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REVIEW

Aging, Hormones and Receptors

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Summary

Ageing is accompanied by deterioration in physical condition and a number of physiological processes and thus a higher risk of a range of diseases and disorders. In particular, we focused on the changes associated with aging, especially the role of small molecules, their role in physiological and pathophysiological processes and potential treatment options. Our previously published results and data from other authors lead to the conclusion that these unwanted changes are mainly linked to the hypothalamic-pituitary-adrenal axis can be slowed down, stopped, or in some cases even reversed by an appropriate treatment, but especially by a life-management adjustment.

Key words

Aging • Small molecules • Hypothalamic-pituitary-adrenal axis • Life-management • Hormonal receptors

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1. Introduction

Aging (Balachandran *et al.* 2020, Chen *et al.* 2019) is associated with an increase in endocrine disorders (Zhavoronkov and Bhullar 2015). On one side, aging is related to changes in hormone secretion mainly in the hypothalamic-pituitary-adrenal axis (HPAA). On the other side there is a decrease in the sensitivity of the HPAA to target hormones and feedback loop mechanisms, as well as decrease in the sensitivity of target tissues to these hormones. Endocrine changes are accompanied by disorders in glucose homeostasis, the loss of muscle and bone mass, and autoimmune and degenerative diseases (Sato and Iemitsu 2018, Watad *et al.* 2017). This review is focused on changes in hormonal homeostasis associated with aging and age-related diseases with particular attention to the role of small molecules like steroids, thyroid hormones, neurotransmitters and their receptors.

2. The hierarchy of endocrine organs/tissues and aging

2.1. Hypothalamus

The anterior hypothalamus produces several releasing hormones such as growth hormone-releasing hormone (GHRH), corticotropin-releasing hormone (CRH), thyroid- releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) and the inhibiting hormones dopamine and somatostatin. The latter leads to inhibition of the pituitary production of somatotropin and also inhibition of the production of gastrointestinal hormones in the gastro-intestinal tract (Pop *et al.* 2018).

2.2. The pituitary gland

The anterior pituitary is connected to the hypothalamus with blood vessels and upon stimulation

produces its hormones. After GHRH stimulation growth hormone (GH) is secreted. After stimulation by CRH, adrenocorticotropic hormone (ACTH) is produced, while after TRH stimulation thyrotropin (TSH) is secreted, and after GNRH stimulation both folitropin (FSH) and lutropin (LH) are produced. The production of tropins by the anterior pituitary regulates the activity of the thyroid gland, the adrenal *zona fasciculata* (ZF), and to a lesser extent also the adrenal *zona reticularis* (ZR), as well as gonadal (both testicular and ovarian) activity (Melmed 2011, Pignatti *et al.* 2017). The hypothalamus has direct connections to the posterior pituitary, which secretes vasopressin, also called antidiuretic hormone (ADH) and oxytocin. The latter declines with age. In addition to its positive effects on social behavior, oxytocin is needed for the regeneration and maintenance of the homeostasis of muscle mass. As oxytocin is a US Food and Drug Administration (FDA) approved drug, it potentially may offer a new way to maintain muscle mass during aging (Elabd *et al.* 2014).

2.3. Target endocrine organs an aging

2.3.1. Thyroid gland

Levels of free trithyronin (fT_3) have a negative correlation with age, however, the TSH activity also declines with age (Strich *et al.* 2016, Surks *et al.* 2004). Aside from these changes, research has found an increasing prevalence of autoimmune complications in the thyroid gland, which can influence the levels of thyroid hormones (Bremner *et al.* 2012, Chaker *et al.* 2016). Changes to the function of the hypothalamic-pituitary-thyroid (HPT) axis with age can also be associated with a range of pathologies, such as cardiovascular diseases (Biondi *et al.* 2015), dementia (Rieben *et al.* 2016), and decreased bone mass (Segna *et al.* 2018). It has been reported that subclinical hypothyroidism, i.e. higher TSH levels correlate with lower mortality in the elderly (Atzmon *et al.* 2009, Selmer *et al.* 2014).

2.3.2. The adrenal medulla

The adrenal medulla produces the catecholamines adrenalin and noradrenalin. In skeletal muscles, catecholamines induce vasodilation, which is a part of the preparation for motor activity. From the point of view of aging, it is important that catecholamine secretion is stimulated by physical stressors and factors such as hypoglycemia, excessive physical stress, injury, emotional swings resulting from fear, anxiety, anger, rage, aggression as well as pain. Sympathetic activation increases with age in the heart, intestines, and liver at rest. In the elderly, sympathetic nerve responses to stressors are increased, while in contrast secretion of adrenalin from the adrenals is lowered, both at rest and during stress (Esler *et al.* 2002).

2.3.3. Adrenal cortex

The adrenal cortex consists of three zones with specific steroid production, with each zone regulated by a different system. In addition to the production of active androgens in men, the primary source of most steroids in the elderly is the adrenal cortex, though steroid metabolism also occurs in other peripheral organs and tissues and to a small degree in nervous system tissues (Labrie *et al.* 2017). In elderly females, steroidogenesis in the non-functional ovaries can be disregarded. Estrogen precursors in both elderly males and females are primarily produced in the adrenal gland, while the sources of active estrogens are peripheral tissues, and particularly adipose tissues, which metabolize primary adrenal steroids. However, some testosterone can be produced directly in the adrenal cortex, which in the zona reticularis (ZR) shows a relatively marked activity of the aldoketoreductase ADR1C3 converting androstenedione to testosterone (Nakamura *et al.* 2009).

