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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.

Keywords

Progesterone; Testosterone; Metabolism; Peripheral neuropathy; Steroidogenesis; Neuroprotection

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.

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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].

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).

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 the myelination process [18,19]. Moreover, PROG also affects axonal outgrowth in DRG neurons. For instance, this neuroactive steroid is able to induce morphological changes, especially in the neuronal growth cones, associated with a rapid reorganization of actin filaments [42]. In agreement, the blockade of PR with the antagonist mifepristone, during development results in axonal impairment in the sciatic nerve of male rats [17].

4. Levels of neuroactive steroids are affected in peripheral neuropathy

Peripheral neuropathy is one of the most common disorders with a prevalence of about 2.4% that rises with aging to 8% in the general population [60]. Different types of peripheral neuropathy have been described. They may be inherited (e.g., Charcot–Marie–Tooth disease including demyelinating and axonal variants) or acquired, such as those occurring during aging process, after physical injury, in diabetes mellitus, vitamin deficiencies, alcoholism, kidney failure, cancer, in infections and autoimmune disorders (e.g., AIDS, hepatitis, Guillain–Barré syndrome, Lyme disease, rheumatoid arthritis, leprosy, sarcoidosis, syphilis, systemic lupus erythematosus, etc.), after exposure to toxic compounds and during drug treatment (e.g., chemotherapeutic, antiretroviral, anti-tuberculosis medications, antimicrobial drugs, lithium, etc.).

Data so far obtained indicate that the levels of several neuroactive steroids are affected in peripheral neuropathy. For instance, in an experimental model of crush injury, the levels of PREG, DHP and THP present in the distal portion of injured sciatic nerve were lowered [61]. Changes in the levels of neuroactive steroids have also been reported in an

experimental model of Charcot–Marie–Tooth type 1 (CMT1A) [33] and in experimental diabetic neuropathy [35,36]. Interestingly, in these experimental models the levels of neuroactive steroids were changed in a sex-dimorphic manner by the pathology. Indeed, as demonstrated in the sciatic nerve of male and female PMP22 transgenic rats (i.e., an experimental model of CMT1A), the levels of 3α-diol were strongly decreased in males and those of isopregnanolone were strongly decreased in females [33]. In the sciatic nerve of streptozotocin (STZ)-treated animals (i.e., an experimental model of diabetes inducing peripheral neuropathy), the levels of PREG, T, DHT and 3α-diol were significantly decreased in males but not in females, while those of PROG, THP and isopregnanolone were decreased only in females [36].

Taken together these results, indicating that neurodegeneration in PNS changes the levels of neuroactive steroids, suggest that these molecules may represent promising neuroprotective agents. Further support of this idea is provided by the relationship between hormonal environment and peripheral neuropathy. Indeed, ovariectomy, but not orchidectomy, significantly counteract STZ-induced alterations on different parameters of the peripheral nerves, such as nerve conduction velocity (NCV), Na^+, K^+-ATPase activity, and expression of P0 and PMP22 [37]. These effects of ovariectomy were associated with an increase in the levels of DHEA, T and DHT in the sciatic nerve of diabetic rats [37]. Thus, as also demonstrated in non-pathological animals, the PNS adapts its local levels of neuroactive steroids in response to castration with sex specificity and depending on the duration of the peripheral modifications [34].

A therapy based on neuroactive steroids could be extremely important because the therapeutic agents available so far for peripheral neuropathies are very limited. Indeed, as discussed below, neuroactive steroids act as protective agents in different experimental models of peripheral neuropathy.

5. Neuroactive steroids as protective agents in the PNS

5.1. Aging

Decrease in the synthesis of P0 and PMP22 and morphological changes in peripheral nerves have been reported during aging [15,20]. Treatment with PROG or its derivatives counteract these alterations [15,20,62,63]. These effects of PROG and its derivatives seem to be a peculiarity of this class of neuroactive steroids because neither T nor its derivatives were able to influence the morphological parameters analyzed in these experiments [15,20].

5.2. Physical injury

As previously mentioned, neuroactive steroids such as PROG and DHP, increase gene expression of P0 after nerve transection [64]. Moreover, PREG and PROG counteract the decrease in the amount of myelin membranes induced by a cryolesion in the sciatic nerve of mice [25]. Furthermore, in guided regeneration of the rabbit facial nerve, PROG treatment increases the number of Schwann cell nuclei, of nonmyelinated and myelinated nerve fibers (also with an increase in their diameters), as well as of the g-ratio of myelinated nerve fibers [65]. Finally, PROG or DHP treatments counteract alterations in myelin proteins and Na^+,K

$^{+}$-ATPase pump, stimulate reelin gene expression and also counteract nociception impairment in a crush injury model [61].

