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Neurosteroids and neuropathic pain management: Basic evidence and therapeutic perspectives

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ABSTRACT

Complex mechanisms involved in neuropathic pain that represents a major health concern make its management complicated. Because neurosteroids are bioactive steroids endogenously synthesized in the nervous system, including in pain pathways, they appear relevant to develop effective treatments against neuropathic pain. Neurosteroids act in paracrine or autocrine manner through genomic mechanisms and/or via membrane receptors of neurotransmitters that pivotally modulate pain sensation. Basic studies which uncovered a direct link between neuropathic pain symptoms and endogenous neurosteroid production/regulation, paved the way for the investigations of neurosteroid therapeutic potential against pathological pain. Concordantly, antinociceptive properties of synthetic neurosteroids were evidenced in humans and animals. Neurosteroids promote peripheral analgesia mediated by T-type calcium and gamma-aminobutyric acid type A channels, counteract chemotherapy-induced neuropathic pain and ameliorate neuropathic symptoms of injured spinal cord animals by stimulating anti-inflammatory, remyelinating and neuroprotective processes. Together, these data open interesting perspectives for neurosteroid-based strategies to manage/alleviate efficiently neuropathic pain.

1. Introduction

Neurosteroids are bioactive steroids endogenously synthesized in neurons and/or glial cells (for reviews, Baulieu et al., 1999; Mensah-Nyagan et al., 1999). The chemical structure of neurosteroids is not necessarily different from that of hormonal steroids but the main criterion required before considering an endogenous steroid as a neurosteroid is its production in the central (CNS) or peripheral (PNS) nervous systems independently from the activity of endocrine glands such as the adrenals and gonads. In addition to the genomic action generally used by all steroidal hormones, neurosteroids modulate the nervous system activity in a paracrine or autocrine manner by acting through various membrane receptors including gamma-aminobutyric acid type A (GABAA), N-methyl-D-aspartate (NMDA), Purinergic 2X (P2X) and sigma receptors as well as voltage-gated calcium channels or VGCCs (Balthazart et al., 2018; Baulieu et al., 1999; Belelli and Lambert, 2005; Gunn et al., 2015; Joksimovic et al., 2018a; Maurice et al., 2006; Mellon and Griffin, 2002; Mensah-Nyagan et al., 1999; Olsen, 2018; Rudolph et al., 2016; Tuem and Atey, 2017). So far, the non-genomic interactions of neurosteroids with the GABAA membrane receptor are the most well documented and neurosteroid binding sites have been identified in the receptor's transmembrane domains mediating the potentiating and direct activation effects of neurosteroids (Belelli and Lambert, 2005; Hosie et al., 2006; Majewska, 1992). In particular, it has been demonstrated that the interactions of neurosteroids with a cavity formed by the α-subunit transmembrane domains allosterically potentiate GABA responses but neurosteroids can also directly initiate GABAA receptor activation from the interfacial residues between α and β subunits and this activation may be increased by steroid binding to the allosteric potentiation site. Thus, significant receptor activation by neurosteroids relies on occupancy of both the activation and potentiation sites (Hosie et al., 2006).

Two main categories of steroids can be distinguished in the neurosteroid family (Patte-Mensah and Mensah-Nyagan, 2008): (i) the non-exclusive neurosteroids such as pregnenolone (PREG), progesterone (PROG) or dehydroepiandrosterone (DHEA) are steroidal hormones that can also be synthesized by neurons or glial cells; (ii) semi-exclusive neurosteroids such as tetrahydroprogesterone (3α,5α-THP) also called allopregnanolone are mainly synthesized in the nervous system even if substantial amounts can be produced in endocrine glands. The existence of exclusive neurosteroids such as epiallopregnanolone (which may only be synthesized in nerve cells) has been suggested but the

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arguments supporting this idea are rare (Higashi et al., 2007). The occurrence of neurosteroidogenesis or neurosteroid production in a neural structure requires the presence of active steroidogenic enzymes such as cytochrome P450side-chain-cleavage (P450scc), cytochrome P450c17 (P450c17), 3α-hydroxysteroid oxidoreductase (3α-HSOR), 3β-hydroxysteroid dehydrogenase (3β-HSD) and 5α-reductase (5α-R) (Baulieu et al., 1999; Compagnone and Mellon, 2000; Mensah-Nyagan et al., 1996a, 1996b). The process of neurosteroidogenesis is well conserved through the vertebrate phylum (Baulieu et al., 1999; Le Goascogne et al., 1987; Mellon and Griffin, 2002; Mensah-Nyagan et al., 1999), suggesting that neurosteroid formation might be crucial for life. This idea raises a great hope for the development of neurosteroid-based therapies to treat effectively complex disorders of the nervous system.

Among chronic disorders of the nervous system that involve complex mechanisms is neuropathic pain which represents a major health concern and the reason for medical consultation in many diseases. The International Association for the Study of Pain defined neuropathic pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede et al., 2008). The etiology of neuropathic pain includes several disorders such as diabetic polyneuropathies, postherpetic neuralgia, trigeminal neuralgia, painful radiculopathies, central post-stroke pain, spinal cord injury pain, traumatic, postsurgical and chemotherapy-induced neuropathies (Colloca et al., 2017; Cruccu and Truini, 2017; Finnerup et al., 2016; Jensen et al., 2011). About 10% of the general population is affected by neuropathic pain that is refractory to current analgesic drugs. This percentage is likely to increase because of the global ageing population and the augmentation of diabetic patients as well as the number of cancer survivors after chemotherapy (Colloca et al., 2017; Cruccu and Truini, 2017; Hershman et al., 2014).

Neuropathic pain is characterized by a diversity of symptoms including burning sensation, sharp, stabbing, allodynia, and/or hyperalgesia. Given to the complexity of the mechanisms involved, the management of neuropathic pain is extremely complicated as the available treatments have only moderate benefits. Thus, the development of effective strategies against neuropathic pain constitutes an urgent medical need. Therefore, to contribute to this objective requiring important global efforts, the present paper has critically reviewed and discussed basic, preclinical and translational evidence suggesting that neurosteroids may represent a relevant tool to exploit for the development of effective treatments against neuropathic pain.

