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**Neuroactive steroids and the new decade**

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Title: **Neuroactive steroids and the new decade**

**Giancarlo Panzica and Roberto C. Melcangi**

The term 'neurosteroids' started to be used in the '80s of the last century, to indicate a family of steroids synthesized within the brain and regulating, via steroid receptors or other receptors, several brain functions. Later on, the term 'neuroactive steroids' was introduced to incorporate also those steroids that are not synthesized in the brain or are only partly metabolized (e.g., the transformation of testosterone into oestradiol via the action of brain aromatase), but that can interact with neural circuits. During the first two decades of the current century, the number of published papers in this field increased by 3,620 (source PubMed, keywords neurosteroid* or neuroactive steroid*), demonstrating a continuous interest in this wide topic. Our international congresses started at the beginning of the century covering the entire scope of this broad research field, and contributions to these biennial meetings were published in a series of special issues of different journals (1-9).

The present special issue includes many of the invited lectures presented during the last edition of the "Steroids and Nervous System" meeting (Torino, February 2019), contributed as contemporary reviews or as original articles. The papers embrace classical themes such as gonadal steroids and glucocorticoids but also very new topics such as the involvement of neuroactive steroids in the control of energy homeostasis and the development of translational models for a variety of neural diseases in which neuroactive steroids are implicated.

The manuscript by Ball et al. (10) illustrates the multiple roles of testosterone in regulating a highly specialized neural circuit (the avian song system) in both males and females. One of the central aspects of reproduction, the switch of oestradiol action from negative to positive feedback in the regulation of the GnRH system, is widely discussed in the paper by Moenter (11). Rapid, non-classical effects of oestradiol on the basal cholinergic neurons in mice are discussed in the paper by Kim and collaborators (12) that demonstrates the presence of a marked sex difference in estradiol-induced non-classical effects and the intracellular distribution of oestrogen receptors in cholinergic neurons of basal forebrain.

Glucocorticoids are used clinically during pregnancy to prevent complications (i.e., prematurity), at the same time as the recreational use of cannabis during pregnancy is increasing; the potential implications of co-exposure to these compounds on the developing brain and later neurodevelopmental consequences are discussed in the review by Franks et al. (13). The study of Lesuis et al. (14) demonstrates that both corticosterone and β-adrenergic receptor activation may cooperate to increase hippocampal spine number.

A very promising new field of research is the involvement of neuroactive steroids in the control of metabolism. In particular, a review by Kammel and Correa (15) elucidates the organization of the hypothalamic ventromedial nucleus (VMH) with particular emphasis on sexual differences involving the presence of phenotypically distinct and sexually differentiated neuron populations within the VMH. In addition, oestrogenic regulation of glucose-excited neurons and how this may affect glucose and energy homeostasis is discussed by Hirschberg and collaborators (16). The review by Hidalgo-Lanussa et al. (17) discusses the relationships between lipotoxicity (a consequence of obesity or of the metabolic syndrome) and the development of neurodegenerative diseases, such as Alzheimer's disease. In this review the authors suggest a cellular and molecular mechanism to explain the neuroprotective effect of oestrogens. Finally, the experimental study of Freire-Regatillo and collaborators (18) demonstrates that peripubertal male and female mice respond differently to short- term dietary changes in a way that is different from that reported in adults. This is also interesting in view of the effects on metabolism and

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neuroendocrine circuits that some molecules termed metabolic disruptors, including several xenoestrogens or xenoandrogens (19, 20), may have when exposure is in adult life or in early life. The neuroprotective effects of neuroactive steroids have been discussed for a long time, but only in recent years have several promising translational models become available. These models may better elucidate the role of neuroactive steroids in neural diseases, and several were presented during the meeting and collected in this special issue. The active form of Vitamin D (called calcitriol) functions as a steroid hormone acting via both genomic and non-genomic pathways. Calcitriol and other Vitamin D analogues affect steroid hormone synthesis and/or signalling in the nervous system as well as cell proliferation. The review by Norlin (21) discusses possible roles for vitamin D analogues as candidates for the future improved treatment of human glioma and possibly also other cancers of the nervous system.

Oestrogens have several functions in the brain. In particular they may enhance extinction learning across species and are considered as risk factors that may slow or accelerate natural ageing processes in women. In the review by Hammond et al. (22) it has been suggested that these neuroactive steroids may have a role in the treatment of posttraumatic stress disorder (PTSD), particularly in women. The review by Miller and collaborators (23) indicates that studies on gonadal hormones as risk factors in humans require the follow up of diverse cohorts over long periods of time as currently under way at the Mayo clinic. Finally, several brain diseases are linked to alterations in mitochondrial function, and gonadal hormones may regulate the metabolism and synthesis of key phospholipids such as cardiolipin. These events could be related to the homeostatic and protective actions of steroids in neural cells, as well as to the manifestation of sex differences in neurodegenerative disorders (24). Progesterone involvement in neuroprotection and immunomodulation in Parkinson's disease is described in a mouse model in the study by Jarras and collaborators (25). Other neuroactive steroids are involved in the complications of sleep deprivation (26), in the imbalance of inhibitory and excitatory actions during pregnancy which program for poor behavioural outcomes in a sex-dependent manner later in life (27), in some psychiatric diseases such as Tourette's syndrome (28), as well as in the regulation of mitochondrial function in tauopathies (29).

Finally, the review by Patisaul (30) describes the first results of a large project (the FDA collaborative project, CLARITY-BPA) on the effects of bisphenol A (BPA), an endocrine disruptor acting principally as an xenoestrogen and found in large amounts in the environment. In particular, in this review, results obtained on the action of BPA on brain and behaviour, have been discussed.

In conclusion, the new decade of studies of neuroactive steroids will certainly be dedicated to the study of their basic properties and mechanisms of action, but, as seen in this special issue, it will also be the time to start clinical trials to explore the real neuroprotective properties of these molecules and develop even more potent analogues.

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