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REVIEW PAPER

Allopregnanolone and Progesterone in Experimental Neuropathic Pain: Former and New Insights with a Translational Perspective

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Abstract
In the last decades, an active and stimulating area of research has been devoted to explore the role of neuroactive steroids in pain modulation. Despite challenges, these studies have clearly contributed to unravel the multiple and complex actions and potential mechanisms underlying steroid effects in several experimental conditions that mimic human chronic pain states. Based on the available data, this review focuses mainly on progesterone and its reduced derivative allopregnanolone (also called 3α,5α-tetrahydroprogesterone) which have been shown to prevent or even reverse the complex maladaptive changes and pain behaviors that arise in the nervous system after injury or disease. Because the characterization of new related molecules with improved specificity and enhanced pharmacological profiles may represent a crucial step to develop more efficient steroid-based therapies, we have also discussed the potential of novel synthetic analogs of allopregnanolone as valuable molecules for the treatment of neuropathic pain.

Keywords Neurosteroids · Neuroactive steroids · Progesterone · Allopregnanolone · Neuropathic pain · Spinal cord · Dorsal root ganglia · Mitochondria

Introduction

Steroids exert a wide range of noteworthy actions in the nervous system during physiological and pathological conditions, including the modulation of diverse biological processes such as memory, aging, stress, anxiety, depression, neuroprotection, and myelination (Balthazart et al. 2018; Baulieu 2001; Brinton 2013; De Nicola et al. 2013; Giatti et al. 2015; Guennoun et al. 2015; McEwen and Kalia 2010; Melcangi et al. 2014; Schumacher et al. 2012, 2014).

Furthermore, an impressive number of studies have demonstrated that several endogenous and synthetic steroids, particularly progesterone and its reduced derivative allopregnanolone (AP), are also implicated in the modulation of both nociceptive (Goodchild et al. 2000; Moradi-Azani et al. 2011; Nadeson and Goodchild 2000; Pathirathna et al. 2005a, b) and neuropathic pain (Cermenati et al. 2010; Coronel et al. 2011a, b, 2014, 2016a; Dableh and Henry 2011; González and Coronel 2016; Kibaly et al. 2008; Kim et al. 2012; Mensah-Nyagan et al. 2008, 2009; Meyer et al. 2008, 2010, 2011; Patte-Mensah et al. 2013, 2014; Wei et al. 2013), opening a fascinating venue to evaluate their potential therapeutic value in a variety of pain conditions.

Steroids are able to exert their multiple actions by binding to intracellular/nuclear receptors thus influencing gene transcription and signaling pathways, or by modulating neuronal excitability through their interaction with ionotropic neurotransmitter receptors, such as gamma-aminobutyric acid type A ($GABA_A$) and N-methyl-D-aspartate receptors (NMDAR), L- and T-type calcium channels, and sigma 1 receptors (Belelli and Lambert 2005; Frye et al. 2014;

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Hosie et al. 2006; Maurice et al. 2006; Mitchell et al. 2007; Pathirathna et al. 2005b; Rudolph et al. 2016; Schumacher et al. 2008), thus acting as "neuroactive steroids" (Paul and Purdy 1992; Porcu et al. 2016). Steroids can also influence second-messenger pathways by directly interacting with specific membrane receptors (Balthazart et al. 2018; Guennoun et al. 2008; Rudolph et al. 2016; Schumacher et al. 2008).

Specifically, progesterone can bind to the "classic" progesterone receptor (PR) that may be directed to the nucleus and act as a ligand-activated transcription factor that regulates the expression of target genes (Brinton et al. 2008; De Nicola et al. 2013; Schumacher et al. 2014). Two isoforms of PR have been described, PRA and PRB, which are products of a single gene (O'Malley et al. 1991), of which, PRB is a more potent transactivator of gene expression than PRA. In addition, PR can interact with the Src/Ras/MAPK and the cAMP signaling pathways leading to the modulation of intracellular signaling cascades (Boonyaratanakornkit et al. 2008; Schumacher et al. 2008).

Additionally, two types of membrane proteins unrelated to nuclear steroid receptors, progesterone membrane receptors (mPRs) and progesterone receptor membrane component 1 (PGMRC1) (Thomas 2008), may mediate progesterone actions in the nervous system. The mPRs, initially discovered in fish ovaries, comprise at least three subtypes, α, β, and γ, and belong to the seven-transmembrane progesterone adiponectin Q receptor (PAQR) family. These receptors, containing seven integral transmembrane domains, are expressed in the nervous system (Frye et al. 2013; Guennoun et al. 2008; Labombarda et al. 2010; Meffre et al. 2013) and mediate signaling via an inhibitory G-protein coupled pathway and stimulation of the MAPK pathway (Thomas and Pang 2012). To further complicate this picture, a putative membrane progesterone receptor 25Dx, later renamed as progesterone receptor membrane component 1 (PGRMC1), was found in the nervous system (Guennoun et al. 2008; Meffre et al. 2005) with a variety of functions (Lösel et al. 2008), including acting as an adaptor protein for steroid receptors (Thomas 2008; Thomas et al. 2014). Progesterone also modulates the activity of the nicotinic acetylcholine receptor (Valera et al. 1992) and may act as an antagonist of the sigma-1 receptor-binding site (Maurice et al. 2006).