2.3.3.1. Zona glomerulosa (ZG) and the renin-angiotensin system

The external zone of the adrenal cortex is the *zona glomerulosa* (ZG), which is part of the renin-angiotensin system. In response to increasing K^+ levels, renin, or lowered blood flow in the kidneys, the ZG produces the mineralocorticoid aldosterone. ZG expresses enzymes enabling the conversion of cholesterol to 11-deoxycorticosterone (DOC), such as cholesterol desmolase (CYP11A1), 21-hydroxylase (CYP21A1), and 3β-hydroxysteroid dehydrogenase type II (HSD3B2), which are also expressed by the *zona fasciculata* (ZF). HSD3B2 is an enzyme specific to the adrenal gland (ZG and ZF). Another enzyme specific to the ZG is aldosterone synthase (CYP11B2). This enzyme converts DOC to 18-hydroxy-corticosterone and then aldosterone, which is the target bioactive steroid. In addition to the physiological production of aldosterone dependent on angiotensin II, low Na^+ levels and high K^+ levels can lead clusters of cells in the ZG (aldosterone-producing cell clusters, APCC) to autonomically express CYP11B2, and at the same time increased the autonomic secretion of

aldosterone, while physiological secretion declines. APCCs are not neoplastic or tumor cells, their activity is not hyperplastic, and they are normally present in the ZG. However, this increased autonomic aldosterone production with age can be associated with an increased risk of cardiovascular disease (Nanba *et al.* 2018, Nanba *et al.* 2017).

2.3.3.2. Zona fasciculata (ZF)

The next, lower level of the adrenal cortex, the ZF is regulated by pituitary ACTH. In addition to the 11β-hydroxylase enzyme (CYP11B1), steroidogenic enzymes in ZF also include the C17-hydroxylase-C17,20 lyase (CYP17A1), the activity of which is stopped in the first step in ZF, i.e. C17-hydroxylation of 17-deoxy-steroids, because of the low expression of a specific hemoprotein for transporting electrons of cytochrome B5 (CYB5). These enzymes (in the sequence) produce pregnenolone, 17-hydroxypregenolone, 17-hydroxyprogesterone, 11-deoxycortisol, and the target product cortisol, which in humans is the key glucocorticoid. ZF express at lower levels the most active isoform of steroid sulfotransferase (SULT2A1) catalyzing the sulfation of pregnenolone and 17-hydroxypregnenolone. A second, lyase step catalyzed by CYP17A1 and the splitting a link between C17 and C20 of the steroid is also underway to a limited extent, with androstenedione thus synthesized in ZF (Seccia *et al.* 2018, Vinson 2016). The age-related alterations in ZF functioning are described latter in the text (see section 3.1.3.).

2.3.3.3. Zona reticularis (ZR)

The innermost zone of the adrenal cortex is the ZR. The ZR is present in only some mammals including humans. Cytochrome B5 (CYB5) is expressed widely in the ZR, and for this reason the lyase step of CYP17A1 is preferred over C17 hydroxylase. Further, as a result of CYB5 activity, the expression of HSD3B2 is blocked in the ZR, while the expressions of SULT2A1 and AKR1C3 are increased. Thus dehydroepiandrosterone (DHEA) sulfate (DHEAS) is the main product of the ZR. Meanwhile, the DHEAS is the most biologically active non-genomic-acting steroid in human (Seccia *et al.* 2018, Vinson 2016). The activity of the ZR is influenced by ACTH, but the reaction of steroidogenic enzymes in the ZR to ACTH is weaker than in ZF. Moreover, CRH directly stimulates ZR activity (Ibanez *et al.* 1999a, Ibanez *et al.* 1999b, Sirianni *et al.* 2005). Aging in both sexes is associated with a decline in adrenal androgens, a decline in CYB5 activity, reduction in the lyase step of CYP17A1 and reduced ZR mass. The decline in adrenal androgen production negatively influences bone density and libido, as well as the immune system and perception ability (Dharia *et al.* 2005).

The skeletal musculature has the ability to synthesize and metabolize sex hormones from DHEA (Sato and Iemitsu 2018). Maximal levels of DHEA are reached between the ages of 20-30 years, and then significantly decline until old age by 75 to 90 % causing similar trends for androgens and estrogens in peripheral target tissues. This could be associated with pathogenic diseases related to age such as obesity and type 2 diabetes (DM2). The expression of steroidogenic enzymes such as HSD3B2 and some isoforms of HSD17B and SRD5A show declines with age from levels found in younger men, as do the levels of both serum and musculature steroids such as DHEA, free testosterone, and 5α-dihydrotestosterone, which show a 30-50 % decline (Sato and Iemitsu 2018). In addition to DHEAS and other adrenal androgens (Sulcova *et al.* 1997, Vermeulen 1995), pregnenolone, 17-hydroxypregnenolone (Hill *et al.* 1999), and especially their sulfates (Havlikova *et al.* 2002) largely declines with advancing age. Moreover, the patients with Alzheimer's disease (AD) compared to corresponding controls show reduced levels of the most important human sulfotransferase SULT2A1, primarily expressed in ZR (Vankova *et al.* 2015).

