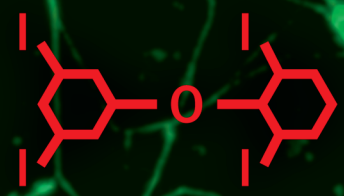
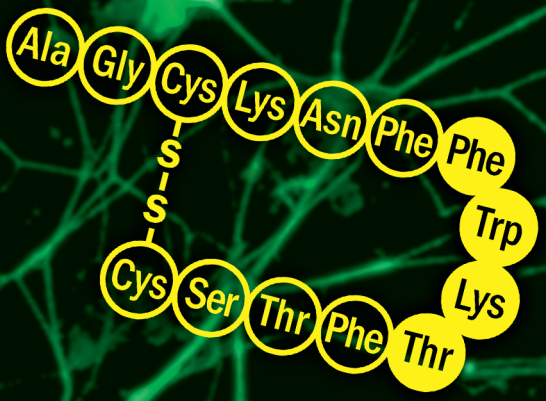
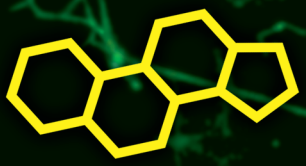
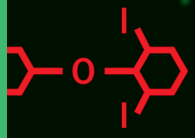
Hormones in Neurodegeneration, Neuroprotection, and Neurogenesis

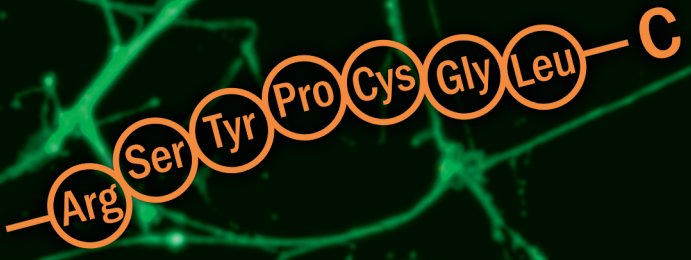
Edited by Achille G. Gravanis
and Synthia H. Mellon











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Cover
The cover photo depicts sympathetic neurons in culture, isolated from superior cervical ganglia (SCG) of E17 mouse embryos (With kind permission from the Dept. of Pharmacology, School of Medicine, University of Crete).

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Foreword

To the scientific keywords of this book, I certainly like to add ''ageing'' and ''hope.'' Clearly, the main risk of neurodegeneration is increased lifespan, which characterizes the current evolution of mankind and, at the same time, today we have hope and even some remedies for improved understanding and means of maintaining active brain function until we die.

The CNS receives, modulates, and transfers to the body information from the environment; it controls our mental and affective life and is therefore largely in command of our behavior and activities. The hormonal system (which includes more than 50 distinct important molecules) is the main vector of the CNS, which gives orders to the rest of the body. Conversely, many hormones synthesized at the ''periphery'' have access to the brain and can modify its (re)actions. Hormones interact between them at levels of regulated synthesis, metabolism and activities. Age-dependent changes in secretion, distribution, receptors, and metabolism of hormones are important to study; they may be responsible for opposite effects according to the ''age.'' If the core of the receptors' structure is the same in most target cells, the receptor-associated proteins vary according to the tissue, physiological state, and so on, including the age of the person.

The CNS is certainly the most complex system of our body. With reference to hormones, not only does it control many glandular productions and therefore their activities, but it itself also synthesizes some of them already produced by peripheral glands, such as in the case of neurosteroids. For example [1], progesterone, made in Schwann cells and oligodendrocytes, is obviously the same as the progesterone coming from ovaries; it is, however, understandable that it works preferentially (probably or even uniquely) in the neighboring nerves and myelin, we even know that ''classical'' glandular progesterone may have the same activities. Does this double origin influence an important secondary sex characteristic explaining the pathological differences between men and women? Up to now, we believe that ''neuroprogesterone'' does not act through receptors different from those found at the periphery (nuclear receptors).

Among neurosteroids (synthesized in the CNS by definition) [2], pregnenolone is globally the most abundant, and it itself displays activities in the CNS, which have not yet been demonstrated elsewhere in the organism. MAP2, an important

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microtubule-associated protein abundant in the brain, is a pregnenolone receptor, binding the steroid specifically, thus stimulating tubulin polymerization [3]. Its derivative ''MAP4343,'' which is not metabolized to progesterone, is active to treat spinal cord injuries (European patent EP15831538, 2008). In addition, pregnenolone, when sulfated at the 3-position, becomes a ligand of the $GABA_A$ receptor, antagonist to allopregnanolone, and also an active ligand of an NMDA receptor [4].

The steroid receptors bind reversibly to the heat shock protein HSP90, and while working on the hetero-oligomeric forms of these receptors, an immunophilin (binding immunosuppressants) protein FKBP52 was discovered. This protein, abundant in the brain, is able to bind to Tau (a microtubule-associated protein) and display an ''anti Tau effect'' on Tau activity on tubulin polymerization [5]. These results deriving from hormonal studies (even without direct action of steroids) have led to unveil novel mechanisms applicable to neurodegenerative diseases (whether hormones will or will not additionally interfere has not been detected so far).

The previously cited examples make logical that this book includes a remarkable variety of functions for hormones acting, from and/or for, on the CNS. An incomplete list includes the interesting actions of estrogens; progesterone (and progestins); androgens themselves or in association with peptides of the insulin-growth hormone – IGF family; the role of leptin; the subtle and varied effects of glucocorticosteroids and dehydroepiandrosterone; and the effects of somatostatin, CRH, PACAP, and erythropoietin. No doubt therapeutic issues may arise from these studies. Hormonal activities can be manipulated at the level of production (an example with etifoxine stimulating the neurosteroid pregnenolone production) [6], at the level of receptors (hormone antagonists), and at the level of their metabolism (via transport protein function and hepatic and renal functions).

I take the liberty to advise the readers of the book to keep it near their desk: they will have the privilege to conveniently obtain information on ''new neuroendocrinology'' as well as on appropriate references of talented authors of the reports.

Kremlin–Bicêtre, November 2010 *Etienne Emile Baulieu*

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