Noteworthy, at least part of progesterone's anxiolytic and anesthetic effects could be due to its conversion to AP (also called 3α,5α-tetrahydroprogesterone). In contrast to progesterone and its first metabolite dihydroprogesterone (DHP), AP does not bind to PR and regulates nerve cell activity through its interaction with membrane receptors such as $GABA_A$ receptors and L- and T-type calcium channels (Balthazart et al. 2018; Belelli and Lambert 2005; Hosie et al. 2006; Mitchell et al. 2007; Pathirathna et al. 2005b) which are expressed in primary afferents and sensory centers that control nociception and pain (Millan 2002). In fact, AP is one of the most potent endogenous positive allosteric modulators of $GABA_A$ receptor function. In addition, the pregnane xenobiotic receptor (PXR) has been shown to act not only as a target of AP in the nervous system but also in the biosynthesis of neuroactive steroids (Cermenati et al. 2010; Frye et al. 2014). In addition, other studies have shown that AP is an effective ligand for mPRα (Thomas and Pang 2012). Such many crossroads of signaling pathways may explain the multiple effects of these steroids in the nervous system and may be relevant in the control of pain processing.

After a brief appraisal on neuropathic pain etiology and pathophysiology, the present review discusses the role of endogenous neurosteroids/neuroactive steroids in neuropathic conditions and, when available, recapitulates the current knowledge on the main mechanisms involved. Specially, we will focus on the potential therapeutic value of progesterone and AP which have been shown to prevent or even correct the complex plastic changes that arise in the nervous system in several experimental chronic pain models (Cermenati et al. 2010; Coronel et al. 2011a, b, 2014, 2016a; Dableh and Henry 2011; González and Coronel 2016; Kibaly et al. 2008; Kim et al. 2012; Mensah-Nyagan et al. 2008, 2009; Meyer et al. 2008, 2010, 2011; Patte-Mensah et al. 2013, 2014; Wei et al. 2013).

Because the currently available pharmacotherapy has poor efficacy and adverse side effects, the treatment and management of neuropathic pain still remain extremely difficult (Finnerup et al. 2016). Therefore, the development and characterization of new molecules exhibiting a safe toxicological profile may represent a crucial step to develop innovative and efficient strategies against neuropathic pain. Based on the available data, the implications of novel synthetic analogs of AP (Karout et al. 2016; Lejri et al. 2017; Taleb et al. 2018) as promising molecules to be used in effective and non-toxic steroid-based therapies for the treatment of neuropathic pain will be discussed.

What is Neuropathic Pain?

The ability to detect noxious stimuli represents a pivotal defense mechanism to ensure an organism's survival and safety (Basbaum et al. 2009; Julius and Basbaum 2001). Noxious stimuli of different modalities, i.e., chemical, mechanical, or thermal are detected by nociceptors, a subpopulation of primary afferent neurons expressing specialized transducer ion channel (Woolf and Ma 2007). These neurons have their cell bodies located either in dorsal root or trigeminal ganglia, for the body and face, respectively. They present a unique morphology, with both a peripheral and a central axonal branch that innervate the target tissues or the spinal cord (Basbaum et al. 2009; Woolf and Ma 2007). Subsets of projection neurons from the dorsal horn of the

spinal cord give rise to ascending pathways, such as the spinothalamic and spinoreticulothalamic tracts, conveying pain information to the somatosensory cortex through the thalamus and the brainstem. Descending pathways originating in the amygdala, hypothalamus, and cingulated cortex relay through brainstem nuclei in the periaqueductal gray matter and the rostroventral medulla to the dorsal horn, where they modulate spinal neurotransmission (Basbaum et al. 2009; Woolf and Ma 2007). The integration of this nociceptive information is considered a warning system that defends an individual from either concrete or potential tissue damage (Basbaum et al. 2009). However, not every type of pain represents an adaptive and defensive response, as is the case of neuropathic pain. The International Association for the Study of Pain has defined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al. 2008). As expected, the etiology of neuropathic pain is complex and includes diabetic polyneuropathies, postherpetic neuralgia, trigeminal neuralgia, painful radiculopathies, central post-stroke pain, and spinal cord injury pain, although traumatic, postsurgical, and chemotherapy-associated neuropathies also represent expected contributors (Colloca et al. 2017; Jensen et al. 2011). This severe type of pain affects 7–10% of the general population and remains refractory to common analgesic drugs. As recently noted, its incidence is likely to increase owing to the aging global population, increased occurrence of diabetes mellitus, and enhanced survival from cancer after chemotherapy (for a review, Colloca et al. 2017).

The symptoms that characterize neuropathic pain include burning sensation, sharp, stabbing pain, allodynia, and/or hyperalgesia, among others. Indeed, allodynia (pain due to a stimulus that does not usually cause pain) and hyperalgesia (increased pain to a stimulus that usually causes pain) are two major neuropathic pain-associated symptoms. Both are observed in several peripheral neuropathies and central pain disorders, affecting 15–50% of patients with neuropathic pain (Jensen and Finnerup 2014).

Despite challenges, mostly associated to the diversity of injuries and diseases involved, active research in the pain field has provided a useful insight on the pathophysiology of neuropathic pain. The increase in the excitability of peripheral or central components of the pain pathway, processes referred to as peripheral or central sensitization (Basbaum et al. 2009), occurs through multiple plastic changes and involves diverse mechanisms such as (a) spontaneous firing of damaged nerve fibers, (b) changes in the expression pattern of different neuropeptides, channels, and receptors, among other molecules, in primary afferent neurons, (c) increased responsiveness of dorsal horn circuits mostly due to increased NMDAR-mediated currents and loss of tonic $GABA_A$ receptor inhibitory control, (d) enhanced neuroimmune reaction, associated with the production of pro-inflammatory mediators, such as cytokines, (e) imbalance between descending facilitatory and inhibitory pathways that influence the transmission of pain messages particularly at the dorsal horn level (Costigan et al. 2009; Jensen et al. 2001, 2011; Truini and Cruccu 2006; Tsuda et al. 2013). More recently, mitochondrial dysfunction has been also pointed out as key player in persistent pain conditions, including diabetic neuropathy, cancer chemotherapy-evoked peripheral neuropathy, spinal cord injury, and inflammatory pain (Flatters 2015; Grace et al. 2016; Guo et al. 2013; Gwak et al. 2013; Park et al. 2006; Schwartz et al. 2008; Sui et al. 2013; Xiao and Bennett 2012).