From the results of many studies it can be generally concluded that there is a positive correlation between adrenal androgens (DHEA/DHEAS) on one side and muscle strength, quality of bone microarchitecture and lower number of falls on the other side in both genders. However, these results differ in some of the details (Carrer *et al.* 2019, Kong *et al.* 2019, O'Donnell *et al.* 2006, Ohlsson *et al.* 2018). Some authors reported that there was a linear relationship between performance results and hormone levels up to a certain threshold concentration of hormone levels, after which the correlation weakened and then disappeared or even slightly reversed in trend polarity (O'Donnell *et al.* 2006).

The decline in DHEA levels is connected with lower physical vitality in women. An early decline might be associated with lower vitality and can predict worsening health as one ages. Female patients with lower-than-average DHEAS and DHEA levels for their age show a higher incidence of chronic diseases and higher levels of chronic pain and higher sensitivity to

pain. In addition, lower DHEAS and DHEA levels positively correlate with poorer results on tests of physical condition and physical functioning in middle ages (Rendina *et al.* 2017).

Physical activity is a proven effective method for preventing a worsening of health due to aging. A 12-day exercise program in older men increased muscular levels of DHEA, free testosterone and 5α-dihydrotestosterone, and led to increased expression of steroidogenic enzymes such as HSD3B2, some isomers of HSD17B, and SRD5A (Sato *et al.* 2014). After the 12-week yoga training, there was a significant increase in GH and DHEAS levels in both sexes compared to before the experiment, while in the control group there were no significant changes found (Chatterjee and Mondal 2014). A combination of DHEA and physical training increases both the levels of circulating and muscle steroid sex hormones, and decreases insulin resistance while simultaneously increasing muscle mass and strength (Sato and Iemitsu 2018).

A U-shaped relationship has been found between mortality and DHEAS. Women with higher DHEAS levels had a tendency for higher mortality from carcinomas, while women with lower DHEAS had a tendency for mortality from cardiovascular disease (Cappola *et al.* 2006).

2.3.4. Testes

In the interstitial tissue surrounding the seminal tubules, Leydig cells are present that produce testosterone. Testicle size in older men positively correlates with serum levels of the testicular hormone inhibin B, secreted by the Sertoli cells, and testosterone (Seevagan *et al.* 2019). The testes have two main functions – spermatogenesis, and steroidogenesis that are not completely independent. Under normal circumstances, the hypothalamus secretes GnRH, which stimulates the secretion of FSH and LH in the pituitary. LH binds to LH receptors in Leydig cells, stimulating the biosynthesis of testosterone. FSH binds to FSH receptors on Sertoli cells, with a consequent sperm production. Both these functions are influenced by age, which leads to changes in hormone levels including lower androgen levels. However, this does not necessarily lead to the complete halt in their production capacity, as in the female sex organs after menopause. In addition to the decline in testicular androgens, the production of inhibin B and the number of Sertoli cells declines in men (Santiago *et al.* 2019). Levels of testosterone in older men are positively correlated with muscle, quality of bone microarchitecture, strength and physical condition, independently of muscle mass (Auyeung *et al.* 2011, O'Donnell *et al.* 2006).

2.3.5. Metabolic hormones, proinflammatory cytokines, and skeletal musculature

Sarcopenia is an age-related loss of skeletal musculature that is characterized by worsening amounts and quality of muscle mass. This leads to a gradual slowing of movement, declines in musculature, and increased risk of injury from falls. In addition to physical exercise with amino acid supplements, inhibition of myostatin (a proteohormone produced in muscle cells that inhibits their growth) seems to be a promising strategy for limiting sarcopenia (Sakuma and Yamaguchi 2012). The aging process is associated with a large decline in the secretion of GH (Sato and Iemitsu 2018). The somatotropic effects of GH are mediated by the production of insulin like peptides and their interaction with plasma membrane receptors of the cells (possibly *via* autocrine or paracrine activity). Most of the activity of circulating somatomedins in humans can be accredited to insulin-like growth factors I and II (IGF-I and IGF-II). Levels of circulating IGFs are influenced by GH, though IGF-I is more sensitive. In humans, levels of circulating IGF-I reach a maximum in adolescence and then decline with age. These lower IGF-I levels are associated with the decreased secretion of GH that accompanies aging (Hammerman 1987). Despite the fact that IGF-I is an effective regulator of muscle mass, its therapeutic use has not been positive. In contrast, ghrelin treatment can lessen the age-related atrophy in muscle mass caused by the decline in GH with age (Sakuma and Yamaguchi 2012). Another hormone, glucagon-like peptide-1 (GLP-1) likely acts protectively, since agonists for its receptor (GLP-1R) effectively reduce muscle atrophy, and in laboratory rodents supports myogenic factors. In seniors, the levels of the proinflammatory cytokines TWEAK and TNF-α positively correlate with the risk of sarcopenia on the one hand, but metabolic hormones such as insulin, IGF-I and adiponectin are associated with lower risks of sarcopenia on the other hand (Li *et al.* 2019).

3. Hormonal receptors and aging

3.1. Nuclear receptors (NRs)

3.1.1. Progesterone receptors (PRs)

Progesterone is in sub-nanomolar levels in men, and postmenopausal women (Bae *et al.* 2019).

