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Review

Neuroactive steroids, nociception and neuropathic pain: A flashback to go forward

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ABSTRACT

The present review discusses the potential role of neurosteroids/neuroactive steroids in the regulation of nociceptive and neuropathic pain, and recapitulates the current knowledge on the main mechanisms involved in the reduction of pain, especially those occurring at the dorsal horn of the spinal cord, a crucial site for nociceptive processing. We will make special focus on progesterone and its derivative allopregnanolone, which have been shown to exert remarkable actions in order to prevent or reverse the maladaptive changes and pain behaviors that arise after nervous system damage in various experimental neuropathic conditions.

Contents

Abbreviations: ALLO, Allopregnanolone; $GABA_A$, γ-aminobutyric acid type A; NMDA, N-methyl-D-aspartate; SP, substance P; CGPR, calcitonin gene-related peptide; KOR, kappa opioid receptor; DOR, delta opioid receptor; MOR, mu opioid receptor; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, 5α-dihydrotestosterone; 3α-diol, 5α-androstane-3α,17β-diol; THP, 3α,5α-tetrahydroprogesterone; P0, myelin protein zero; PMP22, peripheral myelin protein 22; MAL, myelin and lymphocyte protein; PKCγ, gamma isoform of protein kinase C; iNOS, inducible isoform of nitric oxide synthase; COX-2, cyclooxygenase 2; IL, interleukin; TNFα, tumor necrosis factor α; pNR1, phosphorylated form of NR1; PR, progesterone nuclear receptor; mPR, progesterone membrane receptor; PGRMC1, progesterone receptor-membrane component 1; PXR, pregnane xenobiotic receptor; StAR/STARD1, steroidogenic acute regulatory protein; TSPO, 18 kDa translocator protein; PREG, pregnenolone; P450scc, P450 side-chain cleavage; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-R, 5α-reductase; 3α-HSOR, 3α-hydroxysteroid oxidoreductase; LXRs, nuclear liver X receptors.

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1. Introduction

Almost 35 years have gone by since the pioneering works of Baulieu and colleagues showed that the rat nervous system is capable of synthesizing bioactive steroids [1,2]. This discovery gave birth to the term "neurosteroids", e.g. steroids produced by the nervous system [3], while "neuroactive steroids" refers to steroids acting in the nervous system by modulating inhibitory or excitatory neurotransmitter receptors and neuronal excitability [4]. However, this notion has been extended to all steroids that directly act on neurons, either via membrane or nuclear signaling mechanisms [5], and includes those synthesized locally and in the peripheral glands (ovary, testis and adrenal glands) and also synthetic steroids [6].

Among these molecules, progesterone and its derivative allopregnanolone (ALLO) exert a wide range of fascinating actions in the central nervous system. In fact, an impressive number of pharmacological and behavioral studies have demonstrated that these neurosteroids/neuroactive steroids are involved in the control of several and diverse biological mechanisms such as cognition, stress, anxiety, depression, neuroprotection and myelination, which have been extensively reviewed elsewhere [6–12]. Furthermore, an important area of research has been devoted to explore the role of these steroids and related molecules in the modulation of both nociceptive [13–16] and neuropathic [17–30] pain, providing clear evidences towards the development of steroid-based therapies to counteract chronic pain conditions.

The present review discusses the potential role of neuroactive steroids in the regulation of nociceptive and neuropathic pain, and recapitulates the current knowledge on the main mechanisms involved, making reference mainly to those occurring at the spinal cord, a crucial site for nociceptive processing. We will make special focus on progesterone and ALLO, which have been shown to exert remarkable actions tending to prevent or reverse the maladaptive changes and pain behaviors that arise after nervous system damage in various experimental neuropathic conditions.

2. Steroids and nociceptive pain

Nociceptive pain represents a pivotal defensive mechanism intended to warn an individual of recent, ongoing or imminent damage to the body. In this context, the ability to detect noxious stimuli is essential to an organism's survival and wellbeing [31,32]. Mechanical, thermal and chemical noxious stimuli are detected by a subpopulation of primary afferent neurons called nociceptors [31,33]. Nociceptors have cell bodies located in dorsal root ganglia, a peripheral axonal branch that innervates tissues and organs, and a central branch that synapse on second order neurons, and local interneurons, within the dorsal horn of the spinal cord [31,33] (Fig. 1). Some second order neurons act as projection neurons and convey nociceptive information to the somatosensory cortex, via several brainstem and thalamic nuclei [31,34]. Supraspinal control of nociceptive signaling is relayed through the midbrain periaqueductal gray matter, the serotoninergic raphe nucleus, the noradrenergic locus coeruleus and the rostral ventromedial medulla, that directly or indirectly project to the dorsal horn [35,36].

