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Progress in dorsal root ganglion neurosteroidogenic activity: Basic evidence and pathophysiological correlation

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ABSTRACT

Dorsal root ganglia (DRG) which contain glial cells and somas of primary sensory neurons are pivotal for neural transmission between the peripheral and central nervous systems. It is well established that neuropeptides such as substance P and calcitonin gene-related peptide located in DRG neurons control sensory and pain mechanisms. However, contrary to the brain and spinal cord which are extensively investigated, DRG received little attention. Therefore, the current knowledge on DRG may be far to represent their complete neurochemical potential. For instance, until 1997, nothing was known on DRG neurosteroidogenic ability but recently, several investigations have shown that DRG contain various key enzymes synthesizing neuroactive neurosteroids. To provide new advances into DRG neurochemistry, we reviewed and highlighted herein basic and functional evidence showing that neurosteroids are produced in DRG through a neuron-glia crosstalk mechanism. Indeed, key enzymes producing neurosteroids including pregnenolone, progesterone, dihydroprogesterone and estradiol are differentially expressed in DRG cell types. Cytochrome P450side-chain-cleavage is located in DRG neurons and satellite glial cells, 3β-hydroxysteroid dehydrogenase is expressed in Schwann cells and neurons, 5α-reductase is localized in satellite glial and Schwann cells (not in neurons) while aromatase is present in neurons but not in glia. Recent studies also revealed that DRG neurosteroidogenesis is a physiologically relevant process selectively regulated under pathological conditions. Acting through paracrine and autocrine mechanisms, endogenous neurosteroids modulate DRG sensory functions and protect DRG neurons against death. The paper suggests that DRG neurosteroidogenic components may be targeted for the development of therapies against peripheral nerve injury-induced afferent noxious stimulations.

Contents

Abbreviations: CCI, chronic constriction injury; DH, dorsal horn; DHDOC, dihydrodeoxycorticosterone; DHEA, dehydroepiandrosterone; DHP, dihydroprogesterone; DHT, dihydrotestosterone; 3α-diol, 3α-androstanediol; DOC, deoxycorticosterone; DRG, dorsal root ganglia; HPLC, high performance liquid chromatography; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3α-HSOR, 3α-hydroxysteroid oxido-reductase; P450c17, cytochrome P450c17; P450scc, P450side-chain-cleavage; PREG, pregnenolone; PROG, progesterone; 5α-R, 5α-reductase; 3α,5α-THP, tetrahydroprogesterone; TSPO, translocator protein 18 kDa.

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1. Introduction

For several years, the formation of endogenous steroids was exclusively ascribed to the adrenals and gonads but it is now well established that neurons and glial cells, in the central (CNS) or peripheral (PNS) nervous system, are capable of synthesizing bioactive steroids or neurosteroids which regulate several neurophysiological functions (Baulieu et al., 1999; Mensah-Nyagan et al., 1999). The main criterion required for the identification of neurosteroids is their production in the CNS or PNS independently from the activity of endocrine steroidogenic glands including the adrenals and gonads. In addition to the genomic mode of 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 (Baulieu et al., 1999; Mensah-Nyagan et al., 1999; Mellon and Griffin, 2002; Belelli and Lambert, 2005; Melcangi et al., 2008). Different categories can be distinguished in the neurosteroid family. The non-exclusive neurosteroids such as pregnenolone (PREG), progesterone (PROG) or dehydroepiandrosterone (DHEA) are steroidal hormones that can also be synthesized by neurons and glial cells. Semi-exclusive neurosteroids such as tetrahydroprogesterone (3α,5α-THP) also called allopregnanolone are mainly produced in the nervous system although substantial amounts can be produced in endocrine glands. A recent work, which found that epiallopregnanolone was undetectable in plasma, suggested the existence of exclusive neurosteroids such as epiallopregnanolone that may be only synthesized in nerve cells (Higashi et al., 2007). However, other studies succeeded to measure low concentrations of epiallopregnanolone in plasma (Hill et al., 2007; Giatti et al., 2010). Whether these weak epiallopregnanolone plasma levels originated from the peripheral or central nervous tissue or from the classical endocrine glands, remains a matter of speculation. Anyway, further investigations are necessary to characterize genuine neurosteroids which can be considered as exclusively produced in the nervous system. The demonstration of the capacity of a neural center to produce neurosteroids requires the localization in that center of active forms of key steroidogenic enzymes such as cytochrome P450side-chain-cleavage (P450scc), cytochrome P450c17 (P450c17), 3β-hydroxysteroid dehydrogenase (3β-HSD), 5α-reductase (5α-R) and 3α-hydroxysteroid oxido-reductase (3α-HSOR) (Mensah-Nyagan et al., 1996a,b; Baulieu et al., 1999; Compagnone and Mellon, 2000). Occurrence of neurosteroid formation has been investigated in several animal species and it appears that the process of neurosteroidogenesis is well conserved through the vertebrate phylum (Baulieu et al., 1999; Mensah-Nyagan et al., 1999; Mellon and Griffin, 2002). This observation, which suggests that neurosteroidogenesis might be crucial for life, raises a great hope for the development of novel therapies utilizing 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. For instance, elegant studies which have shown the occurrence of neurosteroidogenesis in cortico-limbic circuits revealed that the down-regulation of neurosteroid biosynthesis in corticolimbic pathways mediates social isolation-induced behavior in mice (Agis-Balboa et al., 2007). To investigate whether the process of neurosteroidogenesis may also determine the activity of an extremely important pathway such as the sensory circuit, it appeared crucial to check the existence of neurosteroid biosynthesis in the spinal cord and dorsal root ganglia (DRG) which pivotally control sensory transmission and contains various steroid receptors (Haines et al., 1997; Millan, 1999, 2002; Herd et al., 2007; De Nicola et al., 2009). While the results related to the spinal cord have been discussed in recent comprehensive reviews (Patte-Mensah et al., 2006; Mensah-Nyagan et al., 2009), the data obtained on DRG by various and different research groups have never been reviewed, analyzed or discussed in an integrated manner. Therefore, the first objective of the present paper is to provide this integrated analysis in order to clarify and highlight the current knowledge on the process of neurosteroidogenesis and its physiological relevance in DRG. Prior to the detailed and extensive analysis on DRG neurosteroidogenic activity, a brief recall of key results on the spinal cord is made to give a complete view of the situation. Moreover, as only little is known on the potential of DRG (which compared to the spinal cord and other structures generally received minor attention from neuroscientists), valuable data are also provided in the present review to get new insights into DRG neurochemistry.

2. Brief recall of the spinal cord neurosteroidogenic ability

By using anatomical, immunohistochemical and biochemical approaches, we demonstrated that the rat spinal cord 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 (Patte-Mensah et al., 2003, 2004a,b, 2005, 2006; Kibaly et al., 2005, 2008; Mensah-Nyagan et al., 2008). 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 synthesis, 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 chronic constriction injury (CCI) (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 upregulation of enzymatic pathways (P450scc and 3α-HSOR) leading to 3α,5α-THP biosynthesis in the DH (Patte-Mensah et al., 2004a,b; Meyer et al., 2008). In contrast, the biosynthetic pathway (P450c17) producing DHEA was down-regulated in neuropathic rat DH (Kibaly et al., 2005, 2008). Behavioral studies using 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 CCI-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). Acute DHEA treatment exerted a rapid pro-nociceptive and a delayed anti-nociceptive action. Inhibition of DHEA formation in the DH by intrathecally administered ketoconazole (P450c17 inhibitor) induced analgesia in CCI-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). Taken together, these key results have clearly established that endogenous neurosteroids locally synthesized in the spinal cord pivotally control nociception and pain mechanisms.

3. Rapid view of DRG anatomy and function

DRG contain cell bodies of primary sensory neurons which transmit sensory information from the periphery to the CNS. Indeed, peripheral axons belonging to sensory neuronal cell bodies located in DRG constitute sensory receptors while the central axons of DRG neurons project on the spinal DH (Matthews and Cuello, 1982; Aldskogius et al., 1986). DRG neuronal cell bodies are surrounded by glial cells called satellite glial cells. Also present in DRG are Schwann cell bodies which synthesize myelin wrapping over sensory axons. Due to this anatomical organization, DRG are crucially important structures intervening in sensory processes. It is well established that DRG neurons, which contain nociceptive neuropeptides such as substance P and calcitonin gene-related peptide (Battaglia and Rustioni, 1988; De Biasi and Rustioni, 1988; Ribeiro-da-Silva and Hokfelt, 2000) are involved in pain transmission (Millan, 1999; Zimmermann, 2001). Moreover, it is also well-known that, in the event of nerve injury, cell bodies of DRG neurons generate ectopic neural discharges which probably contribute to neuropathic pain (Wall and Devor, 1983).

