Chapter 36
Neurosteroids

C. Fernando Valenzuela

Abstract Neurosteroids are steroids that are produced locally within the central nervous system independently of adrenal glands and gonads. Enzymes involved in neurosteroid biosynthesis are expressed in the cerebellum. These agents modulate the development of cerebellar neurons as well as glial cells. Neurosteroids exert neuroprotective actions and modulate synaptic transmission and plasticity in mature neurons. Deficits in cerebellar neurosteroid production may play a role in the pathophysiology of neuropsychiatric disorders.

Keywords Neurosteroids • Neuroactive • Steroids • Cerebellum • Neuron • Glia • Purkinje cells • Granule cells

Steroids produced locally in the brain are denoted as neurosteroids. Neurosteroids modulate neuronal and glial cells via regulation extracellular and intracellular receptors. Several of the enzymes involved in neurosteroid biosynthesis are expressed in the cerebellum (Fig. 36.1) (Ukena et al. 1998, 1999; Agis-Balboa et al. 2006; Kiyokage et al. 2014; Sakamoto et al. 2003; Kriz et al. 2005; Yarim and Kabakci 2004).

Purkinje cells (PCs) express cholesterol side chain cleavage enzyme ($P450_{scc}$) during neonatal life and adulthood (Ukena et al. 1998). During neonatal life, rat PCs and external granule cells (GrCs) express 3β-hydroxysteroid dehydrogenase (3β-HSD) and generate progesterone (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. 2001). Progesterone and its metabolites also promote cerebellar myelination (Ghoumari et al. 2003).

Allopregnanolone has also been detected in the neonatal cerebellum where it promotes survival of PCs and GrCs (Tsutsui et al. 2011; Sakamoto et al. 2001;

C.F. Valenzuela (✉)
Department of Neurosciences, MSC08 4740, 1 University of New Mexico, 87131-0001 Albuquerque, NM, USA
e-mail: fvalenzuela@salud.unm.edu

© Springer International Publishing Switzerland 2016

D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_36

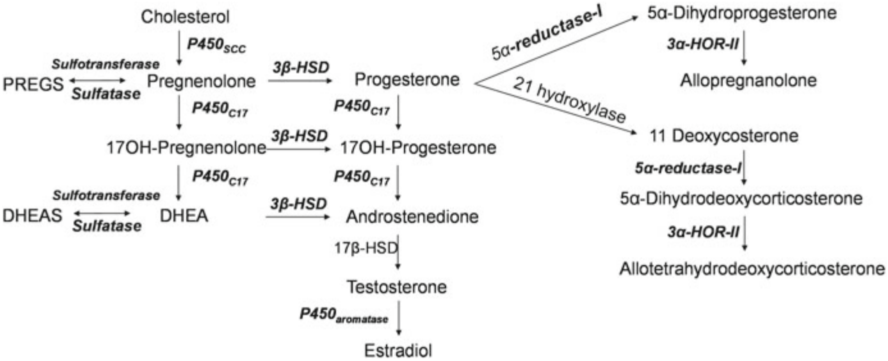

Fig. 36.1 Neurosteroid Biosynthetic Pathway. Enzymes shown in bold and italics have been identified in the cerebellum. Steroid 17 alpha-hydroxylase/17,20 lyase ($P450_{C17}$); pregnenolone sulfate (PREGS); dehydroepiandrosterone (DHEA); DHEA sulfate (DHEAS). For other enzyme abbreviations, see text

Yawno et al. 2009). In juvenile quails, allopregnanolone generated in the pineal gland promotes PC survival (Haraguchi et al. 2012). 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).

In PCs and external GrCs from neonatal rats, high levels of both aromatase ($P450_{aromatase}$) and estrogen can be detected (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). Mice deficient in reelin, which have been used to model some aspects of schizophrenia and autism, displayed alterations in cerebellar neurosteroid levels as well as PC degeneration that could be corrected by estrogen administration (Biamonte et al. 2009).

In GrCs, estrogen rapidly activates ERK1/2 via a G protein-dependent mechanism; protein phosphatase 2A is also activated by estradiol through a different mechanism of action (Belcher 2008). The endocrine disruptor bisphenol A was shown to mimic and occlude these effects. Estrogen regulates the invasiveness of medulloblastoma, a malignant brain tumor that originates at GrC-like precursors (Belcher 2008).

