Neuroactive Steroids

37

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Abstract

Neuroactive steroids regulate neuronal and glial function via non-genomic mechanisms by interacting with ion channels and neurotransmitter receptors. The adrenal glands and gonads are important sources of neuroactive steroids. In addition, neuroactive steroids can be produced locally within the central nervous system and these agents are denoted as neurosteroids. Enzymes involved in neurosteroid biosynthesis are expressed in the cerebellum, where these agents modulate the development of cerebellar neurons as well as glial cells. Neurosteroids also exert neuroprotective actions and modulate synaptic transmission and plasticity in mature neurons. Deficits in cerebellar neuroactive steroid signaling may play a role in the pathophysiology of several conditions involving the cerebellum, including Niemann–Pick type C disease, gestational dietary deficiency of methyl donors (folate and vitamin B12), prenatal stress, brain tumors, schizophrenia, autism, mood disorders, and alcohol use disorder. In addition, neuroactive steroids are emerging as potential therapeutic agents for a number of diseases that impair cerebellar function.

Keywords

Steroid · Neurotransmitter · Receptor · Channel
Synaptic · Plasticity · Enzyme

37.1 Introduction

Steroid hormones are derived from cholesterol and bind to ligand-dependent nuclear receptors that act as transcription factors, controlling the expression of a wide range of genes involved in numerous physiological and pathophysiological processes in many brain regions, including the cerebellum (Mahfouz et al. 2016; Pillerová et al. 2021; Zsarnovszky et al. 2018). Steroids also regulate neuronal function via non-genomic mechanisms by interacting with ion channels and metabotropic receptors; these agents are known as neuroactive steroids. Major sources of neuroactive steroids (or their precursors) are the adrenal glands and gonads; because steroids are lipophilic, they can efficiently cross the blood–brain barrier (Gatta et al. 2021; Guennoun 2020; Kudova 2021; Lloyd-Evans and Waller-Evans 2020). In addition, neuroactive steroids are produced locally in glial and neuronal cells of the central nervous system—independently of peripheral organs—and these compounds are known as neurosteroids (Kudova 2021; Schverer et al. 2018). Neuroactive steroids regulate many neuronal functions including neurotransmitter release, neuronal plasticity, and neuronal excitability (Kudova 2021; Lloyd-Evans and Waller-Evans 2020; Schverer et al. 2018). These agents have important roles in a variety of neuropsychiatric disorders, including epilepsy, substance abuse, multiple sclerosis, depression, and Alzheimer's disease (Lloyd-Evans and Waller-Evans 2020; Gatta et al. 2021). In the next sections, we will discuss the specific roles of neuroactive steroids on cerebellar physiology and pathophysiology.

37.2 Physiological Effects

37.2.1 Developing Cerebellum

Several of the enzymes involved in neurosteroid biosynthesis are expressed in the cerebellum (Fig. 37.1) (Ukena et al.

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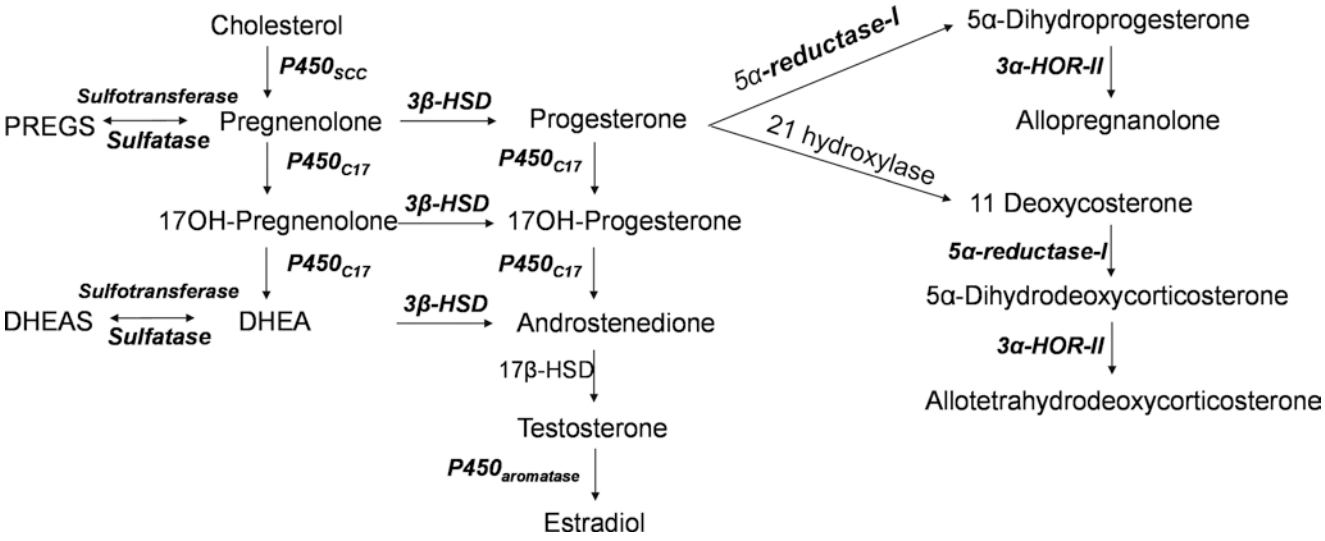

