Frontiers in Neuroendocrinology 55 (2019) 100788

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Neurosteroids as regulators of neuroinflammation

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ARTICLE INFO

Keywords:
Neurosteroids
Estrogens
17β-estradiol
Progestogens
Progesterone
Allopregnanolone
Dehydroepiandrosterone (DHEA)
Neuroinflammation
Microglia
Astrocytes
Multiple sclerosis
Alzheimer's disease
Parkinson's disease
Traumatic brain injury

ABSTRACT

Neuroinflammation is a physiological protective response in the context of infection and injury. However, neuroinflammation, especially if chronic, may also drive neurodegeneration. Neurodegenerative diseases, such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) and traumatic brain injury (TBI), display inflammatory activation of microglia and astrocytes. Intriguingly, the central nervous system (CNS) is a highly steroidogenic environment synthesizing steroids de novo, as well as metabolizing steroids deriving from the circulation. Neurosteroid synthesis can be substantially affected by neuroinflammation, while, in turn, several steroids, such as 17β-estradiol, dehydroepiandrosterone (DHEA) and allopregnanolone, can regulate neuroinflammatory responses. Here, we review the role of neurosteroids in neuroinflammation in the context of MS, AD, PD and TBI and describe underlying molecular mechanisms. Moreover, we introduce the concept that synthetic neurosteroid analogues could be potentially utilized for the treatment of neurodegenerative diseases in the future.

1. Introduction

Several functions of the central nervous system (CNS) are influenced by steroid hormones (Compagnone and Mellon, 2000; Mellon and Griffin, 2002). Circulating steroids produced by the adrenal glands, the gonads and the placenta readily cross the blood brain barrier (BBB) and reach their target cells in the CNS by diffusion; these are termed 'neuroactive' steroids (Mellon and Griffin, 2002; Schumacher et al., 2003; Starka et al., 2015). In addition, the CNS has the capacity to synthesize steroids de novo (Compagnone and Mellon, 2000; Mellon and Griffin, 2002). Of note, in humans, steroids, such as dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), pregnenolone and allopregnanolone, can be found in greater amounts in the brain than in the serum (Maggio et al., 2015; Marx et al., 2006). The prevailing thinking is that steroids synthesized in the CNS and circulation-derived steroids have indistinguishable effects in the CNS (Compagnone and Mellon, 2000; Mellon and Griffin, 2002; Schumacher et al., 2003; Starka et al., 2015; Alexaki et al., 2017; Charalampopoulos et al., 2006; Charalampopoulos et al., 2008). Therefore, in the present review, we discuss the effects of steroids on neuroinflammation independently of their origin; the term 'neurosteroid' is collectively used here for steroids deriving either from the circulation or synthesized de novo in the CNS. Moreover, we focus on the more abundant and best described neurosteroids, such as 17β-estradiol, DHEA, progesterone and allopregnanolone, describing their role in neuroinflammation in the context of four neurodegenerative diseases, in which neuroinflammation is a key component: multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) and traumatic brain injury (TBI).

2. Neurosteroidogenesis

Neurosteroidogenesis starts with the transfer of cholesterol into the mitochondria, a rate-limiting step involving steroidogenic acute regulatory protein (StAR) and translocator protein 18 kDa (TSPO) (Rone et al., 2009). This step is followed by conversion of cholesterol to pregnenolone by the mitochondrial side-chain cleavage enzyme,

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https://doi.org/10.1016/j.yfrne.2019.100788
Received 20 June 2019; Received in revised form 12 August 2019; Accepted 7 September 2019
Available online 09 September 2019

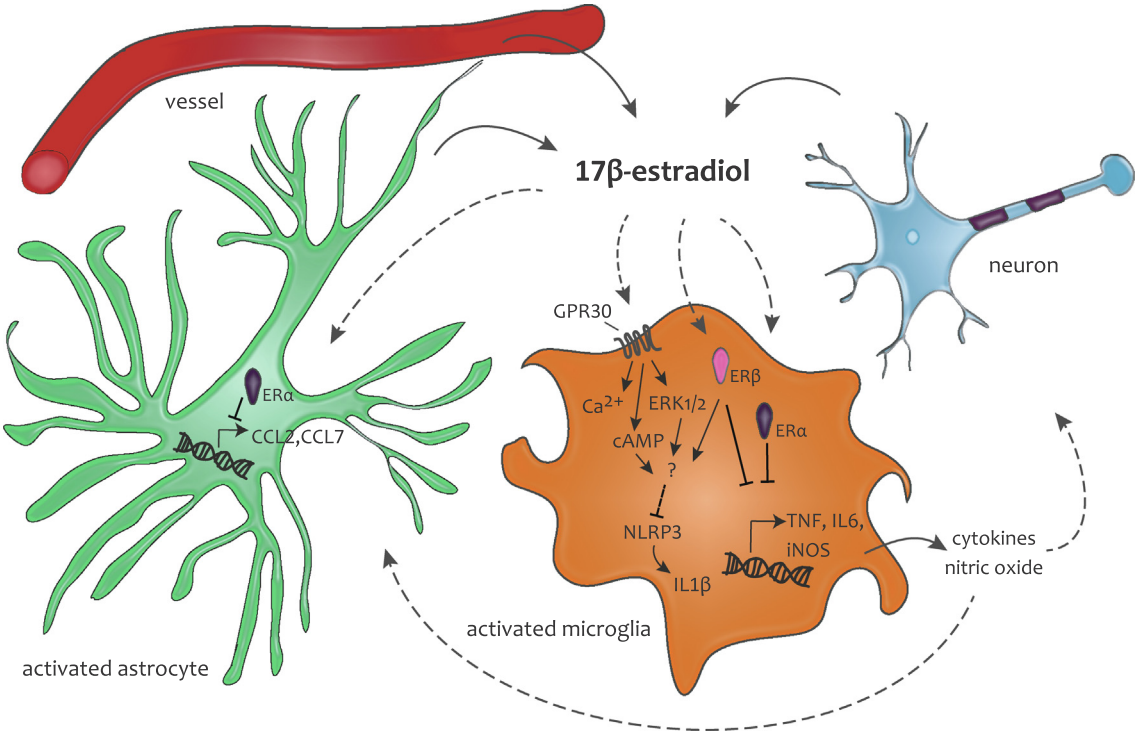

Fig. 1. Functions and signaling of 17β-estradiol in CNS cells. 17β-estradiol derives in the CNS from neurons, astrocytes and the circulation (Zwain and Yen, 1999; Mellon and Griffin, 2002; Schumacher et al., 2003; Starka et al., 2015). In microglia it can activate ERα and ERβ mediating anti-inflammatory effects by suppressing TNF, IL-6 or iNOS expression (Saijo et al., 2011; Smith et al., 2011; Brown et al., 2010; Soucy et al., 2005; Vegeto et al., 2001; Wu et al., 2016; Cerciat et al., 2010; Ishihara et al., 2015; Sarkaki et al., 2013; Barreto et al., 2007; Khaksari et al., 2011; Khaksari et al., 2015; Liu et al., 2005; Bruce-Keller et al., 2000; Sierra et al., 2008). Additionally, through the membrane receptor GPR30 it can activate rapid signaling events, such as Ca^{2+}, cAMP or ERK signaling potentially mediating anti-inflammatory effects (Blasko et al., 2009; Guan et al., 2017; Alexaki et al., 2006; Schaufelberger et al., 2016; Zhang et al., 2018; Prossnitz and Barton, 2014; Prossnitz and Barton, 2011; Liu et al., 2013; Revankar et al., 2005; Filardo et al., 2000; Alexaki et al., 2004). 17β-estradiol was also reported to negatively regulate inflammasome activation by a yet unknown mechanism (Thakkar et al., 2016). In astrocytes it can activate ERα signaling diminishing chemokine expression (Spence et al., 2013; Spence et al., 2011; Kuo et al., 2010). The release of 17β-estradiol is presented by a solid line and its effects by a dashed line. Abbreviations: cAMP: cyclic adenosine monophosphate, CCL2: CC-chemokine ligand 2, CCL7: CC-chemokine ligand 7, ERα: estrogen receptor α, ERβ: estrogen receptor β, ERK1/2: extracellular signal–regulated kinases 1/2, GPR30: G protein-coupled receptor 30, IL1β: Interleukin 1β, IL6: Interleukin 6, iNOS: inducible nitric oxide synthase, NLRP3: NLR family pyrin domain containing 3, TNF: Tumor Necrosis Factor.

P450scc (Mellon and Griffin, 2002). Pregnenolone exits the mitochondria and is metabolized to either progesterone or 17OH-pregnenolone, the latter giving rise to DHEA. DHEA and progesterone can be both metabolized to androstenedione. Androstenedione is subsequently converted to testosterone, which is converted to 17β-estradiol through aromatization (Mellon and Griffin, 2002).

Most of the steroidogenic enzymes expressed in the adrenal glands and the gonads are also present in the CNS, where their expression is cell type-, region-, developmental stage- and gender-specific (Compagnone and Mellon, 2000). Steroidogenesis takes place in both neurons and glia (Gottfried-Blackmore et al., 2008; Zwain and Yen, 1999; Zorumski et al., 2013) (Figs. 1–3). Astrocytes produce pregnenolone, progesterone, DHEA, androstenedione, testosterone, estradiol and estrone (Zwain and Yen, 1999) (Figs. 1–3). Oligodendrocytes synthesize pregnenolone, progesterone and androstenedione (Zwain and Yen, 1999; Gago et al., 2001) (Fig. 2). Microglia can metabolize androgens and estrogens and convert DHEA to 5-androstene-3 beta, 17 beta-diol (ADIOL) (Fig. 3), but lack the enzymes for progesterone and DHEA synthesis (Gottfried-Blackmore et al., 2008; Saijo and Glass, 2011; Saijo et al., 2011). Finally, neurons can produce pregnenolone, DHEA, androstenedione and estrogens (Zwain and Yen, 1999) (Figs. 1 and 3). It needs to be stressed out, that the steroidogenic capacity of these cell types has been mostly examined in purified cells or in vitro in cell cultures (Gottfried-Blackmore et al., 2008; Zwain and Yen, 1999). The manipulations required for cell isolation, such as enzymatic tissue lysis, cell dissociation and suspension, as well as artificial culture conditions, differing substantially from the in vivo cell microenvironment, such as culture in a 2D layer in the absence of the physiological extracellular matrix and network of CNS cell types, high passaging and the inability to mimic in vitro circadian rhythmicity, are few of the reasons which could considerably alter steroidogenesis in vitro (Beaule et al., 2011). At the tissue level, high steroidogenic activity has been observed in the cortex, hippocampus, hypothalamus and the cerebellum (Compagnone and Mellon, 2000).

