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Levels and actions of progesterone and its metabolites in the nervous system during physiological and pathological conditions

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ABSTRACT

Progesterone is synthesized and actively metabolized in the central and peripheral nervous system, into neuroactive steroid metabolites, such as dihydroprogesterone, allopregnanolone and isopregnanolone. Progesterone and/or its metabolites exert a variety of effects acting as physiological regulators of neuronal and glial development and plasticity, controlling reproduction, neuroendocrine events, mood and affection. In addition, these neuroactive steroids maintain neural homeostasis and exert neuroprotective actions. In agreement, metabolic pathways of progesterone are affected by modifications in the level of gonadal hormones and by pathology or injury with a regional specificity and in a sex-dimorphic way. Therefore, observations here summarized may provide a background to design sex-specific therapies based on progesterone metabolites. On this point of view, considering that one of the major limits of a therapy based on neuroactive steroids could be modifications in their plasma levels and their consequent peripheral effects, pharmacological treatments aimed to increase their levels in the nervous system could provide an interesting therapeutic option.

Contents

Abbreviations: 3α-HSOR, 3α-hydroxysteroid oxidoreductase; 3β-HSOR, 3β-hydroxysteroid oxidoreductase; 3α-THP, 3α,5α-tetrahydroprogesterone; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 3β-THP, 3β,5α-tetrahydroprogesterone; 5α-R, 5α-reductase; CNS, central nervous system; DHP, dihydroprogesterone; EAE, experimental autoimmune encephalomyelitis; Iba1, ionized calcium-binding adapter molecule 1; LC-MS/MS, liquid chromatography tandem mass spectrometry; LXR, liver X receptor; MBP, myelin basic protein; P0, glycoprotein zero; P450scc, P450 side-chain cleavage enzyme; PMP22, peripheral myelin protein 22; PNS, peripheral nervous system; PR, progesterone receptor; PREG, pregnenolone; PROG, progesterone; StAR, steroidogenic acute regulatory protein; STZ, streptozotocin; TSPO, translocator protein of 18 kDa; WT, wild type.

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1. Introduction

Neuroactive steroids are steroid molecules acting in the nervous system. These molecules are synthesized by neurons and glial cells (i.e., neurosteroids) and in peripheral glands, such as the testis, the ovary and the adrenal glands (i.e., steroid hormones) (Melcangi et al., 2008). The present review will focus on progesterone (PROG) and its metabolites, dihydroprogesterone (DHP), 3α,5α-tetrahydroprogesterone (3α-THP), also known as allopregnanolone, and 3β,5α-tetrahydroprogesterone (3β-THP), also known as isopregnanolone. Indeed, these neuroactive steroids are synthesized and metabolized in the nervous system and recent studies have shown that their levels can be affected by pathology or injury, as demonstrated in experimental models of Alzheimer's disease, Parkinson's disease, multiple sclerosis, peripheral neuropathies and diabetic encephalopathy (Caruso et al., 2008a, 2010a, 2013; Giatti et al., 2010, 2013; Labombarda et al., 2006b; Meffre et al., 2007; Melcangi et al., 2012; Melcangi and Garcia-Segura, 2010; Pesaresi et al., 2010b).

In turn, as demonstrated in experimental models and in clinical studies, PROG and its metabolites exert a variety of effects acting as physiological regulators of nervous function as well as protective agents. Therefore, a potential role of these molecules as components of therapeutic strategies for neurodegenerative and psychiatric disorders has been recently proposed.