Because only little was known on the neurochemical potential of DRG which pivotally control sensory transmission and pain mechanisms, several studies have recently investigated the capacity of DRG to produce neuroactive neurosteroids (Lauber and Lichtensteiger, 1996; Guennoun et al., 1997; Yokoi et al., 1998; Patte-Mensah et al., 2003; Schaeffer et al., 2009). As mentioned in the introduction, we analyzed below several works showing the presence and activity in DRG of key neurosteroid-synthesizing enzymes. Afterwards, we discussed the physiological relevance and pathophysiological correlation of endogenous neurosteroid production in DRG.

4. Evidence for neurosteroid production in DRG

One of the main criteria required for the demonstration of neurosteroidogenesis occurrence in a neural structure is the localization of key active steroidogenic enzymes in that structure (Baulieu et al., 1999; Mensah-Nyagan et al., 1999). Therefore, the neurosteroidogenic activity of DRG has been demonstrated by various studies which showed the localization of key steroidogenic enzymes such as P450scc, 3β-HSD, 5α-R and aromatase in DRG (Fig. 1).

4.1. Presence and activity of P450scc in DRG

The enzyme P450scc is essential because it catalyzes the conversion of cholesterol into PREG, the rate-limiting step in the biosynthesis of all classes of steroids (Le Goascogne et al., 1987; Baulieu et al., 1999) (Fig. 1). P450scc is a mitochondrial enzyme which functions as a mono-oxygenase using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as electron donor. The

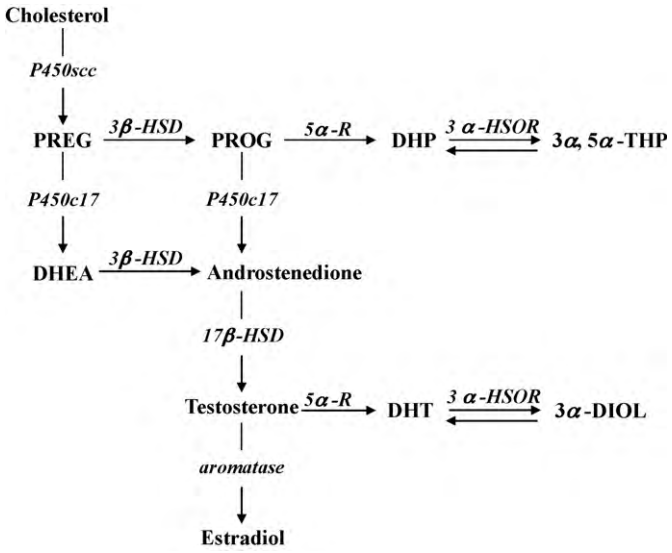

Fig. 1. Biochemical pathways leading to neurosteroid biosynthesis. P450scc, cytochrome P450side-chain-cleavage; P450c17, cytochrome P450c17 or 17α-hydroxylase/17,20lyase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-R, 5α-reductase; 3α-HSOR, 3α-hydroxysteroid oxidoreductase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; PREG, pregnenolone; PROG, progesterone; DHEA, dehydroepiandrosterone; DHP, dihydroprogesterone; 3α,5α-THP, 3α,5α-tetrahydroprogesterone (allopregnanolone); DHT, dihydrotestosterone; 3α-DIOL, 3α-androstanediol.

flavoprotein, adrenodoxin reductase and the iron/sulfur protein adrenodoxin serve as intermediate acceptors in the mitochondrial transport system transferring electrons from NADPH to P450scc. Molecular cloning revealed the existence of a single gene encoding P450scc in the human and rat genome (Matteson et al., 1986; Chung et al., 1987; Morohashi et al., 1987; Oonk et al., 1990). Recently, we studied in adult rats, the expression and biological activity of P450scc in various structures involved in sensory processing including DRG. To this aim we used two different antisera against P450scc. The first antiserum was raised against purified bovine adrenal P450scc (Suhara et al., 1978; Ikushiro et al., 1992; Tsutsui and Yamazaki, 1995; Usui et al., 1995; Ukena et al., 1998) and the second is a polyclonal antibody against carboxy-terminal domain of rat P450scc (Roby et al., 1991). The same anatomical and cellular distribution of P450scc-immunolabeling was observed with both antisera. P450scc-immunoreactivity was detected in several sensory neurons of DRG isolated from cervical, thoracic, lumbar and sacral regions (Patte-Mensah et al., 2003). Moreover, double-labeling experiments showed that P450scc positive cells also contained immunoreactivity for glial fibrillary acidic protein (GFAP) (Fig. 2), a widely used marker of satellite glial cells (Alvarez et al., 1989; Woodham et al., 1989; Stephenson and Byers, 1995; Ohtori et al., 2004; Hanani, 2005; Nascimento et al., 2008). The activity of P450scc in DRG was assessed using a well-validated technique combining pulse-chase experiments, high performance liquid chromatography (HPLC) and flow-scintillation detection (Mensah-Nyagan et al., 1994, 1996a,b, 2001a,b; Patte-Mensah et al., 2003, 2004a, 2005, 2006; Kibaly et al., 2005, 2008; Schaeffer et al., 2006, 2008a,b; Meyer et al., 2008; Venard et al., 2008, 2009). Incubation of DRG homogenates with tritiated cholesterol yielded the formation of several radioactive metabolites. Reversed-phase HPLC analysis coupled to a flow-scintillation characterization showed that one of the newly synthesized tritiated metabolites had the same retention time as PREG (Patte-Mensah et al., 2003). These data indicate that P450scc-immunoreactivity detected in DRG neurons and satellite glial cells corresponds to an active form of the enzyme.

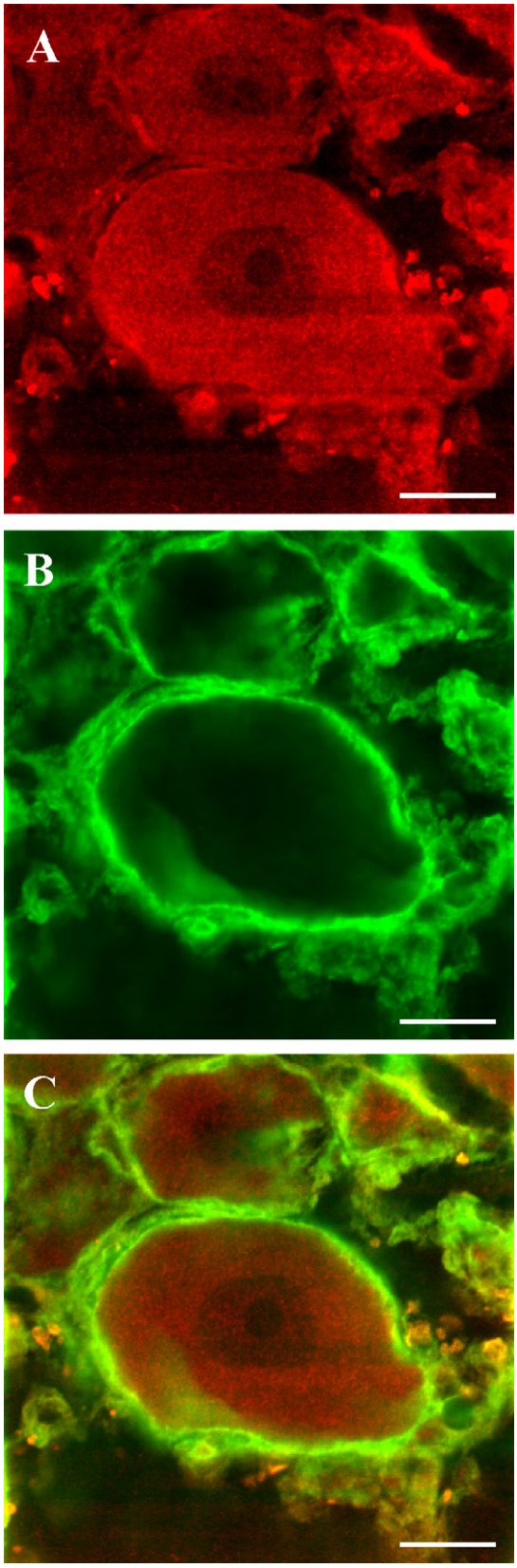

Fig. 2. Cell type identification of P450scc expressing cells in rat DRG. (A) Confocal laser scanning microscope photomicrograph showing P450scc-immunoreactive cells on a transverse section of rat lumbar DRG (used with permission from Patte-Mensah et al., 2003). (B) Photomicrograph of the same section observed in A showing GFAP-positive satellite glial cells. (C) Merged images of A and B showing the expression of P450scc-immunoreactivity in both DRG neuronal cell bodies and satellite glial cells. Scale bars: 10 μm.

