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Role of neuroactive steroids in the peripheral nervous system

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Several reviews have so far pointed out on the relevant physiological and pharmacological role exerted by neuroactive steroids in the central nervous system. In the present review we summarize observations indicating that synthesis and metabolism of neuroactive steroids also occur in the peripheral nerves. Interestingly, peripheral nervous system is also a target of their action. Indeed, as here reported neuroactive steroids are physiological regulators of peripheral nerve functions and they may also represent interesting therapeutic tools for different types of peripheral neuropathy.

Keywords: progesterone, testosterone, metabolism, peripheral neuropathy, steroidogenesis, neuroprotection

INTRODUCTION

Recent studies have shown that peripheral nerves synthesize and metabolize neuroactive steroids. The term neuroactive steroid refers to those steroids acting in the nervous system and includes steroids produced by the nervous system (i.e., neurosteroids) and hormonal steroids coming from classical steroidogenic tissues (i.e., gonads and adrenal glands; Melcangi et al., 2008). Moreover, peripheral nerves express receptors for neuroactive steroids and consequently represent a target for them. Indeed, neuroactive steroids are involved in the regulation of different functions of peripheral nerves, including Schwann cell proliferation and myelination (Chan et al., 1998, 2000; Desarnaud et al., 1998, 2000; Fex Svenningsen and Kanje, 1999; Lubischer and Bebinger, 1999; Guennoun et al., 2001; Mercier et al., 2001; Azcoitia et al., 2003; Rodriguez-Waitkus et al., 2003; Tanzer and Jones, 2004; Melcangi et al., 2005; Magnaghi et al., 2006, 2007).

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 (England and Asbury, 2004). Peripheral neuropathy may be inherited, such as those referred to Charcot–Marie–Tooth (CMT) disease including demyelinating and axonal variants, or acquired, like for instance those occurring during aging process, after physical injury, in systemic or metabolic disorders (e.g., diabetes mellitus, vitamin deficiencies, alcoholism, kidney failure, cancer, etc.), 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, antituberculosis medications, antimicrobial drugs, lithium, etc.). Currently, therapeutic arsenal for these peripheral neuropathies is very limited. Therefore, the finding that neuroactive steroids act as protective agents in different experimental models of peripheral neuropathy is highly promising (Leonelli et al., 2006; Melcangi and Garcia-Segura, 2006, 2010; Roglio et al., 2008b; Schumacher et al., 2008). At present, corticosteroids are the only steroids used for clinical management of peripheral neuropathy, due to their anti-inflammatory actions. However, the design of a randomized controlled trial for the treatment of mild idiopathic carpal tunnel syndrome (CTS) with local injection of 17 alpha-hydroxyprogesterone caproate, a synthetic derivative of progesterone (PROG), has been recently reported (Milani et al., 2010).

We will here review the state of the art on the synthesis, actions, and therapeutic implications of neuroactive steroids in the peripheral nervous system (PNS).

SYNTHESIS OF NEUROACTIVE STEROIDS OCCURS IN THE PERIPHERAL NERVES

Peripheral nerves are a source of neuroactive steroids (Mellon and Deschepper, 1993; Schumacher et al., 2003; Melcangi et al., 2008; Pelletier, 2010). 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, is located. This transport is facilitated by translocator protein-18kDa (TSPO) and steroidogenic acute regulatory protein (StAR), two molecules that, together with P450scc, are expressed by Schwann cells (Benmessahel et al., 2004; Papadopoulos et al., 2006).