2. Historical evidence in favor of a key modulatory action of steroidal compounds on pain sensation

For several years, the production of endogenous steroids was exclusively ascribed to the adrenals and gonads but it is now well established that various other tissues such as the bowel, liver, prostate and nervous system may synthesize or metabolize steroids (Baulieu et al., 1999; Belanger et al., 1989; Dalla-Valle et al., 1992; Martel et al., 1994). The chemical nature of steroids allows them to behave as lipophilic molecules, particularly when they are free or non-conjugated to sulfate radicals. Therefore, unconjugated steroids synthesized by peripheral glands may reach or act on several tissues in the body including the PNS and CNS since free steroids are capable of crossing the blood-brain barrier. Consequently, numerous studies indicate that steroid hormones exert a large array of biological effects including the control of sex behaviors, reproduction, development, stress and the regulation of the activity of various important physiological systems such as the immune, cardiovascular, respiratory and nervous systems (for reviews, Balthazart et al., 2018; Barnes, 1998; Belvisi and Hele, 2003; De Nicola et al., 2018; Fakih et al., 2002; Firestein et al., 1991; McEwen, 1994; Melcangi and Mensah-Nyagan, 2006). Receptors of various steroid hormones are expressed in several neural structures allowing steroids to crucially control the development, growth, maturation, differentiation and plasticity of the CNS and PNS (Balthazart et al., 2018; Green et al., 1997; Jones, 1993; Kimonides et al., 1998; McEwen, 1994; Rudolph et al., 2016; Sapolsky, 1996; Seckl, 1997; Uno et al., 1989; Yu, 1989).

Because of their pleiotropic potential and diverse effects on the CNS and PNS, steroids have early been suspected to modulate pain sensation. Indeed, since 1927, Cashin and Moravek observed that intravenous injections of cholesterol were able to suppress pain sensation by exerting anesthetic effects in mammals. Afterwards, Selye and Masson (1942) demonstrated that certain pregnane steroids such as PROG and deoxycorticosterone can induce sedation and anesthesia in rat. Together, these observations paved the way for the development of various synthetic analogs of pregnane steroids which reduced pain through allosteric activation of GABAA receptors (Belelli and Lambert, 2005; Holzbauer, 1976; Kraulis et al., 1975; Majewska, 1992; Olsen, 2018; Purdy et al., 1991; Taleb et al., 2018). Nowadays, the therapeutic use of glucocorticosteroids and their analogs is considered as the most effective strategy against inflammatory pain in spite of the occurrence of diverse side effects (for reviews, Barnes, 1998; Belvisi and Hele, 2003). Glucocorticosteroids reduce inflammatory pain by inducing anti-inflammatory actions on the damaged peripheral or central tissue which activates nociceptive mechanisms and generate pain sensation. Anti-inflammatory effects of glucocorticosteroids result from their ability to inhibit the expression of collagenase (the key enzyme involved in tissue degeneration during inflammatory mechanisms) and pro-inflammatory cytokines or to stimulate the synthesis of lipocortin which blocks the production of eicosanoids (Barnes and Adcock, 1993; Fakih et al., 2002; Firestein et al., 1991; Sibilia, 2003). There is also clinical evidence supporting the use of glucocorticoids in the treatment of chronic neuropathic pain (Devor et al., 1985; Kingery, 1997; Lussier et al., 2004; Wareham, 2004). Experimental investigations in animals suggest that glucocorticoids may inhibit the initiation of neuropathic pain states or attenuate this pain but the mechanisms of action are unknown (Clatworthy et al., 1995; Devor et al., 1985; Johansson and Bennett, 1997; Kingery et al., 1999; Takeda et al., 2004). It is usually thought that anti-inflammatory actions of glucocorticosteroids may contribute to the inhibition of neuroinflammatory component of neuropathic pain but there is no specific evidence supporting this hypothesis. As an interesting finding revealed that the endoneurial expression of pro-inflammatory cytokines may have a role in the genesis of neuropathic pain, glucocorticosteroids may reduce this pain through the modulation of neuroimmune interactions (Sommer and Kress, 2004). In support of this idea, a recent study showed that the glucocorticoid triamcinolone, which reduced the neuropathic pain seen in the model of post-traumatic peripheral neuropathy, also decreased the number of endoneurial mast cells expressing (in the injured nerve) the pro-inflammatory cytokine tumor necrosis factor-α (Hayashi et al., 2008). Altogether, the findings recapitulated above strongly support the existence of key actions of endogenous and synthetic steroids in the modulation of inflammatory and neuropathic pain.

3. Endogenous neurosteroids and neuropathic pain modulation

The demonstration of the occurrence of neurosteroidogenesis in a neural center/structure requires the localization in that structure of active forms of key steroidogenic enzymes such as P450scc, P450c17, 3α-HSOR, 3β-HSD and 5α-R (Baulieu et al., 1999; Compagnone and Mellon, 2000; Mensah-Nyagan et al., 1996a, 1996b). Among these enzymes, P450scc plays a crucial role since it catalyzes cholesterol conversion into PREG, the first pivotal step for neurosteroid biosynthesis (Baulieu et al., 1999; Le Goascogne et al., 1987). The finding that the CNS and PNS have the ability to locally produce key neuroactive steroids (Baulieu et al., 1999; Le Goascogne et al., 1987; Mellon and Griffin, 2002; Mensah-Nyagan et al., 1999) raises a great hope for the development of novel therapies based on the use of neurosteroids to improve the treatment of various neural disorders.