Interesting results have been also obtained with other neuroactive steroids. Indeed, T and DHT, accelerate regeneration and functional recovery of injured nerves [66–70]. After rat sciatic nerve transection, DHEA reduces the extent of denervation atrophy and induces an earlier onset of axonal regeneration [71]. This neuroactive steroid and also 17β-estradiol promote a faster return to normal values of sciatic function index and increase the number of myelinated fibers and fiber diameters after nerve crush injury in rats [72] and mice [73].

5.3. Chemotherapy-induced peripheral neurotoxicity

DHP or P treatments counteract the effects of docetaxel (i.e., a semisynthetic taxane widely employed as antineoplastic agent for the treatment of breast, ovarian, and non-small cell lung cancer). Thus, neuroactive steroid treatment prevents NCV and thermal threshold changes, degeneration of skin nerves in the footpad as well as changes in gene expression of P0, PMP22, myelin and lymphocyte-associated protein and myelin basic protein [74].

5.4. Diabetic peripheral neuropathy

In STZ-treated rats, treatment with PROG or its derivatives improves alterations in NCV, P0 and PMP22, Na^{+},K^{+}-ATPase activity, thermal threshold and skin innervation density [75] and counteracts the increase in the number of fibers with myelin infoldings [76]. Similar neuroprotective effects are also exerted by treatment with T or its derivatives [77] as well as by DHEA [38]. Interestingly, DHEA exerts sex-depending neuroprotective actions, with more potent effects in female animals [38]. Moreover, DHEA prevents not only neuronal but also vascular dysfunction in this experimental model [78].

Recently, it has been reported that altered levels of neuroactive steroids and morphological changes in peripheral nerves are associated not only with changes in myelin proteins but also in the lipid components. Indeed, we demonstrated that diabetes in peripheral myelin alters phospholipids, fatty acids and cholesterol content in a pattern that can modify membrane fluidity [79,80]. Interestingly, neuroactive steroids, such as DHP or 3α-diol are able to counteract these effects. In particular, these neuroactive steroids reduce myelin structural alterations, decrease the accumulation of myelin saturated fatty acids and promote desaturation [81]. Therefore these results suggest that the myelin lipid compartment can also be considered a target for the action of neuroactive steroids.

5.5. Neuropathic pain

Neuropathic pain, an important consequence of peripheral nerve damage, is also a target for the action of neuroactive steroids [82,83]. Indeed, as reported in different experimental models, T-type calcium channels, GABA-A channels, P2X3 receptors, voltage-gated sodium channels and bradykinin signaling, which exert a role in neuropathic pain, are also affected by different kinds of neuroactive steroids [84–89]. In particular, metabolites of PROG (i.e., DHP and THP) suppress neuropathic symptoms (allodynia/hyperalgesia) evoked by antineoplastic drugs such as vincristine [90] or oxaliplatin [91]. Moreover, metabolites of T have been recently demonstrated as potential agents for the treatment of diabetic neuropathic

pain [92]. Indeed, DHT counteracts the effect of diabetes on mechanical nociceptive threshold, pre- and post-synaptic components, glutamate release, astrocyte immunoreactivity and expression of interleukin-1β, while its metabolite, 3α-diol, was effective on tactile allodynia threshold, glutamate release, astrocyte immunoreactivity and the expression of substance P, toll-like receptor 4, tumor necrosis factor-α, transforming growth factor β−1, interleukin-1β and TSPO [92].