Nevertheless, progestogens and some of their reduced metabolites are neuroprotective molecules that act in both the central (C) and peripheral nervous systems (PNS) (see review Hill *et al.* 2011). They exhibit anti-inflammatory effects, support the myelination and re-myelination of Schwann cells in the PNS, as well as, regulate neurogenesis, protect mitochondrial cells, and influence mood, memory, and recognition. Because of their low polarity, progestogens easily cross the blood-brain barrier to the CNS but are also active in the PNS (Jure *et al.* 2019, Schumacher *et al.* 2014).

3.1.2. Mineralocorticoid receptors (MRs)

Ligands of MRs regulate blood pressure, influencing the balance between electrolytes and water in the kidney. The primary mineralocorticoid is aldosterone, but affinity to nuclear MRs is also shown by its precursors DOC, corticosterone, and the primary human glucocorticoid cortisol. Nuclear MRs are also expressed in extra adrenal tissues, such as the heart, vascular tissue, and adipose tissue (Gorini *et al.* 2019). Aging leads to the activation of nuclear MRs, which acts profibrotically leading to vasoconstriction, lowers arterial elasticity, and subsequently to higher blood pressure (Omar *et al.* 2012).

3.1.3. Nuclear glucocorticoid receptors (GRs) and transmembrane mineralocorticoid receptors (tMRs)

These bioactive steroids are immunosuppressive and anti-inflammatory mediators. In addition to binding to GRs, in the CNS glucocorticoids bind to transmembrane mineralocorticoid receptors (tMRs) (Ruhs *et al.* 2017). While binding to nuclear GRs has a slower effect, binding to tMRs induces a rapid response (de Kloet *et al.* 2018). In addition, the affinity of the glucocorticoids cortisol and corticosterone to tMRs is about an order of magnitude higher than to GRs, and levels of the classic mineralocorticoid aldosterone are about 1-2 orders lower than endogenous glucocorticoids depending on the diurnal rhythm. Finally, like adrenal androgens the secretion of aldosterone and renin depends on age (de Kloet *et al.* 2018). The tMRs are expressed in limbic neurons of the hippocampus (HC), the lateral septum, and amygdalla, and bind, in addition to cortisol and corticosterone, several other steroids such as aldosterone, its precursor DOC, and progesterone (de Kloet *et al.* 2018).

While the response mediated by transmembrane GRs is targeted to emotion and immediate decision making, the slower response mediated by MRs is targeted to contextualization, rationalization, and storing stressful situation into memory. Antagonists of GR therefore impair memory, while antagonists of tMRs slow the storage of situation in memory (de Kloet *et al.* 2018). The HC and prefrontal cortex first inhibit the activity of the stress response, while the amygdala activates them (Yiallouris *et al.* 2019). The tMRs also direct the tonic effects of glucocorticoids in the brain at a basal levels, while activation of GRs inhibit further increases in the activity of the stress response (de Kloet *et al.* 2018, Yiallouris *et al.* 2019). The tMRs mediate the threshold of HPAA reactivity during stress that is considered a "healthy" state (de Kloet *et al.* 2018).

The balance between phases under the control of tMRs and nuclear GRs is related in a U-shaped curve with levels of glucocorticoids. However, in regions with a predominant expression of tMRs this relationship is linear (de Kloet *et al.* 2018). An imbalance between phases of the stress response mediated by tMRs and nuclear GRs leads to damage to the stress response and a predisposition to a range of pathologies (de Kloet *et al.* 2018). In general, aging is associated with a weakening of feedback between cortisol secretion because of impaired HPAA sensitivity (Yiallouris *et al.* 2019). As a result, higher levels of corticoids and a flatter diurnal profile are associated with lower abilities of recognition, anxiety, depression, dementia, and neurodegenerative disorders (Yiallouris *et al.* 2019).

As opposed to the clear decline in the production of adrenal androgens, average corticoid levels have rather the opposite trend (Yiallouris *et al.* 2019). A flatter circadian profile of corticoids with higher levels and night and lower in the morning has been described in a number of studies (de Kloet *et al.* 2018, Roelfsema *et al.* 2017, Yiallouris *et al.* 2019). In addition, the enzyme 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1), which converts non-active 11-oxy-corticoids to their bioactive 11β-hydroxylated forms, is expressed in CNS tissues and its activity increases with age, while lower average glucocorticoid levels are associated with longevity (Yiallouris *et al.* 2019).

3.1.4. Estrogen receptors (ERs)

Estrogens play a central role in regulating lipid metabolism in the CNS, as weakened estrogen receptors α (ERα) function leads to increased food intake. Activation of ERβ has an anti-lipogenic effect, and further lowers insulin resistance and glucose intolerance. ERs also influence the retention of glucocorticoids in

skeletal muscle. In addition, estrogens help increase the production of HDL cholesterol and triglycerides, and in contrast helps lower the production of LDL cholesterol in postmenopausal women. Estrogens are known for their rapid regulatory activity in pancreatic β-cells through the depolarization of cellular membranes with the subsequent flow of calcium ions into the cell and activation of insulin secretion. In addition, estrogens protect β-cells from apoptosis. An absence of ERα leads to a β-cell dysfunction associated with hyperinsulinemia. Therefore, the long-term estrogen therapy has anti-diabetic effects (Jia *et al.* 2015).

