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Neuroactive steroids and the peripheral nervous system: An update

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ABSTRACT

In the present review we summarize observations to date supporting the concept that neuroactive steroids are synthesized in the peripheral nervous system, regulate the physiology of peripheral nerves and exert notable neuroprotective actions. Indeed, neuroactive steroids have been recently proposed as therapies for different types of peripheral neuropathy, like for instance those occurring during aging, chemotherapy, physical injury and diabetes. Moreover, pharmacological tools able to increase the synthesis of neuroactive steroids might represent new interesting therapeutic strategy to be applied in case of peripheral neuropathy.

1. Introduction

Neuroactive steroids are molecules acting in the nervous system including steroids produced by the nervous system (i.e., neurosteroids) and hormonal steroids coming from classical steroidogenic tissues (i.e., gonads and adrenal glands) [1]. Several reviews have extensively considered and discussed this topic in the central nervous system (CNS), because the first observations were obtained in the brain [2–7]. However, more recent results have indicated that the peripheral nervous system (PNS) also synthesizes and metabolizes neuroactive steroids and is a target for these molecules. Indeed, neuroactive steroids exert key physiological roles in the PNS acting on the glial [8–16] and neuronal compartments [17–19]. On this basis, new therapeutic strategies based on neuroactive steroids have been recently proposed for peripheral neuropathy [10,20]. Here, we review the state of the art on the synthesis, actions and therapeutic implications of neuroactive steroids in the PNS.

2. Synthesis of neuroactive steroids

The first step of steroidogenesis is the transport of cholesterol from intracellular stores to the inner mitochondrial membrane, where cytochrome P450 side chain cleavage (P450scc), the enzyme that converts cholesterol to pregnenolone (PREG), is located (Fig. 1). This transport is facilitated by translocator protein-18 kDa (TSPO) and steroidogenic acute regulatory protein (StAR). The machinery of this first step of steroidogenesis (i.e., P450scc, TSPO and StAR) is present in Schwann cells [21,22]. Moreover, Schwann cells as well as neurons in dorsal root ganglia (DRG) are capable of converting PREG further to neuroactive steroids (Fig. 1). Indeed, Schwann cells and DRG neurons express steroidogenic enzymes such as (i) 3β-hydroxysteroid dehydrogenase, which converts PREG into progesterone (PROG) [18,19,23–27]; (ii) 5α-reductase (5α-R) type 1, which converts PROG and testosterone (T) into dihydroprogesterone (DHP) and dihydrotestosterone (DHT) respectively and (iii) 3α-hydroxysteroid dehydrogenase, which converts DHP and DHT into tetrahydroprogesterone (THP) and 5α-androstane-3α, 17β-diol (3α-diol) respectively [1,24,28–31].

Abbreviations: 3α-diol, 5α-androstane-3α, 17β-diol; 5α-R, 5α-reductase; 17β-E, 17β-estradiol; AR, androgen receptor; DHEA, dehydroepiandrosterone; DHP, dihydroprogesterone; DHT, dihydrotestosterone; DRG, dorsal root ganglia; P0, glycoprotein zero; LXR, liver X receptor; NCV, nerve conduction velocity; P450scc, P450 side chain cleavage; PMP22, peripheral myelin protein 22; PNS, peripheral nervous system; PREG, pregnenolone; PROG, progesterone; PR, progesterone receptor; PGRMC1, progesterone receptor membrane component 1; StAR, steroidogenic acute regulatory protein; SRC-1, steroid receptor coactivator-1; T, testosterone; THP, tetrahydroprogesterone; STZ, streptozotocin; TSPO, translocator protein-18 kDa.

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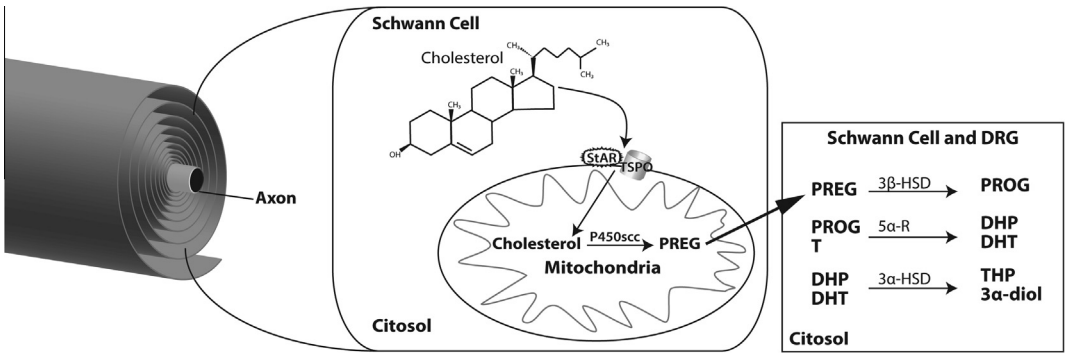

Fig. 1. Synthesis and metabolism of neuroactive steroids in the PNS. Further details are provided in the text. DRG, dorsal root ganglia; StAR, steroidogenic acute regulatory protein; TSPO, translocator protein-18 kDa; PREG, pregnenolone; PROG, progesterone; T, testosterone; DHP, dihydroprogesterone; DHT, dihydrotestosterone; THP, tetrahydroprogesterone; 3α-diol, 5α-androstane-3α, 17β-diol; P450scc, cytochrome P450 side chain cleavage; 5α-R, 5α-reductase; 3β-HSD, 3β-hydroxysteroid dehydrogenase.