Moreover, Schwann cells, as well as dorsal root ganglia (DRG), also express other steroidogenic enzymes such as 3α-hydroxysteroid dehydrogenase (i.e., the enzyme converting PREG into PROG; Koenig et al., 1995; Guennoun et al., 1997; Chan et al., 2000; Schumacher et al., 2001; Coirini et al., 2003; Rodriguez-Waitkus et al., 2003; Schaeffer et al., 2010), 5α-reductase (5α-R), converting PROG and testosterone (T) into dihydroprogesterone (DHP) and dihydrotestosterone (DHT) respectively, and 3α-hydroxysteroid dehydrogenase, converting DHP and DHT into tetrahydroprogesterone (THP) and 5α-androstane-3α, 17β-diol (3α-diol) respectively (Melcangi et al., 1990, 2001a; Yokoi et al., 1998; Schaeffer et al., 2010). Synthesis of neuroactive steroids in peripheral nerves has been also confirmed by the assessment of their levels. For instance, using liquid chromatography tandem mass spectrometry analysis, levels of PREG, PROG, and its derivatives (i.e., DHP, THP and isopregnanolone), dehydroepiandrosterone (DHEA), T, and its derivatives (i.e., DHT and 3α-diol) have been determined in the sciatic nerve of male and female rats (Caruso et al., 2008a,b, 2010; Pesaresi et al., 2010b). These studies have shown that local levels of neuroactive steroids in the peripheral nerve do not directly reflect plasma levels. In addition, these studies have revealed that the PNS adapts its local levels of neuroactive steroids in response to gonadectomy with sex specificity and depending on the duration of the peripheral modifications (Caruso et al., 2010).

PHYSIOLOGICAL CONTROL BY NEUROACTIVE STEROIDS ON PERIPHERAL NERVES

PERIPHERAL NERVES AS TARGETS OF NEUROACTIVE STEROIDS

Peripheral nerves and Schwann cells not only synthesize and metabolize neuroactive steroids, but are also targets for these molecules. Classical intracellular steroid receptors, such as PROG (PR), estrogen, glucocorticoid, and mineralocorticoid receptors, have been detected in rat sciatic nerve and in Schwann cells (Jung-Testas et al., 1996; Melcangi et al., 2001b; Groyer et al., 2006). Also, androgen receptor (AR) expression has been demonstrated in the endoneurial compartment of rat sciatic nerve (Magnaghi et al., 1999; Jordan et al., 2002). Through the activation of these classical steroid receptors, neuroactive steroids such as PROG, DHP, T, DHT, DHEA, estrogens, and corticosteroids, affect the development and function of the PNS.

In addition, in the central nervous system, neuroactive steroids such as 3alpha-hydroxy-derivatives of dihydroprogesterone, dihydrotestosterone, and deoxycorticosterone are known to bind to neurotransmitter receptor channels and to modulate their activity (Lambert et al., 2003; Belelli and Lambert, 2005; Zheng, 2009). This mechanism of action also operates in the PNS, since neurotransmitter receptors modulated by neuroactive steroids, such as GABA-A (i.e., α2, α3, β1, β2, and β3 subunits) and GABA-B (i.e., GABA-B1 and GABA-B2) receptors, have been identified in peripheral nerves and Schwann cells (Melcangi et al., 1999; Magnaghi et al., 2004a). Moreover, rat sural nerve expresses NMDA receptor 1 subunit, glutamate receptor 1 (GluR1), AMPA subunit, and GluR 5, 6, 7 kainate subunits (Coggeshall and Carlton, 1998; Verkhratsky and Steinhauser, 2000). Schwann cells of mammalian peripheral vestibular system express GluR 2, 3, 4 (Dememes et al., 1995; Verkhratsky and Steinhauser, 2000). Finally, the presence of sigma 1 receptor (i.e., an atypical neuro-modulatory receptor) in Schwann cells of rat sciatic nerve has been confirmed (Palacios et al., 2004). Therefore, neuroactive steroids may also regulate PNS physiology through the modulation of the activity of neurotransmitter receptors and by non-classical steroid receptors, such as the sigma 1 receptor.