3.1.5. Vitamin D receptor (VDRs)

The ligand for VDRs is the active form of vitamin D calcitriol (1,25-dihydroxycholecalciferol). The most common disorders associated with aging and VDR/calcitriol deficiency are sarcopenia (a degenerative loss of skeletal muscle mass), and osteoporosis (Garcia *et al.* 2019, Scimeca *et al.* 2018).

3.1.6. Peroxisome proliferator-activated receptors (PPARs)

PPARs are nuclear transcription factors that play a key role in energy homeostasis and in the pathophysiology of many age-related disorders, such as increased oxidative stress, inflammatory reactions, and insulin resistance, and PPAR agonists can be used in the treatment of these disorders. Energy restriction, the most effective intervention in offsetting the effects of aging, leads to declines in oxidative stress and a lessening in inflammatory reaction, reduced adipose tissue and fasting glycemia levels, and thus prolonging life (Erol 2007).

3.1.7. Thyroid receptors (TRs)

The key ligand for TRs is T_3. TRs play a key role in the metabolism of cholesterol and saccharides and the regulation of pulse. T_3 stimulates energy output through thermogenesis in brown adipose tissue, leading to a loss of body weight. T_3 also stimulates increased lipolysis, lowers cholesterol levels, increases the production and induces declines in insulin secretion and increased gluconeogenesis (Mullur *et al.* 2014). Levels of thyrotropin that stimulate the production of T_3 in the thyroid increase with age, while levels of the T_3 precursor thyroxine (T_4) remain unchanged (Bremner *et al.* 2012). Several authors have proposed that slightly reduced thyroid gland activity with aging might be optimal for increasing longevity (Bowers *et al.* 2013).

3.1.8. Transcription factors for protein activation connected to xenobiotic detoxification

Pregnane X receptors (PXRs), constitutive androstane receptors (CARs), liver X receptors (LXRs) and farnesoid receptors (FXRs) act as transcription factors for the activation of proteins connected to xenobiotic and endobiotic detoxification and their eliminations from the organism in coordination with other factors, molecules (e.g. PPAR) and enzymes such as sulfotransferases and some P450 cytochromes (CYPs) (Kodama and Negishi 2013). In addition, these receptors are targets for influence by androgen activities (Zhang *et al.* 2010). The main organs that play a role in detoxification and excretion of xeno and endobiotics are the liver, kidneys and GI tract tissues. From a functional perspective, VDRs can be included in this group of receptors (Kodama and Negishi 2013).

In addition to sulfotransferases, the main target of PXR activation is the gene for the enzyme CYP3A4, which catalyzes the conversion of 16-deoxy steroids to immunoprotective 16α-hydroxy analogs and further converts 7-deoxy androgens to their immunoprotective 7β-hydroxy analogs (Sterzl *et al.* 2017). CYP3A4 expression in seniors of both sexes markedly declines with increasing age, as does PXR expression particularly in men (Uno *et al.* 2014). Ligands for PXR include a wide variety of hydrophobic xenobiotics and endobiotics, the levels of which typically range in μmol/l, and endobiotics such as steroids and bile acids also activate PXRs acids (Kliewer *et al.* 2002). Co-activators of PXRs include for instance PPARγ. Activation of PXRs is associated with a range of pathologies, including diabetes, and osteomalacia (Kodama and Negishi 2013). On the other hand, PXR activation can inhibit some inflammatory processes (Garg *et al.* 2016, Kodama and Negishi 2013). CARs, with several androstane steroids as ligands, and also LXRβ influence the expression of sulfotransferases (Kodama and Negishi 2013).

3.2. Transmembrane receptors (metabotropic, G-protein coupled)

3.2. 1. γ-aminobutyric acid receptors type B ($GABA_BR$)

$GABA_BRs$ are metabotropic transmembrane receptors coupled with $G_{i/o}$ protein. $GABA_BRs$ regulate nerve activity by opening potassium channels or inhibiting calcium channels through the $G_{i/o}$ protein signaling cascade. Successful tests have been done using $GABA_BR$ antagonists to reduce cognitive deficits in patients with Alzheimer's disease (AD) (Li *et al.* 2016).

3.2.2. Dopamine D1 receptors

Dopamine influences skeletal muscle tone through the activation of type D1 receptors on somatic motoneurons (Schwarz and Peever 2011). Aging negatively effects dopamine transporters and receptors, but not on production of dopamine itself (Karrer *et al.* 2017).

3.3. Ionotropic receptors

3.3.1. Nicotinic acetylcholine receptors (nAChRs)

The nAChR ligands are the excitatory endogenous neurotransmitter acetylcholine. nAChRs are expressed in the CNS and PNS, and are the primary receptors for muscle contractions, with changes to their function associated with pathogenic neurodegenerative diseases (Kalamida *et al.* 2007). High levels of acetylcholine and choline acetyltransferases occur in the *nucleus accumbens* (NAc). The cholinergic activity in the NAc is connected to ceasing food intake and with satiation (Salgado and Kaplitt 2015). Thalamic nAChR plays a key role in coordinating attention and speech. The affinity of nAChR to its agonists and its abundance decline with age, and the composition of its subunits changes as well (Sottile *et al.* 2017). Together, agonists of nAChR slow the development of neurodegenerative diseases (Picciotto and Zoli 2002). Endogenous low-molecular-weight compounds inhibiting nAChR include triiodothyronine, progesterone, PregS, and other less-potent steroids such as estradiol and corticosterone (Ke and Lukas 1996).