Further evidence of the steroidogenic activity of the PNS is provided by the analysis of neuroactive steroid levels by liquid chromatography tandem mass spectrometry. Indeed, PREG, PROG and its derivatives (i.e., DHP, THP and isopregnanolone), dehydroepiandrosterone (DHEA), T and its derivatives (i.e., DHT and 3α-diol) and 17β-estradiol (17β-E) are measurable in the sciatic nerve of rats [32–35]. Interestingly, the levels of neuroactive steroids are different in males and females (Fig. 2), with females having higher PREG, DHP, THP, DHEA and 17β-E levels, and males having higher levels of isopregnanolone, T, DHT and 3α-diol [36–39].

Thus, PNS express steroidogenic capability as well as the presence of consistent *in situ* amounts of neuroactive steroids.

3. The PNS as a physiological target of neuroactive steroids

PNS is not only able to synthesize and metabolize neuroactive steroids but it is also a target for their effects. Neuroactive steroids may exert their effects by classical steroid receptors as well as non-classical steroid receptors. Indeed, classical intracellular steroid receptors, such as PROG (PR), androgen (AR), estrogen, glucocorticoid and mineralocorticoid receptors, which bind PROG, DHP, T, DHT, DHEA, estrogens and corticosteroids, have been detected in the glial (i.e., Schwann cells) and neuronal (i.e., DRG) compartments of the PNS [40–47]. Moreover, non-classical steroid receptors, such as progesterone receptor membrane component 1 (PGRMC1), GABA-A, GABA-B, NMDA, AMPA and kainate subunits, as well as sigma 1 receptor are also expressed by the different cellular components of the PNS [42,48–52]. Therefore, neuroactive steroids may regulate PNS physiology through different signaling pathways. Among the physiological effects of neuroactive steroids in the PNS, the regulation of the myelination program has been investigated extensively. For example, an important myelin protein, such as glycoprotein zero (P0) is a target of the action of PROG and its derivatives (i.e., DHP and THP) as well as of T derivatives (i.e., DHT and 3α-diol) [11,16,53,54]. Another myelin protein, the peripheral myelin protein 22 (PMP22) is under the control of THP and 3α-diol [11,16,53,54]. These physiological effects are mediated by activation of classical or non-classical steroid receptors. Observations to date indicate that the expression of P0 is under the control of classical steroid receptors, such as PR and AR, while that of PMP22, is under the control of a non-classical steroid receptor, such as GABA-A receptor [11]. A classical steroid genomic effect on P0 is supported by the presence of putative progesterone responsive elements on the P0 gene [53]. In further support of a classic genomic mechanism, steroid receptor coactivator (SRC)-1, a member of the p160 family of nuclear receptor coactivators [55], is involved in the control of P0 expression [56]. In further support of PR functioning with nuclear receptor coactivators, cells of the sciatic nerve of female rats co-express PR and SRC-2, another member of the p160 family (Fig. 3).

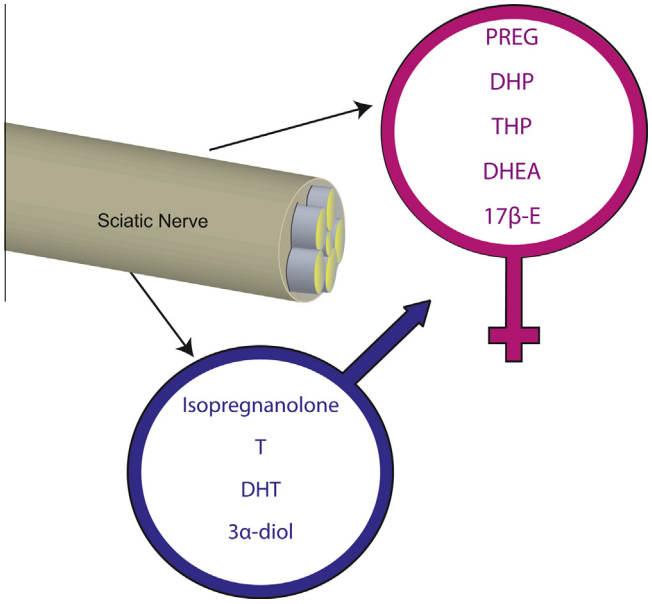

Fig. 2. Neuroactive steroid levels in rat sciatic nerve show sexual dimorphism. Further details are provided in the text. PREG, pregnenolone; DHP, dihydroprogesterone; THP, tetrahydroprogesterone; DHEA, dehydroepiandrosterone; 17β-E, 17β-estradiol; T, testosterone; DHT, dihydrotestosterone; 3α-diol, 5α-androstane-3α, 17β-diol.

P0 and PMP22 play an important role for the maintenance of the multilamellar structure of PNS myelin [57]. Therefore, consistent with the effects exerted on the proteins of peripheral myelin, PROG stimulates the synthesis of myelin membranes accelerating the time of initiation and enhancing the rate of myelin synthesis in Schwann cells co-cultured with DRG neurons [19,58]. Moreover, neuroactive steroids, such as PROG or its metabolites, DHP and THP, stimulate the gene expression of transcription factors with key role in Schwann cells physiology and their myelinating program, such as Krox-20, Krox-24, Egr-3, FosB, and Sox-10 [9,13,59].

PROG also exerts effects on the neuronal compartment. Indeed, in co-cultures of Schwann cells and DRG neurons this neuroactive steroid stimulates the expression of a small Ras-like GTP-binding protein (Rap 1b) and of phosphoribosyl diphosphate synthase-associated protein, that are two neuronal molecules involved in