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Neuroactive steroids: An update of their roles in central and peripheral nervous system

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Summary After five editions, the congress on ''Steroids and Nervous System'' held in Torino, Italy, represents an important international event for researchers involved in this field aimed to recapitulate mechanisms, physiological and pharmacological effects of neuroactive steroids. The present review introduces manuscripts collected in this supplement issue which are based on new interesting findings such as the influence of sex steroids on cannabinoid-regulated biology, the role of steroids in pain, the importance of co-regulators in steroidal mechanisms and the understanding of new non classical mechanism, the emerging role of vitamin D as a neuroactive steroid and the pathogenetic mechanisms mediated by glucocorticoid receptors. Finally, we have integrated these aspects with an update on some of the several and important observations recently published on this hot topic.

1. Introduction

In the last decade the study of the interactions between steroids and the nervous system has received a great attention from scientific community. Indeed, steroids acting on the nervous system, now named neuroactive steroids, reveal the capability to exert a variety of physiological effects through different signaling pathways involving classical and non-classical steroid receptors (Melcangi and Panzica, 2006). Recent observations have also shown that these molecules may represent interesting tools for therapeutic strategies against neurodegenerative and psychiatric disorders. In particular, because many of these disorders show sex differences in their incidence, symptomatology, neurodegenerative outcome, and, interestingly, in the levels of neuroactive steroids, new proposals imply sex-specific neuroprotective therapies based on neuroactive steroids (Melcangi and Garcia-Segura, 2009). Finally, new findings have been recently obtained suggesting that also vitamin D shows features similar to neuroactive steroids and consequently could be tentatively included in their family. All these aspects, which have been also discussed during the 5th International Meeting on Steroids and Nervous System held in February 2009 in Torino, Italy, are here summarized and reported in details in the manuscripts collected in this supplement issue of *Psychoneuroendocrinology*.

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2. New insights in the molecular mechanisms of neuroactive steroids

As recently reviewed by Pfaff and Levine (2008) researches on mechanisms of steroid hormone action during the middle 20th century emphasized at first rapid changes in biochemical reactions in the cytoplasm (Williams-Ashman and Reddi, 1971). Later, starting from the end of sixties, new methodological approaches revealed that steroid hormones may act at genomic level through the mediation of nuclear receptors that were (almost) fully characterized (Greenstein, 1978). Molecular and immunohistochemical techniques demonstrated that these receptors are predominantly located in the nucleus as opposed to the cytoplasm. The idea that steroid hormone receptor could also be localized to the plasma membrane was, at this point, banned as heretic. However, the genomic action of steroid hormones cannot explain all the effects, mainly those classified as rapid effects, therefore in the late eighties several studies started to investigate the putative presence of steroid hormone plasma membrane receptors (Schumacher, 1990). These studies demonstrated that steroids can specifically bind to partially purified synaptic membrane, thus acting as specific ligands (Orchinik et al., 1991; Moore et al., 1995). In addition they can exert a modulatory indirect action to some non-cognate receptor, that is, a receptor specific for another ligand or hormone (Ramirez and Zheng, 1996). For example, progesterone, estradiol, and corticosterone may bind to nicotinic acetylcholine receptor inducing its inhibition without altering the binding activity towards the natural ligand (Valera et al., 1992; Ke and Lukas, 1996). Also other neurotransmitters' systems are influenced by steroid hormones, like glutamate, dopamine, noradrenaline, serotonin and GABA (for a recent review see Zheng, 2009).

A new perspective developed about 20 years ago, based on the studies of Baulieu et al. demonstrated the presence of intermediates of the biosynthetic chain of steroids within the vertebrate brain. These compounds accumulate in the rat brain independently of the supply by peripheral endocrine glands. Several biological functions have been proposed and demonstrated for these metabolites: they may serve as precursors of other steroids (such as progesterone and testosterone and their metabolites) and are implicated in the control of some behavioral activities. Steroids synthesized within the central and peripheral nervous system were collectively called "neurosteroids" (Baulieu and Robel, 1990).

Therefore, the nervous system (both central and peripheral) is a target for two different pools of steroids, one coming from the peripheral glands (i.e., steroid hormones) and the second one originating directly in the nervous system (i.e., neurosteroids). However, it is difficult to discriminate whether the steroid effect is due to *in situ* synthesis, to the peripheral hormones, or to an enzymatic activation of steroids in metabolites which are more active and in some cases use a different mechanism of action, for this reason several researchers use now the term *neuroactive steroids* (Paul and Purdy, 1992; Rupprecht and Holsboer, 1999; Melcangi and Panzica, 2001; Rupprecht et al., 2001).

In addition to these endogenous sources of neuroactive steroids, a third pool of compounds that are biologically active and often mimic endogenous steroid hormones, binding to steroid hormones' receptors thereby altering hormone-modulated responses, has been recently revealed. They belong to the class of the so-called endocrine disrupting chemicals (EDCs) and are of either synthetic (i.e., bisphenol), or biological derivation (i.e., phytoestrogens). Some compounds target neuroendocrine systems, thereby affecting reproductive endocrine systems as well as other endocrine systems. Therefore, exposure to the EDCs during embryonic development has consequences beyond impaired function of the reproductive axis (Panzica et al., 2007). These compounds are therefore a third player within the nervous system (Panzica et al., 2005; Melcangi and Panzica, 2006) and the evolutionary implications of having them in the normal food supply for certain human populations (i.e., phytoestrogen derivatives from soy) (Naftolin and Stanbury, 2002), as well as for wild and farm animals have not yet been discussed.

The presence of such different neuroactive steroids implicates a variety of molecular mechanisms based on different cellular pathways and their understanding is crucial to clarify the role played by these compounds. Some of these actions are summarized in the present issue, as their role in the plasticity of nervous system (Calabrese et al., 2009; Fester et al., 2009; Smith et al., 2009a), in the control of several behaviors (Frye, 2009), in the development of several nervous system's diseases (Fernandes de Abreu et al., 2009), as well as in their use as drugs to counteract these diseases (Jevtovic-Todorovic et al., 2009).

One of the hot topics to understand the mechanisms of action of the steroid nuclear receptors is that of cofactors. In fact, steroid receptors such as estrogen and androgen receptors are nuclear receptors involved in the transcriptional regulation of a large number of target genes: the discovery of a competition between two different nuclear receptors introduced the notion that common cofactors may be involved in the modulation of transcriptional activity of nuclear receptors. These cofactors or coregulatory proteins are functionally divided into coactivators and corepressors and are involved in chromatin remodeling and stabilization of the general transcription machinery. Although a large amount of information has been collected about the in vitro function of these coregulatory proteins, relatively little is known regarding their physiological role in vivo, particularly in the brain (Tetel, 2000, 2009a). A number of reviews on this important topic is presented in this special issue. In particular, the protein SRC-1 is an example of how steroid receptors show region-specific preferences for a set coactivator. In female rat brain SRC-1 from hypothalamus or hippocampus interacts differently with both types of estrogen receptors (ER) and both types of progesterone receptors (PR). Thus suggesting that these brain regions have distinct expression patterns of coregulators involved in these important protein—protein interactions. In addition, SRC-1 could undergo differential post-translational modification in these two brain regions, leading to distinct patterns of interactions with receptors. A series of experiments performed on the quail model suggests that different cell phenotypes underlying sexual behavior, such as aromatase and vasotocin, are differentially affected by the reduction of SRC-1 induced by antisense oligoprobe administration. While the reduction of SRC-1 expression significantly inhibits testosterone-dependent male sexual behavior, the cell phenotypes affected by this reduction is puzzling, raising a large number of questions