Moreover, neurosteroid levels are also different between males and females, not only due to differences in the levels of circulating steroids entering the CNS, but also because of different expression levels of steroidogenic enzymes in the brain (Compagnone and Mellon, 2000). For instance, allopregnanolone and progesterone levels are higher in the CNS of female rats, contrarily to 3α-androstanediol, testosterone and dihydrotestosterone (DHT) levels, which are greater in the male rat CNS (Caruso et al., 2013). In humans, little is known on gender-specific differences in neurosteroid brain levels (Mendell and MacLusky, 2018).

Steroidogenic pathways can be also species-specific. For instance, in humans DHEA is synthesized in high amounts in the adrenal glands; therefore DHEA in the brain does not only derive from local synthesis but also from the periphery (Starka et al., 2015; Maninger et al., 2009). On the contrary, rodent adrenals lack the enzyme P450c17 that converts pregnenolone to DHEA, thus DHEA(S) levels in rodent blood are very low (Maninger et al., 2009; van Weerden et al., 1992). However, in rodents, as in humans, DHEA is synthesized in the brain, and thus DHEA in the rodent brain exclusively derives from local synthesis (Compagnone and Mellon, 2000; Maninger et al., 2009; Corpechot et al., 1981). Despite some species-specific differences,

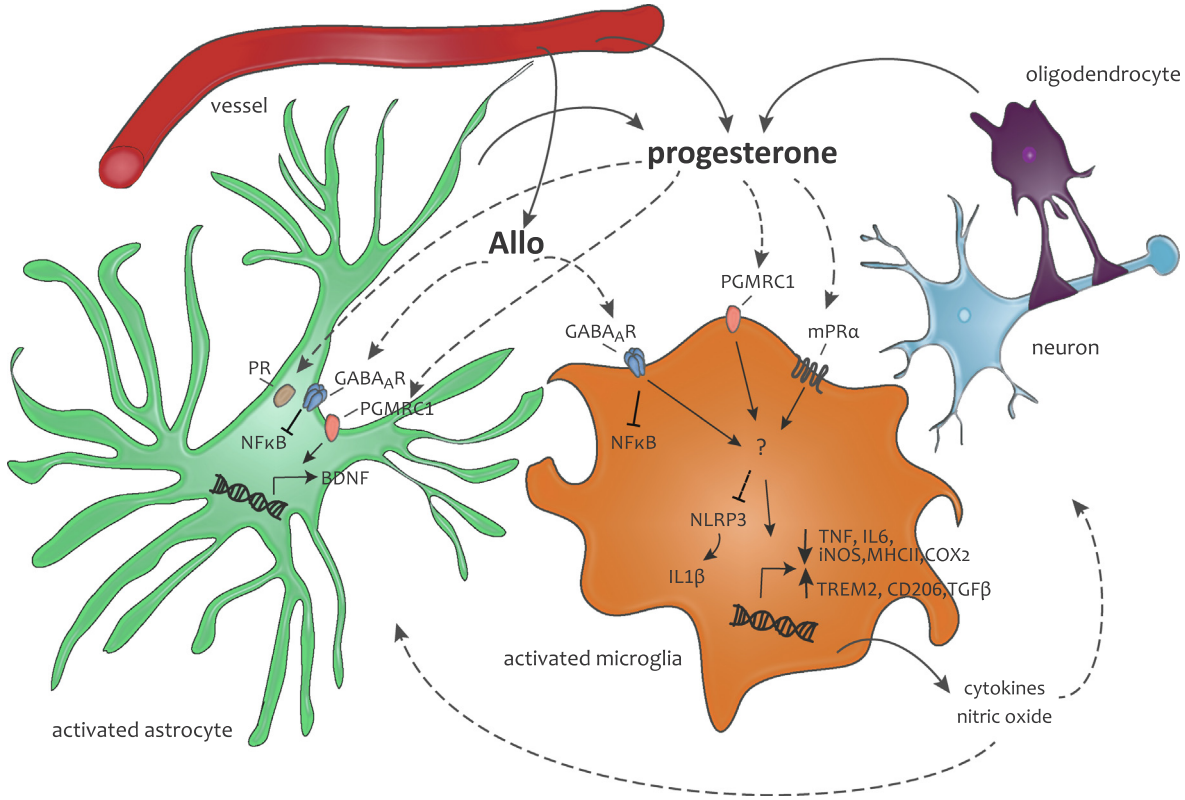

Fig. 2. Functions and signaling of progesterone and allopregnanolone in CNS cells. In the CNS progesterone and allopregnanolone derive from the periphery, astrocytes and oligodendrocytes (Zwain and Yen, 1999; Gago et al., 2001; Mellon and Griffin, 2002; Schumacher et al., 2003; Starka et al., 2015). In microglia progesterone activates membrane PRα and PGMRC1 (Bali et al., 2013; Bali et al., 2013; Roche et al., 2016; Meffre et al., 2013) and can down-regulate inflammasome activation, inhibit the expression of pro-inflammatory genes, such as TNF, IL-6, iNOS, MHCII and COX2, and enhance the expression of TREM2, CD206 or TGFβ (Aryanpour et al., 2017; Lei et al., 2014; Cutler et al., 2007; Hua et al., 2011). Astrocytes express PR and PGMRC1 (Bali et al., 2013; Bali et al., 2013; Meffre et al., 2005) and progesterone might induce BDNF release in a Pgrmc1-dependent manner, thereby promoting cell survival (Jodhka et al., 2009; Su et al., 2012; Sun et al., 2016; Kaur et al., 2007; Atif et al., 2013). On the other hand, allopregnanolone binds to $GABA_A$ receptors in microglia as well as astrocytes mediating anti-inflammatory effects through NFκB inhibition (Singh et al., 2013; Lambert et al., 2003; Lee et al., 2011). The release of progesterone and allopregnanolone is marked by solid lines and their effects by dashed lines. Abbreviations: BDNF: Brain-derived neurotrophic factor, CD206: Cluster of Differentiation 206, COX2: cyclooxygenase 2, $GABA_A$R: γ-aminobutyric acid type A receptor, IL1β: Interleukin 1β, IL6: Interleukin 6, iNOS: inducible nitric oxide synthase, MHCII: major histocompatibility complex class II, NLRP3: NLR family pyrin domain containing 3, mPRα: membrane progesterone receptor α, NFκB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells, NLRP3: NLR family pyrin domain containing 3, PGMRC1: progesterone membrane receptor component 1, PR: progesterone receptor, TGFβ: Transforming Growth Factor β, TNF: Tumor Necrosis Factor, TREM2: Triggering receptor expressed on myeloid cells 2.

neurosteroidogenesis as a whole is a conserved phenomenon across vertebrates (Callard et al., 1978), since non-mammalian vertebrates, such as fish, amphibians and birds also synthesize neurosteroids (Forlano et al., 2001; Schlinger et al., 1994; Diotel et al., 2011; Mensah-Nyagan et al., 1996; Takase et al., 1999; Matsunaga et al., 2004; London et al., 2006; Krentzel and Remage-Healey, 2015; London and Clayton, 2010). Hence, neurosteroids might have acted as ancestral neuromodulators since the early evolution of vertebrates (Pediaditakis et al., 2015).

3. Multiple sclerosis (MS)

MS is a demyelinating disease characterized by axonal degeneration and pathological symptoms, including motor, visual, sensational and cognitive defects. In the relapsing-remitting form of MS (RR-MS), neurological functions remain stable between attacks. However, MS often develops to secondary progressive MS (SP-MS) featured by fewer relapses but gradually increasing and progressively irreversible neurological function deterioration. In fewer cases, MS is primary progressive (PP-MS), characterized by continuous worsening of symptoms from disease onset (Dobson and Giovannoni, 2019). Several risk alleles have been associated with MS development, such as the human leukocyte antigen (HLA) HLA-DRB15 or genes encoding cytokines, cytokine receptors, co-stimulatory molecules and regulators of inflammation (International Multiple Sclerosis Genetics et al., 2011; International Multiple Sclerosis Genetics et al., 2007; Choi et al., 2015; Goris et al., 2003).

MS pathology is featured by infiltration of peripheral auto-reactive immune cells along with activation of innate immune responses of CNS resident cells (Dendrou et al., 2015). The most widely used animal models of MS are EAE, which is induced by immunization of animals with myelin peptides or by adoptive transfer of myelin-reactive T cells, thereby featuring the autoimmune component of the disease (Choi et al., 2015; Bjelobaba et al., 2018; Xie et al., 2006; Langer et al., 2012), and the cuprizone model, in which animals are fed with the copper chelator cuprizone, which induces oligodendrocyte cell death, demyelination and glial activation (Praet et al., 2014). While innate immune responses of resident cells (microglia, resident macrophages and astrocytes) are key drivers in the cuprizone-induced pathology, EAE and MS pathology involves innate as well as adaptive immune responses (Dendrou et al., 2015; Bjelobaba et al., 2018; Praet et al., 2014).

T cells are central players in EAE and MS. The adaptive immune response is initiated by activation of naïve T cells by antigen presenting cells (APC) in secondary lymphoid organs, such as deep cervical lymph nodes. Subsequently, T cells infiltrate the brain parenchyma and get reactivated by antigen presenting microglial cells expressing major

