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Review

Progesterone and allopregnanolone in the central nervous system: Response to injury and implication for neuroprotection

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ABSTRACT

Progesterone is a well-known steroid hormone, synthesized by ovaries and placenta in females, and by adrenal glands in both males and females. Several tissues are targets of progesterone and the nervous system is a major one. Progesterone is also locally synthesized by the nervous system and qualifies, therefore, as a neurosteroid. In addition, the nervous system has the capacity to bio-convert progesterone into its active metabolite allopregnanolone. The enzymes required for progesterone and allopregnanolone synthesis are widely distributed in brain and spinal cord. Increased local biosynthesis of pregnenolone, progesterone and 5α-dihydroprogesterone may be a part of an endogenous neuroprotective mechanism in response to nervous system injuries. Progesterone and allopregnanolone neuroprotective effects have been widely recognized. Multiple receptors or associated proteins may contribute to the progesterone effects: classical nuclear receptors (PR), membrane progesterone receptor component 1 (PGRMC1), membrane progesterone receptors (mPR), and γ-aminobutyric acid type A ($GABA_A$) receptors after conversion to allopregnanolone. In this review, we will succinctly describe progesterone and allopregnanolone biosynthetic pathways and enzyme distribution in brain and spinal cord. Then, we will summarize our work on progesterone receptor distribution and cellular expression in brain and spinal cord; neurosteroid stimulation after nervous system injuries (spinal cord injury, traumatic brain injury, and stroke); and on progesterone and allopregnanolone neuroprotective effects in different experimental models including stroke and spinal cord injury. We will discuss in detail the neuroprotective effects of progesterone on the nervous system via PR, and of allopregnanolone via its modulation of $GABA_A$ receptors.

Contents

Abbreviations: 5α-DHPROG, 5α-dihydroprogesterone; CNS, central nervous system; $GABA_A$ receptors, γ-aminobutyric acid type A receptors; GC/MS, gas chromatography/mass spectrometry; 3α-HSOR, 3α-hydroxysteroid oxidoreductase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; MCAO, middle cerebral artery occlusion; PGRMC1, membrane progesterone receptor component 1; mPR, membrane progesterone receptors; PR, progesterone receptors; PR-A, progesterone receptor isoform A; PR-B, progesterone receptor isoform B; PRE, progesterone response element; SRC1,2,3, steroid receptor coactivator-1,2,3; SCI, spinal cord injury; TBI, traumatic brain injury.

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1. Introduction

Progesterone is a hormone and a neurosteroid. As a hormone, it is synthesized by the ovaries, placenta and adrenal glands. As a neurosteroid, it is synthesized locally within the nervous system by both neurons and glial cells. In addition, progesterone can be metabolized into allopregnanolone (also named 3α,5α-tetrahydroprogesterone). The concentrations of these neurosteroids change under different physiological and pathological states [1–8]. Progesterone and allopregnanolone exert several effects in brain and spinal cord including neuroprotection. Their neuroprotective efficiencies have been demonstrated in different experimental models including traumatic brain injury (TBI), spinal cord injury, ischemic stroke, excitotoxic damage of hippocampal neurons and neurodegenerative diseases [9–26].

However, the mechanisms, targets, and effectors of the neuroprotective effects of progesterone and allopregnanolone are understudied. Clarifying their signaling mechanisms is a prerequisite for their efficient therapeutic use.

2. Progesterone and allopregnanolone in brain and spinal cord: sources, biosynthetic pathways and enzyme distribution

The synthesis of progesterone in the nervous system has been demonstrated in several species, and the enzymes required for progesterone and allopregnanolone synthesis are widely distributed throughout the brain and spinal cord [11,27–42]. Progesterone synthesis involves the conversion of cholesterol to pregnenolone by cytochrome P450scc enzyme (located in the mitochondria), then the conversion of pregnenolone to progesterone by the 3β-hydroxysteroid dehydrogenase (3β-HSD) enzyme (located in the mitochondria and the endoplasmic reticulum) [43,44]. The translocation of cholesterol inside the mitochondria is a rate -limiting step in the synthesis of steroids. It involves the "transduceosome", composed of multiple proteins including the translocase 18 kDa (TSPO, previously known as the peripheral benzodiazepine receptor), and the protein StAR [45].