Given that all these complex mechanisms often coexist, the available treatments for neuropathic pain usually have moderate benefits if any (Finnerup et al. 2016). Undoubtedly, neuropathic pain represents a significant burden for patients and healthcare systems, mainly related to the intricacy of neuropathic symptoms and inadequate outcomes that directly impact quality of life. Consequently, the development of novel strategies aimed to prevent or even reverse these maladaptive events represents an urgent medical need and a challenge for biomedical researchers. Since steroids control the development, activity, and plasticity of the nervous system, these compounds appear as relevant molecules to achieve these purposes. Therefore, in the following sections, we will recall the available data supporting the role of progesterone, AP, and related synthetic analogs as interesting candidates to develop effective and non-toxic strategies against neuropathic pain.

Progesterone and AP are Synthesized in the Sensory Pathways

The remarkable discovery that the nervous system is able to synthesize bioactive steroids gave birth to the term "neurosteroids" (Baulieu and Robel 1990; Corpéchot et al. 1981). "Neurosteroids," including androgens, estrogens, progestogens, and their derivatives, are steroids synthesized within the nervous system either *de novo* from cholesterol or from circulating steroids that serve as precursors for steroidogenic enzymes (Kibaly et al. 2008; Panzica and Melcangi 2008; Schaeffer et al. 2010a). In fact, measurable levels of several neurosteroids such as pregnenolone and progesterone are maintained in the brain (Corpéchot et al. 1983; Robel and Baulieu 1995) and in the rat spinal cord even in the absence of their adrenal and gonadal sources, supporting the notion of their local biosynthesis (Labombarda et al. 2006).

Over the last decades, the study of neurosteroidogenesis in the nervous system has become an active research field (De Nicola et al. 2018; Do Rego et al. 2009; Do Rego and Vaudry 2016; Garcia-Segura and Melcangi 2006; Giatti et al. 2015; Mensah-Nyagan et al. 1996a, b, 1999; Panzica

and Melcangi 2008; Patte-Mensah et al. 2004b; Porcu et al. 2016; Stoffel-Wagner 2003).

Several key steroidogenic enzymes involved in progesterone and AP synthesis are expressed by neurons and glial cells. The rate limiting step for neurosteroidogenesis is the shuttle of cholesterol from intracellular stores to the inner mitochondrial membrane, mediated by steroidogenic acute regulatory protein (StAR) and the 18 kDa translocator protein (TSPO) (King et al. 2002; King and Stocco 2011; Lavaque et al. 2006; Papadopoulos et al. 2006). Then, the enzyme cytochrome P450 side-chain cleavage (P450scc) located on the matrix side of the inner mitochondrial membrane catalyzes the transformation of its substrate cholesterol into pregnenolone (PREG). Finally, progesterone is synthesized by 3β-hydroxysteroid dehydrogenase (3β-HSD) action, using pregnenolone as a precursor molecule (Fig. 1).

AP, the neuroactive metabolite of progesterone, can be synthesized from progesterone by the complementary action of two key enzymes: 5α-reductase (5α-R), which reduces progesterone into 5α-dihydroprogesterone (5α-DHP), and 3α-hydroxysteroid oxido-reductase (3α-HSOR), which either reduces 5α-DHP into AP or converts AP into 5α-DHP (Fig. 1).

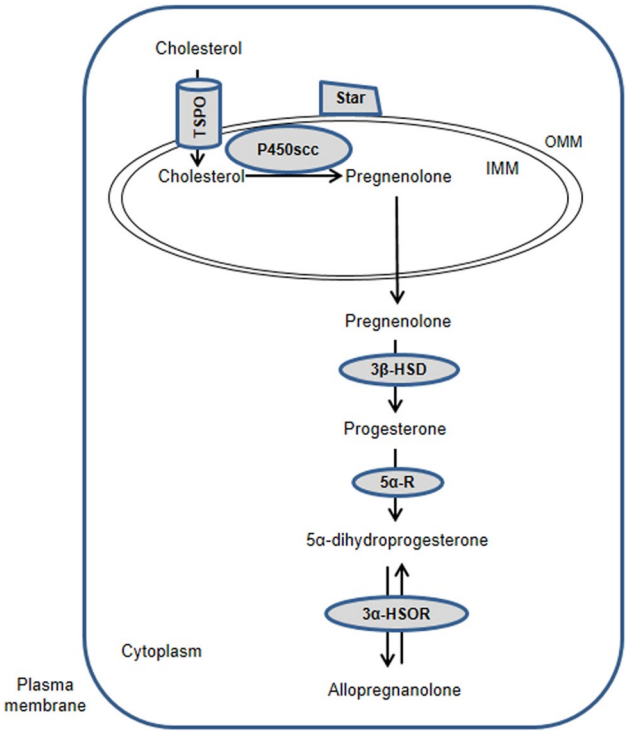

Fig. 1 Schematic representation of progesterone and allopregnanolone biosynthetic pathways in a steroidogenic cell. StAR, steroidogenic acute regulatory protein; TSPO, 18 kDa translocator protein; P450scc, cytochrome P450side-chain cleavage; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-R, 5α-reductase; 3α-HSOR, 3α-hydroxysteroid oxido-reductase; OMM, Outer mitochondrial membrane; IMM, Inner mitochondrial membrane