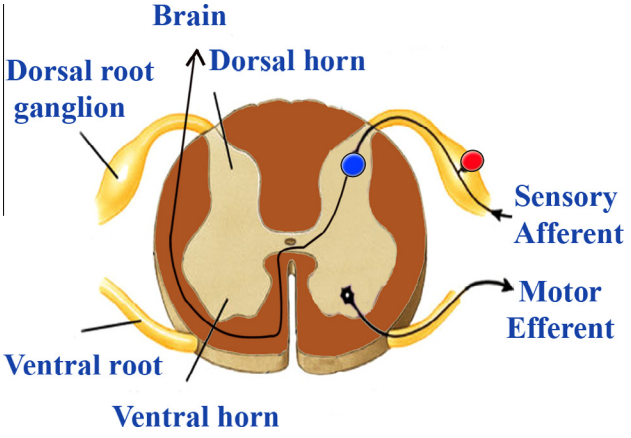

Fig. 1. Schematic representation of the pain pathway. Noxious stimuli are detected by nociceptors, a subpopulation of primary afferent neurons. They are located in dorsal root ganglia and have a peripheral axonal branch that innervates tissues and organs, and a central branch that synapse on second order neurons within the dorsal horn of the spinal cord, which convey nociceptive information to the brain.

Therefore, nociception can be regulated at different levels of the nervous system through facilitating (pronociceptive) or inhibitory (antinociceptive) actions. Particularly, the dorsal horn of the spinal cord stands as a critical site for nociceptive modulation, receiving both information about painful stimuli from the periphery as well as descending feedback from supraspinal centers, which ultimately regulates (with inhibition or further facilitation) the output from the spinal cord [31].

Steroids play pivotal physiological roles in the nervous system, including the modulation of pain sensitivity [8,37,38]. Steroids are able to exert their effects by binding to intracellular/nuclear receptors thus influencing gene transcription and signaling pathways [39,40], or by rapidly modulating membrane excitability and synaptic transmission through their interaction with ionotropic neurotransmitter receptors, such as γ-aminobutyric acid type A ($GABA_A$) and N-methyl-D-aspartate (NMDA) receptors, or voltage-dependent Ca^{2+} or K^+ channels [39–41]. Moreover, several steroids can also influence second-messenger pathways by directly interacting with specific membrane receptors [40,42].

Specifically, the spinal cord is not only a target for circulating steroids, but also an active steroid-producing site, that contains an array of regulatory proteins and enzymes involved in neurosteroid production and metabolism [37,38]. Accordingly, the impact of circulating steroids and neurosteroids on nociceptive processing at the spinal level has been largely studied, mainly in the context of stress response [9,43], pregnancy [44–46], estrous cycle [47,48] and sex-dimorphic responses to both noxious stimuli and opioid administration [49–51].

The impact of the stress response on nociception is multifaceted, and involves a large number of neurotransmitters and neuropeptides [52]. Acute stress is most commonly associated with the induction of analgesia, whereas chronic stress has been more frequently linked with the onset of hyperalgesia [52]. In this context, changes in circulating levels of glucocorticoids, occurring as part of the stress response, may impact on nociceptive processing at spinal level [43,53].

One recent study has shown that high levels of plasma corticosterone produce analgesia, by its conversion into its neuroactive 3α,5α-reduced metabolite in the spinal cord, which enhances GABAergic spinal inhibitory transmission and decreases nociceptive inputs [43]. Further, chronic glucocorticoid administration can also modulate the spinal expression of neuropeptides i.e. substance P (SP) and calcitonin gene-related peptide (CGRP), involved in nociceptive transmission [54], confirming that these steroids regulate physiological pain processing at the dorsal horn level.

Less is known about the participation of aldosterone in nociceptive modulation. Various preclinical and clinical studies have documented the role of the renin–angiotensin–aldosterone system in pain processing [55] and the consequences of experimental activation of the mineralocorticoid receptor, which increases the severity of inflammation [56], a key component in pain generation. However, the participation of the mineralocorticoid receptor in nociception and pain conditions deserves further investigation.