4.2. Presence and activity of 3β-HSD in DRG

The key enzyme 3β-HSD participates to the biosynthesis of all classes of steroids by converting Δ^5-3β-hydroxysteroids such as PREG, 17-hydroxy-PREG and DHEA into Δ^4-3-ketosteroids as PROG, 17-hydroxy-PROG and androstenedione, respectively (Fig. 1). This reaction requires two sequential steps that are both catalyzed by 3β-HSD: (1) the first step is the dehydrogenation of 3β-equatorial hydroxysteroids in the presence of NAD^+, which yields Δ^5-3-keto intermediates and reduced NADH; and (2) the second reaction is the activation by NADH of Δ^5-3-ketosteroid isomerization to generate Δ^4-3-ketosteroids (Payne and Hales, 2004).

The presence of 3β-HSD has been demonstrated in DRG explants obtained from rat embryos (Guennoun et al., 1997). In particular, isolation of neurons and Schwann cells from DRG explants showed that both cell types were immunoreactive for 3β-HSD and are able to convert ^{3}H-PREG into ^{3}H-PROG, suggesting that the enzyme is functional (Guennoun et al., 1997). Similar experiments performed on highly enriched neuronal and Schwann cell cultures established from adult rat DRG indicated that both neurons and Schwann cells contained an active form of 3β-HSD (Guennoun et al., 1997). As these results were obtained from cell cultures, it will certainly be interesting to confirm them with double-labeling experiments performed in DRG tissues using specific markers for neurons, Schwann cells and satellite glial cells. In the meantime, it could reasonably be anticipated that the results provided by the investigations on cell cultures may be similar to those expected with experiments on complete DRG tissues. Indeed, in situ hybridization studies revealed that the mRNA encoding for 3β-HSD is expressed in neuronal cell bodies of complete DRG tissues, an observation which confirmed the data obtained with experiments using neuronal cell cultures (Guennoun et al., 1997).

4.3. Presence and activity of 5α-R in DRG

The enzyme 5α-R is responsible for the transformation of testosterone, PROG and deoxycorticosterone (DOC) into dihydrotestosterone (DHT), dihydroprogesterone (DHP) and dihydrodeoxycorticosterone (DHDOC), respectively (Fig. 1). 5α-R is a microsomal NADPH-dependent protein that acts essentially on steroids possessing a C4–C5 double bond and a ketone group at the C3 position. This enzyme catalyzes the transfer of two hydrogens from NADPH, inducing the reduction of the C4–C5 double bond and the formation of 5α-reduced metabolites (DHT, DHP and DHDOC) from steroid substrates (testosterone, PROG, DOC). Two isoforms of 5α-R, designated type 1 (5α-R1) and type 2 (5α-R2), have been cloned in human and rat (Andersson and Russell, 1990; Andersson et al., 1991; Berman and Russell, 1993). The genes encoding 5α-R1 and 5α-R2 are located on chromosome 5 and 2, respectively, and the two isoenzymes have different optimal pH and sensitivity to substrates (Normington and Russell, 1992; Wilson et al., 1993).

By using in situ hybridization (Lauber and Lichtensteiger, 1996) have detected 5α-R1 mRNA expression in DRG during early fetal development. In the adult rat PNS, immunocytochemical experiments combined with electron microscopic analyses revealed the presence of 5α-R1 protein in Schwann cells and satellite glial cells but not in neuronal perykaria (Yokoi et al., 1998). The absence of 5α-R1-like immunostaining in DRG neuronal cell bodies are contradictory to results showing that DRG sensory neurons can metabolize progesterone to DHP, suggesting the existence of 5α-R enzymatic activity in DRG neurons (Guennoun et al., 1997; Yokoi et al., 1998). Since immunocytochemical studies indicating the absence of 5α-R in neuronal cell perykaria were performed with a polyclonal antibody directed only against 5α-R1 (Yokoi et al., 1998), it is possible that the 5α-R enzymatic activity evidenced in DRG sensory neurons with biochemical methods (Guennoun et al.,

1997) reflects the presence of the isozyme 5α-R type 2 or 5α-R2 in DRG neurons. Altogether, these data indicate that 5α-R enzymatic activity is present in DRG cells. However, additional investigations will be useful to clarify the cellular distribution of each one of the two isozymes 5α-R1 and 5α-R2 in DRG neuronal and glial cells.

4.4. Presence and activity of aromatase in DRG

The conversion of androgens to estrogens is catalyzed by aromatase (Fig. 1), an enzymatic complex which comprises two proteins: (1) a specific form of cytochrome (cytochrome P450aromatase) responsible for the binding of C19 steroid substrate and the formation of the phenolic A-ring characteristic of estrogens and (2) a flavoprotein (NADPH-cytochrome P450reductase) which transfers reducing equivalents from NADPH to any microsomal form of cytochrome (Nelson et al., 1993).

Taking advantage of the availability of a specific monoclonal antibody against aromatase, we have recently investigated the presence and cellular distribution of this enzyme in DRG cells (Schaeffer et al., 2009). By combining immunohistochemical experiments with confocal microscopic analyses, we observed aromatase-immunoreactivity in small, medium and large size cell bodies of the rat DRG. Cell type identification using specific markers for neurons and glial cells revealed that aromatase-immunostaining is exclusively expressed in DRG neurons and not in glial cells (Fig. 3A–F). Moreover, we have used the well-validated