6. The induction of the synthesis of neuroactive steroids as a therapeutic tool

Because a therapeutic strategy that uses exogenous neuroactive steroids could evoke endocrine side effects, an alternative strategy could be the use of pharmacological agents that increase the synthesis of endogenous neuroactive steroids directly in the peripheral nervous system. As reported in the CNS, activation of TSPO or liver X receptor (LXR) may be considered the basis for therapeutic strategy in the neurodegenerative and psychiatric field. Indeed, TSPO ligands, like for instance XBD 173 or etifoxine, increase neurosteroidogenesis and exert anxiolytic effects without causing the classical side effects (i.e., sedation or tolerance) of benzodiazepines [7]. Beneficial effects by midazolam on behavior deficits have been also reported in an experimental model of post-traumatic stress disorder [93]. Moreover, protective effects have been also reported in experimental model of multiple sclerosis [94] or Alzheimer's disease [95]. Similarly, activation of LXR exerts protective effects in global [96] or focal cerebral ischemia [97] as well as in neurode-generative diseases, such multiple sclerosis, Alzheimer and Parkinson diseases [98]. On this basis, similar therapeutic strategies have been also applied in the PNS. For instance, treatment of STZ-induced diabetic neuropathy in rats with the TSPO ligand, Ro5–4864, increased the levels of PREG, PROG and DHT, and counteracted the impairment of NCV and thermal threshold, restored skin innervation density and P0 gene expression, and improved Na^+,K^+-ATPase activity [99]. This TSPO ligand was also able to exert a beneficial effect on morphological parameters of the sciatic nerve of aged male rats by increasing the total number of myelinated fibers and decreasing the percentage of fibers with myelin decompaction [100]. Moreover, another TSPO ligand, SSR180575, has been reported to increase the survival of facial nerve motoneurons after axotomy and the regeneration of peripheral nerves [101]. Furthermore, a TSPO ligand used for the treatment of anxiety disorders, etifoxine, enhances peripheral nerve regeneration and functional recovery, increases axonal growth, causes a marked reduction in the number of macrophages and improves recovery of locomotion, motor coordination and sensory functions in experimental models of peripheral nerve lesion [102,103]. As reported in an experimental model, this ligand is also able to exert a beneficial effect on neurophatic pain evoked by an antitumoral agent, such as vincristine sulphate [104].

Treatment with a synthetic ligand of LXR, such as GW3965, increases the levels of PREG, PROG, DHP and 3α-diol and of molecules and enzymes involved in their synthesis, such as StAR, P450scc and 5α-R in the sciatic levels of STZ-treated animals [105]. These changes are associated with neuroprotective effects on thermal nociceptive activity, NCV and Na^+,K^+-ATPase activity [105]. Interestingly, LXR knock-out mice have an altered pheno-type of

the myelin sheaths surrounding axons (i.e., thinner myelin sheaths), with no change in the diameter or number of axons [106], suggesting that the myelin compartment is also a target for this pharmacological tool.

On the other hand, even if these two pharmacological tools may be considered extremely promising it is also important to recall that they may also induce side-effects. For instance, it has been recently proposed that TSPO may play a role in schizophrenia susceptibility and antipsychotic-induced weight gain [107]. Moreover, an association of TSPO activation with the advancing of breast cancer has been also reported [108]. LXR activation increases triglycerides biosynthesis, an undesirable side effect for a candidate therapeutic drug. Indeed, it has been reported that in db/db mice, a model of type 2 diabetes, the synthetic LXR agonist T0901317 induced severe hepatic lipogenesis and increased plasma triglycerides [109]. In addition, studies with GW3965 and its analog SB742881 in hamster and monkey showed, unexpectedly, that these compounds increased LDL-cholesterol in the species expressing CETP. In addition Hong and colleagues demonstrated that LXR activation in monkeys induces hepatic expression of the E3 ubiquitin ligase IDOL a negative regulator of the LDL receptor thus raising plasma LDL levels [110]. This negative effect together with the hypertriglyceridemic properties are detrimental issues associated with drug discovery targeting LXR [111]. However, new ligands avoiding these side effects may represent a promising strategy for the development of novel interventions targeting LXR. In this context, it is also important to highlight that it is possible to maintain the LXR beneficial properties and avoid hepatic steatosis by changing the administration protocol of GW3965, instead of daily administration we dosed STZ-animals once a week for 4 weeks [105]. Moreover, at least in diabetic animals, activation of LXR [105] seems to be particularly interesting, because at variance to that of TSPO [99], did not induce significant changes of neuroactive steroid levels in plasma.

7. Concluding remarks

The concept that the CNS is able to produce neurosteroids and is a target for neuroactive steroids is well established and discussed in several reviews [1,5,112–115]. Here we have recapitulated this concept in the PNS, highlighting the potential efficacy of a therapeutic strategy based on administration of neuroactive steroids (Fig. 4) or pharmacological strategy that induce the synthesis of endogenous neuroactive steroids (Fig. 5) in different forms of peripheral neuropathies. Indeed, these therapeutic strategies are extremely intriguing given the many situations in which there are no effective treatments that can prevent, arrest or reverse peripheral nerve damage.