Based on the principle that neurosteroids act mainly through

autocrine or paracrine mechanisms, endogenous neurosteroid involvement in the regulation of a neurobiological process is plausible when neurosteroids are locally synthesized in the neural circuit controlling this process. It is true that neurosteroids modulate GABAA, NMDA and P2X receptors which play a crucial role in the regulation of pain (Baulieu et al., 1999; Mensah-Nyagan et al., 2008a; Millan, 1999, 2002; Tuem and Atey, 2017; Wang, 2011) but the local synthesis of neurosteroids near their sites of actions in pain neural centers is a prerequisite to render credible the possible involvement of endogenous neurosteroids in pain modulation. Therefore, we performed a series of studies to investigate whether the spinal cord which pivotally controls pain transmission and also contains potential sites of action for neurosteroids (Haines et al., 1997; Millan, 1999, 2002) may have the enzymatic machinery to locally synthesize neurosteroids. We demonstrated that the rat spinal dorsal horn (DH), which contains various key steroid-synthesizing enzymes such as P450scc, P450c17, 5α-R and 3α-HSOR, is an active center producing neurosteroids including PREG, DHEA, PROG, dihydroprogesterone (DHP) and 3α,5α-THP (Kibaly et al., 2005, 2008; Mensah-Nyagan et al., 2008b; Meyer et al., 2008; Patte-Mensah et al., 2003, 2004a, 2004b, 2005, 2006). In addition, we observed that substance P, a major nociceptive neuropeptide released by primary afferents, inhibited in a dose-dependent manner 3α,5α-THP biosynthesis in the DH (Patte-Mensah et al., 2005). As the neurosteroid 3α,5α-THP is a potent allosteric stimulator of GABAA receptors, our observation suggested that substance P, by reducing 3α,5α-THP production, may indirectly decrease the spinal inhibitory tone and therefore facilitate noxious signal transmission. To further investigate the possible role of neurosteroids endogenously produced in the DH in pain modulation, we performed a multidisciplinary study using the rat experimental model of neuropathic pain generated by sciatic nerve ligatures (Bennett and Xie, 1988). Molecular and biochemical investigations (quantitative real time polymerase chain reaction after reverse transcription, western blot, radioimmunoassay, pulse-chase experiments, high performance liquid chromatography and continuous flow scintillation detection) revealed an up-regulation of enzymatic pathways (P450scc and 3α-HSOR) leading to 3α,5α-THP biosynthesis in the DH (Meyer et al., 2008; Patte-Mensah et al., 2004a, 2004b). Because 3α,5α-THP is well known as a potent activator of the central inhibitory system (Belelli and Lambert, 2005), the observation of an upregulation of 3α,5α-THP production in the DH of neuropathic rats suggested that the increased synthesis of 3α,5α-THP might be involved in endogenous mechanisms triggered by neuropathic animals to cope with their chronic pain condition. However, the endogenous adaptive mechanisms or the level of 3α,5α-THP endogenously produced in the DH may not be sufficient to suppress painful symptoms that is the reason why, in the absence of treatments, neuropathic rats remained allodynic and/or hyperalgesic (Meyer et al., 2008). These data suggest that intrathecal injection of exogenous/synthetic 3α,5α-THP as an external contribution to increase the insufficient endogenous level in the DH may represent an effective strategy to suppress pain symptoms in neuropathic rats. In support of this hypothesis, behavioral studies using the plantar test (thermal nociceptive threshold) and the von Frey filament test (mechanical nociceptive threshold) showed that intrathecal administration of 3α,5α-THP in the lumbar spinal cord induced analgesia in neuropathic pain rats by suppressing the thermal hyperalgesia and mechanical allodynia characterizing these animals. Unlike 3α,5α-THP, intrathecal injection of Provera (3α-HSOR inhibitor) potentiated both thermal hyperalgesia and mechanical allodynia in neuropathic rats (Meyer et al., 2008; Patte-Mensah et al., 2014; Table 1). Contrary to what is observed for 3α,5α-THP production, the biosynthetic pathway (P450c17) producing DHEA was down-regulated in neuropathic rat DH (Kibaly et al., 2005, 2008). Acute DHEA treatment exerted a rapid pro-nociceptive and a delayed anti-nociceptive action. Inhibition of DHEA biosynthesis in the DH by intrathecally administered ketoconazole (P450c17 inhibitor) induced analgesia in neuropathic rats. Chronic treatment of DHEA increased and maintained elevated the basal pain thresholds in neuropathic and control rats, suggesting that androgenic metabolites generated from daily injected DHEA exerted analgesic effects while DHEA itself (before being metabolized) induced a rapid pro-nociceptive action (Kibaly et al., 2008).

In agreement with our findings showing endogenous neurosteroid involvement in pain modulation, various other investigations using synthetic analogs of 3α,5α-THP also revealed antinociceptive properties of neurosteroids in humans and animals (Gambhir et al., 2002; Goodchild et al., 2000, 2001; Nadeson and Goodchild, 2000, 2001). Interestingly, it has been shown that analgesic and antinociceptive effects of neurosteroids are reversed *in vivo* by the GABAA receptor antagonist bicuculline confirming therefore the involvement of this receptor considered as a major neurosteroid target (Belelli and Lambert, 2005; Hosie et al., 2006; Majewska, 1992) in the mediation of neurosteroid actions against pain sensation (Nadeson and Goodchild, 2000, 2001). Furthermore, it has been reported that neurosteroid 3α,5α-THP is capable of suppressing efficiently median nerve injury-induced mechanical hypersensitivity and glial extracellular signal-regulated kinase activation through GABAA receptor modulation in the rat cuneate nucleus (Huang et al., 2016).

Other important contributions are the works which investigated the interactions of 5α- and 5β-reduced steroid analogs with VGCCs and suggested that neurosteroids having combined inhibitory effects on low- and high-voltage-activated (LVA and HVA) calcium currents may be suitable to develop novel therapies against neuropathic pain (Joksimovic et al., 2018a; Pathirathna et al., 2005; Todorovic et al., 1998). Indeed, VGCCs, composed of HVA or sustained currents and LVA or transient (T-type) currents, are expressed in pain neural pathways and pivotally control cellular excitability and synaptic transmission (Catterall, 2000). Inhibition of peripheral T-channels led to potent antinociception in models of somatic (Choi et al., 2007; Todorovic et al., 2001, 2002, 2003) and visceral pain (Kim et al., 2003). Concordantly, it has been shown that 5α-reduced neurosteroids, which interact with both GABAA receptors and T-channels in peripheral nociceptive neurons, induce potent analgesic effects (Pathirathna et al., 2005). Because the upregulation of CaV3.2 isoform of T-channels in dorsal root ganglion sensory neurons caused hyperalgesia after surgical incision, additional studies demonstrated that the endogenous 5β-reduced neurosteroid epipregnanolone which inhibited the CaV3.2 isoform, without modulating GABAA-mediated currents, exerted a potent analgesia in healthy rodents (Ayoola et al., 2014; Joksimovic et al., 2018b; Todorovic et al., 2004). Local intraplantar injection of epipregnanolone decreased both thermal and mechanical nociception in the wild type mice, but was ineffective in CaV3.2 knock-out mice and this observation confirmed the idea that the blockade of CaV3.2 T-type calcium channels in peripheral sensory neurons was indeed involved in analgesia induced by epipregnanolone (Ayoola et al., 2014). Also, intrathecal administration of epipregnanolone that reduced thermal and mechanical nociception in healthy rats, decreased mechanical hyperalgesia in neuropathic animals *in vivo* after surgery; *in vitro* verifications revealed that epipregnanolone blocked isolated HVA currents in nociceptive sensory neurons with in a G-protein-dependent fashion (Joksimovic et al., 2019). Altogether, the aforementioned data strongly support the idea that VGCCs may represent promising targets to explore for the development of neurosteroid-based strategies against neuropathic pain.