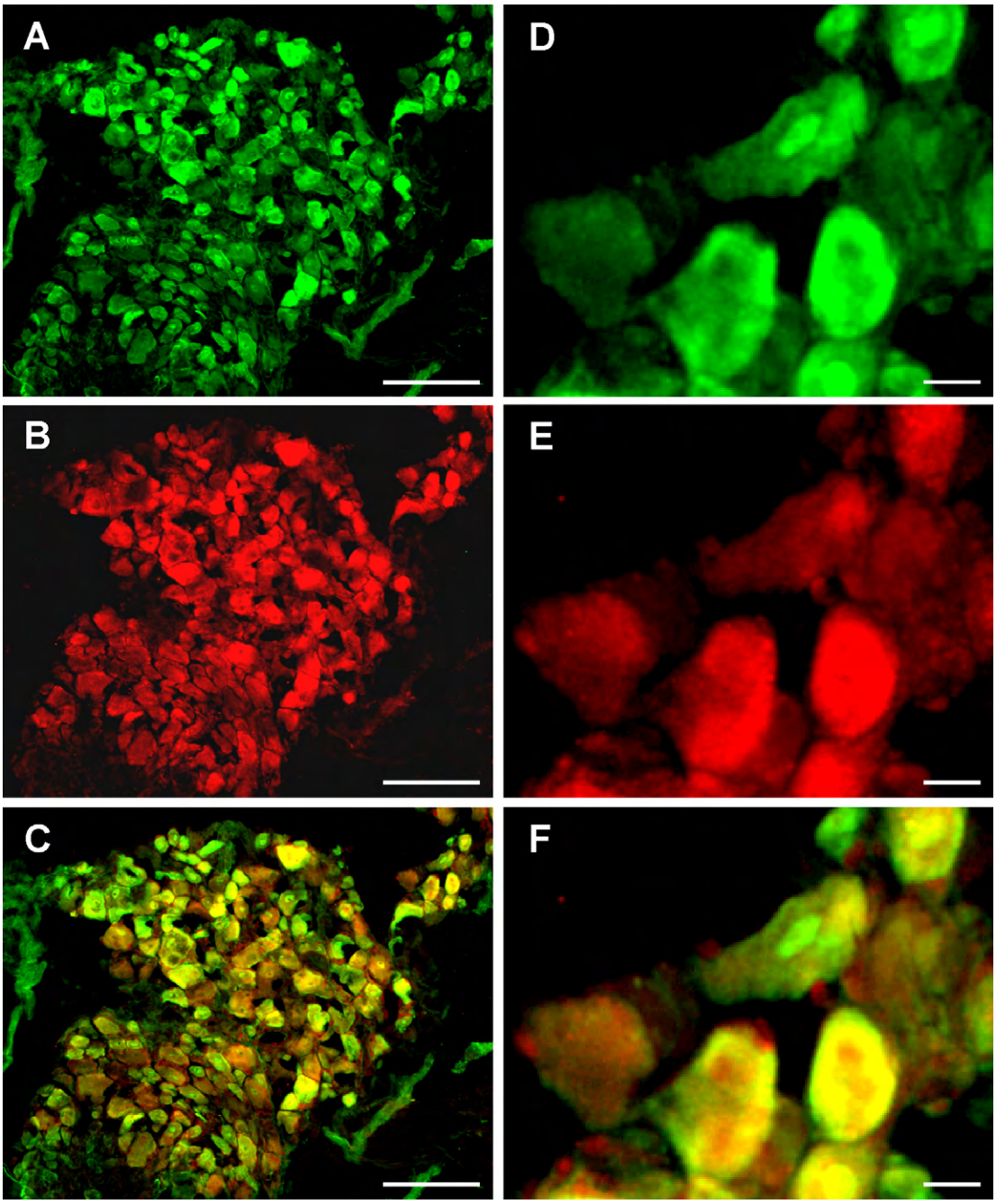

Fig. 3. Cell type identification of aromatase expression in rat DRG. (A and D) Photomicrographs of Neuronal nuclei protein (NeuN)-positive cells revealed in green on transverse sections of rat lumbar DRG. (B and E) Photomicrographs of aromatase-immunoreactive cells revealed in red on the same sections of rat lumbar DRG shown in A and D, respectively. (C and F) Merged images of A and B (C) or D and E (F) showing (in yellow) the co-localization of aromatase and NeuN immunoreactivities in DRG neurons. Scale bars: A–C, 100 μm; D–F, 10 μm.

method associating pulse-chase experiments with HPLC and flow-scintillation detection (Mensah-Nyagan et al., 1994, 1996a,b; Patte-Mensah et al., 2003, 2004a, 2005; Schaeffer et al., 2006, 2008a,b) to demonstrate that aromatase-immunoreactivity detected in DRG sensory neurons corresponds to an active form of the enzyme. Indeed, we observed that DRG isolated from the rat nervous system were capable of converting tritiated PREG into various radioactive neurosteroids including ^{3}H-estradiol; the endogenous production of ^{3}H-estradiol in DRG cells was significantly reduced in the presence of letrozole, a pharmacological inhibitor of aromatase activity (Schaeffer et al., 2009).

4.5. Other steroidogenic enzyme activities in DRG

The biosynthetic pathways transforming PREG into estradiol generate diverse intermediate neurosteroids such as progesterone (3β-HSD), 17-hydroxyprogesterone (P450c17), androstenedione (P450c17) and testosterone (17β-hydroxysteroid dehydrogenase or 17β-HSD) (Fig. 1). The combination of pulse-chase experiments with HPLC and flow-scintillation detection revealed that DRG slices convert ^{3}H-PREG successively into ^{3}H-PROG, ^{3}H-17-hydroxyprogesterone, ^{3}H-testosterone, ^{3}H-estradiol and ^{3}H-3α-androstanediol also called ^{3}H-3α-diol (Schaeffer et al., 2009). These results show that, in addition to P450scc, 3β-HSD, 5α-R and aromatase which were evidenced in DRG by in situ hybridization, immunohistological or biochemical methods (see Sections 4.1–4.4), other key steroidogenic enzyme activities such as P450c17, 17β-HSD and 3α-HSOR are also expressed in DRG cells.

5. Neuron-glia crosstalk and neurosteroidogenesis in DRG

As reported above, the biosynthesis of neurosteroids from cholesterol, the precursor of all classes of steroids, requires complementary activities of various enzymes such as P450scc, 3β-HSD, 5α-R and aromatase (Fig. 1). Several results support the idea that the process of neurosteroid biosynthesis in DRG is a neuron-glia crosstalk dependent mechanism (Guennoun et al., 1997; Yokoi et al., 1998; Patte-Mensah et al., 2003; Schaeffer et al., 2009). Indeed, the aforementioned studies indicate that steroidogenic enzymes producing neurosteroids in DRG are expressed in different cell types. For instance, it has been shown that P450scc and 5α-reductase activities are contained in DRG neurons and satellite glial cells (Guennoun et al., 1997; Yokoi et al., 1998; Patte-Mensah et al., 2003). The enzyme 3β-HSD has been localized in DRG neurons and Schwann cells while aromatase is exclusively expressed in DRG neurons but not in glial cells (Guennoun et al., 1997; Schaeffer et al., 2009). Therefore, it appears that certain neurosteroids cannot be produced by DRG glial cells but once these neurosteroids are released in their vicinity by DRG neurons, DRG glial cell bodies may incorporate and convert them into neuroactive metabolites. For example, DRG Schwann cell bodies do not contain P450scc which catalyzes the conversion of cholesterol into PREG (see above the specific section on P450scc expression in DRG). Therefore, DRG Schwann cells are unable to synthesize the neurosteroid PREG. However, DRG Schwann cells may incorporate PREG (produced by DRG neurons or satellite glial cells) and convert it into active metabolites such as PROG and DHP thanks to 3β-HSD and 5α-R activities that are present in DRG Schwann cells (Guennoun et al., 1997; Yokoi et al., 1998). Another interesting illustration of the neuron-glia cooperation for neurosteroidogenesis in DRG is provided by the endogenous production of estradiol in DRG (Fig. 4). Indeed, estradiol biosynthesis from cholesterol requires several enzymatic activities including P450scc, 3β-HSD, P450c17, 17β-HSD and aromatase (Fig. 1). DRG sensory neurons contain P450scc, 3β-HSD, P450c17 and aromatase (Patte-Mensah et al., 2003; Kibaly et al., 2005; Schaeffer et al., 2009) but do not have 17β-HSD which is known to be preferentially expressed in glial cells (Pelletier et al., 1995; Mensah-Nyagan et al., 1996a,b, 1999). Therefore, DRG sensory neurons may convert cholesterol successively into PREG (P450scc activity), progesterone (3β-HSD) and androstenedione (P450c17). However, because 17β-HSD catalyzing androstenedione conversion into testosterone (the precursor of estradiol) may not be present in DRG neurons, a crosstalk with DRG glial cells is compulsory for endogenous estradiol synthesis in DRG neurons. Thus, androstenedione produced by DRG neurons needs to be incorporated by DRG glial cells which synthesize and release testosterone (17β-HSD activity) in the vicinity of DRG sensory neurons that contain aromatase.

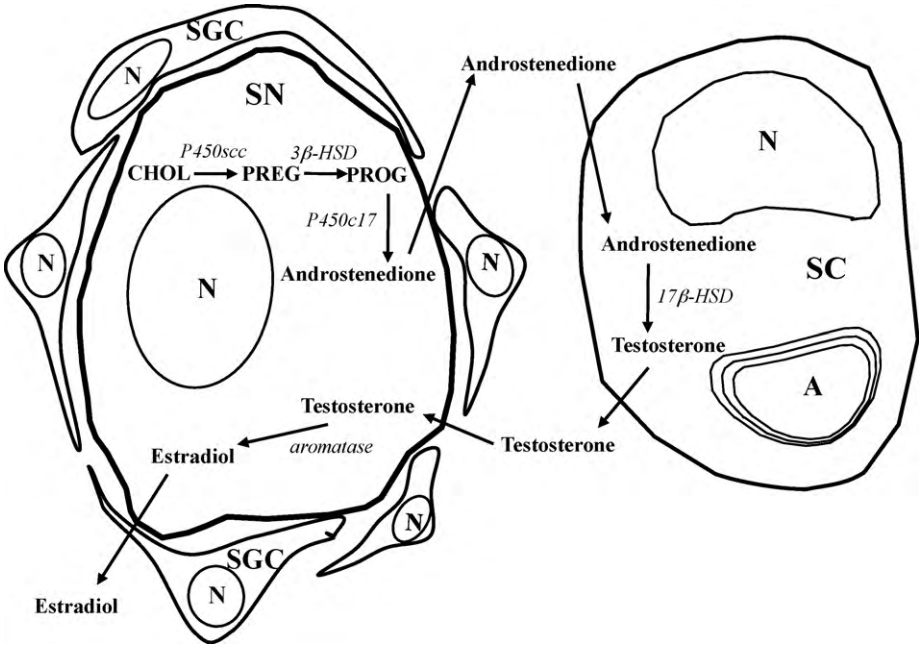

Fig. 4. Hypothetic scheme of neuron-glia crosstalk allowing estradiol production in DRG. (A) Transverse view of an axon surrounded by the myelin sheath generated by a Schwann cell (SC). N: nucleus; SGC: satellite glial cell; SN: sensory neuron.

