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## Editorial - New perspectives for the action of steroids in the brain

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The International Congress "Steroids and Nervous System" held in Torino (Italy) has been held every two years since 2001, for the researcher community in this field of neuroendocrinology (1-8).

The present Special Issue is a collection of some of the lectures presented at the 9th International Meeting on Steroids and the Nervous System, held in February 2017. These reviews provide an update on the state of the art of recent discoveries in three main fields of current research on the role of neuroactive steroids in the brain, with special emphasis on brain development and sexual differentiation, the cellular and molecular mechanisms involved in the action of neuroactive steroids, and clinical implications for the understanding of brain disease and for the potential therapeutic use of these molecules or their analogues.

The Special Issue is opened with a review on the epigenetic and non-epigenetic mechanisms that drive the sexual differentiation of the brain (9). In particular, the mechanisms involving both histone acetylation and DNA methylation in the development of sex differences in the brain and behavior of rodents are discussed, as well as the demonstration that sex differences in the number of neurons of a particular phenotype may be programmed by differences in DNA methylation early in life. The following review discusses improvements in the study of the effects of steroids in the brain by the potential use of human induced pluripotent stem cells (iPSCs) to develop organoids (3D neuronal cultures) to test steroid properties and their therapeutic value (10).

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3 The role of testosterone and the regulation of the enzyme, aromatase, is the theme of the  
4 following three papers (11-13). The expression of aromatase (which converts testosterone  
5 into estradiol) is regulated by several factors including sex hormones, genes and  
6 neurosteroids, therefore these actors may impact on the organizational effects of steroids  
7 during development (11). However, testosterone is not only the source for the local synthesis  
8 of estradiol, but it may itself regulate the development of sexually differentiated circuits, as  
9 revealed by studies in mice with mutations in the androgen receptor (12). Furthermore,  
10 androgens (e.g., testosterone and dehydroepiandrosterone) play a crucial role in sex-specific  
11 cortical growth during development and adolescence (13).  
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19 Also neurosteroids (i.e. brain-derived steroids, such as allopregnanolone) are involved in the  
20 regulation of brain development. One of their roles is represented by the regulation of the  
21 GABA-A receptor, which is one of the major players in both embryonic and neonatal brain  
22 development. Belelli et al. (14) review recent evidence indicating that changes in  
23 neurosteroidogenesis substantially influence neonatal GABA-ergic synaptic transmission, and  
24 discuss how interference of neurosteroids/GABA-A receptor interaction early in life may  
25 contribute to psychiatric conditions later in life. To conclude this part of the Issue dedicated to  
26 the role of steroids in brain development and sex differences, Gagnard et al. (15) review their  
27 recent findings concerning sex differences in brain mitochondrial function in physiological  
28 and pathological conditions, and the influence of endogenous sex steroids.  
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37 The second part of this Special Issue is dedicated to cellular and molecular mechanisms of  
38 steroid action. It is opened by a review on translocator protein of 18 kDa (TSPO), an  
39 ubiquitous mitochondrial protein part of a multiprotein complex involved in cholesterol  
40 transport into the mitochondrion. This is the rate-limiting step in steroidogenesis. Recent  
41 studies have generated controversy about the role of this protein in steroid synthesis,  
42 however recent results using various genetic animal models suggest that TSPO is a unique  
43 pharmacological target for diseases that involve increased mitochondrial activity, including  
44 steroidogenesis (16).  
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52 The three following reviews discuss different aspects of estrogen action in the brain through  
53 their receptors. The first is dedicated to the estrogen receptor beta (ER $\beta$ ), a multifunctional  
54 nuclear receptor with a broad range of physiological functions resulting from the activity of  
55 several alternatively spliced isoforms of ER $\beta$  (17). The second review discusses the tissue,  
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3 cellular and subcellular localization in the brain of a recently discovered estrogen receptor  
4 coregulator (Proline-, Glutamic acid-, and Leucine-rich Protein 1). Recent evidence from  
5 PELP1 forebrain-specific knockout mice demonstrated a critical role of PELP1 in mediating  
6 both extranuclear and nuclear ER signaling in the brain, as well as E2-induced  
7 neuroprotection, anti-inflammatory effects, and regulation of cognitive function (18). The  
8 review of Sheppard et al. (19) examines recent developments in the study of the rapid effects  
9 of  $17\beta$ -estradiol and estrogen receptor (ER) agonists on learning and memory tasks in female  
10 rodents, including activation of intracellular signaling cascades and epigenetic processes.  
11 The rapid non-genomic modulation of dendritic spinogenesis in rat and mouse hippocampal  
12 slices is mediated by sex steroids, including dihydrotestosterone, testosterone, estradiol, and  
13 progesterone. These rapid synaptic modulations are mediated by sex steroid receptors  
14 including rapid non-genomic effects. In the review of Murakami et al. (20), results from  
15 optical imaging of dendritic spines are discussed together with results obtained from other  
16 types of imaging techniques, including electron microscopic imaging.