Moreover, other previous studies have reported that neurosteroids, including PROG, DHP and 3α,5α-THP, improved Na^+K^+ ATPase activity, myelin protein zero and peripheral myelin protein 22 expression levels, thermal nociceptive threshold, skin innervation density and nerve conduction velocity in neuropathic animals (Leonelli et al., 2007). PROG and/or DHP, which counteracted sciatic nerve crush-induced decrease of Na^+K^+ ATPase pump activity and myelin protein expression, also restored normal pain thresholds (Roglio et al., 2008). More importantly, by using a model of incomplete spinal cord injury (SCI)-evoked neuropathic pain, Coronel and coworkers showed that SCI

Table 1
Effects of intrathecal injection of 3α,5α-THP and Provera on the thermal and mechanical pain thresholds of sciatic neuropathic and sham-operated rats. Pre-injection values **(A)** and responses 150 min (for mechanical thresholds) or 165 min (for thermal thresholds) after intrathecal injections **(B)** of 3α,5α-THP (5 mg/kg) or Provera (15 mg/kg). Each value represents the mean ± SEM of 5 observations for mechanical paw withdrawal thresholds (PWT) or 3 observations for thermal paw withdrawal latency (PWL) on each paw of 6 sciatic neuropathic and 6 sham-operated rats. Ipsilateral paw withdrawal responses were compared to contralateral paw withdrawal responses (##p < 0.01; ###p < 0.001). Injections of 3α,5α-THP (5 mg/kg) or Provera (15 mg/kg) were compared to the vehicle group (VEH) (*p < 0.05; **p < 0.01; ***p < 0.001).

	(A) Pre-injection	Sham-operated	Neuropathic Contralateral paw	Neuropathic Ipsilateral paw
	Mechanical PWT (g ± SEM)	116 ± 15	102 ± 9	13 ± 1###
	Thermal PWL (sec ± SEM)	12.25 ± 0.55	11.94 ± 0.49	6.88 ± 0.37###
	(B) Post intrathecal injection	Sham-operated	Neuropathic Contralateral paw	Neuropathic Ipsilateral paw
Vehicle	Mechanical PWT (g ± SEM)	111 ± 15	95 ± 13	15.4 ± 2.6##
	Thermal PWL (sec ± SEM)	9.96 ± 0.43	9.06 ± 0.19	6.2 ± 0.28###
3α,5α-THP	Mechanical PWT (g ± SEM)	207 ± 35*	262 ± 21**	53.6 ± 7.6**,##
	Thermal PWL (sec ± SEM)	11.44 ± 0.34***	11.11 ± 0.49***	8.63 ± 0.26***,###
Provera	Mechanical PWT (g ± SEM)	43.5 ± 9*	56.2 ± 5.3*	11.6 ± 1.4*,##
	Thermal PWL (sec ± SEM)	7.73 ± 0.37***	7.48 ± 0.36***	5.88 ± 0.24**,###

induced an increase in the spinal expression of mitochondrial cholesterol translocator protein (TSPO) and 5α-R that pivotally contribute to endogenous neurosteroid synthesis (Coronel et al., 2016). Previous data have also revealed that PROG and 3α,5α-THP levels were locally increased in the spinal cord 75 h after injury (Labombarda et al., 2006). Because a significant decrease of 5α-R mRNA was determined 28 days after the initial SCI, coinciding with the presence of allodynic behaviors, it has been suggested that the early increase in neurosteroidogenic pathway may represent a primary endogenous protective mechanism tending to control pain development (Coronel et al., 2016). Concordantly, PROG prevented sciatic nerve injury-induced increase expression of key players of pain genesis such as the NR1 subunit of NMDA receptor and the gamma isoform of protein kinase C or PKCγ (Coronel et al., 2011). Also, the early onset and maintenance of PROG therapy for a critical period counteracted peripheral nerve injury-evoked neuropathic pain symptoms (Dableh and Henry, 2011).

Because diabetic neuropathy is also associated with neuropathic pain in about 50% of diabetic patients, various preclinical studies have investigated the potential role of neurosteroid in the modulation of diabetes-induced neuropathic pain. We found an up-regulation of the gene encoding for the key neurosteroidogenic enzyme 3β-HSD as well as an increase of the amount of [^{3}H]PROG newly synthesized in the spinal cord of streptozotocin-induced diabetic rats (Saredi et al., 2005). By using the same animal model, another study, which analyzed testosterone metabolites, dihydrotestosterone (DHT) and 3α- androstanediol (3α-DIOL), on nociceptive and allodynia thresholds showed that diabetes induced a significant decrease in DHT levels in the spinal cord that was reverted by DHT or 3α-DIOL treatments; furthermore, 3α-DIOL systemic therapy promoted 3α-DIOL increase in the spinal cord and both DHT and 3α-DIOL exerted analgesic effects on diabetic neuropathic pain (Calabrese et al., 2014). Interestingly, DHT counteracted the effect of diabetes on mechanical nociceptive threshold, pre- and post-synaptic components, glutamate release, astrocyte immunostaining, and interleukin-1β (IL-1β) expression, while 3α-DIOL was effective on tactile allodynia threshold, glutamate release, astrocyte immunolabeling and the expression of substance P, toll-like receptor 4, tumor necrosis factor-α, transforming growth factor β-1, IL-1β and TSPO (Calabrese et al., 2014). Together, these data suggested that the increase of 3β-HSD expression and PROG production in the spinal cord of diabetic rats (which is insufficient *per se* to suppress pain symptoms) seems also to be an adaptive or compensatory mechanism to reduce the deficit of testosterone metabolites evidenced in these animals since PROG may be a precursor for testosterone synthesis. The data also indicate that testosterone metabolites may potentially constitute beneficial substances for the treatment of diabetic neuropathic pain. Moreover, it has been shown that chronic treatment with 3α,5α-THP prevented diabetes-induced spinal down-regulation of γ2 subunit of GABAA receptor and counteracted thermal hyperalgesia, as well as motor impairment (Afrazi and Esmaeili-Mahani, 2014).

