Of Blind Men and Brain Steroids

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Neurosteroids: A New Regulatory Function in the Nervous System

The first recognized example of the profound influence of steroid hormones on the nervous system was perhaps the observation in prehistoric times that animal behaviour changes dramatically during estrus (the period of female sexual receptivity). In recent years, much specific evidence has accumulated confirming that steroids affect the structure and function of the nervous system through effects on neurogenesis, cell death, cell migration, synaptic formation and neuronal excitability. Why then did Baulieu (the noted French endocrinologist who first proposed the use of the antiprogestin RU486 as an abortifacient) feel the need in 1981 to coin the term ‘neurosteroid’? As is apparent from the definition provided by the editors of this book, the reason was the unexpected discovery that some hormonal steroids could be synthesized de novo from cholesterol in the brain and also in peripheral nerves, thus placing the nervous system firmly on a par with the adrenal gland, gonads and placenta as steroidogenic tissues. Although this perspective might suit the interests of Baulieu and his co-editor — and accordingly many informative chapters in this book are concerned with the activity, localization and regulation of the enzymes for brain steroidogenesis — alternative definitions adopted by many of the chapter authors are as varied as the fancies of the proverbial blind men; each author defines the term neurosteroid according to what happens to be appropriate to their own line of research.

Indeed, no less startling than the recognition that the brain is fully competent to carry out steroid hormone synthesis, was the discovery a few years later that certain reduced progesterone metabolites could act as potent positive modulators of GABA_A receptors. This engendered the rather different view of neurosteroids as those natural steroids that alter neuronal excitability through nongenomic actions on ionotropic neurotransmitter receptors (and also perhaps other ion channels). The all-important GABA_A receptor modulatory neurosteroids allopregnanolone and allo-tetrahydroxy corticosterone would have escaped Baulieu’s strict definition, were it not for the loophole that their precursor (progesterone) can be generated de novo in brain, although of course most allopregnanolone derives from progesterone of ovarian sources. (Some authors have attempted to solve the definitional troubles by calling steroids that are largely synthesized outside the brain or even synthetic steroids that act on the nervous system ‘neuroactive steroids’, but this only emphasizes the lack of understanding of the functional importance of local synthesis for true neurosteroids. Others, such as Majew ska, accept adrenal and gonadal steroids as neurosteroids as long as the actions in the brain are not similar to their classical genomic actions elsewhere.)

Belying the strict definition of the editors, this multi-author volume presents a selection of up-to-date reviews on the burgeoning field of steroid neurobiology. The book covers not only the metabolism of steroids in neural tissues but also their modulatory actions on GABA_A, glutamate and nicotinic acetylcholine receptors, and on voltage-activated Ca^2+ channels, and their effects on behaviour. Additional chapters encompass diverse actions of oestrogens (that, incidentally, do not fall within anyone’s definition of neurosteroid as they derive not by de novo synthesis but from gonadal sources or by local aromatization of androstenedione and testosterone, and the actions discussed occur through genomic mechanisms). However, coverage here is sporadic with detailed descriptions of recent research on the actions of oestrogens on neuronal and glial development, survival and plasticity, but little on the effects of the hormones on brain excitability, seizure susceptibility, regulation of excitatory synaptic transmission or in protecting against Alzheimer’s disease. Similarly, the effects of glucocorticoids in aggravating brain damage resulting from pathological insults and their controversial role in mediating stress-induced hippocampal damage are only briefly mentioned.

The field of neurosteroid research has not yet reached maturity and this book highlights certain key problems in the discipline. In contrast to other steroid hormones, neurosteroids as most authors define them do not act on their own specific receptor, and instead serve as allosteric modulators of ionotropic neurotransmitter receptors, or have other unknown membrane actions mediated by as yet undefined targets. Moreover, there is still not a single example where a neurosteroid has been unequivocally linked to an essential signalling function. Thus, the status of neurosteroids as true hormones, even in the autocrine or paracrine sense, is uncertain. Once it is possible to state in functional terms the physiological roles of the steroids, the definitional problems should resolve themselves. For the time being, however, there is good evidence that neurosteroids have a diversity of behavioural actions and that they perhaps play a part in some pathological states.

The roles of neurosteroids in the determination of mood, personality, aggressiveness and in alcohol dependence are discussed in detail, whereas consideration of the possible roles in menopausal related disorders such as the premenstrual syndrome, postsurgical depression and catecholamine epilepsy is less complete. Finally, the potential uses of neurosteroid-derived agents in therapeutics — for example, in the treatment of insomnia, epilepsy, anxiety, migraine, drug dependence or neurodegenerative disorders — are hardly mentioned. Nevertheless, despite its shortcomings, this book will be referred to often by workers interested in steroids and the brain.

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