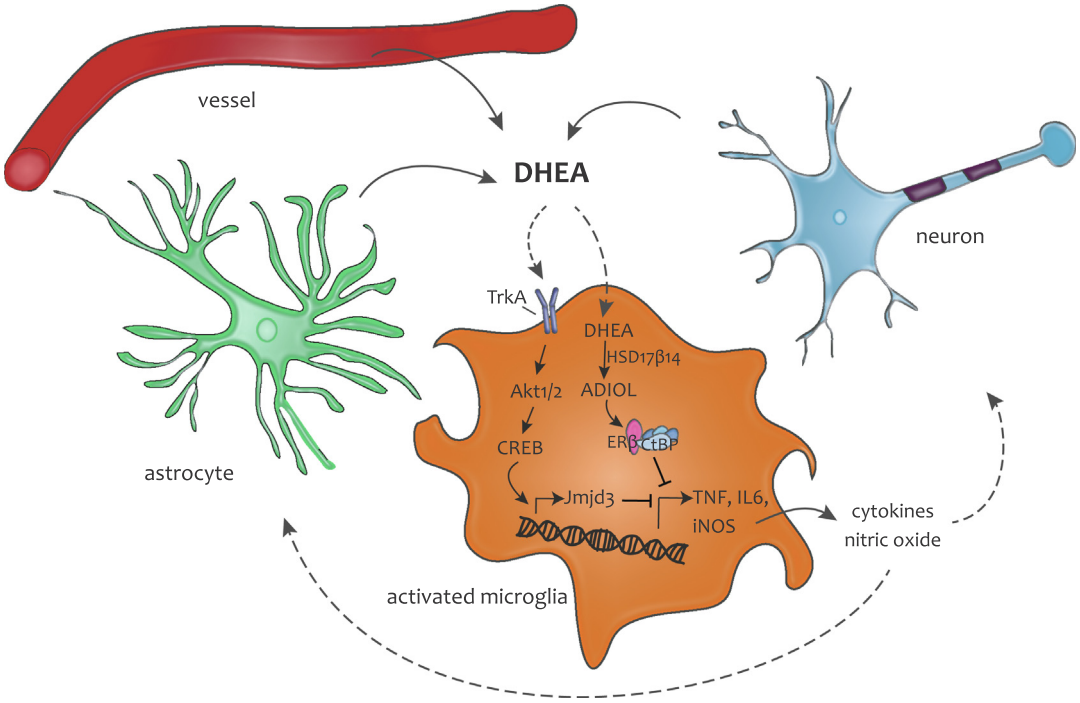

Fig. 3. Functions and signaling of DHEA in CNS cells. DHEA is synthesized in astrocytes and neurons, while it also derives from the circulation (Zwain and Yen, 1999; Mellon and Griffin, 2002; Schumacher et al., 2003; Starka et al., 2015). In microglia it exerts anti-inflammatory effects through activation of the NGF receptor TrkA, which triggers the AKT/CREB signaling cascade leading to enhanced Jmjd3 expression (Lazaridis et al., 2011; Alexaki et al., 2018). Moreover, it can be metabolized to ADIOL, which binds to ERβ thereby negatively regulating pro-inflammatory gene expression (Saijo et al., 2011). Through regulation of cytokine and NO secretion it affects astrocyte activation and neuronal survival (Glass et al., 2010). The release of DHEA is shown by a solid line, its effects by a dashed line. Abbreviations: ADIOL: 5-androstene-3 beta, 17 beta-diol, CREB: cAMP response element-binding protein, CtBP: C-terminal-binding protein 1, DHEA: Dehydroepiandrosterone, ERβ: estrogen receptor β, HSD17β14: 17β14-Hydroxysteroid dehydrogenase, IL6: Interleukin 6, iNOS: inducible nitric oxide synthase, Jmjd3: Jumonji Domain Containing 3, TNF: Tumor Necrosis Factor, TrkA: tropomyosin related kinase.

histocompatibility complex class II (MHCII) and co-stimulatory molecules (B7-1, B7-2, CD40) (Schetters et al., 2017; Almolda et al., 2015). The main autoreactive $CD4^+$ T cell lineages in MS and EAE are Th1 and Th17 cells (Fletcher et al., 2010). $FoxP3^+$ regulatory T cells (Treg) regulate the activity of effector T cells under healthy conditions, while their suppressive function is impaired in MS (Jones and Hawiger, 2017). Inflammation gradually leads to disruption of the BBB, which allows peripheral immune cells, such as monocytes, T and B cells, to gain access to the CNS (Prinz and Priller, 2017). Furthermore, myelin-specific auto-antibodies together with complement factors deposit in lesions and contribute to destruction of myelin and neuronal degeneration (Glass et al., 2010).

Chronic inflammation in MS may be sustained by aberrant innate immune responses of resident cells, such as microglia and astrocytes, having escaped the control mechanisms maintaining homeostasis in the healthy brain (Glass et al., 2010). Among CNS resident cells, microglia are key drivers of innate immune responses (Schetters et al., 2017; Glass et al., 2010; Ransohoff, 2016). They originate from erythromyeloid progenitors (EMPs) in the yolk sac and colonize the CNS in early embryonic development (Ginhoux et al., 2010; Kierdorf et al., 2013). They reside in the CNS for their entire lifespan, self-renewing their population and are not replenished by peripheral monocytes under physiological conditions (Ajami et al., 2007). In the inflamed CNS, microglia acquire an amoeboid morphology, proliferate and secrete pro-inflammatory cytokines, such as TNF, IL-1β, IL-6 and IL-23, chemokines, reactive oxygen species (ROS) and nitric oxide (NO) and express MHCII (Saijo and Glass, 2011; Glass et al., 2010; Ransohoff, 2016). Microglial inflammatory responses escaping regulatory mechanisms can impair neuronal function and survival, thereby propelling progression of neurodegeneration (Glass et al., 2010). However, although destructive when escaping regulatory mechanisms, microglia have primarily a protective role through debris clearance (Yamasaki et al., 2014; Neumann et al., 2009). For instance, blockage of myelin debris clearance by microglia was shown to impair remyelination in the cuprizone-induced MS mouse model (Lampron et al., 2015). On the contrary, monocytes, but not microglia, were shown to be detrimental in EAE, as they induce demyelination by 'tearing off' myelin from neuronal axons, when recruited to the nodes of Ranvier (Yamasaki et al., 2014).

Besides microglia, astrocytes also play a role in MS development. They are the most abundant glial cell type in the CNS and are paramount for maintenance of CNS homeostasis (Colombo and Farina, 2016; Ponath et al., 2018). Among numerous functions they also have immune properties (Colombo and Farina, 2016). They respond to infection or neurodegeneration by a process termed astrogliosis, typified by morphological changes, increased cell numbers and scar formation (Colombo and Farina, 2016; Ponath et al., 2018). Astrocyte scars form boundaries between healthy and damaged or inflamed tissue, thereby protecting the healthy tissue against spreading of inflammatory cells, neuronal loss and demyelination (Sofroniew, 2009). Astrocyte scars frequently surround chronic MS lesions (Colombo and Farina, 2016; Ponath et al., 2018). Furthermore, astrocytes contribute to the BBB structure by sustaining tight junctions and forming the glia limitans, while BBB disruption and infiltration of inflammatory cells is correlated with weakening of the astrocyte structure at the BBB proximity (Alvarez et al., 2013). On the other hand, activated astrocytes can be proinflammatory by secreting cytokines, which can propagate microglia activation and neurodegeneration (Glass et al., 2010; Sofroniew, 2009).

3.1. Estrogens

MS affects women with a greater prevalence than men (Gold and Voskuhl, 2009). Furthermore, increased estrogen levels during the last

trimester of pregnancy correlate with decreased incidences of MS, while postpartum low estrogen levels might predispose to disease progression (Gold and Voskuhl, 2009). Along the same line, administration of 17β-estradiol or estriol reduce EAE severity in both, male and female animals (Gold and Voskuhl, 2009; Ito et al., 2001; Bebo et al., 2001; Garidou et al., 2004; Benedek et al., 2017; Palaszynski et al., 2004). The protective effect of estrogens is attributed to their neuroprotective, as well as anti-inflammatory functions (Gold and Voskuhl, 2009) (Fig. 1). Estrogens downregulate inflammatory cytokine production in the CNS of EAE mice and promote expression of anti-inflammatory markers in microglia (Ito et al., 2001; Bebo et al., 2001; Garidou et al., 2004; Benedek et al., 2017). For instance, administration of 17β-estradiol to female EAE mice reduces expression of the chemokines RANTES (CCL5), MIP-1 alpha, MIP-2, IP-10, and MCP-1, and the chemokine receptors CCR1, CCR2 and CCR5, and decreases TNF and IFNγ expression in spinal cords (Matejuk et al., 2001). In accordance, ERβ-specific synthetic ligands, inhibit IL-6, IL-1β, IL23-p19 and inducible Nitric Oxide Synthase (iNOS) expression in microglia (Saijo et al., 2011) (Fig. 1). Moreover, administration of 17β-estradiol in male mice under cuprizone diet reduces microgliosis and demyelination in the corpus callosum, while it does not affect astrogliosis, recruitment of oligodendrocyte precursor cells or re-myelination (Taylor et al., 2010). Furthermore, selective ERβ agonists inhibit T cell reactivity, suppress Th17 cells, and expand the Treg population (Wu et al., 2013; Aggelakopoulou et al., 2016). On the other hand, treatment with an ERα ligand was reported to decrease EAE severity, microglial activation, astrogliosis and T cell infiltration (Spence et al., 2013; Spence et al., 2011). Moreover, the selective estrogen receptor modulators (SERM), raloxifene and tamoxifen, reduce dendritic cell activation, as evidenced by diminished expression of MHCII and co-stimulatory molecules (Nalbandian et al., 2005). Besides their immunomodulatory effects, estrogens also promote neuronal and oligodendrocyte survival (Kipp and Beyer, 2009). Hence, due to their neuroprotective effects estrogens decrease generation of damage-associated molecular patterns (DAMPs), thereby reducing DAMP-mediated neuroinflammatory reactions (Gadani et al., 2015). Furthermore, a ligand for the G protein-coupled estrogen receptor (GPR30), called G1, reduces EAE severity, associated with decreased expression of proinflammatory cytokines, such as IFNγ and IL-17 (Blasko et al., 2009).

Notably, relapsing-remitting female patients treated orally with estriol (8 mg/day) demonstrated decreased lesion number and volume, associated with increased IL-10 and decreased TNF expression in peripheral blood mononuclear cells (PBMC) (Gold and Voskuhl, 2009; Soldan et al., 2003). In accordance, in a recent phase II study in female MS patients estriol administration combined with glatiramer acetate treatment over a period of 24 months showed a trend for reduced relapse rates compared to patients receiving only glatiramer acetate (Voskuhl et al., 2016). Since estrogen treatments have been proven beneficial in MS models in both, female and male animals, and given the encouraging results of the first clinical trials testing estriol administration in women, similar treatments of male MS patients could be envisioned in the future.

3.2. Progestogens

Among progestogens, progesterone and allopregnanolone are the best-studied neurosteroids (Compagnone and Mellon, 2000; Charalampopoulos et al., 2008; Rossetti et al., 2016; Brinton, 2013). Progesterone administration to female EAE mice delays disease onset, reduces inflammatory cell infiltration and decreases demyelination (Garay et al., 2007). Additionally, in a chronic EAE model, progesterone improves the clinical score and decreases inflammatory markers in the spinal cord in male rats (Giatti et al., 2012). Moreover, progesterone treatment of cuprizone-fed mice decreases microglial inflammatory markers, such as iNOS, CD86, MHCII and TNF, increases anti-inflammatory markers, such as triggering receptor expressed on myeloid cells 2 (TREM2), CD206, arginase 1 (Arg1) and TGF-β, and reduces demyelination in the corpus callosum (Aryanpour et al., 2017). In accordance, progesterone downregulates LPS-induced TNF, iNOS and cyclooxygenase-2 (Cox-2) expression in microglia in vitro (Lei et al., 2014) (Fig. 2).

