



Introduction to the Special Issue “Neuroactive Steroids”

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Abstract

Steroids are complex molecules, exerting known and still unknown effects in the nervous system. Throughout this volume, the reader will find a wide spectrum of articles, giving an up-to-date account of the molecular, physiological, pharmacological, and clinical aspects of steroid action on the nervous system.

Keywords Progesterone · Mineralocorticoid receptors · Glucocorticoid receptors · Mifepristone · Neuroactive steroids · Neuropathology

Introduction

We would like to start this Introduction by quoting Hans Selye’s words (Selye 1947): “The manifold pharmacological activities of the steroids and the fact that almost any of them possess an apparently unpredictable combination of such activities tend to give the impression of a complete lack of orderliness”. This thematic statement of despair was later moderated in the same textbook: “This type of study (referring to steroid effects) is perhaps the most fascinating and, from the practical point of view, the most important aspect of contemporary steroid hormone research”. Stunning words from a man that ahead of his time, revealed the complex world of the steroid field. The idea for gathering new developments on the topic of steroids and nervous system started during an informal café chat with Dr. Juan Maria Saavedra in Buenos Aires. He asked Maria Claudia and me to consider being the editors of a Special Issue on Neuroactive Steroids, to be published in *Cellular and Molecular Neurobiology*. We thought it was a big challenge, considering the

ever-changing cellular and molecular mechanisms appearing in this area of neuroendocrinology. Nevertheless, the challenge was accepted and in the next months we invited top investigators in the steroid field to contribute to this Special Issue. Throughout the volume, the reader will find a wide spectrum of articles, giving an up-to-date account of the physiological, pharmacological, clinical, and molecular aspects of steroid action. Nowadays, we know that steroids are complex molecules, exerting known and still unknown effects in the nervous system. Thus, we cannot expect a unified hypothesis to explain what steroids do, but only watch year after year how preconceived concepts crumbled when new and unexpected discoveries arrive.

The first three articles in the Special Issue refer to the effect of progestins. Guennoun et al. (2018) provide evidence for the pleiotropic and beneficial effects of progesterone in experimental stroke, highlighting the important role of the progesterone receptor in cerebroprotection. Next, the roles of progesterone and its reduced metabolite allopregnanolone are discussed by Gonzalez et al. (2018). These authors explored in their review how these compounds prevent or reverse the maladaptive changes of pain behavior arising after injury or disease. A third article concerns with aromatase, an enzyme metabolizing androgens into estrogens, Brocca and Garcia-Segura (2018) describe the non-reproductive effects of aromatase in the brain, and discuss how brain aromatase is involved in cognition and mood. In pathological conditions, however, this enzyme participates in a reparative response and offers neuroprotection, by increasing the levels of neural-derived estradiol.

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The article by Meijer et al. (2018) gives a full account of potential mechanisms that confer cell type specific effects of the mineralocorticoid and glucocorticoid receptor in the brain. They discuss splice variants for these receptors, interactions with chromatin, target genes, and the importance of coregulators that dictates the specificity of transcription, considering that both receptors share an identical responsive element on the DNA.

The last three papers deal with a role of steroids under pathological conditions. Brocca et al. (2018) describe the proinflammatory role of the mineralocorticoid receptor in the brain of spontaneously hypertensive rats. The encephalopathy of hypertension involves the up-regulation of several proinflammatory mediators and down-regulation of anti-inflammatory factors. They postulate that in hypertension, there is a switch of mineralocorticoid receptor function towards a death receptor. Thereafter, Giatti et al. (2018) review the role of neuroactive steroids in diabetes mellitus. They have found that complications of diabetes mellitus show sex dimorphic features in terms of incidence, functional outcomes, and neuroactive steroid levels. Their findings established principles for sex-oriented therapies to counteract damage of the nervous system caused by diabetes. Finally, the third article along the pathological line is by Dalm et al. (2018) who analyze the causes for the improvement of psychotic depression as due to glucocorticoid/progesterin antagonism using Mifepristone. To understand the underlying mechanism, they analyze in mice changes of corticosterone levels, circadian rhythm, and steroid receptors in relation to Mifepristone treatment. They study the behavioral aspects of this interaction and discuss potential factors involved in the reset of the stress system by the steroid antagonist.

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