EFFECTS, MECHANISMS OF ACTION, AND INFLUENCE OF SEX

One of best characterized actions of neuroactive steroids in peripheral nerves is the regulation of the myelination program. Classical and non-classical steroid receptors mediate physiological actions of neuroactive steroids on the proliferation of Schwann cells and on their expression of myelin proteins and of transcription factors involved in the regulation of myelination (**Figure 1**). Indeed, PROG and its derivatives are able to modulate the expression of myelin proteins of the PNS, such as glycoprotein zero (P0) and the peripheral myelin protein 22 (PMP22). Namely, the expression of P0 in sciatic nerve of adult male rats, as well as that in rat Schwann cell culture, was increased by the treatment with PROG, DHP, or THP, while in case of PMP22, only THP was effective (Melcangi et al., 1999, 2005). Similar effects are also exerted by derivatives of T. Thus, orchidectomy in adult male rat decreased the expression of P0 and PMP22 in the sciatic nerve (Magnaghi et al., 1999, 2004b). The subsequent treatment with DHT or 3α-diol (i.e., two derivatives of T) restored the levels of P0, while in case of PMP22 only 3α-diol was effective (Magnaghi et al., 1999, 2004b). A very similar pattern of effects was also evident in cultures of rat Schwann cells (Melcangi et al., 2005). The mechanism involved in these effects was different depending on the myelin protein considered. Thus, observations performed with receptor agonists or antagonists suggest that the expression of P0 is under the control of classical intracellular receptors, such as PR and AR, while a role for non-classical mechanisms, like the modulation of GABA-A receptor, may be hypothesized in case of PMP22 (Melcangi et al., 2005). Activation of a classical steroid receptor, such as PR, clearly suggests that the effect of PROG derivatives on P0 expression is due to a classical steroid genomic effect. This hypothesis is supported by the finding that putative progesterone responsive elements are present on P0 gene (Magnaghi et al., 1999) and that a coactivator, such as steroid receptor coactivator-1 (SRC-1), participates in the regulation of P0 gene expression by DHP. Indeed, the effect of this neuroactive steroid on P0 expression in an immortalized cell line of Schwann cell (i.e., MSC80 cells) stably transfected to over- or down-express SRC-1 was increased or completely lost, respectively (Cavarretta et al., 2004). A role for AR in controlling expression of P0 may be also hypothesized. Indeed, *in vivo* treatment with an AR antagonist, such as flutamide, decreased the synthesis of P0 in rat sciatic nerve (Magnaghi et al., 2004b). Interestingly, inhibition of AR influenced P0 synthesis in adult age only. This age-linked effect is different from what we have observed after the *in vivo* treatment with mifepristone, where PR antagonist was only able to decrease the synthesis of P0 at postnatal day 20 (Melcangi et al.,

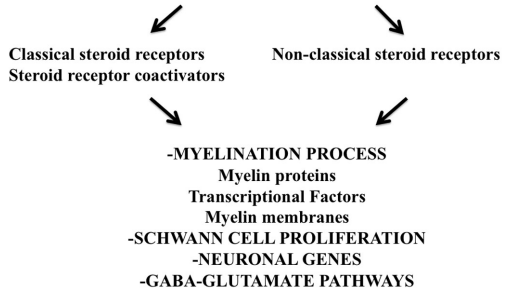

FIGURE 1 | Physiological effects of neuroactive steroids in peripheral nerves.

2003b). A possible hypothesis could be that PROG derivatives may be necessary for inducing P0 synthesis during the first steps of the myelination process, while the subsequent intervention of T derivatives will participate in the maintenance of this process.

At variance to what observed on P0, expression of PMP22 seems to be under the control of GABA-A receptor. As we observed in Schwann cell cultures, treatment with antagonist (i.e., bicuculline) or agonist (i.e., muscimol) of GABA-A receptor abolished or mimicked respectively the stimulatory effect exerted by THP on PMP22 (Melcangi et al., 2005).

Expression of P0 and PMP22 is also affected in a sex-dependent manner. Thus, observations obtained in culture of rat Schwann cells have indicated that PROG or DHP treatment induced a stimulatory effect on P0 mRNA levels only in male, while THP was only effective in female cells. Similarly, the expression of PMP22 was stimulated by PROG in cultures from males and by THP in cultures from females (Magnaghi et al., 2006).