2. Synthesis and metabolism of progesterone in the nervous system

2.1. Synthesis of progesterone

It is now well ascertained that synthesis and metabolism of neuroactive steroids occur in neurons and glial cells (i.e., astrocytes, oligodendrocytes and Schwann cells) of the central (CNS) and peripheral (PNS) nervous system (Garcia-Segura and Melcangi, 2006; Melcangi et al., 2008; Panzica and Melcangi, 2008; Pelletier, 2010). Steroidogenesis is a process highly compartmentalized in a sequence of reactions, which implies as first step the translocation of cholesterol from the cytoplasm to the inner mitochondrial membrane. This is a limiting step hormonally controlled and mediated by the steroidogenic acute regulatory protein (StAR) (Lavaque et al., 2006) and the translocator protein of 18 kDa (TSPO) (Papadopoulos et al., 2006a). In the mitochondria, cholesterol is then converted into pregnenolone (PREG) by the action of P450 side-chain cleavage enzyme (P450scc also known as CYP11A1). PREG is then transformed into progesterone (PROG) by the action of the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) (Melcangi et al., 2008) (Fig. 1).

2.2. Metabolism of progesterone

Enzymes involved in the metabolism of PROG are expressed, in CNS and PNS, by neurons, astrocytes, oligodendrocytes and Schwann cells (Pelletier, 2010). PROG is converted into DHP by (5α-R). In turn, DHP is further converted into 3α-THP or 3β-THP by 3α-hydroxysteroid oxidoreductase (3α-HSOR) and 3β-hydroxysteroid oxidoreductase (3β-HSOR), respectively (Melcangi et al., 2008) (Fig. 1).

The metabolism of PROG has a deep impact on the mechanism of action of this neuroactive steroid. Indeed, while DHP, like PROG, is able to interact with the classical steroid receptor, the PROG receptor (Melcangi et al., 2008), 3α-THP is a potent ligand of a non-classical steroid receptor, such as the GABA-A receptor (Belelli and Lambert, 2005; Lambert et al., 2003). In contrast, 3β-THP, does not bind directly to the GABA-A receptor (Bitran et al., 1991), but it antagonizes the effect of 3α-THP on the GABA-A receptor (Wang et al., 2002). Thus, metabolic conversion of PROG into its derivatives might differently and specifically modulate the mechanism of action of the precursor molecule by recruiting CNS specific pathways.

2.3. Modulation of the synthesis and metabolism of progesterone in the nervous system by steroid hormones

The effects that modifications in the peripheral levels of steroid hormones have on the levels of PROG and its metabolites in nerve tissue have been studied in rats. Data so far obtained have

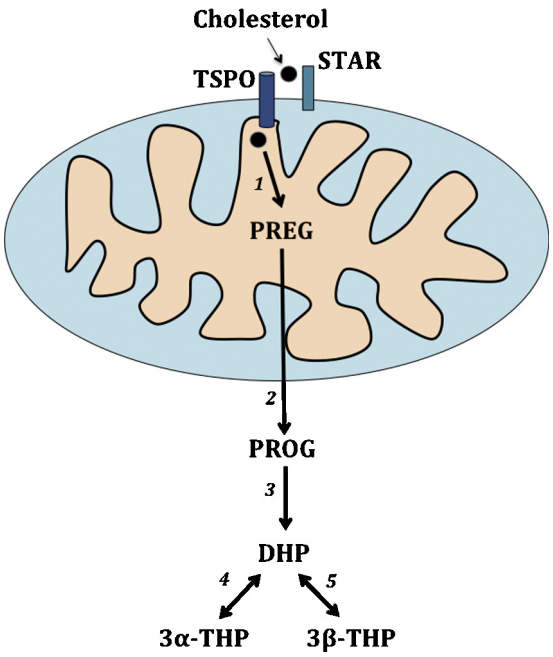

Fig. 1. Formation of progesterone and its metabolism in the nervous system. Details are provided in the text. TSPO: translocator protein of 18 kDa; StAR: steroidogenic acute regulatory protein;1: cytochrome P450scc; 2: 3β-hydroxysteroid dehydrogenase; 3: 5α-reductase; 4: 3α-hydroxysteroidoxidoreductase; 5: 3β-hydroxysteroidoxidoreductase; PREG: pregnenolone; PROG: progesterone; DHP: dihydroprogesterone; 3α-THP: 3α,5α-tetrahydroprogesterone; 3β-THP: 3β,5α-tetrahydroprogesterone.