Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction?

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ABSTRACT **Vitamin D insufficiency is common in the United States; the elderly and African-Americans are at particularly high risk of deficiency. This review, written for a broad scientific readership, presents a critical overview of scientific evidence relevant to a possible causal relationship between vitamin D deficiency and adverse cognitive or behavioral effects. Topics discussed are *1*) biological functions of vitamin D relevant to cognition and behavior; *2*) studies in humans and rodents that directly examine effects of vitamin D inadequacy on cognition or behavior; and *3*) immunomodulatory activity of vitamin D relative to the proinflammatory cytokine theory of cognitive/behavioral dysfunction. We conclude there is ample biological evidence to suggest an important role for vitamin D in brain development and function. However, direct effects of vitamin D inadequacy on cognition/behavior in human or rodent systems appear to be subtle, and in our opinion, the current experimental evidence base does not yet fully satisfy causal criteria. Possible explanations for the apparent inconsistency between results of biological and cognitive/behavioral experiments, as well as suggested areas for further research are discussed. Despite residual uncertainty, recommendations for vitamin D supplementation of at-risk groups, including nursing infants, the elderly, and African-Americans appear warranted to ensure adequacy. McCann, J. C., Ames, B. N. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? *FASEB J.* 22, 982–1001 (2008)**

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A LARGE BODY OF RESEARCH suggests that an inadequate dietary supply of any of a number of essential micronutrients (some 40 vitamins, minerals, and other small molecule essential nutrients) can adversely affect brain function (*e.g.*, refs. 1–4). Some studies also suggest positive effects of multivitamin and mineral supplementation on cognitive function (*e.g.*, refs. 5, 6). A causal relationship between micronutrient deficiencies and suboptimal brain function would have major public health implications. Large segments of the world (including the U.S.) population, particularly the poor, are known to be undernourished for a number of micronutrients (7–9). A major effort to address micronutrient undernutrition as an adjunct to the various programs under way to improve dietary habits, particularly of the poor, would be well justified. One of us has discussed such an approach as a relatively inexpensive and efficacious adjunct to current public health programs (10–12).

This review is part of a series intended to provide critical summaries for a broad scientific readership of expert opinion and the available experimental evidence pertinent to whether there are causal linkages between individual micronutrient deficiencies and brain function. Recently, we reviewed evidence relevant to whether a causal relationship exists between cognitive dysfunction and availability during development of the omega-3 fatty acid docosahexaenoic acid (DHA) (2), choline (3), and iron (4).

It has been only some 25 years since the first reports suggesting that functions of vitamin D extended well beyond its classical role in systemic calcium homeostasis (13). Here, we provide a brief overview of recent mechanistic and direct evidence relevant to whether vitamin D is linked to cognitive or behavioral function. We also discuss the proinflammatory cytokine theory of cognitive/behavioral dysfunction relative to the immunomodulatory activity of vitamin D. Included is a critical summary of rodent studies that have examined cognitive/behavioral performance in mice lacking a functional vitamin D receptor, or in animals that have been restricted for UV light and dietary vitamin D.

Primary resources were recent research reports not yet reviewed, key earlier studies, and a large number of expert reviews and commentaries. We searched the literature by using a combination of techniques, including key word and author searches of the National Library of Medicine's PubMed database and the Science Citation Index Cited References database. We also surveyed citations included in recent research and review articles. Abstracts were not included. Because of the broad subject matter of this review and the fact that some subjects discussed are very active areas of re-

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search, references cited are selective, with preference given to the most recent representative references in order to keep the bibliography of a manageable length.