Neuroactive steroids regulate myelination program by affecting also the expression of transcription factors (**Figure 1**). Data obtained in culture of rat Schwann cells (Guennoun et al., 2001; Mercier et al., 2001) have indicated that PROG stimulates the gene expression of Krox-20, Krox-24, Egr-3, and FosB. Moreover, the expression of Krox-20 was also stimulated by DHP and THP, while that of another transcription factor, such as Sox-10, was only stimulated by DHP (Magnaghi et al., 2007).

P0 and PMP22 play an important role for the maintenance of the multilamellar structure of PNS myelin (D'Urso et al., 1990). Therefore, in agreement with the effect exerted on the proteins of peripheral myelin, PROG is also able to stimulate the synthesis of myelin membranes (**Figure 1**). For instance, PROG accelerates the time of initiation and enhances the rate of myelin synthesis in Schwann cells co-cultured with DRG neurons (Chan et al., 1998, 2000).

Moreover, also the axonal compartment of PNS neurons is a target for the action of neuroactive steroids. Thus, PROG affects the expression of neuronal genes involved in the myelination process by Schwann cells. For instance, in co-culture of Schwann cells and DRG neurons two genes, like a small Ras-like GTP-binding protein (Rap 1b) and phosphoribosyl diphosphate synthase-associated protein, which are induced in co-cultures during myelin synthesis, were also induced by PROG treatment (Chan et al., 2000; Rodriguez-Waitkus et al., 2003). Finally, the blockade of PR by mifepristone during development resulted in axonal impairment in the sciatic nerve of male rats (Melcangi et al., 2003b).

Neuroactive steroids are also able to affect Schwann cell proliferation (**Figure 1**). For instance, a stimulatory effect of PROG has been detected *in vitro* (Fex Svenningsen and Kanje, 1999; Bartolami et al., 2003). Interestingly, also this effect of PROG seems to be dependent on the sex of the animals. Indeed, PROG increased Schwann cell proliferation in cultures of segments of rat sciatic nerve from females, but was ineffective in cultures from males (Fex Svenningsen and Kanje, 1999). Androgens also affect Schwann cell proliferation. For instance, the number of terminal Schwann cells unsheathing the synaptic junction between motor nerve endings and muscles decreased after castration and this effect was counteracted by T replacement (Lubischer and Bebinger, 1999).

Steroid coactivators, which as previously mentioned participate in the effects exerted by neuroactive steroids on myelin proteins, are also able to affect cell proliferation. For instance, cell proliferation in an immortalized line of Schwann cells (i.e., MSC80 cells) overexpressing SRC-1 was slower than in cells in which the coactivator expression was down regulated (Melcangi et al., 2005). In contrast, overexpression of another coactivator, such as steroid receptor RNA activator (SRA), induced an increase in the proliferation of MSC80 cells (Melcangi et al., 2005).

Finally, metabolites of PROG, such as THP, acting on GABA-A receptors are also able to influence GABA and glutamate pathways in Schwann cells (**Figure 1**). Thus, this neuroactive steroid stimulates GABA synthesis by increasing the levels of glutamic acid decarboxylase of 67 kDa (Magnaghi et al., 2010) and the activity of excitatory amino acid carrier 1 and therefore, glutamate uptake (Perego et al., 2011).

THE LEVELS OF NEUROACTIVE STEROIDS IN PERIPHERAL NERVES ARE AFFECTED BY PATHOLOGICAL EVENTS

As demonstrated in several experimental models, the levels of neuroactive steroids present in peripheral nerves are affected by traumatic injury and pathologies. Namely, in the experimental model of crush injury the levels of PREG, DHP, and THP present in the distal portion of injured sciatic nerve were lowered (Roglio et al., 2008a). The drop of DHP was not explained by a decrease in the levels of its first substrate (i.e., PROG) that were unchanged, but by a decrease in the expression of the enzyme 5α-R (i.e., enzyme converting PROG into DHP; Roglio et al., 2008a).