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18 Relationships between spine modulation and modulation of cognition are also discussed. The  
19 anti-inflammatory action of neuroactive steroids is discussed in the following two reviews.  
20 The review of De Nicola et al. (21) discusses the role of neuroactive steroids in experimental  
21 autoimmune encephalomyelitis (EAE), a commonly used model for multiple sclerosis (MS).  
22 Data reviewed in this paper suggest that enhanced synthesis of neurosteroids contributes in  
23 an auto/paracrine manner to reinforce the neuroprotective and anti-inflammatory effects of  
24 exogenous progesterone given to EAE mice. The review of Rizzi et al. (22) illustrates the  
25 results obtained by developing a mouse reporter system (the NF $\kappa$ B-luc2 reporter mouse) to  
26 understand the anti-inflammatory action of estrogens at the molecular level, in order to  
27 evaluate the extent to which the action of this steroid hormone was relevant in models of  
28 pathologies characterized by a strong inflammatory component, and to investigate the  
29 efficacy of novel, synthetic estrogens endowed with anti-inflammatory activity.

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31 Some transient calcium channels (Transient Receptor Potential Channels, TRPC) are regulated  
32 for their tissue- and cell-specific expression in the brain by different neuroactive steroids,  
33 including pregnenolone, progesterone and dihydrotestosterone. In the review of Qiu et al.  
34 (23) the authors discuss their findings of the depolarizing action of insulin and leptin on  
35 proopiomelanocortin neurons of the arcuate nucleus mediated by activation of TRPC5  
36 channels, indicating a potential link among neurosteroids and anorexigenic neuronal systems.

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4 The last paper of this section is an experimental paper describing the properties of BR297 (a  
5 new analog of allopregnanolone) that appears to be a potent neuroprotective compound  
6 devoid of cell-proliferative activity. These results open promising perspectives for the  
7 development of neurosteroid-based selective and effective strategies against neuroendocrine  
8 and/or neurodegenerative disorders (24).  
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14 The last part of the Special Issue is dedicated to the clinical implications of the action of  
15 neuroactive steroids. Moraga-Amaro et al. (25) discuss the current status of Positron  
16 Emission Tomography (PET) imaging for studying sex steroid hormones in the brain. This  
17 technique has been applied to reveal changes in sex hormone receptor expression, to measure  
18 aromatase and to evaluate the effects of hormonal treatment in the brain, and is a useful  
19 technique to facilitate the translation of results from animal studies into clinical trials in  
20 patients.  
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27 Many clinical aspects suggest that sex steroid-nervous system interactions may contribute to  
28 the onset and course of symptoms, and the cognitive impairment displayed by men and  
29 women with schizophrenia. The review of Owens et al. (26) discusses the relationships  
30 between the action of estrogen and testosterone on the brain during adolescent development,  
31 and schizophrenia, and presents evidence of potential beneficial, as well as detrimental,  
32 effects of both testosterone and estrogen.  
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39 Premenstrual dysphoric disorder (PMDD) is characterized by recurrent negative mood  
40 symptoms during the luteal phase of the menstrual cycle with a temporal association with  
41 circulating progesterone and its metabolite, allopregnanolone. Bixo et al. (27) discuss in their  
42 review the results of a randomized, placebo-controlled clinical trial that demonstrates that  
43 isoallopregnanolone (an isomer of allopregnanolone) can ameliorate the symptoms of PMDD  
44 due to its ability to antagonize the allopregnanolone effect on the GABA<sub>A</sub> receptor.  
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51 In the review of Slowick et al. (28), the authors discuss the most recent findings  
52 demonstrating that estrogens selectively suppress the activation of the neuroinflammatory  
53 cascade in the brain in acute and chronic brain disease models. In addition, they discuss the  
54 presence of an inflammatory component in psychiatric disorders such as depression that  
55 could be modulated by estrogen.  
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4 In the last review of the issue, the authors (29) discuss how steroids can influence the gut  
5 microbiota, and in turn how the gut microbiota can influence hormone levels altering the  
6 stress axis and behavior, addressing future research in this new area at the intersection of  
7 steroids, stress, gut-brain axis and human health.  
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