Editorial

Steroid-Dependent Management of Biological Responses in the Nervous System

The existence of corticosteroid receptors in the nervous system was first demonstrated [1] in several structures such as the hypothalamus, hippocampus and the parietal cortex (see [2] for a comprehensive review of that time whose validity still persists today). The potential presence of more than one population of corticosteroid-binding sites in the brain and in anterior pituitary was then suggested based on the differential binding of dexamethasone and corticosterone [3]. These results were also consistent with the view that the dexamethasone blockade of stress-induced adrenocorticotrophic hormone release is mediated by the anterior pituitary, while the high specificity of corticosterone binding in the hippocampus implies a specific, but undetermined effect of the hormone in this brain area, an effect which was thought to be unrelated to regulation of adrenocorticotrophic hormone secretion. These findings led researchers to suggest a role of extrahypothalamic regions in the perception of corticosteroid feedback as well as in the regulation of the hypothalamo-hypophysial-adrenal function.

During the early 80s were identified large quantities of the first brain steroids, i.e. dehydroepiandrosterone (DHEA) and its sulfatedester (DHEA-S) [4]. Then, the immediate precursors of DHEA and DHEA-S, pregnenolone and pregnenolone sulfate, were also identified in rat brains [5]. Interestingly, the concentrations of all these steroids were far greater in the brain than those found in plasma, and their concentrations remained unexpectedly high after adrenalectomy and orchiectomy. This surprising finding suggested that these steroids could be originated through local brain synthesis. Hence, the concept of endogenous steroid synthesis in the brain, neurosteroidogenesis, was consequently born. More recently, it become evident that absence or reduced concentrations of neurosteroids during development (and also in adults) may be associated with the development of psychiatric and behavioral disorders. Accordingly, treatments with physiologic or pharmacologic concentrations of these compounds promote neurogenesis, neuronal survival, myelination, increased memory, and reduced neurotoxicity [6-8].

Since that time, the biological functions for these compounds began to be uncovered, and the mechanisms and receptors through which these compounds mediated their action also began to be extensively studied. Today, we know that steroid hormones exert their biological effects *via* classic soluble receptors associated to molecular chaperones, and also by non-genomic (or fast) mechanisms *via* membrane associated receptors (see [9-11] for recent updates).

Physiological processes are governed in a coordinated and well-balanced manner between all these steroid-dependent signalling cascades, leading to several effects comprising from neuronal differentiation to normal or pathological behavior. Often, steroid hormones show cooperative and even opposing effects to mediate neuronal excitability, development, defense against stress, and behavioral adaptation [12-14]. Emotional arousal, vulnerability to psychotic episodes and cognitive anomalies are frequently linked to the regulation of steroid-dependent circuits and to the level of production or exposure to neurosteroids. The susceptibility pathways underlying these disturbed brain functions are also influenced by genetic factors, early-life priming experiences, and later-life events. Therefore, the imbalance of steroid receptor-mediated actions increases the vulnerability of the individual to stress-related psychiatric disorders [15]. In other cases, the imbalance of receptors [14] and/or their associated chaperones [16] generates improper protein folding leading to disease due to the lack of the proper biological activity of the receptor. Correction of all these classes of imbalances facilitates the recovery process of a diseased brain. Recent developments of animal models and new drugs employed in clinical trials have helped to shed light on many of the molecular mechanisms that govern these brain processes.

The study of hormone action on the brain, as well as the study of how the brain regulates endocrine function, is prompting a re-evaluation of the more traditional views of the separation between psychiatric and systemic medical disorders. The new viewpoint should promote new and more flexible approaches to both treatment and prevention. Importantly, recent findings have linked steroid hormones and their receptors with neuronal differentiation and neuroprotection. Moreover, chaperones and co-chaperones normally associated to steroid receptor complexes appear to be critical during the neurotrophic action of certain drugs as well as during the neuroregeneration process without the need of being associated to the receptor [17, 18].

The articles published in this special issue of *CNS & Neurological Disorders-Drug Targets* analyze both the cellular and molecular implications of both ligand structures and steroid receptor complexes in cell systems and animal models, and explore the implications of these findings for our understanding of normal neuroendocrine function, adaptation to stress, and the consequences on their dysfunctions in both animal models and patients.