Then, DRG sensory neurons can incorporate testosterone and convert it into estradiol thanks to aromatase activity (Fig. 4). So clearly, the process of neurosteroidogenesis in DRG appears as a neuron-glia crosstalk dependent mechanism. Taken together, these data suggest that the neuron-glia cooperation for the production of endogenous neurosteroids in DRG may be of particular importance in the modulation of various physiological processes. In support of this suggestion, neuron-glia crosstalk production of neurosteroids has been evidenced between neurons, oligodendrocytes and astrocytes in the developing brain and also between mature Schwann cells and sciatic nerve axons during the process of progesterone neosynthesis-induced myelination and regeneration of injured peripheral nerves (Melcangi et al., 1994, 1998; Schumacher et al., 2001, 2007).

6. Physiological relevance and pathophysiological correlation

It is well known that neurosteroids modulate neurotransmitter binding sites or receptors including calcium channels, GABAa, NMDA and P2X receptors which have all been evidenced in DRG (Dunn et al., 2001; Mellon and Griffin, 2002; Szekely et al., 2002; Belelli and Lambert, 2005; Jevtovic-Todorovic et al., 2009; Mensah-Nyagan et al., 2009). Therefore, endogenous neurosteroids produced in DRG may act in a paracrine or autocrine manner to control DRG functions through the modulation of neurotransmitter receptors expressed on DRG cells. In support of this hypothesis, a series of data published by Jevtovic-Todorovic and coworkers have successively demonstrated that (i) GABAa receptor modulation in DRG in vivo affects chronic pain after nerve injury and (ii) both T-type calcium channels and GABAa receptors are responsible for the potent peripheral analgesic effects of 5α-reduced neurosteroids (Pathirathna et al., 2005; Naik et al., 2008). Moreover, it has also been shown that neurosteroids, which rapidly inhibit calcium influx in murine embryonic sensory neurons (Viéro et al., 2006), also reduce ATP-induced intracellular calcium via the blockade of L-type calcium channels (Chaban et al., 2003). Together, these results suggest that the process of neurosteroidogenesis in DRG cells may pivotally regulate several calcium-dependent mechanisms involved in the development of immature neural tissue as well as in the functions of the adult nervous system. Furthermore, as several investigations have shown that neurosteroids are efficient neuroprotective molecules, it could be expected that neurosteroidogenesis in DRG may contribute to the protection of DRG cells against cytotoxic events (Guth et al., 1994; Kimonides et al., 1998; Frank and Sagratella, 2000). In particular, studies performed in rodents revealed that PROG, DHP and 3α,5α-THP locally synthesized in the CNS and PNS participate to the protection of nerve cells against degeneration (Koenig et al., 1995; Ghoumari et al., 2003; Martini et al., 2003; Melcangi et al., 2003; Leonelli et al., 2007; Schumacher et al., 2007). Neuroprotective action of endogenously synthesized estradiol has also been demonstrated in various experimental models (Garcia-Segura et al., 1999a,b, 2001, 2003; Azcoitia et al., 2001; McCullough et al., 2003; Veiga et al., 2005; Fester et al., 2006). Since DRG express the key enzymes (3β-HSD and 5α-R, 3α-HSOR and aromatase) required for the biosynthesis of all these neuroprotective neurosteroids their endogenous production may effectively contribute to the protection of DRG cells in cytotoxic situations. In agreement with this hypothesis, we have recently performed a series of investigations which showed that endogenous estradiol locally synthesized in DRG sensory neurons protect them against peripheral nerve injury-induced cell death (Schaeffer et al., 2009). Indeed, we have used the model of neuropathic pain generated by sciatic nerve CCI (Bennett and Xie, 1988) in which we observed apoptosis occurrence in DRG satellite glial cells 30 days after CCI. In this pathological situation, estradiol production was upregulated in DRG sensory neurons surrounded by apoptotic satellite glial cells. This result suggests that, through a paracrine mechanism, pro-apoptotic factors induced in DRG satellite glial cells by sciatic nerve CCI have triggered in DRG sensory neurons a selective increase in the activity of aromatase. The blockade of endogenous estradiol production in DRG neurons with intrathecal injection of letrozole (pharmacological inhibitor of aromatase) induced apoptosis of both satellite glial cells and DRG sensory neurons in CCI-rats (Schaeffer et al., 2009). Altogether, our observations suggest that the up-regulation of estradiol production in CCI-rat DRG neurons surrounded by apoptotic satellite glial cells may be an adaptive mechanism triggered by these neurons to protect themselves against peripheral nerve injury-induced cell death. Therefore, the neuron-glia crosstalk mechanism leading to estradiol formation in DRG sensory neurons (Fig. 4) appears as an extremely important neurochemical process involved in pain modulation and neuroprotection.

Because neurosteroids endogenously synthesized in nervous tissues modulate neurophysiological mechanisms through paracrine and autocrine modes (Frye et al., 2002, 2004; Patte-Mensah et al., 2004a; Agis-Balboa et al., 2007; Kibaly et al., 2008; Meyer et al., 2008), various substances which are capable of controlling neurosteroidogenesis appear as potentially interesting for the development of effective drugs against neural disorders (Pinna et al., 2003; Hirani et al., 2005; Ugale et al., 2007). In particular, recent studies have shown in animal models and humans that the ligands stimulating the translocator protein 18 kDa or TSPO (also called peripheral-benzodiazepine receptor) induce anxiolytic action devoid of side effects by increasing the local production of neurosteroid 3α,5α-THP in the CNS (Verleye et al., 2005; Ugale et al., 2007; Rupprecht et al., 2009). Indeed, TSPO plays a pivotal role in the onset of neurosteroidogenesis by regulating the transfer of cholesterol from the outer to the inner mitochondrial membrane where P450scc enzyme is located. Interestingly, TSPO has been localized in DRG sensory neurons (which contain also P450scc) and its expression increases in DRG neurons after peripheral nerve injury (Mills et al., 2005). Since endogenous estradiol produced in DRG is protective against peripheral nerve injury-induced DRG cell death (Schaeffer et al., 2009), it appears that TSPO and its ligands may control the regenerative response of sensory axons via the stimulation of local production of neurosteroids. In accordance with this idea, it has recently been shown that etifoxine, a TSPO ligand, improves peripheral nerve regeneration and functional recovery after nerve transection (Girard et al., 2008). Taken together, these results demonstrate that the neurosteroidogenic activity of DRG is a physiologically relevant process which may be strategically controlled to improve treatments against peripheral neuropathies.

7. Conclusion

Thanks to a collaborative action between neurons and glial cells, DRG are capable of synthesizing endogenous neurosteroids such as PREG, PROG, DHP and estradiol. This neuron-glia crosstalk allowing neurosteroid production in DRG generates an adequate trophic environment for DRG cells. Endogenous neurosteroids produced in DRG also appear to be pivotally involved in the modulation of DRG functions and the protection of DRG sensory neurons against death. Altogether, the data reviewed here suggest that neurosteroidogenic enzymes or molecular and cellular factors involved in neurosteroid production in DRG may be interesting targets for the development of strategies aiming to suppress afferent noxious stimulations resulting from injured peripheral nerves.

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References

Agis-Balboa, R.C., Pinna, G., Pibiri, F., Kadriu, B., Costa, E., Guidotti, A., 2007. Down-regulation of neurosteroid biosynthesis in corticolimbic circuits mediates social isolation-induced behavior in mice. Proc. Natl. Acad. Sci. U.S.A. 104, 18736–18741.

Aldskogius, H., Elfvin, L.G., Forsman, C.A., 1986. Primary sensory afferents in the inferior mesenteric ganglion and related nerves of the guinea pig. An experimental study with anterogradely transported wheat germ agglutinin-horseradish peroxidase conjugate. J. Auton. Nerv. Syst. 15, 179–190.

Alvarez, M.P., Solas, M.T., Suarez, I., Fernandez, B., 1989. Glial fibrillary acidic protein-like immunoreactivity in cat satellite cells of sympathetic ganglia. Acta Anat. (Basel) 136, 9–11.

Andersson, S., Russell, D.W., 1990. Structural and biochemical properties of cloned and expressed human and rat steroid 5 alpha-reductases. Proc. Natl. Acad. Sci. U.S.A. 87, 3640–3644.

Andersson, S., Berman, D.M., Jenkins, E.P., Russell, D.W., 1991. Deletion of steroid 5 alpha-reductase 2 gene in male pseudohermaphroditism. Nature 354, 159–161.

Azcoitia, I., Sierra, A., Veiga, S., Honda, S., Harada, N., Garcia-Segura, L.M., 2001. Brain aromatase is neuroprotective. J. Neurobiol. 47, 318–329.