Fig. 37.1 Neurosteroid Biosynthetic Pathway. Enzymes shown in bold and italics have been identified in the cerebellum. Steroid 17 alpha-hydroxylase/17,20 lyase ($P450_{C17}$); pregnenolone sulfate (PREGS); dehydroepiandrosterone (DHEA); DHEA sulfate (DHEAS). For other enzyme abbreviations, see text

1998, 1999; Agís-Balboa et al. 2006; Kiyokage et al. 2014; Sakamoto et al. 2003; Kríz et al. 2008; Yarim and Kabakci 2004). Purkinje cells (PCs) express cholesterol side chain cleavage enzyme ($P450_{scc}$) during neonatal life and adulthood (Ukena et al. 1998). Pregnenolone sulfate, a neuroactive steroid formed through the P450scc pathway, potentiates glutamatergic transmission at climbing fiber-PC synapses in neonatal rats, an effect mediated by an increase in presynaptic Ca^{2+} levels acting on steroid-sensitive transient receptor potential melastatin 3 receptors (Zamudio-Bulcock et al. 2011; Zamudio-Bulcock and Valenzuela 2011). During neonatal life, rat PCs and external granule cells (GrCs) express 3β-hydroxysteroid dehydrogenase (3β-HSD) and generate progesterone (Fig. 37.1)(Ukena et al. 1999). Progesterone promotes dendritic outgrowth and increases spine density in PCs via intracrine and/or paracrine activation of nuclear receptors (Sakamoto et al. 2003). Progesterone and its metabolites also promote cerebellar myelination (Ghoumari et al. 2003). Allopregnanolone has also been detected in the neonatal cerebellum where it promotes the survival of PCs and GrCs (Sakamoto et al. 2003; Tsutsui et al. 2011; Yawno et al. 2009). In samples from adolescent rats, immunohistochemical studies showed that 5α-reductase type I protein is expressed in glial cells, indicating that these cells can synthesize 5α-dihydroprogesterone and possibly allopregnanolone (Fig. 37.1) (Kiyokage et al. 2014). In juvenile quails, allopregnanolone generated in the pineal gland promotes PC survival (Haraguchi et al. 2012).

In PCs and external GrCs from neonatal rats, high levels of both aromatase ($P450_{aromatase}$) and estrogen can be detected (Fig. 37.1)(Sakamoto et al. 2003). Estradiol injection near the vermis of postnatal day 6–9 rats increased dendritic growth and spine density in PCs, perhaps via nuclear estrogen receptor-driven production of brain-derived neurotrophic factor (Sakamoto et al. 2003; Sasahara et al. 2007). In 10–12-day-old rats, intracerebral injection of prostaglandin E2 stimulated $P450_{aromatase}$ activity and estradiol synthesis; this was associated with a decrease in dendritic length, reduced spinophilin content, and altered excitability of PCs (Dean et al. 2012). Estrogen administration was found to affect levels of presynaptic (SNAP25, VAMP1, VAMP2) and postsynaptic (PSD95) proteins in developing deep cerebellar nuclei neurons (Manca et al. 2014).

37.2.2 Mature Cerebellum

Adult mice express 5α-reductase type I and 3α-HOR-II mRNA in PCs and to a lesser extent in GrCs (Agís-Balboa et al. 2006). The cerebellum of mature rodents can produce allopregnanolone (Griffin et al. 2004; Caruso et al. 2013). Allopregnanolone and allotetrahydrodeoxycorticosterone potentiate synaptic $GABA_A$ receptor function in PCs and GrCs (Cooper et al. 1999; Kelley et al. 2011). In GrCs and stellate cells, the effect of allotetrahydrodeoxycorticosterone on synaptic $GABA_A$ receptors depends on the presence of δ subunits (Vicini et al. 2002). Allotetrahydrodeoxycorticosterone potentiates tonic currents mediated by δ subunit-containing extrasynaptic $GABA_A$ receptors in rat cerebellar GrCs (Hamann et al. 2002).