The beneficial role of neurosteroids in the treatment of neuropathic pain symptoms was also evidenced significantly in preclinical conditions of anticancer drug-induced painful peripheral neuropathy. Indeed, it is well known that the therapeutic efficacy of anticancer drugs is limited by a major dose-dependent side effect which is painful peripheral neuropathy (Antoine and Camdessanche, 2007; Brewer et al., 2016; Cavaletti and Marmiroli, 2015; Dougherty et al., 2007; Fehrenbacher, 2015; Hershman et al., 2014; Ling et al., 2007a, 2007b; Polomano and Bennett, 2001; Seretny et al., 2014). Vincristine (VINC) and oxaliplatin (OXAL) are two antineoplastics widely used for the treatment of various malignancies including leukemia, ovarian, breast, lung and colorectal cancers (Antoine and Camdessanche, 2007; Baker, 2003; Brewer et al., 2016; Cavaletti and Marmiroli, 2015; Dougherty et al., 2007; Fehrenbacher, 2015; Ling et al., 2007a, 2007b; Polomano and Bennett, 2001; Seretny et al., 2014). However, both VINC and OXAL induce neuropathic pain symptoms such as mechanical hyperalgesia, cold-allodynia and mechanical allodynia (Antoine and Camdessanche, 2007; Dougherty et al., 2007; Hou et al., 2018; Ling et al., 2007a, 2007b; Polomano and Bennett, 2001). These painful symptoms hamper the success of VINC- or OXAL-based therapy as patients, who cannot complete optimal treatment schedules, must also face chronic discomfort and decreased quality of life. Neuroprotective compounds including thiols, neurotrophic factors, anticonvulsants and antioxidants were used to prevent antineoplastic-evoked neuropathy but the clinical data are controversial and these neuroprotective agents induce themselves adverse effects including nausea, reflex dysfunctions, treatment emergent nervousness, insomnia, anorexia or stomach burning (Durand et al., 2005; Finnerup et al., 2015, 2016; Gamelin et al., 2004; Hershman et al., 2014; Hou et al., 2018; Lang et al., 1996; Ling et al., 2007a, 2007b; Marchand et al., 2003). Therefore, it remains crucial to identify other molecules which may treat effectively anticancer drug-evoked neuropathic pain without evoking themselves undesirable effects. Because 3α,5α-THP is a natural neurosteroid exerting various beneficial actions (neuroprotection, neurogenesis, anxiolysis and analgesia) with no toxic side-effects (Bansal and Singh, 2017; Belelli and Lambert, 2005; Bitran et al., 1991; De Nicola et al., 2018; Joksimovic et al., 2018a; Meyer et al., 2008; Pathirathna et al., 2005; Patte-Mensah et al., 2005; Timby et al., 2006; Uzunova et al., 1998; Wang et al., 2010; Zamora-Sanchez et al., 2017), we hypothesized that 3α,5α-THP may be an interesting molecule to develop effective strategies against anticancer drug-induced painful neuropathy (Meyer et al., 2010, 2011). To check this hypothesis, we evaluated the effects of 3α,5α-THP on behavioral, electrophysiological, histological and