Battaglia, G., Rustioni, A., 1988. Coexistence of glutamate and substance P in dorsal root ganglion neurons of the rat and monkey. J. Comp. Neurol. 277, 302–312.

Baulieu, E.E., Robel, P., Schumacher, M., 1999. Contemporary Endocrinology. Totowa, NJ.

Belelli, D., Lambert, J.J., 2005. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat. Rev. Neurosci. 6, 565–575.

Bennett, G.J., Xie, Y.K., 1988. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33, 87–107.

Berman, D.M., Russell, D.W., 1993. Cell-type-specific expression of rat steroid 5 alpha-reductase isozymes. Proc. Natl. Acad. Sci. U.S.A. 90, 9359–9363.

Chaban, V.V., Mayer, E.A., Ennes, H.S., Micevych, P.E., 2003. Estradiol inhibits ATP-induced intracellular calcium concentration increase in dorsal root ganglia neurons. Neuroscience 118, 941–948.

Chung, B.C., Picado-Leonard, J., Haniu, M., Bienkowski, M., Hall, P.F., Shively, J.E., Miller, W.L., 1987. Cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. Proc. Natl. Acad. Sci. U.S.A. 84, 407–411.

Compagnone, N.A., Mellon, S.H., 2000. Neurosteroids: biosynthesis and function of these novel neuromodulators. Front. Neuroendocrinol. 21, 1–56.

De Biasi, S., Rustioni, A., 1988. Glutamate and substance P coexist in primary afferent terminals in the superficial laminae of spinal cord. Proc. Natl. Acad. Sci. U.S.A. 85, 7820–7824.

De Nicola, A.F., Labombarda, F., Deniselle, M.C., Gonzalez, S.L., Garay, L., Meyer, M., Gargiulo, G., Guennoun, R., Schumacher, M., 2009. Progesterone neuroprotection in traumatic CNS injury and motoneuron degeneration. Front. Neuroendocrinol. 30, 173–187.

Dunn, P.M., Zhong, Y., Burnstock, G., 2001. P2X receptors in peripheral neurons. Prog. Neurobiol. 65, 107–134.

Fester, L., Ribeiro-Gouveia, V., Prange-Kiel, J., von Schassen, C., Bottner, M., Jarry, H., Rune, G.M., 2006. Proliferation and apoptosis of hippocampal granule cells require local oestrogen synthesis. J. Neurochem. 97, 1136–1144.

Frank, C., Sagratella, S., 2000. Neuroprotective effects of allopregnenolone on hippocampal irreversible neurotoxicity in vitro. Prog. Neuropsychopharmacol. Biol. Psychiatry 24, 1117–1126.

Frye, C.A., Rhodes, M.E., Rosellini, R., Svare, B., 2002. The nucleus accumbens as a site of action for rewarding properties of testosterone and its 5alpha-reduced metabolites. Pharmacol. Biochem. Behav. 74, 119–127.

Frye, C.A., Edinger, K.L., Seliga, A.M., Wawrzycki, J.M., 2004. 5alpha-reduced androgens may have actions in the hippocampus to enhance cognitive performance of male rats. Psychoneuroendocrinology 29, 1019–1027.

Garcia-Segura, L.M., Naftolin, F., Hutchison, J.B., Azcoitia, I., Chowen, J.A., 1999a. Role of astroglia in estrogen regulation of synaptic plasticity and brain repair. J. Neurobiol. 40, 574–584.

Garcia-Segura, L.M., Wozniak, A., Azcoitia, I., Rodriguez, J.R., Hutchison, R.E., Hutchison, J.B., 1999b. Aromatase expression by astrocytes after brain injury: implications for local estrogen formation in brain repair. Neuroscience 89, 567–578.

Garcia-Segura, L.M., Azcoitia, I., DonCarlos, L.L., 2001. Neuroprotection by estradiol. Prog. Neurobiol. 63, 29–60.

Garcia-Segura, L.M., Veiga, S., Sierra, A., Melcangi, R.C., Azcoitia, I., 2003. Aromatase: a neuroprotective enzyme. Prog. Neurobiol. 71, 31–41.

Ghoumari, A.M., Ibanez, C., El-Etr, M., Leclerc, P., Eychenne, B., O'Malley, B.W., Baulieu, E.E., Schumacher, M., 2003. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. J. Neurochem. 86, 848–859.

Giatti, S., D'Intino, G., Maschi, O., Pesaresi, M., Garcia-Segura, L.M., Calza, L., Caruso, D., Melcangi, R.C., 2010. Acute experimental autoimmune encephalomyelitis induces sex dimorphic changes in neuroactive steroid levels. Neurochem. Int. 56, 118–127.

Girard, C., Liu, S., Cadepond, F., Adams, D., Lacroix, C., Verleye, M., Gillardin, J.M., Baulieu, E.E., Schumacher, M., Schweizer-Groyer, G., 2008. Etifoxine improves peripheral nerve regeneration and functional recovery. Proc. Natl. Acad. Sci. U.S.A. 105, 20505–20510.

Guennoun, R., Schumacher, M., Robert, F., Delespierre, B., Gouezou, M., Eychenne, B., Akwa, Y., Robel, P., Baulieu, E.E., 1997. Neurosteroids: expression of functional 3beta-hydroxysteroid dehydrogenase by rat sensory neurons and Schwann cells. Eur. J. Neurosci. 9, 2236–2247.

Guth, L., Zhang, Z., Roberts, E., 1994. Key role for pregnenolone in combination therapy that promotes recovery after spinal cord injury. Proc. Natl. Acad. Sci. U.S.A. 91, 12308–12312.

Haines, D.E., Mihailoff, G.A., Yezierski, R.P., 1997. The spinal cord. In: Haines, D.E. (Ed.), Fundamental Neuroscience. Livingstone Inc., New York, pp. 129–141.

Hanani, M., 2005. Satellite glial cells in sensory ganglia: from form to function. Brain Res. Brain Res. Rev. 48, 457–476.

Herd, M.B., Belelli, D., Lambert, J.J., 2007. Neurosteroid modulation of synaptic and extrasynaptic GABA(A) receptors. Pharmacol. Ther. 116, 20–34.

Higashi, T., Nagahama, A., Otomi, N., Shimada, K., 2007. Studies on neurosteroids XIX Development and validation of liquid chromatography–tandem mass spectrometric method for determination of 5alpha-reduced pregnane-type neurosteroids in rat brain and serum. J. Chromatogr. B 848, 188–199.

Hill, M., Cibula, D., Havlíkova, H., Kancheva, L., Fait, T., Kancheva, R., Parizek, A., Starka, L., 2007. Circulating levels of pregnanolone isomers during the third trimester of human pregnancy. J. Steroid Biochem. Mol. Biol. 105, 166–175.

Hirani, K., Sharma, A.N., Jain, N.S., Ugale, R.R., Chopde, C.T., 2005. Evaluation of GABAergic neuroactive steroid 3alpha-hydroxy-5alpha-pregnane-20-one as a neurobiological substrate for the anti-anxiety effect of ethanol in rats. Psychopharmacology (Berl) 180, 267–278.

Ikushiro, S., Kominami, S., Takemori, S., 1992. Adrenal P-450scc modulates activity of P-45011 beta in liposomal and mitochondrial membranes. Implication of P-450scc in zone specificity of aldosterone biosynthesis in bovine adrenal. J. Biol. Chem. 267, 1464–1469.

Jevtovic-Todorovic, V., Covey, D.F., Todorovic, S.M., 2009. Are neuroactive steroids promising therapeutic agents in the management of acute and chronic pain? Psychoneuroendocrinology 34 (Suppl. 1), S178–S185.

Kibaly, C., Patte-Mensah, C., Mensah-Nyagan, A.G., 2005. Molecular and neurochemical evidence for the biosynthesis of dehydroepiandrosterone in the adult rat spinal cord. J. Neurochem. 93, 1220–1230.

Kibaly, C., Meyer, L., Patte-Mensah, C., Mensah-Nyagan, A.G., 2008. Biochemical and functional evidence for the control of pain mechanisms by dehydroepiandrosterone endogenously synthesized in the spinal cord. FASEB J. 22, 93–104.

Kimonides, V.G., Khatibi, N.H., Svendsen, C.N., Sofroniew, M.V., Herbert, J., 1998. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. Proc. Natl. Acad. Sci. U.S.A. 95, 1852–1857.

Koenig, H.L., Schumacher, M., Ferzaz, B., Thi, A.N., Ressouches, A., Guennoun, R., Jung-Testas, I., Robel, P., Akwa, Y., Baulieu, E.E., 1995. Progesterone synthesis and myelin formation by Schwann cells. Science 268, 1500–1503.