The presence and bioactivity of several key steroidogenic enzymes have been extensively demonstrated in sensory neural pathways (Baulieu 1999; Coirini et al. 2002; Mensah-Nyagan et al. 1996a, b, 1999, 2008; Patte-Mensah et al. 2003, 2004a, b, 2005). In fact, Mensah-Nyagan and colleagues provided strong evidence of the cellular distribution and bioactivity of fundamental steroidogenic enzymes such as cytochrome P450scc, cytochrome P450c17, 3β-HSD, 5α-R, and 3α-HSOR necessary for progesterone and AP synthesis from cholesterol in nociceptive structures (Mensah-Nyagan et al. 1999, 2008; Patte-Mensah et al. 2003, 2004a, b, 2005). Indeed, Patte-Mensah et al. (2004a) were the first to provide evidence of the anatomical and cellular localization of 5α/3α-reduced steroid-synthesizing enzymes in the spinal cord, which pivotally controls pain transmission. Furthermore, it was the first demonstration that oligodendrocytes and neurons of the spinal cord possess the key enzymatic complex for synthesizing potent neuroactive steroids that may control spinal sensorimotor processes. In line with this concept, these authors also found that substance P, a nociceptive neuropeptide released by sensory neurons, by inhibiting AP production may be involved in the reduction of the inhibitory tone in the spinal cord, facilitating noxious signal transmission (Patte-Mensah et al. 2005).

The Impact of Neuropathic Pain on Neurosteroid Synthesis

The local production of neurosteroids during several pain conditions has been extensively studied in the spinal cord (Kibaly et al. 2008; Mensah-Nyagan et al. 2008; Poisbeau et al. 2005), dorsal root ganglia (Patte-Mensah et al. 2010; Schaeffer et al. 2010a, b), and peripheral nerves (Leonelli et al. 2007; Pesaresi et al. 2010; Roglio et al. 2008b). In this section, we will make special emphasis on the spinal cord dorsal horn, as an active steroid-producing center in different chronic pain conditions.

Using the sciatic nerve ligature experimental model of neuropathic pain, a threefold increase in the spinal cord mRNA levels of the enzyme P450scc has been observed. This increase correlates with a significant higher density of P450scc-immunoreactive fibers in the ipsilateral dorsal horn (Patte-Mensah et al. 2003). In lumbar dorsal horn tissue homogenates from neuropathic animals, newly synthesized PREG is 80% higher than in the corresponding controls (Patte-Mensah et al. 2006). In addition, in animals with peripheral nerve injury-induced neuropathic pain, an increase in the endogenous concentrations of PREG and AP has been described, while their plasma levels do not change (Patte-Mensah et al. 2004a). In good

agreement with these results, the spinal cord mRNA levels of 3α-HSOR, the enzyme involved in the biosynthesis of AP, as well as its biological activity, has been shown to increase in animals subjected to a chronic constriction injury, contributing to reduce thermal hyperalgesia and mechanical allodynia (Meyer et al. 2008). Furthermore, the gene encoding for 3β-HSD shows a ninefold increase and the amount of [^{3}H] progesterone newly synthesized is 200% higher in the spinal cord of streptozotocin-induced diabetic rats than in control animals (Saredi et al. 2005).

An extension of this concept has been recently provided by Coronel et al., using a model of incomplete spinal cord injury (SCI) that induced neuropathic pain (Coronel et al. 2016b). In this work, we provided evidence that SCI induces an early and significant increase in the spinal expression of TSPO and 5α-RII, likely increasing spinal steroidogenic activity. Although in this study the spinal concentrations of neurosteroids were not evaluated, a previous report demonstrated that progesterone and AP levels were increased in the spinal cord 75 h after injury, without a significant increase in plasma (Labombarda et al. 2006), supporting the notion that the regulatory proteins/enzymes detected may correspond to active forms. Therefore, the early activation of neurosteroidogenic pathways appears as a protective and endogenously regulated response tending to control pain development (Mensah-Nyagan et al. 2008, 2009). Even more, the local production of dehydroepiandrosterone (DHEA), a steroid with pronociceptive actions, is reduced in the spinal cord of sciatic nerve-injured animals, due to the down-regulation of the enzyme involved in its biosynthesis (Kibaly et al. 2008). Thus, in several painful states, the activation of these spinal biosynthetic pathways appears to be selectively regulated to balance the levels of anti-nociceptive and pronociceptive neurosteroids.

However, in the chronic phase after spinal cord injury, a significant decrease in the mRNA levels of 5α-RI and 5α-RII was observed, coinciding with the presence of allodynic behaviors (Coronel et al. 2016b). Similarly, in a model of diabetic neuropathy, data obtained by liquid chromatography-tandem mass spectrometry indicate that the levels of neuroactive steroids decrease both in the peripheral and central nervous system (Pesaresi et al. 2010) and is differently affected in male and female rats. Thus, in several pain conditions, the local synthesis of protective steroids cannot be maintained, likely contributing to abnormal sensory processing.

Notably, a direct role of AP on nociception and neuropathic pain was demonstrated in healthy and experimental rat models of neuropathic pain. In both healthy and neuropathic rats, the in vivo knockdown and/or the pharmacological inhibition of spinal 3α-HSOR, which block AP synthesis, exerted a pronociceptive action (Meyer et al. 2008; Patte-Mensah et al. 2010). Importantly, these effects were reverted by intrathecal administration of AP (Meyer et al. 2008).

All these compelling literature studies allow a direct link between the local production of neurosteroids and its regulation in critical pathways controlling of pain transmission, paving the way to investigate their potential use in pathological pain.