Allopregnanolone (5alpha-pregnan-3beta-ol-20-one) is a derivative of progesterone (Compagnone and Mellon, 2000; Noorbakhsh et al., 2014). Its levels are reduced in the cerebrospinal fluid (CSF) of female relapsing-remitting MS patients and in the white matter of male MS patients compared to healthy subjects (Noorbakhsh et al., 2011; Orefice et al., 2016). In accordance, allopregnanolone reduces demyelination, axonal injury, microglial reactivity and lymphocyte infiltration in EAE mice (Noorbakhsh et al., 2011), while it attenuates inflammatory responses of macrophages and microglia in vitro (Noorbakhsh et al., 2014; Noorbakhsh et al., 2011; Muller and Kerschbaum, 2006) (Fig. 2). Furthermore, it protects neuronal survival and induces myelin synthesis in oligodendrocytes, hence supporting remyelination (Charalampopoulos et al., 2008; Brinton, 2013; Noorbakhsh et al., 2014). To date, progestogens have not been clinically tested in MS patients.

3.3. DHEA(S)

DHEA and its sulfate ester, DHEAS, are the most abundant circulating steroids in humans (Maninger et al., 2009). DHEA levels are decreased in CNS tissues of women with MS and female EAE animals (Boghozian et al., 2017). Three independent reports showed that DHEA ameliorates EAE development. Du et al., showed that DHEA administration to female mice, starting from induction of the disease by immunization, reduces EAE severity, demyelination and CNS inflammation and decreases T cell responses (Du et al., 2001). Saijo et al., reported that DHEA inhibits EAE development in female mice due to its anti-inflammatory effects in microglia and astrocytes mediated by its metabolism by 17β-HSD type 14 (HSD17B14) to 5-androsten-3b,17β-diol (ADIOL). ADIOL binds to ERβ inducing recruitment of CtBP co-repressor complexes to AP-1-dependent promoters, thereby repressing expression of cytokines (Fig. 3), which promote Th17 differentiation and activation (Saijo and Glass, 2011; Saijo et al., 2011). Finally, Aggelakopoulou et al., demonstrated in four different EAE models using female mice that DHEA ameliorates clinical scoring also when given after clinical onset, suggesting that DHEA could be of therapeutic interest. This effect is mediated by suppression of Th17 cell responses and expansion of the IL-10-producing Treg population in an ERβ-dependent manner (Aggelakopoulou et al., 2016). Moreover, DHEA reduces microglia-mediated neuroinflammation in vitro and in vivo during LPS-induced brain inflammation (Alexaki et al., 2017) (Fig. 3). Similarly to DHEA, its sulfate ester (DHEAS) is also protective when administered to EAE female animals. DHEAS reduces demyelination and axonal loss, improves clinical scoring and reduces IL-1β and IFNγ levels in the spinal cord (Boghozian et al., 2017). DHEA or DHEAS have not yet been studied in MS clinical trials.

In conclusion, 17β-estradiol, estriol, progesterone, allopregnanolone and DHEA have all been shown in animal MS models to reduce disease severity and neuroinflammation evidenced by reduced demyelination and microglial activation, respectively (Alexaki et al., 2017; Saijo and Glass, 2011; Saijo et al., 2011; Noorbakhsh et al., 2011; Du et al., 2001; Aggelakopoulou et al., 2016; Gold and Voskuhl, 2009; Ito et al., 2001; Bebo et al., 2001; Garidou et al., 2004; Benedek et al., 2017; Palaszynski et al., 2004; Garay et al., 2007; Giatti et al., 2012; Aryanpour et al., 2017). Out of these steroids, only estriol has been tested in clinical studies, with encouraging results (Gold and Voskuhl, 2009; Soldan et al., 2003; Voskuhl et al., 2016). Future clinical studies could examine the efficacy of progesterone, allopregnanolone or DHEA in the treatment of MS.

4. Alzheimer's disease (AD)

AD is one of the most common neurodegenerative diseases with its prevalence increasing with age (Querfurth and LaFerla, 2010). Clinical symptoms are memory loss, cognitive impairment and neuropsychiatric disorders (Citron, 2010). Pathological hallmarks in the brain of AD patients are formation of amyloid plaques composed by amyloid β_{1-42} and β_{1-40} peptides, which are derived from amyloid precursor protein (APP) through cleavage by β and γ secretases, and intraneural neurofibrillary tangles (NFTs), composed by hyper-phosphorylated microtubule-binding protein tau (Querfurth and LaFerla, 2010; Haass and Selkoe, 2007). A significant genetic risk factor for AD is the ε4 allele of the Apolipoprotein E (APOE4) contributing to amyloid β (Aβ) peptide accumulation and increased neuroinflammation (Querfurth and LaFerla, 2010; Newcombe et al., 2018; Bertram and Tanzi, 2008). Other genetic factors are mutations in the genes encoding APP, the γ secretase component presenilin, the microglial phagocytosis-mediator TREM2 and CD33 (Bertram and Tanzi, 2008; Guerreiro et al., 2013; Jonsson et al., 2013; Bradshaw et al., 2013). Finally, toxic environmental factors, traumatic brain injury, infection, diet or type-2 diabetes could also play a role in AD development (Glass et al., 2010; Migliore and Coppede, 2009). Single nucleotide polymorphisms (SNP) in several genes involved in innate immunity are also linked to an increased risk for AD (Tanzi, 2012).

Aβ peptides act as danger signals, activating microglia through Pattern Recognition Receptors (PRRs), such as Toll like Receptor (TLR) 4, Receptor for Advanced Glycation End products (RAGE) and NOD-like receptors (NLR) and inducing NFκB activation and production of pro-inflammatory cytokines, such as TNF, IL-1β and IL-6, prostaglandins, NO and ROS (Glass et al., 2010; Newcombe et al., 2018). A feature of activated microglia is the inflammasome, which is a protein complex mediating activation of caspase 1-dependent cleavage and release of IL-1β and IL-18 (Walsh et al., 2014). Aβ activates the NLRP3 inflammasome in microglia, while NLRP3 or caspase 1 knockdown in an animal model of familial AD reduces brain IL-1β activation, Aβ deposition and development of pathological features associated with AD (Heneka et al., 2013). In turn, inflammatory conditions may induce APP and secretase expression, leading to Aβ aggregation and tau kinase activation, resulting in NFT formation (Newcombe et al., 2018; Sastre et al., 2008; Ballatore et al., 2007). On the other hand, microglia have also a protective role due to Aβ clearance (Glass et al., 2010; Newcombe et al., 2018), while inflammation might attenuate microglial phagocytosis, thereby contributing to Aβ plaque formation (Koenigsknecht-Talboo and Landreth, 2005). Moreover, microglia activate astrocytes through secretion of TNF and IL-1β (Glass et al., 2010), and pro-inflammatory cytokines (TNF, IL-1β, IL-6) may induce neuronal apoptosis (Glass et al., 2010; Verma et al., 2016; Guadagno et al., 2013; Miura et al., 2003; Chen et al., 2016; Tian et al., 2017; Wang et al., 2005; Talley et al., 1995). Thus, neuroinflammation and neurodegeneration create a vicious cycle driving disease progression.

4.1. Estrogens

Several studies in different AD animal models suggest that estrogens might attenuate disease development (Vegeto et al., 2006; Yue et al., 2005; Carroll et al., 2007; Yun et al., 2018). Estrogen levels and aromatase expression are reduced in brains of female AD patients compared to brains of non-AD subjects. In contrast, serum estrogen levels are not different from those of non-AD individuals (Yue et al., 2005). Estrogen depletion via ovariectomy in the APP23 AD mouse model increases pathological signs of the disease and microglial activation, whereas treatment of ovariectomized mice with 17β-estradiol is protective (Vegeto et al., 2006). Along the same line, aromatase knockout in APP23 female mice induces earlier disease onset and increases Aβ deposition, while microglia from these mice display impaired Aβ clearance (Yue et al., 2005). In accordance, ovariectomy in the 3xTgAD mouse model increases Aβ accumulation and worsens memory performance, while administration of 17β-estradiol prevents these effects, however, without improving tau pathology (Carroll et al., 2007). Furthermore, ovariectomy after intracerebroventricular infusion of $A\beta_{1-42}$ in female mice increases AD pathology, cognitive deficit, microgliosis, astrogliosis and NF-κB activation (Yun et al., 2018). In accordance, 17β-estradiol increases phagocytosis of Aβ in human cortex-derived microglia (Li et al., 2002), decreases Aβ-induced microglial inflammatory responses (Yun et al., 2018) and reduces COX2, iNOS, IL-1β and TNF expression in astrocytes stimulated with Aβ (Valles et al., 2010). Moreover, 17β-estradiol was reported to negatively regulate inflammasome formation in microglia *in* vivo in female mice and in vitro (Slowik et al., 2018; Thakkar et al., 2016) (Fig. 1). Although most clinical studies failed to show any improvement in cognitive symptoms in post-menopausal women with AD receiving hormonal replacement therapy (Janicki and Schupf, 2010; Henderson, 2014; Imtiaz et al., 2017), a pilot study demonstrated reduced Aβ deposition in recently postmenopausal women, and particularly in APOE4 carriers, after receiving 17β-estradiol (Henderson, 2014).

4.2. Progestogens

Similarly to estrogens, age-related decline in progesterone levels in women associates with AD risk (Barron and Pike, 2012). $A\beta_{25-35}$ injection into the CA1 hippocampal region of male rats decreases progesterone levels in the prefrontal cortex and the hippocampus, while progesterone administration improves behavioral performance, increases pyramidal neuron survival and decreases TNF and IL-1β expression in a dose-dependent manner (Liu et al., 2013). However, continuous progesterone treatment of female ovariectomized 3xTgAD mice, although reducing tau hyperphosphorylation, has no effect on Aβ accumulation or behavioral improvement, while in co-treatment with 17β-estradiol it reduces the ameliorating effects of the latter (Carroll et al., 2007; Carroll et al., 2010). On the contrary, cyclic administration of progesterone reduces Aβ levels and enhances the protective effects of 17β-estradiol in female 3xTgAD mice (Carroll et al., 2010). Moreover, progesterone attenuates inflammatory responses of astrocytes treated with $A\beta_{1-42}$ in vitro by suppressing ER stress and enhancing autophagy (Hong et al., 2016; Hong et al., 2018). In accordance, progesterone was reported to dampen inflammasome activation in microglia (Slowik et al., 2018) (Fig. 2). Administration of allopregnanolone to male 3xTgAD mice prior to disease manifestation also increases neuronal survival, reduces Aβ plaque formation and decreases microglial activation (Chen et al., 2011). However, combined estrogen and synthetic progestogen therapy does not prevent cognitive impairment but rather increases the risk of dementia in post-menopausal women (Shumaker et al., 2003).