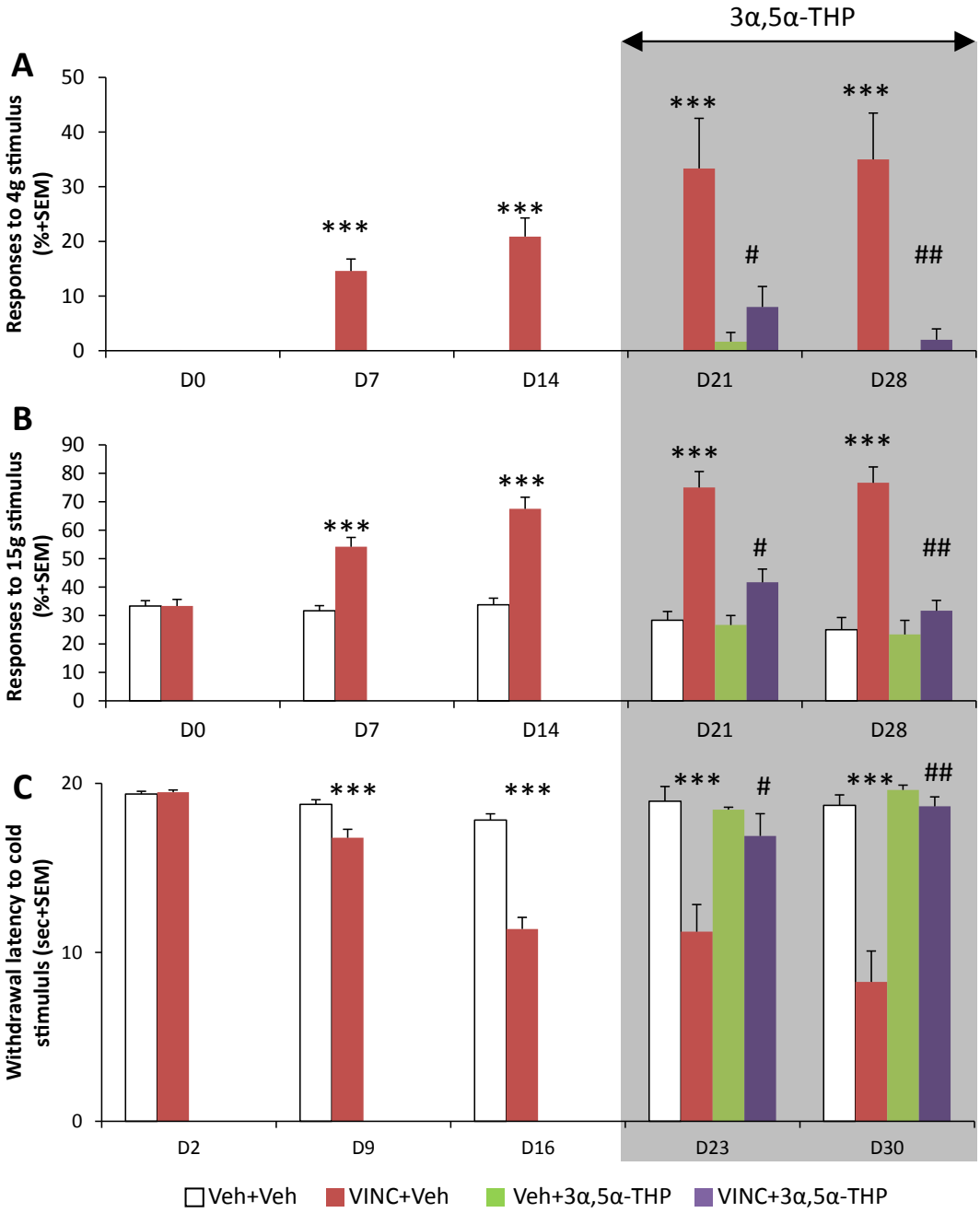

Fig. 1. Effects of 3α,5α-THP (4 mg/kg/2 days) corrective treatment on VINC-induced neuropathic pain symptoms. Corrective 3α,5α-THP treatment, which aimed at suppressing painful neuropathic symptoms persisting after the end of VINC treatment, consisted in starting 3α,5α-THP administration after the two VINC cycles (3α,5α-THP injections started 2 days after VINC cycles and lasted one week). (A, B) Action of 3α,5α-THP against VINC-induced mechanical allodynia (A) and hyperalgesia (B). The curves show the mean + SEM of the percentages of paw withdrawal responses to mechanical stimulation by von Frey filament 4 g (A) or 15 g (B) (n = 6 per group). (C) Effect of 3α,5α-THP against VINC-evoked cold-allodynia. Each point represents the mean + SEM of 6 observations in each of 6 rats. Non-parametric Mann-Whitney *U* test was used for the analysis of the von Frey test results and one-way repeated measures ANOVAs followed by Newman-Keuls *post hoc* comparisons were used for the acetone test. *p < 0.05, **p < 0.01, ***p < 0.005. * vs (Veh + Veh), # vs (VINC + Veh). Veh: Vehicle.

neurochemical parameters altered by VINC or OXAL treatment. Our results revealed that the prophylactic or corrective 3α,5α-THP treatment (4 mg/kg/2days) respectively prevented or abolished VINC or OXAL-induced mechanical hyperalgesia, mechanical allodynia and cold-allodynia (Meyer et al., 2010, 2011; Patte-Mensah et al., 2014; Fig. 1). Electrophysiological analyses allowed the determination of the effects of VINC or OXAL treatment on key functional parameters of the rat sciatic nerve including the conduction velocity (CV), the nerve action potential (NAP) onset and peak amplitude. We observed that VINC induced about 25% CV reduction without any significant change in the NAP peak amplitude. In contrast, the main effect of OXAL treatment was seen at the peak amplitude level which was reduced by about 62%. OXAL also decreased the nerve CV but the significant effect was only observed for the fastest conducting fibers. Prophylactic treatment with 3α,5α-THP prevented VINC- or OXAL-induced sciatic nerve functional alterations. In addition, when VINC- or OXAL-evoked nerve dysfunctions are well established before the onset of 3α,5α-THP treatment, the administration of 3α,5α-THP corrective treatment (4 mg/kg/2days) during one week was able to restore normal or control values of nerve CV and NAP peak amplitude in VINC- and OXAL-treated rats (Meyer

et al., 2010, 2011; Patte-Mensah et al., 2014). In the line of previous histological studies describing various nerve tissue damages induced by anticancer drug treatments (Authier et al., 2009; Jamieson et al., 2009; Lauria et al., 2005; Ravula et al., 2007; Siau et al., 2006), we have used the indirect immunofluorescence approach and laser scanning confocal microscopic quantifications to show that VINC or OXAL treatment, which dramatically decreased the density of intraepidermal nerve fibers (IENF) in hind paw intraplantar skins, also repressed neurofilament 200 kDa expression level in sciatic nerve axons and dorsal root ganglion neurons (Meyer et al., 2010, 2011; Patte-Mensah et al., 2014). The occurrence of such cellular alterations was prevented by prophylactic administration of 3α,5α-THP. Furthermore, corrective 3α,5α-THP treatment repaired VINC or OXAL-induced nerve tissue damages by restoring normal density of IENF in hind paw intraplantar skins and control expression level of neurofilament 200 kDa in VINC- or OXAL-treated rat dorsal root ganglia and sciatic nerves (Meyer et al., 2010; Patte-Mensah et al., 2014).

