

Low vitamin D concentration exacerbates adult brain dysfunction^{1,2}

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The links between vitamin D and brain function have strengthened considerably in the past decade (1). The empirical evidence includes the following: 1) convincing data from *in vitro* and animal experimental studies, 2) inconsistent findings from observational and analytic epidemiology, and 3) inconsistent findings from the handful of randomized controlled studies done in the field. Occasionally, the evidence from these different research domains converges. In this issue of the Journal, Suzuki et al (2) report the outcomes of a double-blind, placebo-controlled trial of vitamin D supplementation (1200 IU/d, for 1 y) on various Parkinson disease (PD)-related outcomes. Although the sample size was modest ($n = 114$), there were clear group differences in several of the outcomes. In addition, there were tantalizing findings showing that vitamin D supplementation interacted with common polymorphisms in the gene coding for the vitamin D receptor (VDR) to prevent decline. The findings are informative: those who received placebo (and thus those who were more likely to have persisting 25-hydroxyvitamin D insufficiency or deficiency) had a steady worsening on PD outcomes. In contrast, those who received vitamin D supplements had no change in PD outcomes over the year. The results strongly suggest that low vitamin D status exacerbates disease progression.

The active form of vitamin D (1,25-dihydroxyvitamin D) operates via the VDR, the smallest member of the family of nuclear receptors (which includes other brain-critical signaling pathways such as retinoic acid, thyroid hormone, sex hormones, etc). The brain distributions of the VDR, and the key enzyme required for the conversion of the prohormone (25-hydroxyvitamin D) to 1,25-dihydroxyvitamin D, have been mapped (3). Of particular relevance to the target article, VDR was most strongly expressed in dopamine-rich areas such as the substantia nigra. We have recently confirmed that all large tyrosine hydroxylase-positive (dopaminergic) neurons in the human substantia nigra also express VDR (4). In addition, there is *in vitro* evidence that 1,25-dihydroxyvitamin D increases the expression of tyrosine hydroxylase (5).

The timing of vitamin D deficiency produces variable effects on the brain. There is a growing body of convergent evidence linking low prenatal vitamin D to an increased risk of neurodevelopmental disorders such as schizophrenia (6). It is thought that the mechanisms linking developmental vitamin D deficiency with neurodevelopmental disorders probably relates to the well-described pro-differentiation, antiproliferative properties of the active form of vitamin D (and of steroids in general). Thus, the absence of vitamin D deprives the developing brain of an expected signal.

The links between vitamin D deficiency and adult brain function suggest that other mechanisms may be involved. Animal experiments that have examined the impact of transient vitamin D deficiency on adult brain outcomes suggest relatively modest neurochemical and behavioral phenotypes (7). However, there is convergent evidence that vitamin D may have “neuroprotective” properties (8). For example, vitamin D has a direct neuroprotective action against excitotoxic insults by downregulating L-type calcium channels (9), and pretreatment with vitamin D attenuates the effects of various stressors of interest in PD disease, including 6-hydroxydopamine-induced neurotoxicity (10). An experimental study based on a rodent ischemic stroke model reported that animals allocated to a vitamin D-deficient diet (before the stroke lesion) subsequently had significantly greater ischemic brain damage and worse functional impairments (compared with rodents fed vitamin D-replete chow) (11). Overall, these findings suggest that low vitamin D affects adult brain function in subtle ways but may exacerbate “second hit” stressors. This hypothesis is entirely consistent with the findings from Suzuki et al (2). Vitamin D insufficiency or deficiency exacerbated the progression of an underlying brain disorder (the PD-related outcomes worsened in the placebo arm). In contrast, those who received the vitamin D supplement had no disease progression over the year of the study (but still required ongoing L-dopa treatment).

From a neuroscience perspective, there is a growing body of evidence showing that developmental vitamin D deficiency alters brain development—it may be a “sufficient cause” with respect to neurodevelopmental disorders such as schizophrenia. In contrast, adult vitamin D deficiency leaves the brain more vulnerable to second hits and/or exacerbates the progression of concurrent brain disorders—but as a cause, it is neither necessary nor sufficient. Regardless, because vitamin D deficiency is prevalent in the community, and may exacerbate a range of adverse brain outcomes (eg, PD and stroke), optimizing vitamin D status could translate to important gains from a public health perspective. The consequences of persistent vitamin D deficiency on adult brain outcomes may be delayed (ie, have a long latency) and

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First published online March 27, 2013; doi: 10.3945/ajcn.113.061176.

interact with a range of other exposures and risk factors. We speculate that adult vitamin D deficiency could exacerbate the progression of a wide range of other brain disorders such as multiple sclerosis, dementia, and depression.

If the findings of Suzuki et al (2) are replicated, and if future studies confirm that the treatment of vitamin D deficiency is not associated with unintended adverse outcomes, then there is a case to translate this treatment promptly. Even if optimal vitamin D status delays PD progression by a small degree, this treatment is cheap, simple to access (eg, across the counter), relatively safe, and publicly acceptable.

The authors did not declare any conflicts of interest.

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