Jason P. Chua and Andrew P. Lieberman analyze the genetic and clinical features of the spinobulbar muscular atrophy, a progressive neuromuscular disorder also known as Kennedy's disease that is caused by a CAG/glutamine tract expansion in the androgen receptor. A unique feature of this disease is the initiation of pathogenesis by androgens, the natural ligands of the androgen receptor. The authors analyze cellular and animals models that have been used to study this disorder, and discuss emerging therapeutic targets that have been reported in recent studies and were translated to clinical trials.

Chad Dickey group discusses recent advances on the possible mechanism of action of the immunophilin FKBP51 (FK506-binding protein) on stress related psychiatric disorders. During the last decade, it was found that dysregulation of steroid hormone receptors can cause mood disorders. Since the hypothalamus-pituitary-adrenal axis has been linked to depression and the Hsp90-binding immunophilin is able to regulate the function of steroid receptors, FKBP51 is to date at the heart of the

research of psychiatric disorders. The use of animal models leading to a better understanding of the role for this cochaperone in neurological diseases is discussed.

The Mario Galigniana laboratory examines structural aspects of preganesteroids that may favor the mechanism of action of the mineralocorticoid receptor *via* aldosterone despite the overwhelming presence of glucocorticoids in the nervous system. It is discussed a recently postulated novel mechanism of action for primarily cytoplasmic steroid receptors, and the potential relative contribution of several factors that may permit the fine tuning of aldosterone and cortisol actions according to the integrative cooperation between steroid ligands, receptors, and chaperones associated to these receptors, which are imbalanced during the development of stressing situations.

Sheela Vyas and Layal Maatouk discuss the contribution of glucocorticoids and glucocorticoid receptors to the regulation of neurodegenerative processes. It is pointed out the involvement of chronically high cortisol levels in Alzheimer's, Parkinson's or Huntington's diseases and how chronic stress or glucocorticoid treatment exacerbate neurodegenerative processes in animal models. This observation is contrasted with more recent evidences showing that cortisol and the glucocorticoid receptor may also exert neuroprotective rather than neurodegenerative effects.

The Theo Rein laboratory reports a recent research of the group aimed at identifying genes that are regulated by the glucocorticoid receptor and also display epigenetic features of transcriptional control in a neuronal cell line system. By microarray analyses, the authors reveal a network of glucocorticoid receptor-dependent genes that are under control of epigenetic factors, and by gene set enrichment analysis obtain insights into functional mechanisms implicated in stress hormone physiology. The study introduces a conceptual approach and incipient proof-of-concept for the identification of candidate genes that might be epigenetically programmed by the glucocorticoid receptor.

A multidisciplinary study led by Dr. Alejandro De Nicola and Dr. Michael Schumacher present a comprehensive review on the most recent advances on the therapeutic actions of progesterone in neurological disorders. The authors analyze the protective and promyelinating effects of progesterone in both spinal cord injury and amyotropic lateral sclerosis mouse models, as well as the protective and anti-inflammatory effects of progesterone in an experimental autoimmune encephalomyelitis model of multiple sclerosis. The progesterone prevention of nociception and neuropathic pain, and the protective effect of progesterone in experimental ischemic stroke are also discussed.

István Ábrahám laboratory review the neuroprotective effects of non-classical estrogen-like signaling activators by estradiol-induced non-classical signaling cascades. It is discussed the importance and potential therapeutic use of these type of compounds, and is described the molecular characteristics of them and possible mechanisms underlying the ameliorative actions for selective non-classical estrogen-like signaling activators. The pitfalls and future aspects of non-classical-line activators and its clinical relevance are also analyzed.

Despite the great advances reached in the field and the exciting novel findings that are shaping a new landscape on daily bases, it is clear that we still have more questions than answers, a state of the art that keeps feeding our thoughts proposing new hypothesis or models and, above all, stimulating us to overcome the new rising challenges shown in the course of our careers. Certainly, not bad for a field that is still in its young adolescence. Finally, I wish to thank all authors for their conspicuous and priceless efforts to contribute to this special issue, which I aimed to be useful and enjoyable to read.

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