Pregnenolone sulfate potentiates glutamatergic transmission at climbing fiber-PC synapses in neonatal rats, an effect that is mediated by an increase in presynaptic Ca^{2+} levels mediated by steroid-sensitive transient receptor potential melastatin 3 receptors (Zamudio-Bulcock et al. 2011).

Adult mice express 5α-reductase type I and 3α-HOR-II mRNA in PCs and to a lesser extent in GrCs (Agis-Balboa et al. 2006). In samples from adolescent rats, immunohistochemical studies showed that 5α-reductase type I protein is expressed in glial cells (Kiyokage et al. 2014). 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). The potentiating effects of allopregnanolone and related neurosteroids on $GABA_A$ receptors may exert neuroprotective actions in the cerebellum (Ardeshiri et al. 2006; Kelley et al. 2011).

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 et al. 1989). Estradiol facilitates the induction of long-term potentiation and increases synaptic density at parallel fiber-PC synapses; activation of β-estrogen receptors in PCs enhances gain-decrease vestibulo-occular reflex learning (Andreescu et al. 2007). Optical imaging studies indicate that endogenous estrogen facilitates glutamatergic transmission at parallel fiber-PC synapses (Hedges et al. 2012). Cerebellar injury upregulates expression of $P450_{aromatase}$ in birds (Mirzatoni et al. 2010). Estrogen treatment reduced PC death and improved motor coordination in ethanol withdrawn rats (Jung et al. 2002).

References

Agis-Balboa RC, Pinna G, Zhubi A, Maloku E, Veldic M, Costa E, Guidotti A (2006) Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. Proc Natl Acad Sci U S A 103:14602–14607

Andreescu CE, Milojkovic BA, Haasdijk ED, Kramer P, De Jong FH, Krust A, De Zeeuw CI, De Jeu MT (2007) Estradiol improves cerebellar memory formation by activating estrogen receptor beta. J Neurosci 27:10832–10839

Ardeshiri A, Kelley MH, Korner IP, Hurn PD, Herson PS (2006) Mechanism of progesterone neuroprotection of rat cerebellar Purkinje cells following oxygen-glucose deprivation. Eur J Neurosci 24:2567–2574

Belcher SM (2008) Rapid signaling mechanisms of estrogens in the developing cerebellum. Brain Res Rev 57:481–492

Biamonte F, Assenza G, Marino R, D'Amelio M, Panteri R, Caruso D, Scurati S, Yague JG, Garcia-Segura LM, Cesa R, Strata P, Melcangi RC, Keller F (2009) Interactions between neuroactive steroids and reelin haploinsufficiency in Purkinje cell survival. Neurobiol Dis 36:103–115

Caruso D, Pesaresi M, Abbiati F, Calabrese D, Giatti S, Garcia-Segura LM, Melcangi RC (2013) Comparison of plasma and cerebrospinal fluid levels of neuroactive steroids with their brain, spinal cord and peripheral nerve levels in male and female rats. Psychoneuroendocrinology 38:2278–2290

Cooper EJ, Johnston GA, Edwards FA (1999) Effects of a naturally occurring neurosteroid on GABAA IPSCs during development in rat hippocampal or cerebellar slices. J Physiol 521(Pt 2):437–449

Dean SL, Wright CL, Hoffman JF, Wang M, Alger BE, McCarthy MM (2012) Prostaglandin E2 stimulates estradiol synthesis in the cerebellum postnatally with associated effects on Purkinje neuron dendritic arbor and electrophysiological properties. Endocrinology 153:5415–5427

Ghoumari AM, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'Malley BW, Baulieu EE, Schumacher M (2003) Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. J Neurochem 86:848–859

Griffin LD, Gong W, Verot L, Mellon SH (2004) Niemann-Pick type C disease involves disrupted neurosteroidogenesis and responds to allopregnanolone. Nat Med 10:704–711

Hamann M, Rossi DJ, Attwell D (2002) Tonic and spillover inhibition of granule cells control information flow through cerebellar cortex. Neuron 33:625–633