Mature cerebellar PCs and GrCs express estrogen receptors (Hedges et al. 2012). Estrogen exerts rapid modulatory effects on locomotor activity-induced PC firing in female rats (Smith 1989). Gonadal estradiol facilitates the induction of long-term potentiation and increases synaptic density at

parallel fiber-to-PC synapses; activation of β-estrogen receptors in PCs enhances gain-decrease vestibulo-ocular reflex learning in mice (Andreescu et al. 2007). Subsequent optical imaging studies demonstrated that endogenous estrogen facilitates glutamatergic transmission at parallel fiber-to-PC synapses (Hedges et al. 2012). More recently, Dieni et al. (2018a, b) found that blockade of 17β-estradiol synthesis with a $P450_{aromatase}$ inhibitor (letrozole, administered orally) in adult (150–170 days old) male rats abolished gain increases and decreases in vestibulo-ocular reflex adaptation (similar effect was observed in 30–34 days old rats). Letrozole prevented long-term potentiation but not long-term depression at parallel fiber-to-PC synapses (Dieni et al. 2018a). Interestingly, $P450_{aromatase}$ is expressed at low levels in adult PCs, suggesting that localized synthesis of 17β-estradiol mediates its effects on PC synaptic plasticity, contributing to the regulation of vestibulo-ocular reflex adaptation (Dieni et al. 2020, b; Tozzi et al. 2020).

37.3 Roles in Cerebellar Diseases

37.3.1 Developing Cerebellum

In a mouse model of Niemann–Pick type C disease, a lysosomal lipid storage disorder, expression of 3α-hydroxysteroid oxidoreductase II (3α-HOR-II) activity was found to be reduced in the cerebellum and neonatal administration of allopregnanolone increased survival of both PCs and GrCs by a mechanism involving nuclear pregnane X receptors (Griffin et al. 2004; Langmade et al. 2006).

Using a rat model of gestational dietary deficiency of methyl donors (folate and vitamin B12), El Hajj Chehadeh et al. (2014) detected a reduction in the levels of the steroidogenic acute regulatory protein (involved in the transfer of cholesterol from the outer to the inner mitochondrial membrane), $P450_{aromatase}$, estrogen receptors α and β, and luteinizing hormone receptors in PCs of postnatal day 21 female offspring. Progesterone and estradiol levels were also found to be decreased in the cerebellum of these female rats. These findings indicate that methyl donor deficiency during gestation induces persistent deficits in neuroactive steroids synthesis and function in PCs.

Mice pups deficient in reelin, which have been used to model some aspects of schizophrenia and autism, display alterations in cerebellar neuroactive steroid levels at postnatal day 5 (increased testosterone and 17β-estradiol levels and decreased dihydrotestosterone levels) as well as PC degeneration at postnatal day 15 that could be corrected by 17β-estradiol administration at postnatal day 5 (Biamonte et al. 2009).

The effect of prenatal stress on the actions of neurosteroids in the cerebellum was studied in guinea pigs (Bennett et al. 2017). The investigators hypothesized that the developing cerebellum could be vulnerable to prenatal stress because of its relatively high levels of glucocorticoid receptor expression. Guinea pigs were exposed to strobe light for 2 hr. on gestational days 50, 55, 60, and 65 (average guinea pig pregnancy duration is 67 days). Advantages of using guinea pigs include that the placental structure and function is more similar to that of humans, gestation duration is more prolonged than in rodents, and newborns are more mature (Morrison et al. 2018). It was found that prenatal stress produced age-dependent reductions in mature oligodendrocyte numbers and reactive astrocytes in cerebellar lobule VIII of term female offspring, but this effect disappeared by postnatal day 21. Levels of neurosteroid-sensitive $GABA_A$ receptors expressed in the extra-synaptic compartment of GrCs (i.e., containing α_6 and δ subunits) were reduced in a sex- and age-dependent manner, whereas cerebellar 5α-reductase levels (Fig. 37.1) were increased, which may represent a compensatory mechanism to maintain tonic GABAergic inhibition (Bennett et al. 2017). These findings indicate that prenatal stress disrupts the actions of neurosteroids in the developing cerebellum.