3.3.2. Glycine receptor (GlyR)

GlyRs are neuroinhibitory chloride channels influencing the rapid transduction of nerve signals in the spine and brain stem (Schaefer *et al.* 2018). Glycine receptors also play an important role in physiological hearing and speech (Caspary *et al.* 2008) and in pathophysiological disorders of the same (Richardson *et al.* 2012, Wang *et al.* 2009). With aging there is a decline in the total number of GlyR binding sites and changes to the expression of their subunits in the dorsal cochlear nucleus, leading to worsening hearing (Wang *et al.* 2009). Some endogenous steroids such as allopregnanolone or pregnenolone positively modulate GlyR (Jiang *et al.* 2006, Maksay *et al.* 2001), while others are negative modulators (PregS, DHEAS, androsterone sulfate, epiandrosterone sulfate, progesterone, pregnenolone) (Jiang *et al.* 2006, Maksay *et al.* 2001, Weir *et al.* 2004, Wu *et al.* 1990).

3.3.3. γ-aminobutyric acid receptors types A and C ($GABA_AR$, $GABA_CR$)

In the CNS, $GABA_AR$ ensures the rapid inhibition of open ion channels for the flow of chloride ions into the cell. Subunits of $GABA_AR$ have relatively different function. For instance, the α_1 subunit allows the sedative effects of diazepam, the α_2 subunit mediates anxiolytic effects, while the α_5 subunit is associated with worsening recognition and memory. In AD, hyperexcitation is considered one of the toxic factors leading to neuron death. For this reason, $GABA_AR$ agonists have been successfully tested in mitigating the AD manifestation (Li *et al.* 2016).

Similarly to dopamine, antagonists to $GABA_AR$ increase mobility (Salgado and Kaplitt 2015). As the γ-aminobutyric acid (GABA) is also a key inhibitory neurotransmitter in the primary motor cortex, the lowering of extrasynaptic $GABA_AR$ activity with age very likely contributes to dysfunctions of motor abilities (Mooney *et al.* 2017). Furthermore, increases in dopamine and GABA levels in rats arising from the activation of glutamate receptors in the NAc and basal ganglia decline as the animals age (Segovia and Mora 2005). In addition to motor activity, NAc is responsible for motivation and emotional processes. It is interesting that giving GABA in small doses increases mobility, but at higher doses induces hypoactivity (Mora *et al.* 2008, Salgado and Kaplitt 2015).

Some unconjugated endogenous neuroactive steroids and neurosteroids such as 5α/β-reduced pregnanes and androstanes with hydroxyl at position 3α can be positive GABAergic modulators, while other steroids can be their antagonists (PregS, 20α-dihydro-PregS, isopregnanolone sulfate, DHEAS, androsterone sulfate) (Belelli *et al.* 1996, Li *et al.* 2007, Lundgren *et al.* 2003, Park-Chung *et al.* 1999, Rahman *et al.* 2006, Sullivan and Moenter 2003, Wang *et al.* 2002).

3.3.4. Glutamate receptor

3.3.4.1. AMPA receptor (AMPAR)

AMPARs (2-amino-3-3-hydroxy-5-methyl-isoxazol-4-yl propanoic acid receptors) are glutamate receptors with the fastest excitatory transmission in the CNS and they play a key role in the regulation of brain function including learning and memory. For this reason, one of the first biological signs of AD is reduced synaptic AMPARs and dysfunctions of synaptic plasticity. NMDAR-dependent plasticity is the basis for processing information, learning, and memory, which are slightly

worsened in seniors, though normally with non-harmful outcomes. This natural cognitive decline is not likely associated with significant nerve loss, but rather with the reorganization of synaptic structures. In general, long-term potentiation of AMPARs in older individuals is less robust and requires a stronger initial stimulus. On the other hand, the long-term depression is facilitated (Jurado 2017). Endogenous steroids acting as negative modulators of AMPARs include primarily PregS and DHEAS (declining with advancing age) (Havlikova *et al.* 2002, Sulcova *et al.* 1997), and further sulfates of allopregnanolone and pregnanolone (see reviews Jurado 2017, Ratner *et al.* 2019).

3.3.4.2. N-methyl-D-aspartate receptor (NMDAR)

Like the AMPARs NMDARs play a key role in learning and functioning of spatial memory. Several studies have shown a decline in NMDAR functionality and a lowered expression of subunits in the nervous system with increasing age (Clayton *et al.* 2002, Kumar 2015, Newcomer *et al.* 2000). Some endogenous steroids such as PregS, 17-hydroxy-PregS, DHEAS and 20α-dihydro-PregS, can be positive modulators of NMDARs. Others, such as pregnanolone sulfate, act as negative modulators (see review Vyklicky *et al.* 2014).