Haraguchi S, Hara S, Ubuka T, Mita M, Tsutsui K (2012) Possible role of pineal allopregnanolone in Purkinje cell survival. Proc Natl Acad Sci U S A 109:21110–21115

Hedges VL, Ebner TJ, Meisel RL, Mermelstein PG (2012) The cerebellum as a target for estrogen action. Front Neuroendocrinol 33:403–411

Jung ME, Yang SH, Brun-Zinkernagel AM, Simpkins JW (2002) Estradiol protects against cerebellar damage and motor deficit in ethanol-withdrawn rats. Alcohol 26:83–93

Kelley MH, Kuroiwa M, Taguchi N, Herson PS (2011) Sex difference in sensitivity to allopregnanolone neuroprotection in mice correlates with effect on spontaneous inhibitory post synaptic currents. Neuropharmacology 61:724–729

Kiyokage E, Toida K, Suzuki-Yamamoto T, Ishimura K (2014) Cellular localization of 5alpha-reductase in the rat cerebellum. J Chem Neuroanat 59–60:8–16

Kriz L, Bicikova M, Hill M, Hampl R (2005) Steroid sulfatase and sulfuryl transferase activity in monkey brain tissue. Steroids 70:960–969

Langmade SJ, Gale SE, Frolov A, Mohri I, Suzuki K, Mellon SH, Walkley SU, Covey DF, Schaffer JE, Ory DS (2006) Pregnane X receptor (PXR) activation: a mechanism for neuroprotection in a mouse model of Niemann-Pick C disease. Proc Natl Acad Sci U S A 103:13807–13812

Mirzatoni A, Spence RD, Naranjo KC, Saldanha CJ, Schlinger BA (2010) Injury-induced regulation of steroidogenic gene expression in the cerebellum. J Neurotrauma 27:1875–1882

Sakamoto H, Ukena K, Tsutsui K (2001) Effects of progesterone synthesized de novo in the developing Purkinje cell on its dendritic growth and synaptogenesis. J Neurosci 21:6221–6232

Sakamoto H, Mezaki Y, Shikimi H, Ukena K, Tsutsui K (2003) Dendritic growth and spine formation in response to estrogen in the developing Purkinje cell. Endocrinology 144:4466–4477

Sasahara K, Shikimi H, Haraguchi S, Sakamoto H, Honda S, Harada N, Tsutsui K (2007) Mode of action and functional significance of estrogen-inducing dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell. J Neurosci 27:7408–7417

Smith SS, Woodward DJ, Chapin JK (1989) Sex steroids modulate motor-correlated increases in cerebellar discharge. Brain Res 476:307–316

Tsutsui K, Ukena K, Sakamoto H, Okuyama S, Haraguchi S (2011) Biosynthesis, mode of action, and functional significance of neurosteroids in the Purkinje cell. Front Endocrinol (Lausanne) 2:61

Ukena K, Usui M, Kohchi C, Tsutsui K (1998) Cytochrome P450 side-chain cleavage enzyme in the cerebellar Purkinje neuron and its neonatal change in rats. Endocrinology 139:137–147

Ukena K, Kohchi C, Tsutsui K (1999) Expression and activity of 3beta-hydroxysteroid dehydrogenase/delta5-delta4-isomerase in the rat Purkinje neuron during neonatal life. Endocrinology 140:805–813

Vicini S, Losi G, Homanics GE (2002) GABA(A) receptor delta subunit deletion prevents neurosteroid modulation of inhibitory synaptic currents in cerebellar neurons. Neuropharmacology 43:646–650

Yarim M, Kabakci N (2004) Neurosteroidogenesis in oligodendrocytes and Purkinje neurones of cerebellar cortex of dogs. Anat Histol Embryol 33:151–154

Yawno T, Hirst JJ, Castillo-Melendez M, Walker DW (2009) Role of neurosteroids in regulating cell death and proliferation in the late gestation fetal brain. Neuroscience 163:838–847

Zamudio-Bulcock PA, Everett J, Harteneck C, Valenzuela CF (2011) Activation of steroid-sensitive TRPM3 channels potentiates glutamatergic transmission at cerebellar Purkinje neurons from developing rats. J Neurochem 119:474–485