More importantly, our studies have evidenced the fact that the local activity of neurosteroidogenic enzymes in pain neural pathways is pivotal for the induction of a beneficial action of neurosteroids against anticancer drug-evoked neuropathic pain. Indeed, the inhibition of PROG conversion into 5α-reduced metabolites (DHP and 3α,5α-THP) by finasteride (Finn et al., 2006; Stoner, 1990) completely blocked antinociceptive, analgesic and neuroprotective effects exerted by PROG against VINC-induced painful neuropathy. In fact, in the absence of finasteride, PROG may be converted to the potent PROG nuclear receptor agonist DHP (Brann et al., 1990) and to the neuroprotector 3α,5α-THP (Melcangi et al., 2008), allowing therefore a strong stimulation or optimal activities of biochemical and neuroanatomical/neurochemical components in peripheral nerves such as CNPase, axonal constitutive proteins/transporters and IENF. In the presence of finasteride, PROG (or its non-5α-reduced metabolites), exerted only 3% increase on CNPase expression in control rat nerves and this slight stimulatory action failed to reverse the severe CNPase repression evoked by VINC treatment (Meyer et al., 2010). In agreement with our observations, other investigations have shown that DHP restored to normal values decreased levels of myelin-associated glycoprotein, peripheral myelin protein 22 and myelin basic protein in sciatic nerves of docetaxel-treated rats while PROG rescue effect was weak or undetectable (Roglio et al., 2009). Moreover, by using a model of brain traumatism *in vivo*, Sayeed et al. (Sayeed et al., 2006) have shown that 3α,5α-THP is more effective than PROG in reducing cortical damages after transient middle cerebral artery occlusion. Interestingly, it is well demonstrated that DHP may be inter-converted into 3α,5α-THP thanks to the enzymatic activity of 3α-HSOR abundantly expressed in the nervous system (Patte-Mensah et al., 2004b, 2005). Collectively, these data indicate that the conversion into 5α,3α-reduced metabolites is critical for the expression of PROG analgesic and neuroprotective effects. During our studies which revealed an efficient effect of 3α,5α-THP against anticancer-induced neuropathic pain, we did not measure plasma levels of 3α,5α-THP and its metabolites after the prophylactic or corrective 3α,5α-THP treatment (Meyer et al., 2010, 2011). However, a recent report has shown that subcutaneous injection of 3α,5α-THP to male Wistar rats at the dose of 1.25 or 2.5 mg/kg led to the increase of 3α,5α-THP plasma level which reached 97 or 252 nM, respectively (Holmberg et al., 2013). Therefore, it appears reasonable to estimate that 3α,5α-THP dose regimen investigated in our studies, namely 4 mg/kg/2days, may generate similar plasma concentration ranges as those detected by Holmberg and coworkers (Holmberg et al., 2013; Meyer et al., 2010, 2011). Moreover, it has been demonstrated that 3β-hydroxylated isopregnanolone or epipregnanolone did not affect formalin-induced pain and that the antinociceptive effect of 5α- and 5β-DHP in the formalin test is dependent on their conversion into 3α,5α-THP or PREG (Ocvirk et al., 2008). Altogether, these results, which confirm the crucial role played by 5α,3α-reduced neurosteroids in pain modulation, also suggest that 3α,5α-THP may offer an interesting possibility to develop effective strategy against neuropathic pain. 3α,5α-THP treatment also successfully corrected motor behaviors altered by OXAL-chemotherapy, indicating that 3α,5α-THP-based therapy may be relevant for the treatment of both painful/sensory and motor peripheral neuropathies (Taleb et al., 2017).

Among the family of 3α,5α-neurosteroids is also 3α-androstanediol or 3α-DIOL synthesized from the 5α-reduction of testosterone into DHT followed by the conversion of DHT into 3α-DIOL by the enzyme 3α-HSOR. Similarly to 3α,5α-THP, 3α-DIOL also activates allosterically the GABAA receptor and potentiates the central inhibition (Belelli and Lambert, 2005; Bitran et al., 1996; Edinger and Frye, 2004; Frye et al., 1996, 2007; Frye and Seliga, 2001; Hosie et al., 2006; Olsen, 2018; Reddy, 2008; Rhodes and Frye, 2004). While 3α,5α-THP has extensively been investigated in several experimental models and in humans as a neuroprotective, neurogenic, anaesthetic, anxiolytic or analgesic compound, the neurosteroid 3α-DIOL has received little attention (Akwa et al., 1999; Belelli and Lambert, 2005; Ciriza et al., 2004, 2006; Griffin et al., 2004; Meyer et al., 2008; Patte-Mensah et al., 2006; Uzunova et al., 1998; Wang et al., 2010). We have therefore investigated whether 3α-DIOL may also be a neuroprotective neurosteroid offering effective possibilities for the treatment of chemotherapy-induced painful neuropathy and neuropathological symptoms (Meyer et al., 2013). Thus, we assessed the potential of 3α-DIOL to prevent or suppress paclitaxel (PAC)-evoked neurochemical and functional abnormalities in rat peripheral nerves. Prophylactic or corrective 3α-DIOL treatment (4 mg/kg/2days) prevented or suppressed PAC-evoked heat-thermal hyperalgesia, cold-allodynia and mechanical allodynia/hyperalgesia, by reversing to normal, decreased thermal and mechanical pain thresholds of PAC-treated rats. Electrophysiological studies demonstrated that 3α-DIOL restored control values of nerve conduction velocity and action potential peak amplitude significantly altered by PAC-treatment. 3α-DIOL also repaired PAC-induced nerve damages by restoring normal neurofilament-200 level in peripheral axons and control amount of 2′,3′-cyclic-nucleotide-3′-phosphodiesterase in myelin sheaths. Decreased density of IENF evoked by PAC-therapy was also counteracted by 3α-DIOL treatment. More importantly, 3α-DIOL beneficial effects were not sedation-dependent but resulted from its neuroprotective ability, nerve tissue repairing capacity and long-term analgesic action. Interestingly, previous works reported that 3α-DIOL may exert estrogenic activity by interacting with estrogen receptors or may increase intracellular cAMP levels through binding to the sex hormone binding globulin (Ding et al., 1998; Pettersson et al., 2009). It has also been shown that the stimulatory effect of testosterone on learning and memory may partially be mediated through actions of its metabolite 3α-DIOL at estrogen receptors in the dorsal hippocampus (Edinger and Frye, 2007). Estrogens acting via classical and/or non classical receptors/targets have recognized neuroprotective properties in several experimental models of neurodegenerative/neurological disorders (for reviews, Arevalo et al., 2015; Baez-Jurado et al., 2019). Furthermore, we have previously observed that neurosteroid estradiol endogenously produced in the spinal pain circuit is pivotal for the protection of dorsal root ganglion sensory neurons against sciatic nerve chronic constriction injury-induced apoptosis (Schaeffer et al., 2010a, 2010b). Therefore, the aforementioned beneficial effects exerted by 3α-DIOL against PAC-evoked peripheral nerve damages and neuropathic pain may involve interactions of 3α-DIOL with various targets including estrogen and GABAA receptors.

Altogether, these data confirmed the idea that 5α,3α-reduced neurosteroids may offer promising options for the management of neuropathic pain evoked by chemotherapeutic drugs, spinal cord or peripheral nerve injuries.