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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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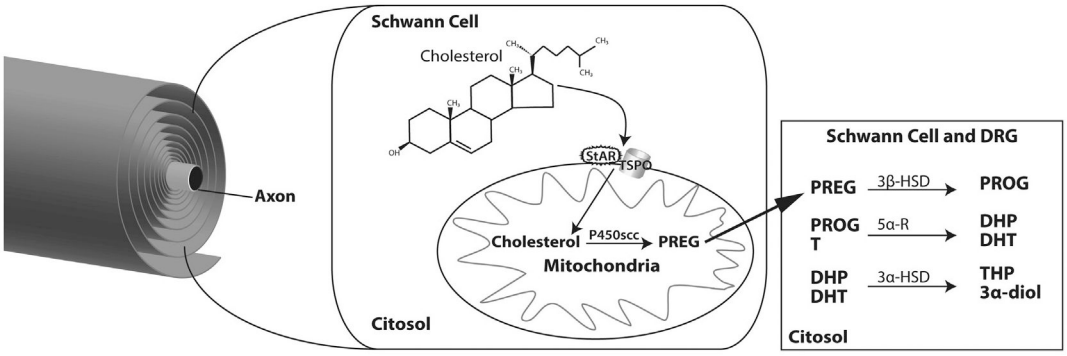

Fig. 1.

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.

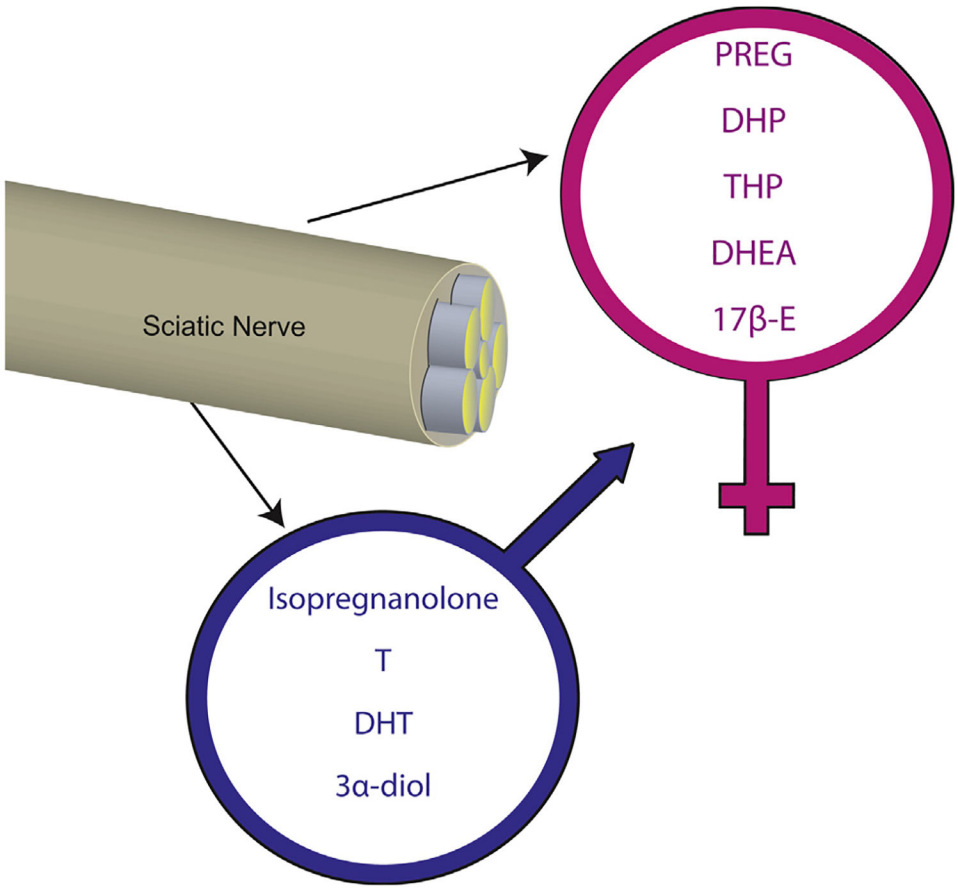

Fig. 2.

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.