Effects of Progesterone and AP in Neuropathic Pain Conditions

It is now a well-consolidated concept that progesterone and its reduced derivatives are neuroprotective agents in the central and peripheral nervous system (De Nicola et al. 2013; Fréchou et al. 2015; Guennoun et al. 2015; Melcangi et al. 2014; Schumacher et al. 2014), showing outstanding effects in experimental models of Alzheimer and Parkinson disease, multiple sclerosis, and traumatic brain and spinal cord injury (Garay et al. 2012; Garcia-Ovejero et al. 2014; González et al. 2004; Irwin et al. 2014; Labombarda et al. 2009, 2011, 2015; Stein 2006). Moreover, as it will be detailed below, an active area of research has shown that these steroids can also modulate pain behaviors in several experimental pain models, such as peripheral nerve injury, diabetic neuropathy, and spinal cord injury.

Progesterone and AP in Peripheral Nerve Injury and Diabetic Neuropathy

An overwhelming amount of evidence indicates that progesterone and its reduced metabolites are able to restore biochemical, morphological, and functional parameters after peripheral nerve injuries of different etiologies, e.g., physical trauma, diabetes, chemotherapy, among others (Afrazi and Esmaeili-Mahani 2014; Coronel et al. 2011b; Dableh and Henry 2011; Meyer et al. 2010, 2011; Patte-Mensah et al. 2014; Roglio et al. 2008a).

Indeed, by using animal models of diabetic neuropathy (Leonelli et al. 2007; Veiga et al. 2006), sciatic nerve crush (Roglio et al. 2008a), or docetaxel administration (Roglio et al. 2009), progesterone, DHP, and/or AP treatment have been shown to restore the activity of Na^+K^+ ATPase pump (Leonelli et al. 2007; Roglio et al. 2008a), counteract the injury-induced decrease in the expression of several myelin proteins in the sciatic nerve (Leonelli et al. 2007; Roglio et al. 2008a, 2009; Veiga et al. 2006) and the expression of calcitonin gene-related peptide in the spinal cord (Roglio et al. 2009). The steroids have been also able to prevent the degeneration of nerve endings in the footpad (Leonelli et al. 2007; Roglio et al. 2009) and improve functional parameters such as nerve conduction velocity (Leonelli et al. 2007;

Roglio et al. 2009) and thermal nociceptive threshold (Leonelli et al. 2007; Roglio et al. 2008a, 2009). Furthermore, a more recent report has shown that chronic AP treatment prevents the diabetes-induced spinal down-regulation of γ2 subunit of $GABA_A$ receptor, which in parallel counteracts both thermal hyperalgesia and motor impairment (Afrazi and Esmaeili-Mahani 2014).

In addition, Pathirathna et al. (2005a, b) demonstrated that AP is able to alleviate thermal and mechanical hyperalgesia after sciatic nerve ligature by potentiating $GABA_A$ receptor activity and blocking T-type Ca^{2+} channels (Pathirathna et al. 2005b), while Coronel et al. (2011a) recently showed that progesterone prevents allodynic behaviors in male rats subjected to sciatic nerve chronic constriction injury by preventing the injury-induced increase in the expression of two key players involved in pain generation: the NR1 subunit of NMDAR and the gamma isoform of protein kinase C (PKCγ) (Coronel et al. 2011b). In line with these findings, Dableh and colleagues (2011) found that, in order to prevent neuropathic pain-associated behaviors, progesterone treatment needs to be initiated early and maintained for a critical period after peripheral nerve injury (Dableh and Henry 2011).

AP Effects Against Anti-neoplastic Drug-Induced Neuropathic Pain

Recently it was hypothesized that AP, which exerts a wide range of beneficial actions in the nervous system with no toxic side effects, could be also an interesting molecule to counteract anti-neoplastic drug-induced painful neuropathy, a major limitation of anti-cancer treatment efficacy (Meyer et al. 2010, 2011). Meyer et al. showed that prophylactic or corrective AP administration, respectively, prevented or abolished mechanical hyperalgesia and allodynia induced by vincristine (VIN) and oxaliplatin (OXAL), two drugs commonly used for cancer chemotherapy. AP treatment also successfully corrected motor behaviors altered by OXAL-chemotherapy, indicating that AP-based therapy may be relevant for the treatment of both painful/sensory and motor peripheral neuropathies (Taleb et al. 2017).

Progesterone in Spinal Cord Injury-Induced Neuropathic Pain

Over the past decades, and using diverse experimental models of trauma and neurodegeneration, our laboratory and others have shown that progesterone exerts concerted actions on multiple processes in the injured spinal cord, resulting in better functional and histological outcomes (Garcia-Ovejero et al. 2014; Thomas et al. 1999), promoting neuroprotection (Gonzalez Deniselle et al. 2011; González et al. 2009), remyelination (Labombarda et al. 2009, 2011, 2015), and reducing inflammatory mediators and glial activation (Labombarda et al. 2011, 2015).

Furthermore, we have found that early progesterone administration prevents mechanical allodynia and significantly reduces the number of painful responses to cold stimulation in male rats subjected to SCI (Coronel et al. 2011a, 2014, 2016a).

