the accumulation of aberrant, neurotoxic forms of host proteins in the brain for which there is no known cure. In the landmark study reported in *Proc. Natl. Acad. Sci. U. S. A.* [(2001) 98, 9295–9299], a mouse cell line was chronically infected with a strain of mouse scrapie causing the massive accumulation of neurotoxic scrapie prion protein (PrP^{Sc}), a defective variant of a surface protein found in brain cells (PrP^{C}). Using this model, Enari *et al.* showed that exposure of the cells to an antibody directed against the prion protein blocked the infection of neighboring susceptible cells and further abolished the accumulation of PrP^{Sc} in the chronically infected cells. Encouraged by the findings *in vitro*, the research team will now test the prion antibody in mice, in the hope that the approach might soon be used in the treatment of prion diseases. *SS*

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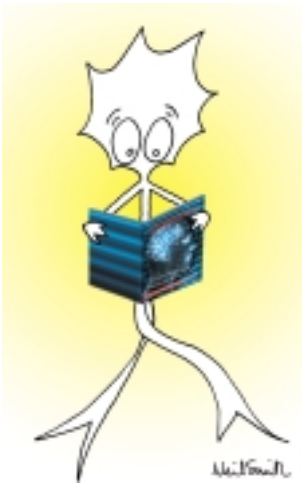

Letters

Vitamin D: the neglected neurosteroid?

Recent articles in this journal[1,2] have focused attention on the growing body of evidence showing that steroid hormones can alter brain function in novel ways. The autocrine and paracrine roles played by steroids synthesized in the brain (also known as neurosteroids) are yet to be fully elucidated. The physiological properties of known neurosteroids are diverse, and differ temporally (neurodevelopment versus adult brain) and regionally within the brain[3].

We wish to draw attention to vitamin D as a neuroactive steroid whose probable synthesis in the CNS qualifies it as a neurosteroid. A precursor of vitamin D is generated from a cholesterol derivative by the action of ultraviolet light on the skin[4]. Its active form, calcitriol, is formed by two hydroxylation reactions. The expression of mRNA coding for the 1∝-OH hydroxylase (the P450 enzyme required in the final step to produce the active form 1,25-dihydroxyvitamin D_3) has been

observed in the CNS (Ref. 5). Apart from traditional roles in Ca^{2+} homeostasis, vitamin D induces the expression of many CNS genes[6]. 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 brain[14]. 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 ≤ 38 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 mood[17] (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 adulthood[20]]. Several studies have also linked vitamin D with general neuroprotection[21,22] and changes associated with Alzheimer's disease[23]. 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 'soltriol', 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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References

1 Rupprecht, R. and Holsboer, F. (1999) Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci*. 22, 410–416
2 Melcangi, R.C. and Panzica, G.C. (2001) Steroids in the nervous system: a Pandora's box? *Trends Neurosci*. 24, 311–312
3 Baulieu, E.E. (1998) Neurosteroids: a novel function of the brain. *Psychoneuroendocrinology* 23, 963–987
4 Holick, M.F. (1995) Environmental factors that influence the cutaneous production of vitamin D. *Am. J. Clin. Nutr*. 61, 638S–645S
5 Miller, W.L. and Portale, A.A. (2000) Vitamin D 1∝-OH hydroxylase. *Trends Endo. Metabol*. 11, 315–319
6 Darwish, H. and DeLuca, H.F. (1993) Vitamin D-regulated gene expression. *Crit. Rev. Eukaryot. Gene Expr*. 3, 89–116
7 Saporito, M.S. *et al.* (1994) Chronic 1,25-dihydroxyvitamin D3-mediated induction of nerve growth factor mRNA and protein in L929 fibroblasts and in adult rat brain. *Brain Res*. 633, 189–196
8 Cornet, A. *et al.* (1998) 1,25-Dihydroxyvitamin D3 regulates the expression of VDR and NGF gene in Schwann cells *in vitro*. *J. Neurosci. Res*. 53, 742–746
9 Musiol, I.M. and Feldman, D. (1997) 1,25-dihydroxyvitamin D3 induction of nerve growth factor in L929 mouse fibroblasts: effect of vitamin D receptor regulation and potency of vitamin D3 analogs. *Endocrinology* 138, 12–28
10 Baas, D. (2000) Rat oligodendrocytes express the vitamin D(3) receptor and respond to 1,25-dihydroxyvitamin D(3). *Glia*. 31, 59–68
11 Veenstra, T.D. *et al.* (1998) 1,25-Dihydroxyvitamin D3 receptors in the central nervous system of the rat embryo. *Brain Res*. 804, 193–205
12 Prufer, K. *et al.* (1999) Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. *J. Chem. Neuroanat*. 16, 135–145
13 Langub, M.C. *et al.* (2001). Evidence of functional vitamin D receptors in rat hippocampus *Neuroscience* 104, 49–56
14 Sutherland, M.K. *et al.* (1993) Reduction of calbindin-28k mRNA levels in Alzheimer as compared to Huntington hippocampus. *Brain Res. Mol. Brain Res*. 18, 32–42
15 Looker, A.C. and Gunter, E.W. (1998) Hypovitaminosis D in medical inpatients. *New Engl. J. Med*. 339, 344–345
16 McGrath, J.J. *et al.* (2001) Vitamin D insufficiency in south-east Queensland. *Med. J. Australia* 174, 150–151
17 Lansdowne, A.T. and Provost, S.C. (1998) Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacol (Berl.)* 135, 319–323
18 McGrath, J. (1999) Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr. Res*. 40, 173–177
19 McGrath J. (2001) Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders? *Med. Hypotheses* 56, 367–371
20 Hayes, C.E. *et al.* (1997) Vitamin D and multiple sclerosis. *Proc. Soc. Exp. Biol. Med*. 216, 21–27
21 Brewer, L.D. *et al.* (2001) Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J. Neurosci*. 21, 98–108
22 Garcion, E. *et al.* (1998) Expression of inducible nitric oxide synthase during rat brain inflammation: regulation by 1,25-dihydroxyvitamin D3. *Glia* 22, 282–294
23 Landfield, P.W. and Cadwallader-Neal, L. (1998) Long-term treatment with calcitriol (1,25(OH)2 vit D3) retards a biomarker of hippocampal aging in rats. *Neurobiol. Aging* 19, 469–477

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 receptors[1]. 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 sources[2].

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 hormones[3]. 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 belong[3]. 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 1α, 25-dihydroxyvitamin D_3, the steroid hormone metabolite of vitamin D_3 (Ref. 4). However, whereas a variety of ligand-gated ion channels have been shown to be steroid-sensitive[1], an allosteric modulation