Changes in the levels of neuroactive steroids have been also reported in an experimental model of Charcot–Marie–Tooth type 1 (CMT1A; Caruso et al., 2008b) or of diabetic neuropathy (Caruso et al., 2008a; Pesaresi et al., 2010b). Interestingly, in these experimental models the levels of neuroactive steroids were affected in a sex-dimorphic way by the pathology. For instance, as demonstrated in the sciatic nerve of male and female PMP22 transgenic rats (i.e., an experimental model of CMT1A) the levels of isopregnanolone and of 3α-diol, which are exclusively detectable in sciatic nerve of female and male rats respectively, were strongly decreased (Caruso et al., 2008b). In 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

PROG, THP, and isopregnanolone were decreased only in females (Pesaresi et al., 2010b).

NEUROACTIVE STEROIDS AS PROTECTIVE AGENTS IN PERIPHERAL NERVOUS SYSTEM

Neuroactive steroids are not only protective agents in the central nervous system as extensively demonstrated in several experimental models (Melcangi et al., 2000a; Lapchak and Araujo, 2001; McCullough and Hurn, 2003; Ciriza et al., 2004, 2006; Griffin et al., 2004; Melcangi and Mensah-Nyagan, 2006; Aguado-Llera et al., 2007; Schumacher et al., 2007; Pesaresi et al., 2010a), but they are also effective on peripheral neuropathies (**Figure 2**).

AGING

Aging induces important biochemical (e.g., a decrease in the synthesis of P0 and PMP22) and morphological changes in peripheral nerves, such as atrophy of the large myelinated fibers, myelin sheaths increase in thickness and show various irregularities (i.e., myelin ballooning, splitting, infolding, reduplication, and remyelination; Azcoitia et al., 2003; Melcangi et al., 2003a). Neuroactive steroids, such as PROG or its derivatives, are able to stimulate the low expression of P0 and PMP22 in the sciatic nerve of aged rats (Melcangi et al., 1998, 2000c, 2003a). Moreover, they have also clear beneficial effects on the number and shape of myelinated fibers as well as on the frequency of myelin abnormalities (Azcoitia et al., 2003; Melcangi et al., 2003a).

All these effects seem to be a peculiarity of PROG and its derivatives, because neither T nor DHT or 3α-diol were able to influence the morphological parameters analyzed in these experiments (Azcoitia et al., 2003; Melcangi et al., 2003a).

PHYSICAL INJURY

Protective and regenerative effects of neuroactive steroids have been well characterized in experimental models of degeneration occurring after physical injury of peripheral nerves. For instance, (1) PROG or DHP, increase gene expression of P0 after nerve transection (Melcangi et al., 2000b); (2) PREG and PROG counteract the decrease of the amounts of myelin membranes induced by a cryolesion in the sciatic nerve of the mouse (Koenig et al., 1995); (3) In guided regeneration of facial nerve of rabbit, PROG induces an increase in the number of Schwann cell nuclei, of non-myelinated and myelinated nerve fibers (with increase also in their diameters), as well as in the g-ratio of myelinated nerve fibers (Chavez-Delgado et al., 2005); and (4) In crush injury model, DHP and/or P counteract biochemical alterations (i.e., myelin proteins and Na^+,K^+-ATPase pump) and stimulate reelin gene expression. These two neuroactive steroids also counteract nociception impairment, and DHP treatment significantly decreases the up-regulation of myelinated fibers' density occurring in crushed nerves (Roglio et al., 2008a).

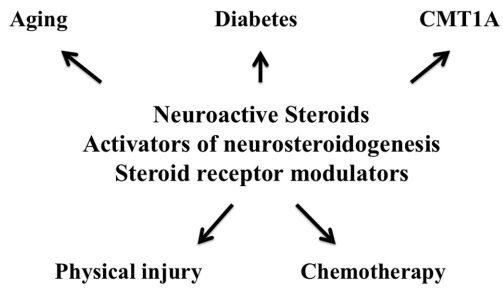

FIGURE 2 | Pathological targets of neuroactive steroids in the peripheral nervous system.