BACKGROUND

The term "vitamin D" refers to either vitamin D2 (ergocalciferol) or D3 (cholecalciferol). A major source of vitamin D3 is fortified foods such as milk and some cereals. Vitamin D3 is naturally present in few foods, primarily fatty fish such as salmon, mackerel, and sardines, whereas some vitamin D2 is found in yeast and plants (14). Vitamin D2 is less active than vitamin D3 (15). The major source of vitamin D3 for most people is the action of UV radiation from the sun on a chemical in the skin related to cholesterol (7-dehydrocholesterol) to form cholecalciferol, which is then enzymatically converted to 25-hydroxycholecalciferol ($25OHD_3$, or calcidiol). $25OHD_3$ is a stable circulating form of vitamin D that is usually measured in serum to indicate vitamin D status. The primary active form of vitamin D is calcitriol (1α,25-dihydroxycholecalciferol), which is formed from $25OHD_3$ by the mitochondrial enzyme 1,α-hydroxylase (CYP27B1). Throughout this review, we use the terms "calcitriol" and "25OHD3" to refer to the active form of vitamin D and its immediate biosynthetic precursor, respectively. The final activation step of calcitriol takes place in the kidney and in many other tissues throughout the body, as well as in white blood cells. (Vitamin D2 is also converted to a dihydroxy active form.) Calcitriol synthesized in the kidney is released into the bloodstream as a hormone, and circulates bound to a vitamin D-binding protein. Calcitriol is also synthesized in or adjacent to regulated cellular targets, thus acting in an autocrine and paracrine fashion as well. Calcitriol binds to the vitamin D receptor (VDR), which, in turn, binds to a vitamin D response element (VDRE) in the promoter region of regulated genes. Many calcitriol target genes have been identified (16–21). Calcitriol also binds to cell membrane receptors (22–24), initiating rapid nongenomic signaling, including rapid Ca^{2+} translocation through voltage-gated ion channels, and up-regulation of the mitogen-activated protein kinase (MAPK) cascade *via* a protein kinase C signaling pathway (25). A membrane receptor distinct from the VDR has been described (26, 27), but the VDR may also be involved (23, 28, 29).

The classical hormonal function of calcitriol is to control blood levels of calcium by regulating the expression of genes involved in its intestinal absorption, renal excretion, and movement in and out of bone. More recently, many other so-called noncalcemic functions of calcitriol have been identified, which include regulation of proliferative and apoptotic activity, immunomodulatory and prodifferentiation activity, and interaction with the rennin-angiotensin system (involved in the regulation of blood pressure), insulin secretion, and neuroprotective functions. These diverse functions are discussed in many general reviews; a few are cited here (13, 22, 23, 30–39). In this review, we will discuss a subset of these functions as they relate to the possible need for vitamin D for cognitive or behavioral function.

VITAMIN D STATUS, INSUFFICIENCY, AND DEFICIENCY

Vitamin D status is currently indicated by $25OHD_3$ concentration in serum (14). The National Academy of Sciences (NAS) used a cutoff value of 27.5 nmol/L (<11 ng/ml) $25OHD_3$ to indicate "vitamin D deficiency" for the purposes of setting Dietary Reference Intakes for vitamin D (14). The term "vitamin D insufficiency" represents the $25OHD_3$ concentration below which a subclinical deficiency is considered to exist; the cutoff value has generally been considered to correspond to the lower limit of the range of $25OHD_3$ in a normal population. The NAS cites several cutoff values determined from different populations, ranging from 37.5 nmol/L (15 ng/ml) to 77.5 nmol/L (31 ng/ml). Some experts have suggested that these cutoff values be raised (*e.g.*, refs. 40, 41). In this review, we use the general terms "low vitamin D" or "vitamin D inadequacy" to indicate either vitamin D insufficiency or deficiency. In discussing specific studies, we specify $25OHD_3$ concentrations when reported. Since calcitriol is synthesized and acts locally in a paracrine or autocrine fashion in the brain (as well as in many other tissues), it is likely that circulating concentrations of $25OHD_3$ will have a complex relationship to localized concentrations of calcitriol.

EXPERIMENTAL DESIGNS

The evidence to be discussed involves primarily three basic experimental designs. First, the supply of vitamin D or calcitriol were manipulated *in vitro* or *in vivo* by creating the conditions of vitamin D inadequacy through restricting exposure to UV radiation and limiting dietary intake or through increasing supply by supplementing the cell culture medium or treating subjects orally or by injection. Second, the functionality of calcitriol was restricted by using a mouse knockout strain (42) lacking a functional VDR (VDR-KO) (43). And third, experimental or population groups were examined for associations between blood concentrations of 25OHD3 and behavioral or biochemical endpoints.