4.3. DHEA(S)

Serum DHEA(S) levels also decline with increasing age in men and women, which could be associated with AD development (Barrou et al., 1997; Hampl and Bicikova, 2010; Aldred and Mecocci, 2010), while serum DHEA levels are lower in AD patients compared to age-matched healthy individuals (Hillen et al., 2000; Sunderland et al., 1989; Luchetti et al., 2011). Furthermore, DHEAS administration was shown to improve cognitive performance in male SAMP8 mice, an AD animal model with age-dependent accumulation of APP and Aβ (Farr et al., 2004). In accordance, DHEA exerts anti-apoptotic effects (Charalampopoulos et al., 2008; Charalampopoulos et al., 2006; Lazaridis et al., 2011; Charalampopoulos et al., 2004; Cardounel et al., 1999) and rescues neurons in the dentate gyrus after Aβ infusion in adult male mice (Li et al., 2010). However, DHEA does not affect APP- or Aβ-induced NO production in microglial cells (Barger et al., 2000). Moreover, in a pilot study, DHEA treatment did not significantly improve cognitive performance or disease severity in female AD patients

(Wolkowitz et al., 2003). To our knowledge, DHEA administration has not been tested in male AD patients.

Summarizing, ovariectomy and aromatase gene deletion have detrimental effects in AD models evidenced by increased Aβ deposition and neuroinflammation, while 17β-estradiol replacement in ovariectomized AD animals is protective (Vegeto et al., 2006; Yue et al., 2005; Carroll et al., 2007; Yun et al., 2018). Moreover, cyclic, but not continuous, administration of progesterone in combination with estrogen protects female AD animals from disease progression (Carroll et al., 2007; Carroll et al., 2010). In contrast, cyclic administration is not necessary for progesterone to be protective in male AD animals (Chen et al., 2011). DHEA(S) administration is also protective in male AD mice (Farr et al., 2004; Li et al., 2010). However, most clinical studies conducted so far, enrolling mainly female AD patients, failed to show any improvement of cognition or AD symptoms by estrogen, progestogen or DHEA administration (Shumaker et al., 2003; Wolkowitz et al., 2003; Janicki and Schupf, 2010; Henderson, 2014; Imtiaz et al., 2017).

5. Parkinson's disease (PD)

PD is a common neurodegenerative disease with clinical features including bradykinesia, rigidity, tremor and postural instability, as well as non-motor-related symptoms, like depression, cognitive deficits and sleep disorders (Troncoso-Escudero et al., 2018; Jankovic, 2008; Langston, 2006). Its pathology involves aggregation of misfolded α-synuclein in intracellular formations, called Lewy bodies, and death of dopaminergic neurons mainly in the substantia nigra (SN) of the midbrain (Glass et al., 2010; Troncoso-Escudero et al., 2018; Fuzzati-Armentero et al., 2019). Rare mutations in the α-synuclein gene are one of the causes of familial PD forms (Polymeropoulos et al., 1997), while most of the cases of the disease are idiopathic (Troncoso-Escudero et al., 2018). Evidence that neuroinflammation contributes to PD development or progression derives from the observation that chronic users of non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase inhibitors present a lower incidence of idiopathic PD development (Chen et al., 2003; Chen et al., 2005). Activated microglia, enhanced NF-κB activation and increased cytokine levels (such as TNF, IL-6 and IL-1β) are observed in the brain of PD patients (Fuzzati-Armentero et al., 2019; McGeer et al., 1988; Tansey et al., 2007; Caggiu et al., 2019). Moreover, α-synuclein can trigger ROS release in microglia (Zhang et al., 2005), leading to death of SN dopaminergic neurons, which are particularly vulnerable to oxidative stress (Glass et al., 2010; Tansey et al., 2007; Zhang et al., 2005). In turn, microglia get activated by DAMPs, such as high mobility group box 1 (HMGB1) and ATP, which derive from dying neurons (Ferreira and Romero-Ramos, 2018), and produce pro-inflammatory cytokines, ROS and NO, thereby sustaining a neurotoxic environment (Glass et al., 2010; Troncoso-Escudero et al., 2018; Fuzzati-Armentero et al., 2019; Ferreira and Romero-Ramos, 2018) and promoting astrocyte inflammatory activation (Glass et al., 2010; Troncoso-Escudero et al., 2018; Ferreira and Romero-Ramos, 2018). Similarly to microglia, astrocytes can also be activated by α-synuclein (Fellner et al., 2013; Kortekaas et al., 2005). Moreover, during disease development BBB integrity can be compromised allowing recruitment of peripheral immune cells, such as $CD4^+$ and $CD8^+$ T cells, which could further propel neuroinflammation (Kortekaas et al., 2005; Brochard et al., 2009).

PD-like pathology can be induced in rats by intrastriatal injection of 6-hydroxydopamine (6-OHDA), while in another model the toxin MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine) is administrated to mice inducing mitochondrial damage and cell death of dopaminergic neurons (Blesa and Przedborski, 2014). Both models are featured by microglia- and astrocyte-mediated neuroinflammation (Troncoso-Escudero et al., 2018; Fuzzati-Armentero et al., 2019; Morales et al., 2016; Garcia-Dominguez et al., 2018). Furthermore, intracranial infusion of LPS induces loss of dopaminergic neurons in rodents and microglia-mediated inflammation (Castano et al., 1998), further suggesting a role of neuroinflammation in PD progression. On the other hand, microglia might also play a protective role supporting neuronal survival, since loss of the fractalkine receptor CX3CR1, through which microglia interact with neurons (Sheridan and Murphy, 2013), dysregulates microglial responses and augments LPS-induced toxicity and neurodegeneration in the SN following MPTP administration (Cardona et al., 2006). Furthermore, microglia and astrocytes can secrete neurotrophic factors, such as Neural Growth Factor (NGF), Brain-Derived Growth Factor (BDNF) or Glial-Derived Growth Factor (GDNF), thereby supporting neuronal survival (Troncoso-Escudero et al., 2018; Batchelor et al., 1999; Frade and Barde, 1998).

5.1. Estrogens

Several lines of evidence suggest a negative association of estrogen levels with PD development. Women show a lower risk for developing PD than men, while disease symptomatology is gender dimorphic (Villa et al., 2016; Bourque et al., 2018). Notably, an ERβ gene polymorphism correlates with early age disease onset (Westberg et al., 2004). Furthermore, women who underwent either unilateral or bilateral oophorectomy before the onset of menopause show increased risk of parkinsonism (Bourque et al., 2018; Rocca et al., 2008). Moreover, expression of markers of microglial activation, such as CD14, CD18, TLR2, TLR4, CCL2 or complement factors C1q and C3, is up-regulated, while expression of genes associated with microglia-mediated phagocytosis and neuroprotection (CD36, CX3CR1, CX3CL1 and CD200) is downregulated in the postcentral and the superior frontal gyrus of postmenopausal compared to pre-menopausal women (Sarvari et al., 2012). Accordingly, ovariectomized animals present greater neuronal damage in the SN, as well as stronger astrocyte activation and microgliosis compared to non-ovariectomized animals in the 6-OHDA and MPTP models (Siani et al., 2017; Morale et al., 2006). Additionally, male mice display a more rapid increase in iNOS expression and a greater reduction of SN dopamine after MPTP treatment compared to female mice (Joniec et al., 2009). In accordance, treatment with estradiol prevents dopamine reduction, neuronal loss and glial activation in the striatum of MPTP-treated animals (Morale et al., 2006; Tripanichkul et al., 2006). The GPR30 ligand G1 also decreases microglial activation and increases dopaminergic neuronal cell survival in male MPTP-treated mice (Guan et al., 2017). Furthermore, 17β-estradiol decreases LPS-induced neuroinflammation, by reducing brain levels of proinflammatory cytokines (IL-1, TNF, IL-6, IL-12p40) and the chemokine RANTES in the female mouse brain (Brown et al., 2010; Soucy et al., 2005) (Fig. 1). Accordingly, 17β-estradiol downregulates LPS-induced expression of iNOS, prostaglandin-E(2) [PGE(2)] and metalloproteinase-9 (MMP-9) in microglia and IL-6 and IFNγ-inducible protein-10 (IP-10) in astrocytes in vitro (Vegeto et al., 2001; Wu et al., 2016; Cerciat et al., 2010). Moreover, SERMs are also able to suppress production of proinflammatory cytokines and chemokines, such as TNF, IL-1β, monocyte chemotactic protein-1 or macrophage inflammation protein-2 (MIP2) in microglia (Ishihara et al., 2015; Wu et al., 2015). However, according to one study SERMs but not 17β-estradiol limit microglial inflammatory responses (Suuronen et al., 2005). It was even reported, that endotoxin-induced microglial activation is inhibited in ovariectomized animals and is restored after 17β-estradiol replacement (Soucy et al., 2005). In accordance, 17β-estradiol was demonstrated to increase LPS-induced macrophage activation in female mice in vivo (Calippe et al., 2010), perhaps through up-regulation of TLR4 cell surface expression (Rettew et al., 2009). However, clinical studies have failed to show an association of estrogen hormone therapy with lower PD risk in women (Bourque et al., 2018; Liu and Dluzen, 2007; Strijks et al., 1999; Liu et al., 2014).

5.2. Progestogens

Reduced progestogen levels associate with PD development. For instance, allopregnanolone is reduced in the CSF of PD patients (di Michele et al., 2003), and in 6-OHDA - treated male rats pregnenolone and dihydroprogesterone levels are lower in the striatum and cortex, respectively (Melcangi et al., 2012). In accordance, some studies have shown protective effects of progesterone, alone or in combination with 17β-estradiol in PD animal models (Yu and Liao, 2000; Bourque et al., 2016; Litim et al., 2017; Casas et al., 2011). Specifically, progesterone administrated before MPTP treatment prevents MPTP toxicity in male mice (Bourque et al., 2016), and when given one, but not five, days after MPTP stimulation, it decreases astrocyte activation and restores BDNF expression and dopamine levels (Litim et al., 2017). Along the same line, progesterone suppresses NF-κB and JNK activation, as well as TNF and iNOS production in microglia in vitro (Lei et al., 2014). Moreover, progesterone was shown to prevent depression-like behavior in 6-OHDA – treated male rats (Casas et al., 2011). Allopregnanolone was also shown to prevent PD-like disease development and improve cognition when administrated orally for two months to rats challenged with 6-OHDA (Nezhadi et al., 2016). In accordance treatment with allopregnanolone restores dopaminergic neurons and improves the motor performance in MPTP-lesioned male mice (Adeosun et al., 2012). However, no improvement of dyskinesia was observed after treatment with progesterone in MPTP-treated female monkeys (Gomez-Mancilla and Bedard, 1992). Moreover, in a double-blind trial progesterone administration for two weeks had a rather anti-dopaminergic effect (Strijks et al., 1999), while medroxyprogesterone acetate co-administration with estrogen improved dyskinesia in female PD patients (Nicoletti et al., 2007).