4. Neurosteroids and sex dimorphism in pain sensitivity?

The ability of the nervous system to synthesize neurosteroids has been demonstrated in both male and female but the occurrence of sex dimorphism in neurosteroidogenic pathways remains a matter of speculation (for reviews Baulieu et al., 1999; Melcangi et al., 2008; Mensah-Nyagan et al., 1999). A recent study, which investigated sex differences in the brain expression of steroidogenic molecules under basal conditions and after gonadectomy, suggested that mRNA expression of steroidogenic molecules in the adult rat brain is sexually dimorphic and presents regional specificity, both under basal condition and after gonadectomy (Giatti et al., 2019). Although protein levels were not investigated in this study, it raises interestingly the hypothesis that local neurosteroidogenesis may contribute to sex and regional differences in brain levels of neurosteroids and may cause sex differences in the adult brain function (Giatti et al., 2019). Most investigations showing a key role of endogenously-produced neurosteroids in the modulation of neuropathic pain symptoms essentially used male animals and only few females have been tested to confirm the fact that the local manipulation of neurosteroidogenesis affects pain sensitivity thresholds in both sexes (Gonzalez et al., 2019; Meyer et al., 2008, 2010, 2011, 2013; Patte-Mensah et al., 2010, 2014; Schaeffer et al., 2010a, 2010b). However, whether selective differences may exist in the local production of neurosteroids in pain neural pathways of males versus females and whether these differences may sexually determine the efficacy of each neurosteroid in preventing pain symptoms remains an open question. Future investigations will certainly clarify this point in order to establish, in comparison with gonadal steroids, the specific contribution of endogenous neurosteroids (locally produced in the brain, spinal cord or peripheral nervous system) to sex differences in pain perception. Indeed, several lines of clinical and basic evidence showed that female and male gonadal steroids are key factors accounting for the gender differences in pain and analgesia (for reviews, Aloisi and Bonifazi, 2006; Aloisi et al., 2003; Arendt-Nielsen et al., 2004; Chakrabarti et al., 2010; Craft et al., 2004; Fillingim and Gear, 2004). Variations in sex steroid levels, receptor expression and mechanisms of action in the nervous system have been correlated with the development of chronic pain (Aloisi, 2003; Craft et al., 2004). Androgens, particularly testosterone, which are higher in males exert analgesic effects in humans and experimental models while estrogens were found to have both hyperalgesic and analgesic effects depending on the experimental conditions (Aloisi and Bonifazi, 2006; Aloisi et al., 2004; Ceccarelli et al., 2003; Hau et al., 2004). In addition, direct evidence has been provided for the occurrence of sex differences in the expression of steroid receptors in the periaqueductal gray that pivotally controls nociception and responsiveness to pain in male and female through interactions with the rostral ventromedial medulla which in turn projects to the spinal DH to elaborate the descending pathway driving pain inhibition (Loyd and Murphy, 2006, 2008). The differential expression of steroid receptors in the male and female brain and/or pain neural circuits may probably contribute to sex dimorphism in endogenous neurosteroid-induced antinociceptive and/or analgesic effects. Moreover, sex differences have also been well identified in both basal and stress -induced activity of the hypothalamic-pituitary-adrenal (HPA) axis which is more responsive to physical and psychological stressors in females than males (Critchlow et al., 1963; Frederic et al., 1993; Goel and Bale, 2008; Iwasaki-Sekino et al., 2009; Mitsushima et al., 2003; Seale et al., 2004). Stress can exert a complex modulatory action on pain leading either to an adaptive (stress-induced analgesia) or a maladaptive (stress-induced hyperalgesia) response depending on the nature, intensity, and duration of the stressful or aversive stimulus (Ferdousi and Finn, 2018). In particular, psychological stress in early life has been evidenced as a predisposing factor for the development of chronic pain and various studies showed that early-life stress is associated with long-term changes in the activity of the HPA axis which exhibits dysfunctions in chronic pain patients (Burke et al., 2017; Catley et al., 2000; Heim et al., 2008; Maccari et al., 2014; Riva et al., 2010; Vachon-Presseau et al., 2013). Because stress stimulates the secretion of adrenal steroids that cross the blood-brain-barrier to serve as precursors for the production of brain neurosteroids which can modulate the HPA axis function, a recent work investigated whether neurosteroid levels in the brain display sex- and/or region-specific differences under basal and acute stress conditions (Sze et al., 2018). This study which showed the existence of sex and regional differences in the brain concentrations of 5α-reduced steroids following acute stress, also suggested a sex-specific expression of steroidogenic enzymes in the brain (Sze et al., 2018). Thus, it appears that differential neurosteroidogenesis may contribute to sex differences in HPA axis responses to stress which in turns influence pain sensations. Therefore, future sex-based comparative investigations and elucidation of the specific role of neurosteroids endogenously synthesized in the female and male brain and/or spinal cord in normal and pathological pain conditions will certainly provide important insight to improve the current knowledge on sex dimorphism in pain sensitivity.

5. Conclusion

The data reviewed in the present paper show that 5α,3α-reduced neurosteroids, which possess a high therapeutic potential and a good toxicological profile, may be used to develop effective and safe strategies against neuropathic pain. Moreover, steroidal compounds in general, including hormonal steroids, neurosteroids and synthetic analogs of neuroactive steroids that control various mechanisms involved in pain sensation, deserve further attention to develop effective steroid-based strategies against neuropathic and chronic pain. In particular, several works that revealed a pivotal role of GABAA receptors (Gambhir et al., 2002; Goodchild et al., 2000, 2001; Nadeson and Goodchild, 2000, 2001) and VGCCs (Joksimovic et al., 2018a, 2018b, 2019; Pathirathna et al., 2005; Todorovic et al., 1998) in the mediation of analgesic and antinociceptive effects of neurosteroids suggest that further preclinical and clinical exploration of interactions between neurosteroids and these receptors/channels in various pain models/conditions may offer interesting opportunities to develop effective neurosteroid-based therapies against neuropathic pain. Finally, it is well known that mitochondrial dysfunction represents a major source of oxidative imbalance in persistent pain conditions (Flatters, 2015; Grace et al., 2016; Guo et al., 2013; Gwak et al., 2013; Lee et al., 2007; Park et al., 2006; Schwartz et al., 2008; Sui et al., 2013; Xiao and Bennett, 2012). Therefore, pharmacological strategies aim to protect mitochondrial function may also represent an effective strategy to alleviate deleterious consequences of oxidative stress and promote functional neuroprotection in patients at risk for neuropathic pain. Interestingly, various natural neurosteroids or newly characterized analogs of neurosteroids have recently been shown to improve mitochondrial bioenergetics/activities and to increase neuronal survival under pathological conditions (Grimm et al., 2014, 2016; Karout et al., 2016; Lejri et al., 2017; Taleb et al., 2018). Altogether, these data open interesting perspectives for the therapeutic exploitation of neurosteroids for the effective management of neuropathic pain.

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Declaration of Competing Interest

Authors declare that they have no conflict of interest.

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