RELEVANCE OF THE EXPERIMENTAL DATABASE TO HUMANS

The majority of evidence concerning the biology and mechanisms of action of vitamin D in the brain and most of the direct evidence for effects of vitamin D inadequacy on cognitive or behavioral function rely on experiments conducted in laboratory rats or mice. The

rodent strains used were all derived from species (*Rattus norvegicus* and *Mus musculus*) (44), known to be largely, though not exclusively, nocturnal (45). They are thus expected to be less exposed to sunlight than humans. It is unclear how this difference between rodents and humans might be reflected in differences in vitamin D biology or in sensitivity to limited availability of vitamin D. On the one hand, there is a large body of evidence indicating that vitamin D plays a key role in many important biological processes in both the development and function of the rodent nervous system, as will be briefly summarized here. And, on the basis of the very few comparative studies of which we are aware, there is evidence to suggest some striking similarities between humans and rodents. For example, vitamin D is synthesized in the skin in both rats and humans (46, 47), the distribution of VDR in human and rat brains is very similar (48), apoptotic effects of calcitriol on brain glial cells appear to be similar whether cells are from humans or rats (49), and serum concentrations of vitamin D-binding protein are similar in laboratory rats and humans (50). On the other hand, all of calcitriol's effects in humans and rodents are not the same. For example, calcitriol stimulates the production of the antimicrobial peptide cathelicidin in humans, but not mice (51, 52). Also, it has recently been demonstrated that, in rats, lithocholic acid can substitute for vitamin D under conditions of deficiency (53). It is not known if this mechanism exists in humans. Throughout the review, we have attempted to take the possibility of significant species differences in vitamin D biology into account in presenting and discussing experimental results.

MECHANISTIC EVIDENCE THAT LINKS VITAMIN D TO BRAIN DEVELOPMENT AND FUNCTION

Below are brief summaries of immunohistochemical, biochemical, and molecular biological evidence that point to the involvement of calcitriol in brain development and function. Because of the enormous size of the relevant literature, several examples have been selected for discussion, and references to more detailed treatment of specific topics are provided. The sections below point to: the ubiquitous presence of VDR and 1,α-hydroxylase (the terminal rate-limiting enzyme in the synthesis of calcitriol) in the brain; examples illustrating the involvement of calcitriol and its target gene products in neuronal differentiation and brain function; and the involvement of calcitriol-mediated membrane processes in brain function.

VDR and 1,α-hydroxylase, the terminal calcitriol-activating enzyme, are distributed throughout both the fetal and adult brain

VDR have been identified in more than 50 tissues (54). VDR and 1,α-hydroxylase (55) are distributed throughout the human adult brain (48, 56) and the rodent adult (57–61) and fetal (62–64) brain. The distribution of VDR in human and rodent brains is very similar (48). VDR have been reported in the nuclei of a number of cell types in the central nervous system (CNS), including microglia, astrocytes, oligodendrocytes (the cells that make myelin), and Schwann cells, their counterpart in the peripheral nervous system (60, 65–67). VDR have been detected in the rat fetal brain at all times examined (as early as ED12) (62, 64), increasing in number until birth (64). Calcitriol can cross the blood-brain barrier (68), but it is also synthesized in the brain (48). Calcitriol injected into hamster brains was found strongly concentrated in the nuclei of neurons in several brain regions involved in memory and cognition (59).

Vitamin D target genes in the brain

As indicated above, the expression of many genes has been shown to be affected by calcitriol treatment, but only a relatively small number of studies have investigated target genes in brain tissues or cells. Specific gene products whose expression in the brain or brain cells has been shown to be altered by calcitriol treatment are summarized in **Table 1** (57, 68–81). Recently, effects on expression of multiple genes and proteins in brain tissue from offspring restricted for dietary vitamin D and UV radiation during fetal development were reported (21, 82). These are the first studies of which we are aware that examined effects of vitamin D deficiency on gene or protein expression. For general discussion of calcitriol target genes, see several reviews (30, 36–38, 83, 84).

Several gene products that have specific relevance to cognitive or behavioral function are discussed further below.

Neurotrophins (NGF, NT-3, NT4/5) and the neurotrophic factor GDNF

Neurotrophins are secreted proteins that support the survival and differentiation of neurons (85, 86) and also function in the adult brain. Of the 4 neurotrophins in mammals (NGF, BDNF, NT-3, and NT4/5), calcitriol affects the expression of 3 of them, as indicated above. NGF is present mainly in the hippocampus and neocortex, where it affects neurotransmission and synaptic plasticity (85). Functions of the other neurotrophins linked to calcitriol include enhancement of synaptic transmission in the hippocampus by NT-3 (87), and involvement in calcium signaling by NT4/5 (88).