5.3. DHEA

DHEA was shown to attenuate microglia-mediated neuroinflammation in male mice treated with LPS by decreasing the expression of proinflammatory cytokines (TNF, IL-6, IL-23p40) and iNOS and increasing the expression of anti-inflammatory markers, such as Arg1, Ym1, Fizz1 and IL-10 (Alexaki et al., 2017; Saijo et al., 2011) (Fig. 3). In accordance, administration of DHEA to female monkeys and male mice with PD-like disease has beneficial effects (Belanger et al., 2003; D'Astous et al., 2003; Belanger et al., 2006; Belanger et al., 2006) and associates with decreased microgliosis (Tomas-Camardiel et al., 2002).

Summarizing, despite their in vitro and in vivo anti-inflammatory and neuroprotective effects (Morale et al., 2006; Tripanichkul et al., 2006; Brown et al., 2010; Soucy et al., 2005; Vegeto et al., 2001; Wu et al., 2016; Cerciat et al., 2010; Yu and Liao, 2000; Bourque et al., 2016; Litim et al., 2017; Casas et al., 2011; Nezhadi et al., 2016; Adeosun et al., 2012), estrogens and progestogens administrated to female PD patients did not ameliorate disease progression (Bourque et al., 2018; Liu and Dluzen, 2007; Strijks et al., 1999; Liu et al., 2014). To our knowledge, no clinical studies using estrogens or progestogens have been conducted in male PD patients, while DHEA has not been tested in neither female nor male PD patients.

6. Traumatic brain injury (TBI)

TBI results from an acute mechanical injury and can involve focal intracranial hemorrhage, epidural and subdural hematoma, hypoxemia, hypotension, edema, axonal damage, neuronal death, gliosis and BBB disruption. The initial pathogenesis is followed by biochemical events, the so-called 'secondary injury', exacerbating neurological impairment (Jassam et al., 2017; Corps et al., 2015). The 'secondary injury' is mainly driven by innate immune responses of microglia and astrocytes (Jassam et al., 2017; Corps et al., 2015). Brain injury induces release of endogenous DAMPs, such as HMGB1 and ATP (Jassam et al., 2017; Corps et al., 2015). HMGB1 binds to TLR4 and RAGE, thereby initiating inflammatory responses (Klune et al., 2008). Accordingly, expression of TLR4, its adaptor protein MyD88 and RAGE, is enhanced in brain tissue after TBI (Lee et al., 2013; Li et al., 2013; Gao et al., 2012), while TLR4 knockdown associates with less neuroinflammation and injury in a TBI animal model (Ahmad et al., 2013). ATP binds to purinergic receptors inducing microglial motility and pro-inflammatory responses (Davalos et al., 2005; Roth et al., 2014; Eltzschig et al., 2012). Moreover, DAMPs also bind to NLRs, which can activate inflammasome formation in microglia and macrophages, with subsequent IL-1β and IL-18 maturation (Gadani et al., 2015; Walsh et al., 2014). Upon TBI microglia extend processes toward the site of damage (Davalos et al., 2005; Roth et al., 2014; Nimmerjahn et al., 2005). On the one hand, microglia are protective by clearing dead cells (Yamasaki et al., 2014; Neumann et al., 2009; Hernandez-Ontiveros et al., 2013; Elkabes et al., 1996), they assist in the maintenance of the integrity of the glial limitans and the vasculature (Roth et al., 2014; Lou et al., 2016) and they can release neurotrophins, which might contribute to neural tissue regeneration (Frade and Barde, 1998; Elkabes et al., 1996; Nagamoto-Combs et al., 2007; Ceni et al., 2014). On the other hand, after TBI microglia secrete pro-inflammatory cytokines, such as IL-1β, IL-18, IL-6 and TNF, and release ROS and NO, thereby creating a neurotoxic environment (Jassam et al., 2017) and disrupting BBB integrity allowing recruitment of peripheral immune cells (Shlosberg et al., 2010). Astrocytes can also have a dual role in TBI. On the one hand, they form structural barriers and isolate the injured from the healthy tissue (Sofroniew, 2015), while on the other hand, they contribute to the inflammatory response of TBI by secreting chemokines, cytokines, NO, ROS and MMP-9 (Jassam et al., 2017). Finally, TBI can be featured by infiltration of neutrophils through the blood-CSF barrier guided by chemokines (CXCL1, CXCL2, CXCL3) (Jassam et al., 2017; Gyoneva and Ransohoff, 2015). Neutrophils are recruited to the meninges, perivascular spaces and the brain parenchyme, followed by monocyte and T cell recruitment (Jassam et al., 2017; Corps et al., 2015; Roth et al., 2014).

6.1. Estrogens

Animal studies have shown improved survival and cognitive function in females after TBI compared to males (Brotfain et al., 2016; Clevenger et al., 2018; Spani et al., 2018). Female mice subjected to controlled cortical impact (CCI) show decreased injury compared to males, while ovariectomized females exhibit increased microglial activation and astrogliosis in the peri-injury cortical area (Clevenger et al., 2018). In accordance, in a model of brain injury in the zebra finch, aromatase inhibition increases and estrogen replacement decreases the extent of damage and neuroinflammation (Pedersen et al., 2017; Pedersen et al., 2016). Mechanistically, estrogens decrease IL-1β, IL-6 and TNF expression and $MHCII^+$ microglial numbers, and increase TGF-β and IL-10 levels in different TBI animal models (Sarkaki et al., 2013; Barreto et al., 2007; Khaksari et al., 2011; Khaksari et al., 2015). Estrogens might also affect microglia phagocytic capacity, since 17β-estradiol promotes phagocytosis in Kupffer cells, the macrophages of the liver (Hsieh et al., 2009). Moreover, they decrease astrogliosis and glial scar formation in the vicinity of the wound (Lopez Rodriguez et al., 2011; Garcia-Estrada et al., 1993; Martin-Jimenez et al., 2018). They also improve motor function and reduce cortical lesions and neuronal loss due to their neuroprotective effects in both, male and female animals (Brotfain et al., 2016; Raghava et al., 2017; Engler-Chiurazzi et al., 2017), which are mediated by attenuation of neuronal apoptosis, glutamate excitotoxicity and oxidative stress, and enhanced release of neurotrophic factors (Martin-Jimenez et al., 2018; Raghava et al., 2017; Engler-Chiurazzi et al., 2017; Lu et al., 2018; Gatson et al., 2012). Furthermore, estrogen administration decreases aquaporin-4 and IL-6 expression, thereby reducing brain edema formation (Soltani et al., 2016). The effects of estrogens in TBI might be sex-specific. Intriguingly, estrogen administration before TBI was reported to improve neurological outcome in male, but not female rats (Emerson et al.,

1993). Other studies showed no protective role of estrogen replacement after ovariectomy in rodents with TBI (Bruce-Keller et al., 2007; Lebesgue et al., 2006). Along the same line, estrogen withdrawal in a zebra finch TBI model decreases NFκB complex expression, suggesting estrogen requirement for the neuroinflammatory response (Cook et al., 2018). Phase I to III clinical trials did not show any effect of estrogen administration on TBI development (Khaksari et al., 2018).

6.2. Progestogens

Progesterone brain levels decrease in female mice after TBI and correlate with neurological recovery (Lopez-Rodriguez et al., 2015). Progesterone administration was shown to ameliorate TBI in different animal models (Spani et al., 2018). Its administration immediately after injury decreases brain lesions, secondary neuronal loss and edema and improves cognitive function in both, male and female animals (Spani et al., 2018). The ameliorating effects of progesterone correlate with its neuroprotective function as well as its anti-inflammatory effects (Spani et al., 2018; Stein, 2008). Progesterone, administrated immediately after prefrontal cortical contusion in male rats, reduces IL-1β and TNF levels early after injury (He et al., 2004). It also decreases COX-2, IL-6, CCL-2 and CXCL-10 up to 3 days after TBI induction in male rodents (Cutler et al., 2007; Hua et al., 2011). Furthermore, in male rats subjected to repeated mild fluid percussion injuries, progesterone treatment attenuates microgliosis, astrogliosis, oxidative stress and grey and white matter damage (Webster et al., 2015) and reduces astrogliosis after penetrating brain injury (Garcia-Estrada et al., 1993; Tang et al., 2013; Garcia-Estrada et al., 1999). Moreover, progesterone reduces inflammatory reactions and increases anti-inflammatory gene expression in cultured primary microglia under hypoxia (Habib et al., 2014). However, in an in vitro scratch model of co-cultured glial and neuronal cells, progesterone hampers estradiol-induced neurite outgrowth (Bali et al., 2013). Also in male songbirds suffering TBI progesterone administration decreases the injury size (Blackshear et al., 2018). Nevertheless, despite the promising results of animal studies, randomized controlled phase II and III trials showed no clinical benefit of progesterone treatment in either, male or female patients with mild, moderate-to-severe or severe TBI (Wright et al., 2014; Skolnick et al., 2014; Lin et al., 2015).

6.3. DHEA(S)

DHEA brain levels transiently decrease after TBI in female mice (Lopez-Rodriguez et al., 2015). Weekly treatment with DHEAS after induction of mild TBI improves long-term cognitive and behavioral deficits in mice (Milman et al., 2008). Administration of DHEAS even seven days after induction of brain injury was shown to improve behavioral performance in male rats (Hoffman et al., 2003). Also treatment with the DHEA analog fluasterone after TBI induction ameliorates neurological effects and cognition in male rats (Malik et al., 2003). DHEA has not been tested yet in clinical studies in TBI patients.

In conclusion, out of the tested neurosteroids, progesterone had the most potent protective effects in TBI animal models (Spani et al., 2018; Stein, 2008; He et al., 2004; Cutler et al., 2007; Hua et al., 2011). Nevertheless, clinical studies testing the efficacy of progesterone as a treatment in TBI were rather unsuccessful (Wright et al., 2014; Skolnick et al., 2014; Lin et al., 2015).