3.3.5. Inward rectifier potassium channels (K_{ir})

3.3.5.1. ATP-sensitive K_{ATP} potassium channels

K_{ATP} channels play an important role in the pathophysiology of DM2 in association with L-type calcium channels (Fridlyand *et al.* 2013, Jia *et al.* 2015). Similarly, estrogens regulate K_{ATP} in β-cells. The closing of K_{ATP} is a key step in glucose-induced insulin secretion. At low glucose levels calcium channels are closed and K_{ATP} channels open, and potassium ions (K^+) can flow into β-cells, while at high glucose levels K_{ATP} channels close and L-type calcium channels are opened. The flow of calcium ions (Ca^{2+}) into β-cells induces insulin secretion (Fridlyand *et al.* 2013, Jia *et al.* 2015). Regardless of the presence or absence of ERα, estrogens reduce the permeability of K_{ATP}, which stimulates insulin secretion. However, in the absence of ERβ estrogens lose their ability to affect K_{ATP} permeability. K_{ATP} channels also contribute to the regulation of blood flow in arteries, and with increasing age the response of K_{ATP} channels to agonists declines, and vasoreactivity along with it. In heart K_{ATP} channels, there is an age-related decline in surface density and an increase in sensitivity to adenosine triphosphate (ATP), which lowers the adaptivity to stress impulses such as physical strain and cardiac ischemia (Yang *et al.* 2016).

3.3.5.2. *$Kir_{2.3}$ channels*

$Kir_{2.3}$ channels are an important subfamily of K_{ir} channels, produced mainly in the forebrain, an area associated with cognitive abilities, memory, emotions, but also with neuropsychiatric disorders. It has been shown that age dependent steroids PregS and to a lesser extend DHEAS are important positive modulators of K_{ir} channels (Kobayashi *et al.* 2009).

3.3.6. *Calcium-activated potassium channels*

3.3.6.1. *Mitochondrial BKCa channels (large-conductance voltage- and calcium-activated K^+ channels)*

Aging leads to the downregulation of BKCa channels in coronary arteries, resulting in a decline in vasodilation and an increase in the risk of coronary disease. This trend can be reduced by low-intensity physical exercise (Albarwani *et al.* 2010). BKCa channels in the circulatory system are modulated by endogenous compounds such as angiotensin II, high levels of glucose, and arachidonic acid brought on by oxidative stress. This mechanism contributes to the development of DM2 (Albarwani *et al.* 2010, Hermann *et al.* 2015). BKCa channels are also connected to the physiology of sleep and hearing. Activators of BKCa can be protective in the heart circulatory system (Bentzen *et al.* 2014).

3.3.6.2. *SKCa channels (small-conductance Ca^{2+}-activated K^+ channels)*

SKCa channels are a subfamily of calcium-activated potassium channels. Calcium does not bind directly to the SKCa channels, but Ca^{2+} binds to the protein calmodulin, which changes conformation and leads to SKCa opening (Adelman *et al.* 2012). SKCa channels are activated by type N calcium channels and allow potassium ions to pass the cellular membrane. SKCas are expressed in CNS tissue, and are associated with synaptic plasticity, playing an important role in learning and memory. Increased expression of SKCA with age contributes to reductions in LTP and cognitive abilities (Blank *et al.* 2003, Stackman *et al.* 2002). SKCa regulates glucose-activated action potentials in pancreatic β-cells (Jacobson *et al.* 2010).

3.3.7. L-type voltage gated calcium channels (VGCCs)

These channels are responsible for the excitation

of cells in skeletal, smooth, and heart muscle, and for the secretion of aldosterone (Felizola *et al.* 2014, Wang *et al.* 2004). Similarly to K_{ATP}, they play an important role in the pathophysiology of diabetes (Fridlyand *et al.* 2013, Jia *et al.* 2015). With increasing age there is an increase in the flow of calcium ions and an increase in the expression of L-type VGCCs, which is related to disorders in neuronal activity, cognitive decline, and particularly to a worsening of contextual and emotional memory (Zanos *et al.* 2015).

3.3.8. Transient receptor potential channels (TRPs)

TRPM channels (TRPV1, TRPV2, TRPM2, TRPM4 and TRPM5) direct insulin secretion and glucose homeostasis through the flow of Ca^{2+} ions, metabolites of nicotinamide adenine dinucleotide (NAD), or hormone-activated hormone receptors. TRPV2 contributes not only to insulin secretion, but also to cellular proliferation. At the same time, it is regulated in an autocrine manner by insulin (Dhakal and Lee 2019, Uchida and Tominaga 2011).

TRPA1 receptors play an important role in detecting potentially dangerous compounds. Similarly as with TRPV1 activation, activation of TRPA1 in humans produces pain (Heber *et al.* 2019). TRPA1 receptors also play a key role in the pathogenesis of AD (Lee *et al.* 2016).

Capsaicin receptors (TRPV1) are expressed in spinal ganglia, and carry stimuli from their endings in the periphery to the CNS (Cho *et al.* 2002). PregS inhibits TRPV1 receptors at the peripheral level, and another Δ^5 steroid DHEA and its reduced metabolites epiandrosterone and etiocholanolone inhibit the transfer of capsaicin-induced pain, independently of the opioid and cannabinoid system (Chen *et al.* 2004, Chen *et al.* 2006). TRPV1, in sensory neurons, is associated with pathophysiological β-cell inflammation. In addition, TRPV1-TRPV4 receptors inhibit adipogenesis (Dhakal and Lee 2019, Uchida and Tominaga 2011).

Activation of capsaicin receptors in young mice inhibits the production of tumor necrotic factor α (TNFα), and thus weakens inflammatory processes. On the other hand, in older animals this has a negative impact, as lower TNFα leads to a weakened immune response, inhibiting the organism's ability to protect itself against microbial infection (Wanner *et al.* 2012). Mice lacking TRPV1 receptors have been shown to live longer, and in old age had metabolic profiles typical for younger individuals. TRPV1-KO mice, this also lowered the production of the CGRP neuropeptide from sensory endings innervating Langerhans islands and subsequently stimulating insulin secretion (Riera *et al.* 2014).

