal cells expressing human tau, J. Neurochem. 107 (2008) 385–397.
[70] Y.L. Arshavsky, Alzheimer's disease, brain immune privilege and memory: a hypothesis, J. Neural Transm. 113 (2006) 1697–1707.
[71] B.S. McEwen, H. Coirini, A. Westlind-Danielsson, M. Frankfurt, E. Gould, M. Schumacher, C. Woolley, Steroid hormones as mediators of neural plasticity, J. Steroid Biochem. Mol Biol. 39 (1991) 223–232.
[72] R. Lathe, Steroid and sterol 7-hydroxylation: ancient pathways, Steroids 67 (2002) 967–977.
[73] R. Morfin, Involvement of steroids and cytochromes P(450) species in the triggering of immune defenses, J. Steroid Biochem. Mol. Biol. 80 (2002) 273–290.
[74] S.B. Solerte, M. Fioravanti, N. Schifino, G. Cuzzoni, I. Fontana, G. Vignati, S. Govoni, E. Ferrari, Dehydroepiandrosterone sulfate decreases the interleukin-2-mediated overactivity of the natural killer cell compartment in senile dementia of the Alzheimer type, Dement. Geriatr. Cogn. Disord. 10 (1999) 21–27.
[75] G. Sala, G. Galimberti, C. Canevari, M.E. Raggi, V. Isella, M. Facheris, I. Appollonio, C. Ferrarese, Peripheral cytokine release in Alzheimer patients: correlation with disease severity, Neurobiol. Ageing 34 (2003) 909–914.
[76] S. Yu, F. Holsboer, O.F. Almeida, Neuronal actions of glucocorticoids: focus on depression, J. Steroid Biochem. Mol. Biol. 108 (2008) 300–309.
[77] M. Ogundare, S. Theofilopoulos, A. Lockhart, L.J. Hall, E. Arenas, J. Sjovall, A.G. Brenton, Y. Wang, W.J. Griffiths, Cerebrospinal fluid steroidomics: Are bioactive bile acids present in the brain? J. Biol. Chem. (December) (2009) (ahead of print).
[78] F. Gilardi, N. Mitro, C. Godio, E. Scotti, D. Caruso, M. Crestani, E. De Fabiani, The pharmacological exploitation of cholesterol 7alpha-hydroxylase, the key enzyme in bile acid synthesis: from binding resins to chromatin remodelling to reduce plasma cholesterol, Pharmacol. Ther. 116 (2007) 449–472.
[79] R.A. Davis, J.H. Miyake, T.Y. Hu, N.J. Spann, Regulation of cholesterol-7alpha-hydroxylase: BAREly missing a SHP, J. Lipid Res. 43 (2002) 533–543.
[80] T. Li, A. Jahan, J.Y. Chiang, Bile acids and cytokines inhibit the human cholesterol 7 alpha-hydroxylase gene via the JNK/c-jun pathway in human liver cells, Hepatology 43 (2006) 1202–1210.
[81] J. Dulos, A. Kaptein, A. Kavelaars, C. Heijnen, A. Boots, Tumour necrosis factor-alpha stimulates dehydroepiandrosterone metabolism in human fibroblast-like synoviocytes: a role for nuclear factor-kappaB and activator protein-1 in the regulation of expression of cytochrome p450 enzyme 7b, Arthritis Res. Ther. 7 (2005) R1271–R1280.
[82] V. Dhikav, K.S. Anand, Glucocorticoids may initiate Alzheimer disease: a potential therapeutic role for mifepristone (RU-486), Med. Hypotheses 68 (2007) 1088–1092.
[83] J.K. Belanoff, J. Jurik, L.D. Schatzberg, C. DeBattista, A.F. Schatzberg, Slowing the progression of cognitive decline in Alzheimer disease using mifepristone, J. Mol. Neurosci. 19 (2002) 201–206.
[84] C. DeBattista, J.K. Belanoff, C-1073 (mifepristone) in the adjunctive treatment of Alzheimer disease, Curr. Alzheimer Res. 2 (2005) 125–129.
[85] N. Pomara, R.T. Hernando, C.B. de la Pena, J.J. Sidtis, T.B. Cooper, S. Ferris, The effect of mifepristone (RU 486) on plasma cortisol in Alzheimer disease, Neurochem. Res. 31 (2006) 585–588.
[86] E. Martignoni, A. Costa, E. Sinforiani, A. Liuzzi, P. Chiodini, M. Mauri, G. Bono, G. Nappi, The brain as a target for adrenocortical steroids: cognitive implications, Psychoneuroendocrinology 17 (1992) 343–354.
[87] J.P. Herman, K. Seroogy, Hypothalamic–pituitary–adrenal axis, glucocorticoids, and neurologic disease, Neurol. Clin. 24 (2006) 461–481.
[88] N.R. Nichols, D. Agolley, M. Zieba, N. Bye, Glucocorticoid regulation of glial responses during hippocampal neurodegeneration and regeneration, Brain Res. Brain Res. Rev. 48 (2005) 287–301.
[89] I. Charalampopoulos, V.I. Alexaki, C. Tsatsanis, V. Minas, E. Dermitzaki, I. Lasaridis, L. Vardouli, C. Stournaras, A.N. Margioris, E. Castanas, A. Gravanis, Neurosteroids as endogenous inhibitors of neuronal cell apoptosis in ageing, Ann. N. Y. Acad. Sci. 1088 (2006) 139–152.