Moreover, promising results have been also obtained with other neuroactive steroids. For instance, T and its derivative, DHT, accelerate regeneration, and functional recovery of injured nerves (Yu, 1982; Vita et al., 1983; Jones et al., 2001; Tanzer and Jones, 2004; Huppenbauer et al., 2005). DHEA is protective after rat sciatic nerve transection, reducing the extent of denervation atrophy and inducing an earlier onset of axonal regeneration (Ayhan et al., 2003). DHEA also promotes a faster return to normal values of sciatic function index and increases the number of myelinated fibers and of fiber diameters after nerve crush injury in rats (Gudemez et al., 2002). Similar results have been obtained after crush injury in mice, using 17β-estradiol (Islamov et al., 2002).

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY

Effects of neuroactive steroids have been also evaluated in an experimental model of chemotherapy-induced peripheral neurotoxicity, such as those due to docetaxel (i.e., a semisynthetic taxane widely employed as antineoplastic agent for the treatment of breast, ovarian, and non-small cell lung cancer; Roglio et al., 2009). We demonstrated that treatment with DHP or P counteracted docetaxel-induced neuropathy, preventing nerve conduction velocity (NCV) and thermal threshold changes, and degeneration of skin nerves in the footpad. Neuroactive steroids also counteracted the changes in gene expression of several myelin proteins, such as P0, PMP22, myelin, and lymphocyte-associated protein and myelin basic protein (MBP) induced by docetaxel in sciatic nerve. Most nerve abnormalities observed during the treatment with docetaxel spontaneously recovered after drug withdrawal, similarly to what occurs in patients. However, results of midterm follow-up experiments indicate that animals treated with DHP or P show a faster recovery (Roglio et al., 2009).

Neuropathic pain is another important consequence of peripheral nerve damage. Indeed, neuroactive steroids exert a beneficial effect also on this component. For instance, DHP or THP treatment suppresses neuropathic symptoms (allodynia/hyperalgesia) evoked by antineoplastic drugs such as vincristine (Meyer et al., 2010) or oxaliplatin (Meyer et al., 2011).

DIABETIC NEUROPATHY

Another experimental model in which protective effects of neuroactive steroids have been ascertained is diabetic neuropathy. Thus, in STZ-treated rats, PROG or its derivatives improve sciatic NCV, myelin protein mRNA levels (i.e., P0 and PMP22), Na^+, K^+-ATPase activity, thermal threshold, skin innervation density (Leonelli et al., 2007) and counteract the increase in the number of fibers with myelin infoldings (Veiga et al., 2006). Androgens, such as T or its derivatives exert similar effects (Roglio et al., 2007), while DHEA prevents not only neuronal but also vascular dysfunction in the sciatic nerve of STZ-rats (Yorek et al., 2002).

INFLUENCE OF HORMONAL ENVIRONMENT

As recently demonstrated, endogenous glucocorticoids exert a role in myelination after sciatic nerve injury. For instance, crush injury performed in adrenalectomized rats affects myelination processes in term of MBP expression and morphological parameters of myelin sheaths (Morisaki et al., 2010). Thus, adrenalectomized animals showed reduced MBP mRNA and protein levels and decreased myelin thickness in comparison to sham-operated animals. These alterations were prevented by low-dose corticosterone replacement.

Recent results have shown that gonadal steroid hormonal environment also influences diabetic neuropathy. Interestingly, this effect is sex-dimorphic. Thus, ovariectomy, but not orchidectomy, significantly counteract STZ-induced alterations on NCV, Na^+, K^+-ATPase activity, and expression of myelin proteins, such as P0 and PMP22 (Pesaresi et al., 2011). The effect of ovariectomy is associated with an increase in the levels of neuroactive steroids (e.g., DHEA, T, and DHT) in the sciatic nerve of diabetic rats (Pesaresi et al., 2011).

These observations, together with the finding that peripheral neuropathies show sex differences in their incidence, symptomatology, and nerodegenerative outcome (Melcangi and Garcia-Segura, 2010) may have strong implications for the development of new sex-oriented therapies based on the use of neuroactive steroids.