GDNF (73, 89) is another type of neurotrophic factor. It is a distant member of the transforming growth factor β (TGFβ) superfamily. GDNF is expressed in neural and non-neural tissues (85). In the brain, GDNF affects the survival and differentiation of dopaminergic cells (90, 91) and is present at relatively high levels in the developing striatum of the rat (91).

TABLE 1. *Calcitriol target genes in the brain*

Gene products whose expression in the brain or brain cells has been reported to be affected by calcitriol
Neurotrophins and other growth factors
NGF (69–71), NT-3 and NT-4/5 (72), GDNF (73, 74), TGF-β_2 (75)
Calcium-binding proteins
Calbindin D28K, parvalbumin, calretinin (76, 111)
Protein subunits for L-TYPE VOLTAGE-SENSITIVE Ca^{2+} channels (L-TYPE VSCCs) (141, 148)
Transcription factors or enzymes involved in signal transduction pathways
N-myc, c-myc, protein kinase C family (PKC) (75)
Other enzymes
Choline acetyltransferase, responsible for synthesis of the neurotransmitter acetylcholine (77)
γ-Glutamyltranspeptidase, involved in recyling of the reactive oxygen species scavenger glutathione (78)
Hormones
Oxytocin, the "trust hormone"[a]
Biochemical or cellular brain functions in which calcitriol target gene products are involved
Synaptogenesis (formation of synaptic connections)
Synaptic plasticity (*e.g.*, memory formation)
Calcium signaling and homeostasis
Neurotransmission and neurotransmitter synthesis
Survival and differentiation of dopaminergic and other neurons
Control of toxic free radicals
Behavior affected by target gene product dysfunction
Learning and memory
Motor control
Maternal or social behavior
Aging (neuronal density)

See text for additional references and discussion. [a]Recently, an *in silico* study identified the VDR DNA binding sequence in the oxytocin receptor gene (16). On the basis of the colocalization of the VDR receptor with oxytocin immunoreactivity in the rat hypothalamus, it was suggested that calcitriol may affect the expression of oxytocin (79). Oxtocin, termed the "trust hormone," is involved in a variety of physiological processes, including labor induction and the milk-eject reflex, as well as stimulating the feeling of trust (80).

Recent evidence indicates its probable involvement in synaptogenesis (92). In striatal neurons *in vitro*, GDNF treatment activated intracellular signaling involving the p42/p44 MAPK pathway and increased dendritic arborization of the neurotransmitter γ-aminobutryric acid (GABA)- and calbindin-positive neurons (93).

GDNF treatment rescued damaged dopamine neurons and associated functions in rodent and primate Parkinson's models (94–98), possibly by reducing oxidative stress (99). In the Parkinson's model in rats, calcitriol treatment also attenuated neurotoxicity (100, 101). Results of GDNF treatment in alleviating Parkinson's symptoms in human clinical trials have been mixed (102–106); treatment with calcitriol or calcitriol analogues has not been investigated. In a different rodent model of neurotoxicity, neuroprotective effects were dose dependent and were elicited with calcitriol at the same concentrations that also increased GDNF levels (107).

Calcium-binding proteins

Many calcium-binding proteins are present throughout the body (108) and in the CNS (109, 110). As indicated above, three have been shown to be modulated by vitamin D in brain tissues or cells—calbindin-D28K, parvalbumin, and calretinin (76, 111). All three of these calcium-binding proteins are widely distributed in both the adult and fetal brain. In the adult brain, each of these proteins is uniquely distributed, and they also exhibit temporal patterns during development (112–115) and aging (116). They fill the cytoplasm of neuronal processes, are commonly used as neuronal markers (117), and are present in some areas of the brain at very high concentrations. For example, calbindin-D28k comprises some 15% of the total protein in adult Purkinje cells in the cerebellum (110). All three proteins are believed to serve a neuroprotective role as calcium buffers (*e.g.*, ref. 118), but they are also involved in critical brain functions. Additional information on the functions of parvalbumin and calretinin in the brain can be found in refs. 109 and 119.

In addition to its calcium-buffering properties, calbindin-D28k undergoes a conformational change on binding Ca^{2+} and functions as a Ca^{2+} sensor (120, 121). It is required for normal signaling of synaptically evoked calcium transients (122) and is involved in synaptic plasticity (123), long-term potentiation (LTP) (124), and memory formation (125, 126), and possibly in the regulation of exocytosis (synaptic secretion of neurotransmitters) (127). Also, in Purkinje cells in the cerebellum, calbindin-D28k appears to be directly involved in motor control (122, 128), which could suggest a possible mechanism explaining motor deficits observed in vitamin D-deficient rats (see below).