7. Altered neurosteroidogenesis in neurodegenerative diseases

Neurodegenerative diseases can significantly alter neurosteroidogenesis. Increased TSPO levels in microglia and astrocytes associate with neuroinflammation (Liu et al., 2014; Lavisse et al., 2012; Abourbeh et al., 2012). In AD, allopregnanolone levels are reduced in the prefrontal and temporal cortex of male and female patients and reduction correlates with AD pathology (Marx et al., 2006; Luchetti et al., 2011; Naylor et al., 2010). On the contrary, AD patients display increased DHEA levels in the hypothalamus, hippocampus and cortex (Luchetti et al., 2011; Naylor et al., 2010). Dihydroprogesterone (DHP) and DHT brain concentrations decrease in the cerebral cortex in both, male and female rats with EAE in a region-specific manner, while allopregnanolone increases in male and remains unaltered in female EAE rats in these CNS regions (Giatti et al., 2010). Moreover, DHEA concentrations are lower in CNS tissues from MS patients and EAE animals, associated with diminished expression of the DHEA-synthesizing enzyme P450c17 in oligodendrocytes (Boghozian et al., 2017). In contrast, DHEA levels are increased in CSF of male and female RR-MS patients compared to control subjects (Orefice et al., 2016). The concentration of allopregnanolone is also decreased in white matter of MS patients correlating with reduced 5-α-reductase and aldo-keto reductase family 1 Member C2 (AKR1C2) expression (Noorbakhsh et al., 2011; Orefice et al., 2016). Moreover, allopregnanolone levels are lower in female compared to male RR-MS patients (Orefice et al., 2016). Alterations in neurosteroidogenesis in the proximity of MS lesions have been also reported to display gender-specificity: Aromatase and 3β-hydroxysteroid-dehydrogenase (3β-HSD) is up-regulated in males and females, respectively (Luchetti et al., 2014). Interestingly, neurosteroid levels can also be affected by exercise in EAE animals in a gender-specific manner: voluntary wheel running increases pregnenolone levels in female more than in male EAE mice (Mifflin et al., 2018). Also in PD neurosteroidogenesis is affected, since gene expression of 5α-reductase type 1 (SRD5A1) and sulfotransferase 2B1 (SULT2B1) is downregulated in the substantia nigra (SN) of PD patients (Luchetti et al., 2011). Finally, in the zebra finch cerebellar injury causes significant changes in the transcription of steroidogenic enzymes in a gender-specific fashion (Mirzatoni et al., 2010). Moreover, brain injury in the same animal model induces aromatase expression in astrocytes in the proximity of the injury, in females faster than in males, a phenomenon which is abrogated by a COX1/2 inhibitor, suggesting a mediating role of inflammation in the induction of aromatase (Pedersen et al., 2017; Pedersen et al., 2017). Overall, based on the existing studies it is difficult to draw a common pattern of regulation of neurosteroigenesis across the different disease models and cell types, while the mechanisms regulating changes in neurosteroidogenesis in the different disease states, and their pathological significance, remain poorly understood.

8. Receptors and mechanisms of action of neurosteroids

8.1. Estrogens

Estrogens mediate their effects through two estrogen receptor (ER) isoforms, ERα and ERβ, encoded by two different genes, *ESR1* and *ESR2*, respectively (Dahlman-Wright et al., 2006). Upon ligand binding, ERs in association with co-activators or repressors bind to the promoter of genes regulating their transcription (Yasar et al., 2017). However, estrogen can also induce rapid, non-genomic signaling events, which are thought to be mediated by ERα located at the plasma membrane or the estrogen receptor GPR30 (Kampa et al., 2008; Alexaki et al., 2006; Kampa et al., 2013). GPR30 resides at the plasma membrane and the endoplasmic reticulum, and can trigger Ca^{2+} mobilization, cAMP signaling and ERK1/2 activation (Alexaki et al., 2006; Prossnitz and Barton, 2014; Prossnitz and Barton, 2011; Liu et al., 2013; Revankar et al., 2005; Filardo et al., 2000; Alexaki et al., 2004) (Fig. 1). Although most of our knowledge on estrogen signaling derives from studies in the human and murine system, signaling through ERα and ERβ, as well as induction of rapid signaling events, such as ERK and CREB phosphorylation, were also reported in the bird brain (Krentzel and Remage-Healey, 2015). Estrogen rapid signaling events were even shown to regulate neurosteroidogenesis in the brain of songbirds in a sex-specific manner (Pradhan et al., 2008).

Microglia and astrocytes were reported to express all three

receptors, ERα, ERβ and GPR30 (Saijo et al., 2011; Ishihara et al., 2015; Schaufelberger et al., 2016; Zhang et al., 2018; Liu et al., 2005; Bruce-Keller et al., 2000; Sierra et al., 2008; Pawlak et al., 2005; Kuo et al., 2010) (Fig. 1). Using ERα and ERβ knockout animals it was shown that both receptors regulate pro-inflammatory cytokine and chemokine production in LPS-induced neuroinflammation (Brown et al., 2010). In addition, isoform-specific agonists of both receptors induce similar anti-inflammatory effects in microglia, such as attenuation of IL-1β, TNF and COX-2 expression (Smith et al., 2011). However, several studies described different effects of ERα and ERβ in the regulation of neuroinflammation. ERα but not ERβ was shown to mediate the anti-inflammatory effects of 17β-estradiol in mice receiving intraventricular LPS injections (Vegeto et al., 2003). Using conditional knockout animals, it was shown that the neuroprotective effects of estrogen mimetics in EAE were mediated by ERα in astrocytes and not neurons (Spence et al., 2011). In accordance, treatment with an ERα but not an ERβ ligand decreases expression of CCL2 and CCL7 in astrocytes in EAE (Spence et al., 2013). Moreover, ERα but not ERβ is required for 17β-estradiol-mediated inhibition of p65 nuclear translocation in LPS-stimulated macrophages (Ghisletti et al., 2005). On the other hand, an ERβ-selective agonist was reported to suppress inflammatory gene expression in microglia and $CD3^+$ T cells in EAE animals (Wu et al., 2013). Moreover, an ERβ but not an ERα or a GPR30 agonist was shown to inhibit microglial proliferation in vitro (Schaufelberger et al., 2016). In addition, ADIOL, which is a selective ERβ ligand, diminishes TLR4-induced inflammatory responses in microglia via recruitment of CtBP corepressor complexes to AP-1-dependent gene promoters (Saijo et al., 2011) (Fig. 3). Similarly, specific ERβ ligands attenuate IL-1β-induced expression of proinflammatory genes, such as B-cell activating factor (BAFF), IL-23p19 and iNOS, in astrocytes (Saijo et al., 2011). Furthermore, GPR30 activation reduces proinflammatory cytokine and chemokine expression in splenocytes in EAE mice and halts disease progression (Blasko et al., 2009). It also reduces inflammation and improves neural damage in a model of ischemic injury (Zhang et al., 2018). Finally, rapid signaling events, such as p38 and ERK1/2 activation, were described to transmit the anti-inflammatory effects of 17β-estradiol in microglia (Bruce-Keller et al., 2000) (Fig. 1), while in astrocytes, 17β-estradiol and SERMs activate PI3K/Akt signaling and induce TGF-β release (Dhandapani et al., 2005).

8.2. Progestogens

Progesterone, similarly to 17β-estradiol, exerts genomic and non-genomic signaling effects (Jacobsen and Horwitz, 2012; Singh et al., 2013; Petersen et al., 2013; Garg et al., 2017). There are two isoforms of the classical progesterone receptor (PR), PRA and PRB (Jacobsen and Horwitz, 2012). In their inactive state PRs associate with Heat Shock Proteins (HSPs), from which, upon ligation with progesterone, they are released to regulate gene transcription (Jacobsen and Horwitz, 2012). On the other hand, progesterone can activate rapid signaling events, such as Ca^{2+} influx, PKA, ERK or PI3K/AKT activation (Singh et al., 2013). Such rapid events are mediated by two types of distinct membrane receptors, membrane PRs (mPRα-δ) and progesterone membrane receptor components (PGMRC) 1 and 2 (Singh et al., 2013; Petersen et al., 2013; Thomas, 2008) (Fig. 2).

Microglia lack the classical PR (Bali et al., 2013; Sierra et al., 2008), but express PGMRC1 (Bali et al., 2013; Bali et al., 2013; Roche et al., 2016) and mPRα (Meffre et al., 2013), while astrocytes express PR and PGMRC1 (Bali et al., 2013; Bali et al., 2013; Meffre et al., 2005) (Fig. 2). Retinal microglia express PGRMC1, PGRMC2 and mPRα, β and γ (Roche et al., 2016). However, the mechanisms of action of progesterone in the context of neuroinflammation have been poorly studied. Progesterone administered to cuprizone mice or an ex vivo demyelination model promotes remyelination in the corpus callosum and enhances oligodendrocyte numbers in a PR-dependent manner (El-Etr et al., 2015; Hussain et al., 2011). Moreover, progesterone in combination with estrogen treatment reduces LPS-induced IL-18 expression in the midbrain, an effect which is inhibited by the PR antagonist mifepristone (Kipp et al., 2007). Furthermore, progesterone induces BDNF release by astrocytes in a Pgrmc1-dependent manner, thereby potentially promoting cell survival under stress conditions, such as glutamate–induced toxicity, ischemia or post-stroke infection (Jodhka et al., 2009; Su et al., 2012; Sun et al., 2016; Kaur et al., 2007; Atif et al., 2013; Yousuf et al., 2013) (Fig. 2). Recently, selective mPR ligands were shown to increase proinflammatory cytokine expression (TNF, IL-1β) in PBMC and monocytes, while decreasing IL-2 and TNF in Jurkat T cells (Polikarpova et al., 2019), suggesting that the effects of progesterone might be cell type-specific.

Finally, allopregnanolone does not bind to PR but to γ-aminobutyric acid (GABA) A receptors (Singh et al., 2013; Lambert et al., 2003). $GABA_A$ receptors are present in both, astrocytes and microglia (Lee et al., 2011) (Fig. 2). Treatment with GABA reduces microglial and astroglial inflammatory responses to LPS and IFNγ by inhibiting NF-κB and p38 activation (Lee et al., 2011) (Fig. 2). Similarly, $GABA_A$ receptors are also expressed in macrophages and mediate anti-inflammatory effects of GABA (Reyes-Garcia et al., 2007; Bhat et al., 2010). Furthermore, T cells also express $GABA_A$ receptors and GABA downregulates effector $CD4^+$ T cell responses (Bhat et al., 2010; Tian et al., 2004). In accordance, GABAergic agents inhibit inflammation and halt disease development in EAE mice (Bhat et al., 2010).