Lauber, M.E., Lichtensteiger, W., 1996. Ontogeny of 5 alpha-reductase (type 1) messenger ribonucleic acid expression in rat brain: early presence in germinal zones. Endocrinology 137, 2718–2730.

Le Goascogne, C., Robel, P., Gouezou, M., Sananes, N., Baulieu, E.E., Waterman, M., 1987. Neurosteroids: cytochrome P-450scc in rat brain. Science 237, 1212–1215.

Leonelli, E., Bianchi, R., Cavaletti, G., Caruso, D., Crippa, D., Garcia-Segura, L.M., Lauria, G., Magnaghi, V., Roglio, I., Melcangi, R.C., 2007. Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: a multimodal analysis. Neuroscience 144, 1293–1304.

Martini, L., Magnaghi, V., Melcangi, R.C., 2003. Actions of progesterone and its 5alpha-reduced metabolites on the major proteins of the myelin of the peripheral nervous system. Steroids 68, 825–829.

Matteson, K.J., Chung, B.C., Urdea, M.S., Miller, W.L., 1986. Study of cholesterol side-chain cleavage (20,22 desmolase) deficiency causing congenital lipoid adrenal hyperplasia using bovine-sequence P450scc oligodeoxyribonucleotide probes. Endocrinology 118, 1296–1305.

Matthews, M.R., Cuello, A.C., 1982. Substance P-immunoreactive peripheral branches of sensory neurons innervate guinea pig sympathetic neurons. Proc. Natl. Acad. Sci. U.S.A. 79, 1668–1672.

McCullough, L.D., Blizzard, K., Simpson, E.R., Oz, O.K., Hurn, P.D., 2003. Aromatase cytochrome P450 and extragonadal estrogen play a role in ischemic neuroprotection. J. Neurosci. 23, 8701–8705.

Melcangi, R.C., Celotti, F., Martini, L., 1994. Progesterone 5-alpha-reduction in neuronal and in different types of glial cell cultures: type 1 and 2 astrocytes and oligodendrocytes. Brain Res. 14, 202–206.

Melcangi, R.C., Poletti, A., Cavarretta, I., Celotti, F., Colciago, A., Magnaghi, V., Motta, M., Negri-Cesi, P., Martini, L., 1998. The 5alpha-reductase in the central nervous system: expression and modes of control. J. Steroid Biochem. Mol. Biol. 65, 295–299.

Melcangi, R.C., Ballabio, M., Cavarretta, I., Gonzalez, L.C., Leonelli, E., Veiga, S., Martini, L., Magnaghi, V., 2003. Effects of neuroactive steroids on myelin of peripheral nervous system. J. Steroid Biochem. Mol. Biol. 85, 323–327.

Melcangi, R.C., Garcia-Segura, L.M., Mensah-Nyagan, A.G., 2008. Neuroactive steroids: state of the art and new perspectives. Cell. Mol. Life Sci. 65, 777–797.

Mellon, S.H., Griffin, L.D., 2002. Neurosteroids: biochemistry and clinical significance. Trends Endocrinol. Metab. 13, 35–43.