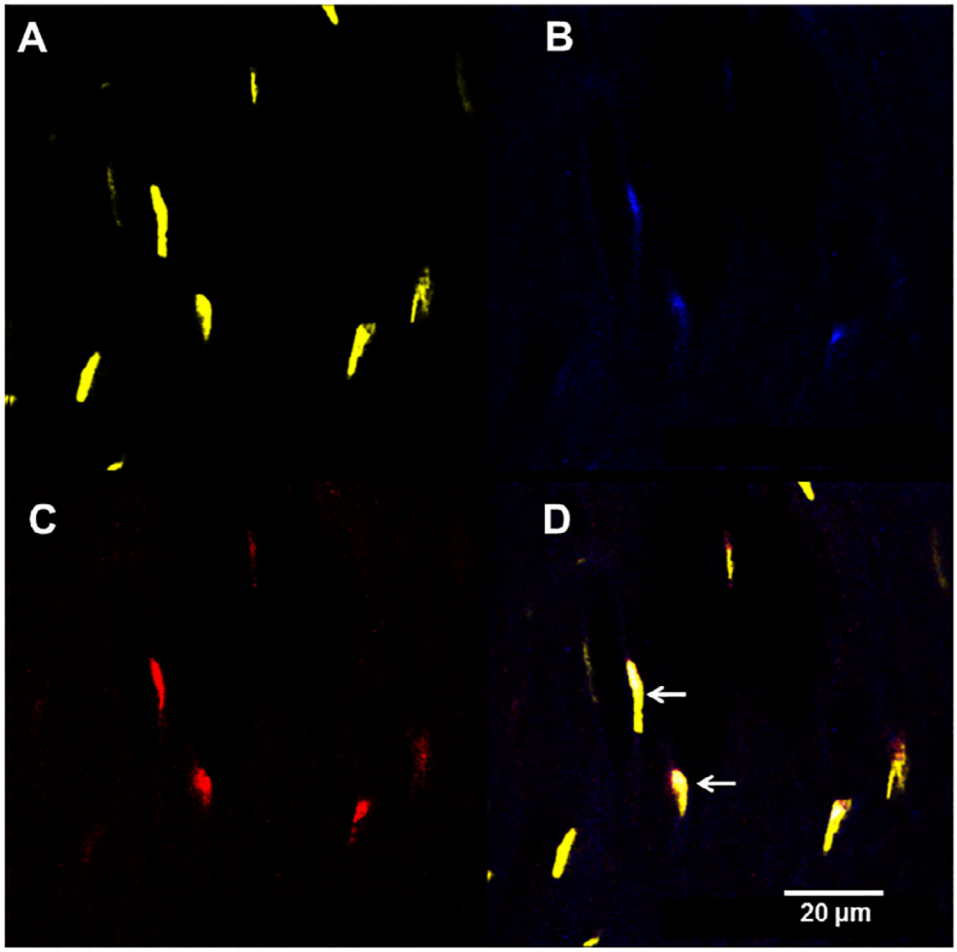

Fig. 3.

Sciatic nerve cells coexpress progesterone receptor (PR) and steroid receptor coactivator-2 (SRC-2) in female rats. Sciatic nerve from ovariectomized rats treated with estradiol benzoate (10 µg, sc) were immunostained for (A) nucleic acids (DAPI), (B) PR, (C) SRC-2 and (D) merged. White arrows in D point to nuclei of cells that coexpress PR and SRC-2.

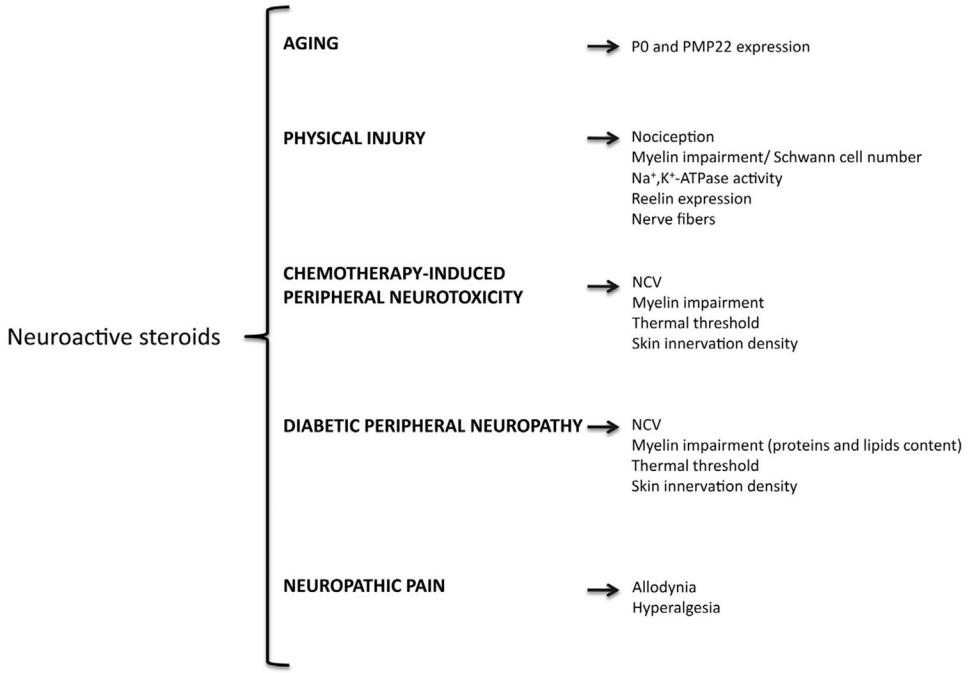

Fig. 4.