8.3. DHEA

DHEA can bind with low affinity to several nuclear receptors, such as PPAR, pregnane X receptor (PXR), ERα, ERβ and AR (Prough et al., 2016; Chen et al., 2005). However, such interactions have not been studied in depth and could reflect binding of downstream metabolites of DHEA to these receptors (Prough et al., 2016). For instance, the derivative of DHEA, ADIOL, was reported to bind to ERβ exerting anti-inflammatory effects in microglia (Saijo et al., 2011) (Fig. 3). On the other hand, DHEA was shown to bind with high affinity to membrane receptors. For instance, it can bind with high affinity to membrane G protein-coupled receptors (GPCRs) triggering rapid signaling events (Liu and Dillon, 2002; Liu and Dillon, 2004; Alexaki et al., 2009). Moreover, DHEA binds with high affinity to isolated PC12 cell membranes and protects against serum deprivation-induced apoptosis in a G protein-dependent manner (Charalampopoulos et al., 2006; Charalampopoulos et al., 2004; Charalampopoulos et al., 2006). The anti-apoptotic effect of DHEA associates with induction of CREB and enhanced Bcl-2 and Bcl-xL protein expression (Charalampopoulos et al., 2004). Furthermore, we discovered that DHEA binds with high affinity (K_D at the nM range) to both NGF receptors, the high affinity tropomyosin related kinase (TrkA) receptor and the pan-neurotrophin receptor p75 ($p75^{NTR}$) (Lazaridis et al., 2011; Reichardt, 2006). DHEA induces TrkA phosphorylation and subsequently Shc, ERK1/2 and Akt activation, while it alters the interaction of $p75^{NTR}$ with TRAF6, RIP2 and RhoGDI (Lazaridis et al., 2011; Pediaditakis et al., 2016). TrkA silencing reverses the anti-apoptotic effect of DHEA in PC12 cells, while administration of DHEA during embryonic development of NGF null mice reduces apoptosis of TrkA-positive sympathetic neurons (Lazaridis et al., 2011). Moreover, DHEA also binds to the BDNF receptor, TrkB, and the NT-3 receptor, TrkC (Pediaditakis et al., 2015). Along the same line, we demonstrated that microglia express TrkA and DHEA reduces microglial inflammatory responses (Alexaki et al., 2017; Fodelianaki et al., 2019). Specifically, DHEA triggers through TrkA Akt1/2 activation, followed by CREB phosphorylation, which induces the expression of histone 3 lysine 27 (H3K27) demethylase, Jumonji Domain Containing 3 (Jmjd3) (Alexaki et al., 2017) (Fig. 1). Jmjd3 downregulates inflammation and promotes anti-inflammatory gene expression in microglia and macrophages (Tang et al., 2014; Ishii et al., 2009; Alexaki et al., 2018) (Fig. 3). Also the prototype ligand of TrkA, NGF, attenuates the inflammatory responses of LPS-stimulated microglia, which

associates with less NF-κB and JNK activation and reduced glycolysis (Fodelianaki et al., 2019). Moreover, NGF promotes TrkA-dependent Aβ clearance by microglia and attenuates microglial Aβ-induced proinflammatory activation (Rizzi et al., 2018). Collectively, these findings suggest that DHEA promotes neuronal survival and down-regulates neuroinflammation through TrkA signaling in neurons and microglia, respectively.

9. Synthetic DHEA analogues with neurotrophic activity

Since DHEA is a precursor of androgens and estrogens, its metabolites might mediate or mask some of its effects (Compagnone and Mellon, 2000; Saijo et al., 2011). Moreover, although DHEA could be a promising candidate in the treatment of neurodegenerative diseases due to its neuroprotective and anti-inflammatory properties (Alexaki et al., 2017; Charalampopoulos et al., 2008; Gravanis et al., 2017), its potential clinical use could be linked to increased risk of hormone–related cancer development due to its metabolism to androgens and estrogens. To overcome these burdens, Calogeropoulou et al (Calogeropoulou et al., 2009) synthesized a series of DHEA analogues with modifications at C3 or C17, which are key positions for the metabolic transformation of DHEA to androgens or estrogens (Calogeropoulou et al., 2009). Out of these analogues, one C17-spiroepoxy steroid derivative, called BNN27, was shown to bind to TrkA, but not ERα or ERβ, exerting neuroprotection, and to synergize with NGF in promoting axonal growth, while exhibiting TrkA-dependent anti-inflammatory properties in microglia (Calogeropoulou et al., 2009; Pediaditakis et al., 2016). BNN27 also binds and activates $p75^{NTR}$ altering its interaction with RIP2 and RhoGDI (Pediaditakis et al., 2016). Moreover, in a $p75^{NTR}$-dependent manner, it protects mouse cerebellar granule neurons against serum deprivation-induced apoptosis and decreases JNK phosphorylation and caspase-3 cleavage (Pediaditakis et al., 2016). In the cuprizone MS mouse model, BNN27 treatment reduces microgliosis, astrogliosis and demyelination and increases oligodendrocyte survival (Bonetto et al., 2017). Anti-inflammatory effects of BNN27 were also demonstrated in the rat streptozotocin model of diabetic retinopathy, where BNN27 treatment reverses the diabetes-induced astrogliosis and microgliosis, reduces pro-inflammatory (TNF and IL-1β) and increases anti-inflammatory (IL-10 and IL-4) cytokine levels in diabetic rat retinas (Iban-Arias et al., 2018). Moreover, BNN27 induces TrkA phosphorylation in treated retinas and attenuates loss of function of amacrine and ganglion cells in a TrkA-dependent manner, correlating with reduced caspase-3 cleavage and $p75^{NTR}$ expression (Iban-Arias et al., 2018). BNN27 also protects motor neurons co-cultured with astrocytes derived from patients with amyotrophic lateral sclerosis (ALS) carrying superoxide dismutase 1 (SOD1) mutations, but does not alter the behavioral outcome or expression of neuropathological markers in G93A SOD1 mice (Glajch et al., 2016). Nonetheless, BNN27 failed to induce TrkA phosphorylation and reduce gliosis and neuronal cell death in a model of retinal detachment (Tsoka et al., 2018). Furthermore, it was shown that BNN27 might be metabolized in mouse and human hepatocytes to molecules, which await to be characterized (Bennett et al., 2016). Another DHEA analogue, called BNN20, which also binds to TrkA, TrkB and $p75^{NTR}$ neurotrophin receptors, reverses the loss of dopaminergic neurons, restores BDNF levels and reduces iNOS expression in the midbrain of the 'weaver' PD mouse model (Botsakis et al., 2017). Finally, both analogues, BNN27 and BNN20, were demonstrated to induce expression of neurotrophin-related genes in induced pluripotent stem cells (iPSC)-derived motor neurons (Bennett et al., 2016).

In view of their small molecular size and their selective functions through NGF receptors, we termed these synthetic DHEA analogues 'microneurotrophins' (Gravanis et al., 2017). The neuroprotective and anti-inflammatory properties of microneurotrophins, in conjunction with their small molecular size, allowing them to readily cross the BBB when administrated systemically (Bennett et al., 2016), render them interesting candidates in the treatment of neurodegenerative diseases (Gravanis et al., 2017). Their therapeutic applicability will be further examined in future studies.

10. Conclusions and future prospects

In summary, neurons and glia synthesize neurosteroids, and in turn, neurosteroids, produced de novo in the CNS or deriving from the circulation, can regulate CNS functions. In neurodegenerative diseases neurosteroidogenesis can be significantly altered. Whether these changes reflect an adaptation favoring reestablishment of homeostasis or epiphenomena of neurodegeneration, stress conditions or inflammation, is not clear. However, increasing amount of evidence suggests that neurosteroids, such as 17β-estradiol, DHEA and allopregnanolone, might regulate neurodegeneration and neuroinflammation, in several cases supporting neuronal survival either through a direct effect on neurons and/or by halting inflammatory responses of microglia and astrocytes (Figs. 1–3). This evidence mainly derives from in vitro culture systems, as well as animal models for neurodegenerative diseases, such as MS, AD, PD or TBI. In summary, across the different disease animal models and in vitro culture systems, 17β-estradiol, progesterone, allopregnanolone and DHEA were shown to reduce microglial inflammation. Despite the fact that all four described neurodegenerative diseases involve microglia-mediated neuroinflammation, the final outcome of steroid administration on disease development is different for each steroid hormone and disease model, since this depends on many different factors, such as the experimental setting, the gender or the steroid dose.

In contrast to the many successful animal studies, most of the clinical studies have failed to show an effect of systemically applied steroid hormones in the progression of neurodegenerative diseases. This could be attributed to the fact that steroids were in most cases administered to patients in an advanced disease stage and in relatively low concentrations, compared to the high concentrations used in animal studies. These conditions (drug concentrations applicable to humans, steroid administration in an advanced disease stage) should be taken under consideration in future animal studies. Other reasons for the discrepancies between animal and human studies could be the heterogeneity in the pool of enrolled patients, different mechanisms driving human diseases and those involved in animal models, as well as differences in the human versus murine physiology. Nevertheless, in vivo studies have allowed the investigation of mechanisms involved in the regulation of neuroinflammation by neurosteroids, which could be therapeutically harnessed in the future. To this end, the use of induced pluripotent stem cells (iPS) deriving from patients with a known neurodegenerative disease-associated genetic background for the generation of neurons, microglia or astrocytes could greatly enhance our knowledge on the regulation of neuroinflammation (McKinney, 2017; Abud et al., 2017; Perriot et al., 2018).

A drawback of clinical and animal studies is the conversion of the administered steroids to downstream metabolites, which could mediate, mask or even antagonize the effects of the applied or endogenous neurosteroids. The use of non-metabolizable steroids, which would share similar functions with their prototype molecules, would overcome this obstacle. Moreover, in vivo studies in which steroids were systemically applied provide little information on the role of endogenous neurosteroids in the CNS. Therefore, studies in conditional knockout animals lacking expression of steroidogenic enzymes or target receptors in certain CNS cells would substantially contribute to our knowledge on the role of endogenous neurosteroids in neurodegenerative diseases. Cell-specific Cre lines for microglia (Cx3Cr1-Cre/ERT2) (Goldmann et al., 2013), astrocytes (Aldh1l1-Cre/ERT2, GFAP-Cre/ERT2) (Srinivasan et al., 2016; Casper et al., 2007) and oligodendrocytes (Pdgfra-Cre/ERT2, PLP-Cre/ERT2) (Zawadzka et al., 2010; Doerflinger et al., 2003) were developed and could be key implements in these studies. Furthermore, following the spatiotemporal progression of

neuroinflammation in vivo would significantly advance our understanding of neurodegenerative diseases. In this aspect, engagement of animal models, such as the zebrafish larvae, allowing noninvasive imaging inside the brain, could be of great benefit (Oosterhof et al., 2015). Of note, neuroinflammation in zebrafish, similarly to mammals, is driven by microglia and astrocytes (Oosterhof et al., 2015; Kyritsis et al., 2012; Sieger et al., 2012), while the zebrafish brain is also steroidogenic (Diotel et al., 2011). Lastly, taking into account the recently revealed great heterogeneity of CNS cell populations, such as microglial cells (Bottcher et al., 2019; Li et al., 2019; Mathys et al., 2017), the study of neurosteroids in the context of neuroinflamamtion could substantially profit from cutting edge technology, such as single-cell transcriptomics, proteomics and metabolomics. These approaches would unravel in great detail the mechanisms regulated by neurosteroids and could thus offer valuable knowledge for the treatment of neurodegenerative diseases.

Funding

Supported by grants from the Deutsche Forschungsgemeinschaft Germany (SFB-TR 205 to T.C. and V.I.A.) and the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement (No 765704 to I.C. and V.I.A.).

Declaration of Competing Interest

None.

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