Possible linkages to vitamin D in the brain have not been specifically examined for calmodulin, another important calcium-binding protein in the brain (129), although two studies reported that calcitriol treatment shifted the intracellular distribution of calmodulin (130) and that calmodulin is involved in calcitriol-regulated intracellular calcium homeostasis (131) in chick embryo muscle cells. In the brain, calmodulin is involved in neurotransmitter activity (132), NMDA-induced synaptic plasticity (133), and short-term plasticity (transient alteration of the efficiency of synaptic transmission between neurons) (134). Calcium/calmodulin-dependent protein kinase II (CAM kinase II) is highly concentrated in neurons and is believed to play a central role in a variety of brain functions, including learning and memory; it has been suggested that CAM kinase II is the molecular basis of long-term synaptic memory (135–138).

Other effects of calcitriol on intracellular calcium homeostasis

One mechanism by which calcitriol regulates cellular calcium homeostasis is by down-regulating the expression of voltage-sensitive calcium channel transcripts (139, 140), which has been demonstrated in primary rat hippocampal cells (141). Fluxes in intracellular calcium concentration regulate many essential cellular signaling processes throughout the body, including cell cycle progression, apoptosis, and transcription (142–144). In the brain, neuronal firing depends on intracellular calcium flux, which also appears to play an important role in developmental processes, including neurogenesis, synaptogenesis, myelination, and neurotransmitter release (142, 145–147). In addition, disturbed calcium homeostasis is a characteristic of the neurotoxicity of neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) (76). Effects on L-type voltage-sensitive calcium channels and neuroprotection were observed to occur at the same concentrations of calcitriol treatment (148). Increased L-type voltage-sensitive calcium channel current is associated with neuron aging; treatment of aged rats with calcitriol restored current activity to that seen in younger animals (141).

Neurogenesis is stimulated by calcitriol and some of its target gene products

As discussed in several reviews (14, 149–151), calcitriol acts as a prodifferentiation hormone in many tissues. With reference to the brain, it is of interest that the increase in apoptotic cells and decrease in mitosis in the developing rat brain correlates with the appearance of VDR (64). Chronic treatment with calcitriol or its analogs increased neurite outgrowth (and some other markers of differentiation) in human neuroblastoma cells in some experiments (61, 152), but not others (153, 154), possibly due to the use of different neuroblastoma cell lines (153). In rodents, calcitriol treatment stimulated neurite outgrowth in embryonic hippocampal explant cultures (155) and in a hippocampal progenitor cell line (156).

Some vitamin D target gene products have also been observed to stimulate neurite outgrowth in rodent brain cells *in vitro*. For example, GDNF treatment of embryonic striatal (93) or ventral mesencephalic (91) cells resulted in biochemical and morphological evidence of differentiation. In rodent systems, overexpression of calbindin-D28k resulted in neurite outgrowth of dopaminergic neuronal cells (157) and hippocampal progenitor cells (158).

Adult neurogenesis is a very active area of research (159, 160). Adult stem cells are believed to be located in only two regions of the adult brain. One group of neural stem cells originates in the subventricular region of the forebrain and migrates to the olfactory bulb; the second group originates in the subgranular zone of the hippocampus and differentiates into neural and glial cells in the dentate gyrus (161, 162). In both cases, new neurons are local-circuit interneurons that link motor and sensory neurons (163).

To our knowledge, the possible involvement of calcitriol in adult neurogenesis has not been examined. It is of interest that VDR appear to be essential for the function of at least one type of non-neural stem cell (keratinocyte stem cells) (164). With specific reference to the brain, VDR are widespread in both the olfactory bulb and the dentate gyrus in rodents (65) and were recently observed in the subventricular zone of the neonatal brain (165). Furthermore, an increased density of hippocampal neurons was observed in some rat strains supplemented for 6–12 mo with calcitriol (20 ng/rat, administered subcutaneously 5×/wk) (166). Collectively, this evidence suggests the possibility that calcitriol could stimulate adult neurogenesis.