NEUROPROTECTIVE EFFECTS BY STEROID RECEPTOR MODULATORS

An alternative to the use of P, DHP, and THP may be the use of molecules that target PR and/or GABA-A receptor (Melcangi et al., 2005). Indeed, it has been demonstrated that the treatment with a PR antagonist (i.e., onapristone) was able to reduce the overexpression of PMP22 and to improve CMT phenotype in an experimental model of CMT1A (i.e., PMP22-transgenic rats; Sereda et al., 2003; Meyer zu Horste et al., 2007). This opens the possibility of using selective PR modulators, perhaps in combination with GABA-A ligands, for the treatment of peripheral neuropathy. Selective estrogen receptor modulators may also offer a potential therapeutic interest since the selective estrogen receptor modulator LY117018 has been shown to enhance functional recovery after injury of the sciatic nerve (McMurray et al., 2003).

IN SITU INDUCTION OF NEUROACTIVE STEROIDS AS THERAPEUTIC TOOLS

Another alternative for a therapeutic strategy with neuroactive steroids themselves, or with specific synthetic ligands of their receptors, might be the use of pharmacological agents that increase the synthesis of endogenous neuroactive steroids within the nervous system. For instance, this is possible with ligands of TSPO, which promoting the translocation of cholesterol to the inner mitochondrial membrane increase the synthesis of neuroactive steroids. As reported, a TSPO ligand like SSR180575 was able to increase the survival of facial nerve motoneurons after axotomy and the regeneration of peripheral nerves (Ferzaz et al., 2002). Another TSPO ligand, such as Ro5-4864, exerted a beneficial effect on morphological parameters of the sciatic nerve of aged male rats, significantly increasing the total number of myelinated fibers and decreasing the percentage of fibers with myelin decompaction (Leonelli et al., 2005). Moreover, Ro5-4864 is effective on STZ-induced diabetic neuropathy and significantly stimulates the low levels of PREG, PROG, and DHT observed in the sciatic nerves of diabetic rats (Giatti et al., 2009). In agreement with the protective actions of these neuroactive steroids, activation of TSPO counteracted the impairment of NCV and thermal threshold, restored skin innervation density and P0 gene expression, and improved Na^+, K^+-ATPase activity (Giatti et al., 2009).

Etifoxine (i.e., a TSPO ligand used for the treatment of anxiety disorders) has been demonstrated to activate neuroactive steroid synthesis (Verleye et al., 2005). In experimental models of peripheral nerve lesion, etifoxine treatment improved peripheral nerve regeneration and functional recovery, increasing axonal growth, causing a marked reduction in the number of macrophages and improving recovery of locomotion, motor coordination and sensory functions (Girard et al., 2008).

Finally, also liver X receptors (LXRs) might be an interesting therapeutic target (Cermenati et al., 2010). LXRs are ligand activated transcription factors that belong to the nuclear receptor superfamily that serving as cholesterol sensors prevent excessive intracellular accumulation of cholesterol.

As recently demonstrated, sciatic nerve expresses functional LRXα and β isoforms. Treatment with a synthetic ligand of this receptors (i.e., GW3965) resulted in an increase of neurosteroidogenesis in the sciatic levels of diabetic animals. Thus, an increase of 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, as well as of classical LXR targets involved in cholesterol efflux, such as ABCA1 and ABCG1 was observed. These changes in neurosteroidogenesis machinery were associated with neuroprotective effects on thermal nociceptive activity, NCV and Na^+, K^+-ATPase activity (Cermenati et al., 2010). Interestingly, recent results have indicated that LXRs may also affect peripheral myelination opening new perspectives in the treatment of peripheral neuropathy. Indeed, knock-out of LXR in mice results in an alteration of the phenotype of myelin sheaths surrounding axons (i.e., thinner myelin sheaths), without affecting the diameters and number of axons (Makoukji et al., 2011).

CONCLUDING REMARKS

Observations here reviewed indicate that the PNS is a target for the effects of neuroactive steroids. In addition, neuroactive steroids themselves or pharmacological approaches acting on their receptors or their synthesis might represent potential therapeutic tools for different forms of peripheral neuropathies. This is extremely interesting because in many situations there are no effective treatments that can stop or reverse peripheral nerve damage. Thus, a sustained research and development effort on this experimental field might permit in a close future a promising translation to clinical research.

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