[90] V.I. Alexaki, I. Charalampopoulos, M. Kampa, A.P. Nifli, A. Hatzoglou, A. Gravanis, E. Castanas, Activation of membrane estrogen receptors induce pro-survival kinases, J. Steroid Biochem. Mol. Biol. 98 (2006) 97–110.
[91] I. Charalampopoulos, A.N. Margioris, A. Gravanis, Neurosteroid dehydroepiandrosterone exerts anti-apoptotic effects by membrane-mediated, integrated genomic and non-genomic pro-survival signalling pathways, J. Neurochem. 107 (2008) 1457–1469.
[92] L. Zhang, B. Li, W. Ma, J.L. Barker, Y.H. Chang, W. Zhao, D.R. Rubinow, Dehydroepiandrosterone (DHEA) and its sulfated derivative (DHEAS) regulate apoptosis during neurogenesis by triggering the Akt signalling pathway in opposing ways, Brain Res. Mol. Brain Res. 98 (2002) 58–66.
[93] S.Y. Lin, H. Cui, B. Yusta, D.D. Belsham, IGF-I signalling prevents dehydroepiandrosterone (DHEA)-induced apoptosis in hypothalamic neurons, Mol. Cell. Endocrinol. 214 (2004) 127–135.
[94] C.J. Pike, Estrogen modulates neuronal Bcl-xL expression and beta-amyloid-induced apoptosis: relevance to Alzheimer disease, J. Neurochem. 72 (1999) 1552–1563.
[95] E.R. Peskind, M.A. Raskind, D. Wingerson, M. Pascualy, L.J. Thal, D.J. Dobie, C.W. Wilkinson, Hypothalamic–pituitary–adrenocortical axis responses to physostigmine: effects of Alzheimer disease and gender, Biol. Psychiatry 40 (1996) 61–68.
[96] X. Zhu, B. Su, X. Wang, M.A. Smith, G. Perry, Causes of oxidative stress in Alzheimer disease, Cell. Mol. Life Sci. 64 (2007) 2202–2210.
[97] I. Onyango, S. Khan, B. Miller, R. Swerdlow, P. Trimmer, P. Bennett Jr., Mitochondrial genomic contribution to mitochondrial dysfunction in Alzheimer disease, J. Alzheimer's Dis. 9 (2006) 183–193.
[98] T.B. Shea, D. Ortiz, 17 Beta-estradiol alleviates synergistic oxidative stress resulting from folate deprivation and amyloid-beta treatment, J. Alzheimers Dis. 5 (2003) 323–327.
[99] J. Nilsen, Estradiol and neurodegenerative oxidative stress, Front. Neuroendocrinol. 29 (2008) 463–475.
[100] S. Bastianetto, C. Ramassamy, J. Poirier, R. Quirion, Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage, Brain Res. Mol. Brain Res. 66 (1999) 35–41.
[101] C. Behl, F. Lezoualc'h, T. Trapp, M. Widmann, T. Skutella, F. Holsboer, Glucocorticoids enhance oxidative stress-induced cell death in hippocampal neurons in vitro, Endocrinology 138 (1997) 101–106.
[102] S. Yamamoto, T. Wajima, Y. Hara, M. Nishida, Y. Mori, Transient receptor potential channels in Alzheimer disease, Biochim. Biophys. Acta 1772 (2007) 958–967.
[103] X.X. Dong, Y. Wang, Z.H. Qin, Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases, Acta Pharmacol. Sin. 30 (2009) 379–387.
[104] K. O'Neill, S. Chen, R.D. Brinton, Impact of the selective estrogen receptor modulator, raloxifene, on neuronal survival and outgrowth following toxic insults associated with ageing and Alzheimer disease, Exp. Neurol. 185 (2004) 63–80.
[105] C.D. Foradori, S.B. Werner, U.S. Sandau, T.R. Clapp, R.J. Handa, Activation of the androgen receptor alters the intracellular calcium response to glutamate in primary hippocampal neurons and modulates sarco/endoplasmic reticulum calcium ATPase 2 transcription, Neuroscience 149 (2007) 155–164.
[106] R. Rupprecht, C.A. Hauser, T. Trapp, F. Holsboer, Neurosteroids: molecular mechanisms of action and psychopharmacological significance, J. Steroid Biochem. Mol. Biol. 56 (1996) 163–168.
[107] M. Schumacher, S. Weill-Engerer, P. Liere, F. Robert, R.J. Franklin, L.M. Garcia-Segura, J.J. Lambert, W. Mayo, R.C. Melcangi, A. Parducz, U. Suter, C. Carelli, E.E. Baulieu, Y. Akwa, Steroid hormones and neurosteroids in normal and pathological ageing of the nervous system, Prog. Neurobiol. 71 (2003) 3–29.
[108] N.A. Compagnone, S.H. Mellon, Neurosteroids: biosynthesis and function of these novel neuromodulators, Front. Neuroendocrinol. 21 (2000) 1–56.
[109] T. Maurice, Improving Alzheimer disease-related cognitive deficits with sigma1 receptor agonists, Drug News Perspect. 15 (2002) 617–625.
[110] S.B. Kim, M. Hill, Y.T. Kwak, R. Hampl, D.H. Jo, R. Morfin, Neurosteroids: cerebrospinal fluid levels for Alzheimer's disease and vascular dementia diagnostics, J. Clin. Endocrinol. Metab. 88 (2003) 199–206.