Notably, and in parallel with lessening pain behaviors after SCI, progesterone also avoids the injury-induced increase in the expression of spinal NMDAR subunits (NR1, NR2A, and NR2B) and PKCγ (Coronel et al. 2011a), major players for chronic pain generation (Basbaum et al. 2009; Lan et al. 2001; Lim et al. 2005; Martin et al. 2001). Indeed, experimental diabetes (Tomiyama et al. 2005), spinal cord (Caudle et al. 2003; Grossman et al. 2000; Hulsebosch et al. 2009), and peripheral nerve injuries (Inquimbert et al. 2018) or morphine tolerance (Lim et al. 2005) show altered expression of spinal NMDAR subunits in clear association with abnormal pain processing. Remarkably, progesterone administration after SCI also resulted in lower number of dorsal horn neuronal profiles exhibiting the phosphorylated form of NR1 (pNR1) (Coronel et al. 2011a). This post-translational modification is critical to enhance NMDAR activity, increase neuronal responsiveness and pain (Caudle et al. 2003; Gao et al. 2005; Ultenius et al. 2006). Since several neuroactive actions of progesterone may involve the activity of NMDAR (Ren et al. 2000) and PKCγ (Balasubramanian et al. 2008), this steroid could have the ability to influence pain sensitivity through the modulation of these molecules.

More recently, we showed that progesterone is able to attenuate the SCI-induced increase in the number of reactive astrocytes and microglial cells, and to regulate the expression of pro-inflammatory enzymes, such as the inducible isoform of nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) (Coronel et al. 2014). Moreover, preclinical evidence strongly supports the notion that reactive gliosis along with the release of pro-inflammatory cytokines (Burda and Sofroniew 2014) are critically placed at the crossroads of neuroinflammation and neuropathic pain (Tsuda 2017, 2018; Walters 2014). For this reason, we have also explored the effects of progesterone on the expression of cytokines such as interleukin (IL) IL-1β, its functional IL-1RI and decoy IL-1RII receptors, the antagonist IL-1ra, IL-6, and tumor necrosis factor (TNF)-α during spinal injury-induced pain. Progesterone administration resulted in lower IL-1β, IL-6, and TNFα mRNA levels and caused a further increase in IL-1RII expression, sustaining the SCI-induced high levels of IL-1ra expression in the acute phase after injury (Coronel et al. 2016a). After SCI, secondary injury and the early neuroinflammatory cascade orchestrated by glial cells not only potentiate SCI damage (Mietto et al. 2015) but also may drive the transition to chronic pain (Cairns et al. 2015; Ji et al. 2018; Walters et al. 2014). Hence, early progesterone

administration may avoid the release of pro-inflammatory mediators responsible for altered neuronal function and widespread central sensitization at spinal level, a maladaptive process responsible of maintaining chronic pain. Our results also showed that, in the chronic phase after SCI, all injured animals—either receiving progesterone or not—showed a basal cytokine expression profile, which appeared to be in discrepancy with the high expression levels of these pro-inflammatory mediators described in neuropathic conditions. Notably, only the injured animals receiving vehicle exhibited a significant increase in IL-1RI expression.

It is well known that IL-1RI is expressed in glial cells but also in neurons (Gardoni et al. 2011). This allows IL-1β to facilitate pain via neural–glial interactions (Ji et al. 2013; Viviani et al. 2014), through the participation of the neuronal IL-1RI that may act as a coordinating factor to mediate spinal NMDAR phosphorylation in pain conditions (Gardoni et al. 2011). This may result particularly relevant in the context of SCI neuronal–glial interactions, a complex process responsible for several maladaptive spinal synaptic changes that contribute to enhanced persistent pain (Gwak et al. 2017).

Therefore, we evaluated the neuronal expression of IL-1RI after SCI. By using double immunofluorescence labeling, we found a higher percentage of NR1 positive neurons co-labeled with IL-1RI in the dorsal horn during the neuropathic phase after SCI (Coronel et al. 2016a). These observations were consistent with our previous results showing increased NR1 mRNA levels and higher number of pNR1 immunoreactive neurons in the dorsal horn associated with painful behaviors (Coronel et al. 2011a). All these literature studies suggest a potential interaction between IL-1β signaling and reinforced glutamatergic transmission, even at basal IL-1β levels, contributing to neuropathic pain after SCI. Remarkably, progesterone administration to injured animals reduced the number of IL-1RI/NR1 positive neurons in the dorsal horn, and prevented the aversive responses to mechanical and cold stimuli (Coronel et al. 2016a). As a result, progesterone might be decreasing the responsiveness of dorsal neurons to IL-1β and contributing to attenuate pain behaviors. Furthermore, these effects were maintained in the long-term, even after the treatment has stopped (Coronel et al. 2014), underlining the significance of targeting several key components of the central injury cascade occurring after SCI (Fig. 2).

Progesterone may influence target gene transcription through direct binding of PR to progesterone response elements in their promoters. In addition, PR can cross-talk with members of the AP-1, NF-κB, and Sp families of transcription factors and/or interact with several signaling pathways (for a review, Schumacher et al. 2014), allowing the transcriptional control of genes lacking these steroid-response elements. By using PR knockout (PRKO) mice, Labombarda et al. (2015) have recently explored the role of PR in the regulation of glial activation and the production of pro-inflammatory mediators after SCI. In these animals, progesterone could not reduce the high expression of inflammatory cytokines such as IL-1β and TNFα and showed a reduced index of NF-kB transactivation. Therefore, progesterone regulation of pro-inflammatory cytokines and enzymes could be mediated through PR modulation of NF-κB transactivation potential after SCI (Coronel et al. 2014; Labombarda et al. 2015).