TRPM3 channels also play an important role in stimulating the activity of pancreatic β-cells and the subsequent insulin secretion (Wagner *et al.* 2008). As for relationships to aging, these channels are positively and rapidly reversibly modulated by age-dependent sulfates of Δ^5 steroids such as PregS and to a lesser extent DHEAS (Havlikova *et al.* 2002, Sulcova *et al.* 1997, Wagner *et al.* 2008).

TRPC5 channels are expressed primarily in the brain. These excitatory non-selective cation channels are regulated with G-protein and phospholipase C (PLC) coupled proteins and they potentiate responses to fear. It is known that TRPC5-KO mice show lowered levels of natural fear to pain stimuli (Riccio *et al.* 2009). The extracellular application of sex and age-related endogenous steroids such as PregS, pregnanolone sulfate, pregnanolone, progesterone, and dihydrotestosterone inhibits the activity of TRPC5 for 1-2 min while DHEAS and estradiol have a weaker inhibitory effect (Majeed *et al.* 2011).

3.4. σ1 receptors (σ1Rs)

σ1Rs are in the membrane-associated protein family. They are distributed mainly in the CNS in neurons, astrocytes, oligodendrocytes, and microglial cells. σ1R is able to bind to a range of pharmacologically active compounds, such as antipsychotics, opioids, antidepressants, antagonists of muscarine, D2 dopamine and N-methyl-D-aspartate (NMDA) receptor ligands, monoamine transport inhibitors, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors. After activation, σ1R is able to translocate to other cellular compartments and bind to membrane proteins including ion channels, kinases, transmembrane receptors, and receptors for tropic factors. The σ1R primarily strengthens glutamatergic synapses, cholinergic synapses, and increases the activity of tropic factors, particularly brain-derived neurotropic factor (BDNF), which is a key component of memory. Cholinergic neurons in the forebrain innervate the grey matter, amygdaloid complex and the HC, which are important for forming memories. The activity of σ1R indirectly influences cholinergic pathways through the modulation of NMDARs in the HC, septum and cortex, but also directly, as agonists of σ1R modulate the release of acetylcholine. This depends on σ1R stimulating the

mobilization of calcium ions through modulation of IP3 receptors and voltage-gated K^+ and Ca^{2+} channels.

During healthy aging, there is no change in the binding potential of σ1R. Nevertheless, σ1R is a target of neuroprotective therapy for AD and other neurodegenerative diseases. In addition, recent studies have found lower densities of σ1R in the brains of AD patients than in age-matched controls. Moreover, some steroid agonists of σ1R such as PregS protect pyramidal cells in the HC from loss due to application of the neurotoxic amyloid β-peptide fragment in rats (see review Maurice and Goguadze 2017).

4. Anti-glucocorticoid immunoprotective steroids

Δ^5C19 steroids, their 7α/β-7-oxo- and 16α-hydroxy-metabolites in particular, are well known as anti-glucocorticoid and immunoprotective substances (Ahlem *et al.* 2011, Hennebert *et al.* 2009, Sterzl *et al.* 2017). In our recent study (Honcu *et al.* 2019) focused on the influence of age on the steroid metabolome and possible improvements using lifestyle changes and spa therapies, results obtained on changes to the steroid metabolome and somatic, psychosomatic, and psychic parameters have allowed us to model the relationships between age and steroidogenesis, the relationships between steroidogenesis and somatic, psychosomatic and psychic indicators, as well as the possible positive reversible changes achievable. Initial levels of immunoprotective steroids were positively correlated with declines in somatic and psychosomatic symptoms and total score on the N-5 neurotic questionnaire (Honcu *et al.* 2019). These results indicate that at the least, the activity of the ZR was increased after intervention, and its activity at the start of treatment predicted the improvement of somatic and psychosomatic components of the N-5 questionnaire. In addition to these bioactive compounds, other adrenal C19 steroids and their 5α/β-reduced metabolites showed similar relationships with the decline in somatic and psychosomatic symptoms after intervention. As mentioned above, levels of Δ^5C19 steroids are markedly age-dependent (Hampl *et al.* 2001, Sulcova *et al.* 1997), and over life they are closely associated with cell death in the ZR (Staton *et al.* 2004). Therefore, the increase in circulating C19 steroids (and their 5α/β-reduced metabolites) after physical activity and an appropriate lifestyle in 50+ women resulted in their ZR becoming "younger" (Bicikova *et al.* 2018, Honcu *et al.* 2019).

5. Conclusions

In this review work, we focused on hormonal changes accompanying aging in relation to functional changes in their receptors, both at peripheral and central levels. The emphasis was particularly on the role of small molecules in these changes. We also discussed the physiological and pathophysiological consequences of these changes mostly linked to changes in hypothalamic-pituitary-adrenal axis (HPAA) with regard to the possible treatment of certain impairments accompanying aging. The data available in the literature, including our own, suggest that unwanted changes associated with ageing can be slowed, stopped and, in some cases, reversed by appropriate treatment, but in particular by life-management adjustment.

Conflict of Interest

There is no conflict of interest.

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