Mensah-Nyagan, A.G., Feuilloley, M., Dupont, E., Do-Rego, J.L., Leboulenger, F., Pelletier, G., Vaudry, H., 1994. Immunocytochemical localization and biological activity of 3 beta-hydroxysteroid dehydrogenase in the central nervous system of the frog. J. Neurosci. 14, 7306–7318.
Mensah-Nyagan, A.G., Do-Rego, J.L., Feuilloley, M., Marcual, A., Lange, C., Pelletier, G., Vaudry, H., 1996a. In vivo and in vitro evidence for the biosynthesis of testosterone in the telencephalon of the female frog. J. Neurochem. 67, 413–422.
Mensah-Nyagan, A.G., Feuilloley, M., Do-Rego, J.L., Marcual, A., Lange, C., Tonon, M.C., Pelletier, G., Vaudry, H., 1996b. Localization of 17beta-hydroxysteroid dehydrogenase and characterization of testosterone in the brain of the male frog. Proc. Natl. Acad. Sci. U.S.A. 93, 1423–1428.
Mensah-Nyagan, A.G., Do-Rego, J.L., Beaujean, D., Luu-The, V., Pelletier, G., Vaudry, H., 1999. Neurosteroids: expression of steroidogenic enzymes and regulation of steroid biosynthesis in the central nervous system. Pharmacol. Rev. 51, 63–81.
Mensah-Nyagan, A.G., Beaujean, D., Luu-The, V., Pelletier, G., Vaudry, H., 2001a. Anatomical and biochemical evidence for the synthesis of unconjugated and sulfated neurosteroids in amphibians. Brain Res. Brain Res. Rev. 37, 13–24.
Mensah-Nyagan, A.G., Do-Rego, J.L., Beaujean, D., Luu-The, V., Pelletier, G., Vaudry, H., 2001b. Regulation of neurosteroid biosynthesis in the frog diencephalon by GABA and endozepines. Horm. Behav. 40, 218–225.
Mensah-Nyagan, A.G., Saredi, S., Schaeffer, V., Kibaly, C., Meyer, L., Melcangi, R.C., Patte-Mensah, C., 2008. Assessment of neuroactive steroid formation in diabetic rat spinal cord using high-performance liquid chromatography and continuous flow scintillation detection. Neurochem. Int. 52, 554–559.
Mensah-Nyagan, A.G., Meyer, L., Schaeffer, V., Kibaly, C., Patte-Mensah, C., 2009. Evidence for a key role of steroids in the modulation of pain. Psychoneuroendocrinology 34, S169–S177.
Meyer, L., Venard, C., Schaeffer, V., Patte-Mensah, C., Mensah-Nyagan, A.G., 2008. The biological activity of 3alpha-hydroxysteroid oxido-reductase in the spinal cord regulates thermal and mechanical pain thresholds after sciatic nerve injury. Neurobiol. Dis. 30, 30–41.
Millan, M.J., 1999. The induction of pain: an integrative review. Prog. Neurobiol. 57, 1–164.
Millan, M.J., 2002. Descending control of pain. Prog. Neurobiol. 66, 355–474.
Mills, C.D., Bitler, J.L., Woolf, C.J., 2005. Role of the peripheral benzodiazepine receptor in sensory neuron regeneration. Mol. Cell. Neurosci. 30, 228–237.
Morohashi, K., Sogawa, K., Omura, T., Fujii-Kuriyama, Y., 1987. Gene structure of human cytochrome P-450(SCC), cholesterol desmolase. J. Biochem. 101, 879–887.
Naik, A.K., Pathirathna, S., Jevtovic-Todorovic, V., 2008. GABAA receptor modulation in dorsal root ganglia in vivo affects chronic pain after nerve injury. Neuroscience 154, 1539–1553.
Nascimento, R.S., Santiago, M.F., Marques, S.A., Allodi, S., Martinez, A.M., 2008. Diversity among satellite glial cells in dorsal root ganglia of the rat. Br. J. Med. Biol. Res. 41, 1007–1011.
Nelson, D.R., Kamataki, T., Waxman, D.J., Guengerich, F.P., Estabrook, R.W., Feyereisen, R., Gonzalez, F.J., Coon, M.J., Gunsalus, I.C., Gotoh, O., et al., 1993. The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. DNA Cell. Biol. 12, 1–51.
Normington, K., Russell, D.W., 1992. Tissue distribution and kinetic characteristics of rat steroid 5 alpha-reductase isozymes. Evidence for distinct physiological functions. J. Biol. Chem. 267, 19548–19554.
Ohtori, S., Takahashi, K., Moriya, H., Myers, R.R., 2004. TNF-alpha and TNF-alpha receptor type 1 upregulation in glia and neurons after peripheral nerve injury: studies in murine DRG and spinal cord. Spine (Phila Pa 1976) 29, 1082–1088.
Oonk, R.B., Parker, K.L., Gibson, J.L., Richards, J.S., 1990. Rat cholesterol side-chain cleavage cytochrome P-450 (P-450scc) gene. Structure and regulation by cAMP in vitro. J. Biol. Chem. 265, 22392–22401.
Pathirathna, S., Brimelow, B.C., Jagodic, M.M., Krishnan, K., Jiang, X., Zorumski, C.F., Mennerick, S., Covey, D.F., Todorovic, S.M., Jevtovic-Todorovic, V., 2005. New evidence that both T-type calcium channels and GABAA channels are responsible for the potent peripheral analgesic effects of 5alpha-reduced neuroactive steroids. Pain 114, 429–443.
Patte-Mensah, C., Kappes, V., Freund-Mercier, M.J., Tsutsui, K., Mensah-Nyagan, A.G., 2003. Cellular distribution and bioactivity of the key steroidogenic enzyme, cytochrome P450side chain cleavage, in sensory neural pathways. J. Neurochem. 86, 1233–1246.
Patte-Mensah, C., Kibaly, C., Boudard, D., Schaeffer, V., Begle, A., Saredi, S., Meyer, L., Mensah-Nyagan, A.G., 2006. Neurogenic pain and steroid synthesis in the spinal cord. J. Mol. Neurosci. 28, 17–31.
Patte-Mensah, C., Kibaly, C., Mensah-Nyagan, A.G., 2005. Substance P inhibits progesterone conversion to neuroactive metabolites in spinal sensory circuit: a potential component of nociception. Proc. Natl. Acad. Sci. U.S.A. 102, 9044–9049.
Patte-Mensah, C., Li, S., Mensah-Nyagan, A.G., 2004a. Impact of neuropathic pain on the gene expression and activity of cytochrome P450side-chain-cleavage in sensory neural networks. Cell. Mol. Life Sci. 61, 2274–2284.
Patte-Mensah, C., Penning, T.M., Mensah-Nyagan, A.G., 2004b. Anatomical and cellular localization of neuroactive 5 alpha/3 alpha-reduced steroid-synthesizing enzymes in the spinal cord. J. Comp. Neurol. 477, 286–299.
Payne, A.H., Hales, D.B., 2004. Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocr. Rev. 25, 947–970.
Pelletier, G., Luu-The, V., Labrie, F., 1995. Immunocytochemical localization of type I 17 beta-hydroxysteroid dehydrogenase in the rat brain. Brain Res. 704, 233–239.
Pinna, G., Dong, E., Matsumoto, K., Costa, E., Guidotti, A., 2003. In socially isolated mice, the reversal of brain allopregnanolone down-regulation mediates the anti-aggressive action of fluoxetine. Proc. Natl. Acad. Sci. U.S.A. 100, 2035–2040.
Ribeiro-da-Silva, A., Hokfelt, T., 2000. Neuroanatomical localisation of Substance P in the CNS and sensory neurons. Neuropeptides 34, 256–271.
Roby, K.F., Larsen, D., Deb, S., Soares, M.J., 1991. Generation and characterization of antipeptide antibodies to rat cytochrome P-450 side-chain cleavage enzyme. Mol. Cell. Endocrinol. 79, 13–20.
Rupprecht, R., Rammes, G., Eser, D., Baghai, T.C., Schule, C., Nothdurfter, C., Troxler, T., Gentsch, C., Kalkman, H.O., Chaperon, F., Uzunov, V., McAllister, K.H., Bertaina-Anglade, V., La Rochelle, C.D., Tuerck, D., Floesser, A., Kiese, B., Schumacher, M., Landgraf, R., Holsboer, F., Kucher, K., 2009. Translocator protein (18 kD) as target for anxiolytics without benzodiazepine-like side effects. Science 325 (5939), 490–493.
Schaeffer, V., Patte-Mensah, C., Eckert, A., Mensah-Nyagan, A.G., 2006. Modulation of neurosteroid production in human neuroblastoma cells by Alzheimer's disease key proteins. J. Neurobiol. 66, 868–881.
Schaeffer, V., Meyer, L., Patte-Mensah, C., Eckert, A., Mensah-Nyagan, A.G., 2008a. Dose-dependent and sequence-sensitive effects of amyloid-beta peptide on neurosteroidogenesis in human neuroblastoma cells. Neurochem. Int. 52, 948–955.
Schaeffer, V., Patte-Mensah, C., Eckert, A., Mensah-Nyagan, A.G., 2008b. Selective regulation of neurosteroid biosynthesis in human neuroblastoma cells under hydrogen peroxide-induced oxidative stress condition. Neuroscience 151, 758–770.
Schaeffer, V., Meyer, L., Patte-Mensah, C., Eckert, A., Mensah-Nyagan, A.G., 2009. Sciatic nerve injury induces apoptosis of dorsal root ganglion satellite glial cells and selectively modifies neurosteroidogenesis in sensory neurons. Glia 58, 169–180.
Schumacher, M., Guennoun, R., Mercier, G., Desarnaud, F., Lacor, P., Benavides, J., Ferzaz, B., Robert, F., Baulieu, E.E., 2001. Progesterone synthesis and myelin formation in peripheral nerves. Brain Res. Brain Res. Rev. 37, 343–359.
Schumacher, M., Guennoun, R., Ghoumari, A., Massaad, C., Robert, F., El-Etr, M., Akwa, Y., Rajkowski, K., Baulieu, E.E., 2007. Novel perspectives for progesterone in hormone replacement therapy, with special reference to the nervous system. Endocr. Rev. 28, 387–439.
Stephenson, J.L., Byers, M.R., 1995. GFAP immunoreactivity in trigeminal ganglion satellite cells after tooth injury in rats. Exp. Neurol. 131, 11–22.
Suhara, K., Gomi, T., Sato, H., Itagaki, E., Takemori, S., Katagiri, M., 1978. Purification and immunochemical characterization of the two adrenal cortex mitochondrial cytochrome P-450-proteins. Arch. Biochem. Biophys. 190, 290–299.
Szekely, J.I., Torok, K., Mate, G., 2002. The role of ionotropic glutamate receptors in nociception with special regard to the AMPA binding sites. Curr. Pharm. Des. 8, 887–912.
Tsutsui, K., Yamazaki, T., 1995. Avian neurosteroids. I. Pregnenolone biosynthesis in the quail brain. Brain Res. 678, 1–9.
Ugale, R.R., Sharma, A.N., Kokare, D.M., Hirani, K., Subhedar, N.K., Chopde, C.T., 2007. Neurosteroid allopregnanolone mediates anxiolytic effect of etifoxine in rats. Brain Res. 1184, 193–201.
Ukena, K., Usui, M., Kohchi, C., Tsutsui, K., 1998. Cytochrome P450 side-chain cleavage enzyme in the cerebellar Purkinje neuron and its neonatal change in rats. Endocrinology 139, 137–147.
Usui, M., Yamazaki, T., Kominami, S., Tsutsui, K., 1995. Avian neurosteroids. II. Localization of a cytochrome P450scc-like substance in the quail brain. Brain Res. 678, 10–20.
Veiga, S., Azcoitia, I., Garcia-Segura, L.M., 2005. Extragonadal synthesis of estradiol is protective against kainic acid excitotoxic damage to the hippocampus. Neuroreport 16, 1599–1603.
Venard, C., Boujedaini, N., Belon, P., Mensah-Nyagan, A.G., Patte-Mensah, C., 2008. Regulation of neurosteroid allopregnanolone biosynthesis in the rat spinal cord by glycine and the alkaloidal analogs strychnine and gelsemine. Neuroscience 153, 154–161.
Venard, C., Boujedaini, N., Mensah-Nyagan, A.G., Patte-Mensah, C., 2009. Comparative analysis of gelsemine and gelsemium sempervirens activity on neurosteroid allopregnanolone formation in the spinal cord and limbic system. Evid. Based Complement Alternat. Med., doi:10.1093/ecam/nep083.
Verleye, M., Akwa, Y., Liere, P., Ladurelle, N., Pianos, A., Eychenne, B., Schumacher, M., Gillardin, J.M., 2005. The anxiolytic etifoxine activates the peripheral benzodiazepine receptor and increases the neurosteroid levels in rat brain. Pharmacol. Biochem. Behav. 82, 712–720.
Viéro, C., Mechaly, I., Aptel, H., Puech, S., Valmier, J., Bancel, F., Dayanithi, G., 2006. Rapid inhibition of Ca2+ influx by neurosteroids in murine embryonic sensory neurones. Cell Calcium 40, 383–391.
Wall, P.D., Devor, M., 1983. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. Pain 17, 321–339.
Wilson, J.D., Griffin, J.E., Russell, D.W., 1993. Steroid 5 alpha-reductase 2 deficiency. Endocr. Rev. 14, 577–593.
Woodham, P., Anderson, P.N., Nadim, W., Turmaine, M., 1989. Satellite cells surrounding axotomised rat dorsal root ganglion cells increase expression of a GFAP-like protein. Neurosci. Lett. 98, 8–12.
Yokoi, H., Tsuruo, Y., Ishimura, K., 1998. Steroid 5alpha-reductase type 1 immunolocalized in the rat peripheral nervous system and paraganglia. Histochem. J. 30, 731–739.
Zimmermann, M., 2001. Pathobiology of neuropathic pain. Eur. J. Pharmacol. 429, 23–37.