Studies suggest that neuroactive steroids play an important role in the pathophysiology of childhood tumors. One of the most common malignant pediatric tumors is medulloblastoma, which originates in GrC-like precursors that express elevated estrogen receptor levels (Belcher 2008). Activation of these receptors with low physiologically relevant concentrations of estradiol rapidly activates extracellular signal-regulated kinase (ERK)1/2 via a G protein-dependent mechanism and stimulates migration in a cell line of cerebrocortical origin (Belcher 2008). More recently, it was shown that estrogen stimulates growth of medulloblastomas via estrogen receptor β-induced insulin-like growth factor-1 receptor signaling that increases survival of tumor cells (Cookman and Belcher 2015). Estrogen and soy isoflavonoids reduce medulloblastoma cell sensitivity to chemotherapy (Belcher et al. 2017). Antagonism of estrogen receptors blocked the tumor-promoting effects of estrogen in cultured cells and medulloblastoma human xenograft models (Belcher et al. 2009). These studies suggest that estrogen receptor β signaling contributes to medulloblastoma tumorigenesis and that adjuvant antiestrogen therapy could be beneficial in the management of these tumors. It is important to determine if neuroactive steroids play a role in the biology of other cerebellar pediatric tumors (e.g., juvenile pilocytic astrocytomas and ependymomas). A recent review indicates that astrocytomas are also hormone-sensitive tumors (Hirtz et al. 2020).

37.3.2 Mature Cerebellum

Cerebellar neurosteroid levels were measured during normal aging in wild-type mice and heterozygous staggerer mice, which display precocious aging (Janmaat et al. 2011). Aging-related decreases in 17β-estradiol, progesterone, and testosterone levels were correlated with Purkinje cell loss in these mice; these effects occurred earlier in the staggerer mice. Interestingly, locally produced cerebellar neurosteroids (pregnenolone, 5α-dihydroprogesterone, and allopregnanolone) did not decline with age in either wild-type or staggerer mice.

The cerebellum is also an important target of many abused substances and plays an important role in the pathophysiology of substance use disorders (Moulton et al. 2014). A recent study characterized neurosteroid pathways in human male postmortem brains from alcohol-use disorder patients and matching controls (Gatta et al. 2021). In samples from patients with alcohol use disorder, cerebellar mRNA levels for the 18-kDa translocator protein (involved in outer to inner mitochondrial membrane transport of cholesterol), 3α-hydroxysteroid dehydrogenase (Fig. 37.1), and the steroid-sensitive $GABA_A$ receptor δ subunit were significantly reduced. The cerebellar 3α-hydroxysteroid dehydrogenase promoter exhibited elevated DNA methylation levels. Cerebellar allopregnanolone and pregnanolone levels were decreased. These findings suggest that chronic alcohol exposure disrupts neurosteroid signaling in the cerebellum. It is important to determine if other abused substances produce similar effects.

37.4 Conclusions and Future Directions

The cerebellum is an important target of neuroactive steroids produced in peripheral glands, other brain regions (i.e., the pineal gland), and the cerebellum itself. Developing PCs are a major source of locally produced neurosteroids (i.e., progesterone and allopregnanolone), which contribute to the maturation of dendrites, spines, and synapses in these neurons (Tsutsui and Haraguchi 2020). $GABA_A$ receptor-modulating neurosteroids (e.g., allopregnanolone) are produced in the mature cerebellum and regulate synaptic transmission and excitability of PCs and GrCs. The function of mature PCs and GrCs is modulated by estrogen receptors that regulate synaptic transmission and plasticity, as well as vestibulo-ocular reflex adaptation that is mediated, in part, by modulation of vestibulo-cerebellar function by estrogen.

Studies suggest that neuroactive steroids contribute to the pathophysiology of several diseases that involve the cerebellum, including Niemann–Pick type C disease, gestational dietary deficiency of methyl donors (folate and vitamin B12), prenatal stress, brain tumors, schizophrenia, autism, mood disorders, and alcohol use disorder. Future studies should examine if disruptions in cerebellar neuroactive steroid signaling are related to other conditions such as preterm birth, attention deficit hyperactivity disorder, fetal alcohol spectrum disorder, traumatic brain injury, stroke, substance use disorders, sleep disorders, and multiple sclerosis (Dean and McCarthy 2008; Valenzuela et al. 2008; Caldeira et al. 2004; Fanelli et al. 2013; Potts et al. 2009; Mirzatoni et al. 2010; Caruso et al. 2014; Tsutsui and Haraguchi 2020). It is also important to investigate the potential utility of neuroactive steroids in the treatment of diseases that affect the cerebellum (Ardeshiri et al. 2006; Kelley et al. 2011; Jung et al. 2002; Murugan et al. 2019; Xu et al. 2022; Yan et al. 2015). Another exciting area of research is the regulation of the cerebellar actions of neuroactive steroids by the gut microbiota (Diviccaro et al. 2021).

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