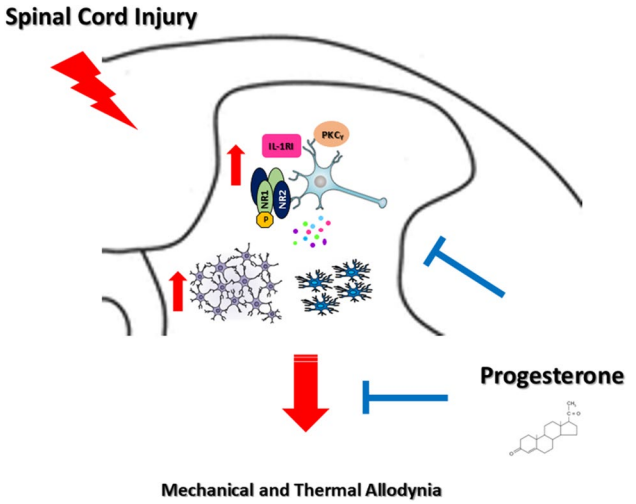

Fig. 2 Progesterone prevents neuropathic pain after experimental spinal cord injury. Spinal cord injury induces glial activation, enhances the expression of NMDAR subunits, IL-1βR and PKCγ, and increases neuronal NR1 phosphorylation, leading to enhanced neuronal responsiveness and allodynia. Progesterone by targeting the key components of this central injury cascade is able to prevent pain-related behaviors (for further details, see the text)

Moreover, progesterone's anti-allodynic effects after SCI could be due to its rapid conversion to AP, metabolite that reinforces inhibitory neurotransmission (Belelli and Lambert 2005; Peng et al. 2009). Recent reports further support this idea, showing that progesterone administration produces a clear increase in the expression of TSPO, StAR, 5α-RI, and 5α-RII in the chronic phase after SCI (Coronel et al. 2016b), and enhances the spinal TSPO expression/activity in animals exposed to nerve injury that also exhibited a lessened pain sensitivity (Liu et al. 2014). Due to the fact that PR response elements have been formerly described in the promoter region of the 5α-RII gene (Matsui et al. 2002), its transcriptional control by progesterone could be mediated through the binding of PR to these regulatory sites (Matsui et al. 2002). Hence, progesterone appears as promoting its own transformation into reduced metabolites for effective pain control (Coronel et al. 2016b).

Recent reports have also point to the critical role of sigma-1 receptor in central neuropathic pain after SCI

(Castany et al. 2018; Choi et al. 2016). Castany et al. (2018) showed that mechanical and thermal hypersensitivity were attenuated in sigma-1 receptor knockout mice following SCI, accompanied by reduced expression of TNFα and IL-1β as well as decreased activation/phosphorylation of the NR2B subunit of NMDAR. Moreover, SCI activates astrocyte sigma-1 receptors, leading to increases in the expression of Cx43, a gap junction protein that contributes to the early spread of astrocyte activation in the dorsal horn, and the induction of mechanical allodynia. Since progesterone was found to act as a competitive antagonist of sigma-1 receptor-binding site (Maurice et al. 2006), further research is needed to clarify the potential role of sigma-1 receptors in mediating progesterone actions in central pain models.

Our knowledge of the multiple cellular and molecular mechanisms acting as potential targets of progesterone actions to prevent the onset/development of neuropathic pain is still limited. However, the preclinical evidence shown here is promising and supports the notion that progesterone can achieve pain relief without interfering with functional improvements after SCI.

Novel Synthetic Analogs of AP: Potential Neuroprotective Candidates for a Targeted Strategy Against Mitochondrial Dysfunction in Pain Conditions

It is well known that mitochondria take part in a multitude of cellular processes including adenosine triphosphate (ATP) synthesis via oxidative phosphorylation, biosynthetic pathways, cellular redox homeostasis, ion homeostasis, oxygen sensing, synaptic plasticity, and regulation of cell survival and programmed cell death (Adam-Vizi and Chinopoulos 2006; Scheffler 2001).

Moreover, mitochondria also play a central role in the pathogenesis of several neurological disorders (Knott et al. 2008; Lin and Beal 2006). In pathological conditions, mitochondrial homeostatic alterations may lead to a failure of aerobic energy metabolism, less efficient production of ATP, decrease in mitochondrial membrane potential, increased generation of reactive oxygen species (ROS), and onset of mitochondrial permeability transition; all of which constitute severe mitochondrial dysfunction.

Under physiological conditions, the production of mitochondrial ROS, such as superoxide anion radicals, hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical (Adam-Vizi and Chinopoulos 2006; Jezek and Hlavatá 2005; Turrens 2003), is balanced by several competent anti-oxidant mechanisms, mainly mediated by the mitochondrial superoxide dismutase SOD2 (or MnSOD) that catalyzes the dismutation of superoxide anions to H_2O_2 and by the reduced glutathione (GSH) pool that allows the detoxification of H_2O_2 into H_2O. Nevertheless, after nervous system injury or disease, levels of ROS may exceed the neutralizing capacity of these endogenous anti-oxidant systems, leading to disruption of the functional and structural integrity of cells (Adam-Vizi and Chinopoulos 2006).

Specially, mitochondrial dysfunction and ROS overproduction represent a major source of oxidative imbalance in persistent pain conditions, including diabetic neuropathy, cancer chemotherapy-evoked peripheral neuropathy, spinal cord injury, and inflammatory pain (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). Indeed, ROS primarily produced in mitochondria have emerged as powerful pronociceptive mediators in oxidative stress and inflammation (Salvemini and Neumann 2009). Together with nitroxidative species, such as peroxynitrite, ROS contribute to the central sensitization associated with pain (Kim et al. 2004, 2008) and to the development of morphine anti-nociceptive tolerance (Doyle et al. 2010; Muscoli et al. 2007). In fact, inhibition of mitochondrial-derived peroxynitrite attenuates morphine hyperalgesia and reduces mitochondrial nitroxidative stress in the spinal cord (Little et al. 2013). Moreover, mitochondrial ROS induce spinal long-term potentiation (Lee et al. 2010), affect redox sensitive signaling pathways (Grace et al. 2016), and NMDAR phosphorylation (Gao et al. 2007; Ye et al. 2016) mediating the sensitization of neurons (Grace et al. 2016; Lee et al. 2007, 2010).

