

observed in the CNS (Ref. 5). Apart from traditional roles in Ca^{2+} homeostasis, vitamin D induces the expression of many CNS genes⁶. Vitamin D is one of the most potent up-regulators of nerve growth factor^{7–9} and can also induce the low affinity neurotrophin receptor (p75^{NTR})¹⁰. Vitamin D receptors (VDR) are widely distributed throughout the developing and adult rat brain^{11–13} and have been identified in the human brain¹⁴. Thus, there is great scope for Vitamin D to act on the CNS in a developmental-, cell- and tissue-specific manner, depending not only on the expression of VDR-target genes but also on interactions with other growth factor signalling pathways.

Because the crucial rate-limiting step in the production of vitamin D is the action of ultraviolet light on the skin, an individual's behaviour (e.g. outdoor activity, dress) and place of residence (e.g. latitude) can interact with seasonal fluctuations in the intensity of ultraviolet light to determine levels of vitamin D. Hypovitaminosis D is common in the community, with a large US community-based survey finding 9% of adults to be deficient (i.e. 25-hydroxyvitamin D levels $\leq 38 \text{ nmol/L}$)¹⁵. Even in subtropical regions, dress and behaviour can result in hypovitaminosis D (Ref. 16).

In the absence of hypocalcaemia, hypovitaminosis D has no apparent immediate impact on brain function, however there is evidence to suggest vitamin D can improve mood¹⁷ (and, therefore, might be associated with seasonal affective disorders). Low vitamin D has also been proposed as a risk factor for schizophrenia (low prenatal vitamin D)¹⁸ and multiple sclerosis [low prenatal vitamin D (Ref. 19) and low vitamin D during childhood and adulthood²⁰]. Several studies have also linked vitamin D with general neuroprotection^{21,22} and changes associated with Alzheimer's disease²³. Thus, chronic hypovitaminosis D should be examined in more detail as a candidate risk factor for neurodevelopmental and neurodegenerative disorders.

Vitamin D is also known as 'solatriol', because of its association with sunshine. With respect to the recent interest in neurosteroids, we feel that it is now time for vitamin D to 'emerge from the shadows'. In view of the prevalence of hypovitaminosis D in the general public, the impact of this neurosteroid on the developing and adult brain requires clarification.

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Response – Vitamin D: the neglected neurosteroid?

In the past decades firm evidence has emerged that steroids, in addition to their effects on gene expression via intracellular steroid receptors, might directly modulate neuronal excitability through allosteric modulation of neurotransmitter receptors¹. Steroids with these particular properties have been called 'neuroactive steroids', whereas the term 'neurosteroids' has been reserved for steroids that are synthesized in the brain itself without the aid of peripheral sources².

In their comment, McGrath et al. address the putative role of vitamin D as a neurosteroid. Vitamin D acts via intracellular receptors on the regulation of gene expression, similar to classical steroid hormones³. Vitamin D receptors are members of the steroid receptor superfamily to which the receptors for steroid hormones and also thyroid hormone receptors or retinoic acid receptors also belong³. Although Vitamin D is formed from cholesterol it is a matter of debate whether vitamin D should really be called a steroid. Rapid non-genomic effects have been described for 1 α , 25-dihydroxyvitamin D₃, the steroid hormone metabolite of vitamin D₃ (Ref. 4). However, whereas a variety of ligand-gated ion channels have been shown to be steroid-sensitive¹, an allosteric modulation

of neurotransmitter receptors by vitamin D, for example, 1α , 25-dihydroxyvitamin D₃, has not yet been demonstrated. Although it remains questionable whether vitamin D fulfills the strict formal criteria of a neurosteroid or a neuroactive steroid, 1α , 25-dihydroxyvitamin D₃ shares common mechanisms of action with steroid hormones, such as the intracellular cross-talk between genomic and non-genomic effects.

In view of the multiple effects of vitamin D on gene expression in the brain described by McGrath *et al.*, vitamin D plays an important role for CNS function and plasticity. Thus, the impact of vitamin D for CNS development and for neuropsychiatric disorders undoubtedly deserves further attention as suggested by McGrath and colleagues. We therefore support the effort of McGrath *et al.* to shed further light on the 'sunshine compound' vitamin D.

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the definition of the term 'neurosteroids'. This term was coined by E.E. Baulieu to define steroids of nervous origins. In particular, the original definition was coined in 1981 as a result of the unexpected discovery that some steroid hormones (i.e. progesterone) could be synthesized *de novo* from cholesterol in the brain¹. Recently, other observations have indicated that such synthesis is also present in the PNS. Following this definition, Vitamin D should strictly not be considered a 'neurosteroid' because this molecule is originally synthesized in the skin.

However, during the past 20 years an impressive body of experimental data has been collected depicting a totally new scenario for the roles played by steroids in the brain. On the one hand, steroid hormones (irrespective of either their nervous or extra-nervous origin) might act through the interaction with the 'classical' cytoplasmic receptors and could directly regulate the expression of steroid-dependent genes. On the other hand, it was discovered that some reduced steroid metabolites (i.e. 3α - 5α -derivatives from progesterone, testosterone and corticoids) could act as potent modulators of GABA_A receptors, and in this way could alter the neuronal excitability. This second method of action of steroids is obviously fast (compared with the long-term effects as a result of the genomic effect) and strictly dependent upon the local availability of the active molecule. Some authors now include in the term 'neurosteroids' those steroids acting in the nervous system through non-genomic mechanisms². Moreover, further observations suggest that some steroids are also able to exert their effects via interaction with different neurotransmitter receptors (e.g. NMDA, cholinergic receptors), putative membrane receptors, and receptors, such as sigma 1 that have not yet been fully characterized.

It is clear that the discovery of new and different molecular targets and alternative signaling pathways has expanded and complicated our understanding of the mechanisms of actions of steroids in the nervous system^{3–5}. In particular, it is difficult to understand the functional importance of local synthesis and consequently to discriminate whether the steroid effect is the result of *in situ* synthesis or to an enzymatic activation in metabolites, which are more active and in some cases possess a different mechanism of action. The term 'neurosteroids' is

becoming more and more difficult to qualify as our knowledge of nervous system–steroid interactions expands. Consequently some of the investigators involved in this field now utilize the term 'neuroactive steroids'⁴. Accordingly, because the last biosynthetic step (i.e. the formation of the active form, 1,25-dihydroxyvitamin D) of Vitamin D also occurs in the brain, it might also be considered as a 'neuroactive steroid'. Such a situation could be similar to the generation of 17β -estradiol, formed from the androgens by the action of the enzyme aromatase, or to the generation of 5α -dihydrotestosterone and 5α -dihydroprogesterone, formed respectively from testosterone and progesterone by the action of the 5α -reductase, these are also considered as 'neuroactive steroids'.

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Response – Vitamin D: the neglected neurosteroid?

The letter of J. McGrath and co-workers proposing that Vitamin D might be considered a neurosteroid, points to one of the 'core' problems for researchers working in the field of the interactions among steroids and the nervous system, that is,

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