Protective effects of neuroactive steroids in healthy aging and different pathological conditions. Details are provided in the text. P0, glycoprotein zero; PMP22, peripheral myelin protein 22; NCV, nerve conduction velocity.

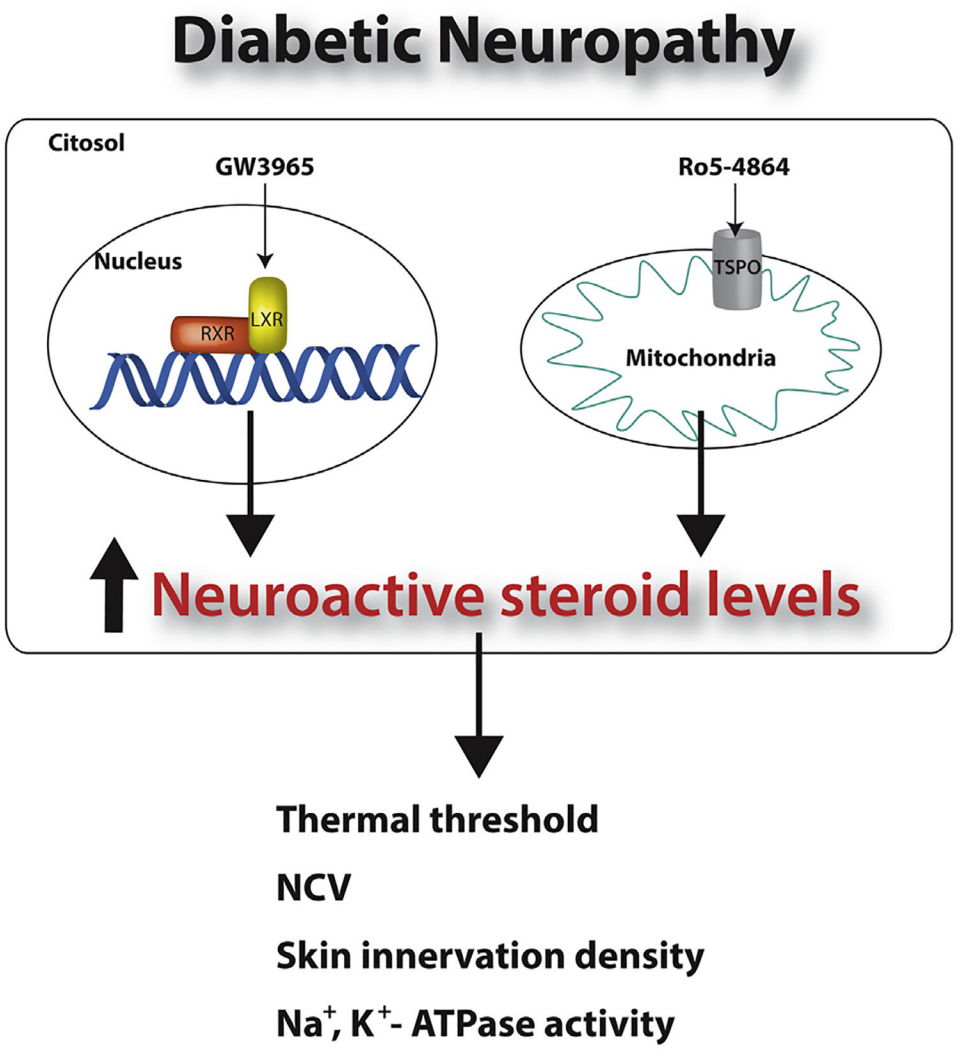

Fig. 5.

Pharmacological tools, able to increase neuroactive steroid levels, are able to exert protective effects in sciatic nerve of diabetic animals. LXR, liver X receptor; RXR, retinoic X receptor; TSPO, translocator protein-18 kDa; NCV, nerve conduction velocity.