From these insights, the pharmacological strategies aimed to protect mitochondrial function may represent an effective strategy to alleviate the deleterious consequences of oxidative stress and promote functional neuroprotection in patients at risk of developing chronic pain.

Of note, mitochondria are the target of sex steroid actions. Indeed, sex steroids influence numerous functions of mitochondria: energy production, oxidative stress regulation, calcium homeostasis, cell proliferation, or apoptosis (Chen et al. 2009; Gaignard et al. 2017; Nilsen and Diaz Brinton 2003; Rettberg et al. 2014; Sayeed et al. 2009).

Further, mitochondria are also the site of the first step of steroidogenesis. Thus, mitochondria energetic dysfunction may lead to a decline in steroidogenesis, which in turn may impact mitochondrial function. Notably, a recent report suggested that sex-specific decrease in neuroactive steroid levels in male diabetic animals may cause an alteration in their mitochondrial function that in turn might influence axonal transport, contributing to the sex difference observed in diabetic neuropathy (Pesaresi et al. 2018).

Interestingly, the ability to improve mitochondrial bioenergetics seems to be a common mechanism of different steroids. In fact, Grimm et al. have recently showed that several structurally diverse neurosteroids improve cellular bioenergetics by increasing mitochondrial respiration, ATP

generation, and regulating redox homeostasis in cultured neuronal cells (Grimm et al. 2012, 2014, 2016a, b). In particular, AP was able to protect neuronal cultures against oxidative stress-induced cell death and prevent peroxide-induced apoptosis and NF-κB activation, balancing the increase of ROS production via improved mitochondrial anti-oxidant activity and intracellular redox state (Grimm et al. 2014, 2016a, b; Lejri et al. 2017; Zampieri et al. 2009).

However, the exploitation of these advantageous properties of AP for targeted therapies remains a difficult matter. Indeed, its proliferation-promoting effects on stem cells may raise serious concerns, in particular when considering its administration to treat chemotherapy-induced pain (Velasco and Bruna 2010). Another obstacle to overcome is the difficulty for AP to pass the liver that hinders the development of oral treatments, so only parenteral routes of AP administration are currently under investigation (Irwin et al. 2015). Moreover, the therapeutic use of AP may be limited by its rapid clearance after sulfation or glucuronidation of the 3-hydroxyl group (Reddy 2010; Schumacher et al. 2014).

Because of the limitations of current pharmacological therapies against neuropathic pain, the development of novel analogs of AP with improved pharmacological profiles appears as an interesting option to produce an effective mitochondrial neuromodulation and neuroprotection for the treatment of pain conditions.

To promote advance, Mensah-Nyagan and colleagues have recently modified the chemical structure of AP to synthesize a new set of compounds generally termed analogs of neurosteroids (ANS) by introducing either an oxo-group in position 12 or an O-allyl as substituent of the 3 hydroxyl group. These modifications allow to obtain a set of more stable compounds and individually designated BR053 (12 oxo-epiAP), BR297 (O-allyl-epiAP), BR351 (O-allyl-AP), and BR338 (12 Oxo-AP). Further details of the chemical synthesis and structures of these 4 ANS were published in the patent number WO 2012127176 A1 (Mensah-Nyagan et al. 2012). Therefore, in order to characterize ANS and select the best compounds, they also compared AP and ANS actions against oxidative stress and mitochondrial dysfunctions leading to cellular death (Lejri et al. 2017).

These novel compounds exhibit notable advantages over AP (Lejri et al. 2017). Indeed, BR297 acts as a potent neuroprotective compound totally devoid of cell-proliferative activity (Lejri et al. 2017; Taleb et al. 2018). Under oxidative stress, both BR297 and BR351 decrease ROS levels, improve mitochondrial respiration and cell survival, and emerge more potent than AP to protect cells against H_2O_2-induced death (Karout et al. 2016; Lejri et al. 2017; Taleb et al. 2018). All these findings lend support to the neuroprotective effects of ANS and emphasize their potential as powerful tools to counteract mitochondrial bioenergetics deficits in several pathological conditions.

Therefore, it could be hypothesized that due to their multiple properties, BR297 and BR351 will achieve a high level of neuroprotection against oxidative stress during pain conditions, representing a promising strategy to be translated from the laboratory to the bedside. Further research is guaranteed to evaluate these new mitochondrial neuromodulators and neuroprotective drugs for the treatment of diverse pain conditions.

Conclusions/Concluding Remarks

Neuropathic pain, a chronic disorder with a complex etiology, affects millions of patients worldwide. Because the treatment and management of neuropathic pain are extremely complicated, the characterization of novel compounds with safe toxicological profiles is a crucial need to develop efficient therapies. The data reviewed herein reveal interesting perspectives for the therapeutic exploitation of natural and synthetic neuroactive steroids for the treatment of peripheral and central neuropathies. Since a variety of standard therapies usually block individual mechanisms and exhibit reduced effectiveness, progesterone, AP and its synthetic analogs, by targeting simultaneous and major pain-related processes, might represent a valuable tool to prevent chronic pain in the clinical setting. However, major challenges for steroid-based therapy include the appraisal of pharmacokinetics, bioavailability, and sex-related differences and a better understanding of the mechanisms involved in their actions. These points should be confronted to produce a successful translational approach for the treatment of severe neuropathic conditions.

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Compliance with Ethical Standards

Conflict of interest None to declare.

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