In the brain, the expression of P450scc is well documented [36,46]. 3β-HSD mRNA showed a wide distribution throughout the rat brain. It is principally expressed in neurons of the olfactory bulb, striatum, cortex, thalamus, hypothalamus, septum, habenula, hippocampus and cerebellum [29]. This suggests a broad role of progesterone in regulating neural functions. *In vitro* studies using highly purified cell types have shown that both neurons and glial cells express P450scc and 3β-HSD and can convert pregnenolone to progesterone. Purkinje cells (a typical cerebellar neuron) have been shown to express P450scc and 3β-HSD during postnatal development and in the adulthood and were demonstrated to be a source of progesterone [47,48]. The brain has also the capacity to metabolize progesterone; the major metabolic pathway in the nervous system is 5 α-reduction [49–54]. Progesterone is first converted by the enzyme 5α-reductase into 5α-dihydroprogesterone, which is converted into allopregnanolone by the 3α-hydroxysteroid oxidoreductase (3α-HSOR) enzyme [55,56]. In mouse and rat brain, these enzymes have been shown to be co-expressed in neurons. *In situ* hybridization combined with immunofluorescence analysis allowed the identification of these neurons as mainly glutamatergic neurons in the cortex, hippocampus and olfactory bulb and as GABAergic output neurons in the striatum, thalamus and cerebellum [52].

In the spinal cord, significant levels of pregnenolone and progesterone remained detectable after the removal of gonads and adrenal glands suggesting their local synthesis [53,57]. Several groups have shown that spinal cord possesses the enzymatic set to synthesize pregnenolone, progesterone and allopregnanolone [51,53,57–60]. P450scc enzyme is expressed and is bioactive in the dorsal horn, nociceptive supraspinal nuclei and somatosensory cortex [59,60]. 3β-HSD mRNA is expressed in motoneurons in the ventral horn and small neurons of the dorsal horn [57]. 5α-reductase type 1 is expressed only by glial cells while 5α-reductase type 2 and 3α-HSOR are expressed by oligodendrocytes, neurons and astrocytes [51].

3. Progesterone receptors: PR, PGRMC1 and mPR in brain and spinal cord

Progesterone uses multiple signaling pathways: the classical one is the regulation of gene expression after binding to intracellular progesterone receptors (PR) which belong to the nuclear receptor super-family of transcription factors. Progesterone may also bind to specific membrane sites (mPR/PGRMC1 complex) and activate intracellular signaling pathways. Finally, progesterone may modulate $GABA_A$ receptor activity after conversion to allopregnanolone [11,61–65]. Both brain and spinal cord express all these receptors and have the capacity to metabolise progesterone into allopregnanolone. This suggests that, one or the other mechanism may be triggered in these tissues according to the physiological or pathological conditions, depending on the available concentration and the expression of the different receptors.

3.1. Intracellular progesterone receptors (PR)

The transcriptional ("genomic" or "classical") effects of progesterone are mediated by at least two intracellular receptor isoforms (PR-A and PR-B). They are transcribed from two distinct promoter regions of a single gene and differ by an additional 164-amino-acid segment in the N-terminal region of PR-B [66–68]. Four functional domains can be distinguished in the structure of PR: the N-terminal domain, the DNA binding domain (DBD), the hinge region and the ligand binding domain (LBD) at the C-terminus. PR contain also a transcription activation function (AF) domain and inhibition function (IF) domains [69]. According to the classical view, gene transcription is activated by PR dimers bound to palindromic response elements (PRE) in the promoter region of the target genes. The detailed PR signaling was recently reviewed in [11].

PR expression is regulated by estrogens and progesterone. Estrogens induce PR but not in all brain regions. Indeed, estrogen