Morphological and biochemical effects of vitamin D restriction

Some morphological and biochemical changes were observed in the brains of newborn Sprague-Dawley rats whose serum 25OHD3 levels were >90% lower than controls after dams were restricted for dietary vitamin D and UV radiation 6 wk prior to and during pregnancy (167). These changes included a longer cortex and enlarged ventricles, reduced expression of NGF and GDNF, and the low-affinity p75 receptor (83), an increased number of mitotic cells, and a decreased number of apoptotic cells (168). Using the same dietary restriction protocol, at 10 wk of age, enlarged ventricles and reduced expression of nerve growth factor were also observed (169). In an experiment in which 3-wk-old rats were fed a vitamin D-deficient diet for 4 wk, one-half of the animals were also injected i.p. with calcitriol (300 ng/100g b.w.) (170). In the diet-restricted groups not injected with calcitriol, results included decreased phosphorus and increased citrate concentrations in cortical homogenates, increased acetylcholinesterase, glucose-6-phosphate dehydrogenase, and acyl phosphatase activities in cortical synaptosomes, and increased NAD^+-dependent isocitrate dehydrogenase in cortical mitochondria. None of these changes occurred in the diet-restricted groups injected with calcitriol (170). Finally, reduced concentrations of brain calcium (10–24%) were observed in vitamin D diet-restricted rats under conditions that resulted in a 50% reduction in serum calcium (171).

EVIDENCE THAT LINKS VITAMIN D INADEQUACY TO COGNITIVE OR BEHAVIORAL DYSFUNCTION

Humans

A possible linkage of low vitamin D to schizophrenia was hypothesized (172) and reviewed by J. J. McGrath and colleagues (173–175). Evidence includes the association of schizophrenia with winter births, its greater

frequency in dark-skinned migrants to cold climates, and the variation in incidence and prevalence of schizophrenia with latitude (172, 175, 176). It is also noteworthy, as investigators point out (83), that two morphological changes observed in the brains of rats diet-restricted for vitamin D (see above) are enlarged ventricles and a thinner cortex, both of which are consistent with changes consistently observed in the brains of humans with schizophrenia (177). Two small studies directly tested for an association between low $25OHD_3$ and schizophrenia in humans (178, 179). One of these studies (179) retrospectively compared the use of vitamin D supplements during the first year of life with subsequent development of schizophrenia. A significantly reduced risk of developing schizophrenia was observed in males who consumed supplements, but not in females (179). The second study (178) compared $25OHD_3$ concentrations in banked sera from the third trimester of mothers of offspring with schizophrenia and healthy controls, and concluded that results in an African-American subgroup (only 7 individuals) were suggestive of an association, although it was not statistically significant. Another study (180) searched for VDR gene variants in a small (n=100) population of individuals with schizophrenia. Two of 14 African-American patients contained a novel variant compared to none in African-American controls; the result was not significant, but was suggestive (P=0.08). Studies examining VDR polymorphisms (181) and cosegregation of psychosis and rickets phenotypes in an inbred family (182) were also negative.

The initial suggestion that low vitamin D might be linked to depression was based on the higher incidence of seasonal affective disorder (SAD) in winter, when exposure to UV in sunlight is low (183). Currently, the most effective treatment for SAD is treatment with bright light that does not include UV (184). Most current research assumes that SAD is a circadian disorder and that light acts through the eye (185–187), although this has not been proven. One randomized controlled trial (RCT) that specifically tested for the effectiveness of vitamin D2 treatment (10^5 IU, single dose) on SAD patients reported positive results (188). Four other RCTs compared measures of perceived well-being before and after treatment with vitamin D3, with mixed results: positive (1000 IU/day for 6 mo (189), 400–800 IU/day for 5 days (190); negative (800 IU/day for 6 mo (191), 1000 IU/day for 6 mo (192). It is difficult to directly compare these RCTs since patient populations, supplementation protocols, durations, and endpoints differed. A recent small (n=80) cross-sectional study reported an association between lower serum concentrations of $25OHD_3$ and depression in a group with mild symptoms of Alzheimer's disease (AD) compared to normal controls (193), but since neither subjects nor controls were institutionalized, it is difficult to rule out obvious confounders such as less exposure to sunlight in the AD group. Thus, while the seasonal and latitudinal associations of SAD are intriguing observations and are to some extent supported by RCTs, results are mixed.

We also note several additional recent studies in humans: *1*) an interesting report of differences in performance of 563 elderly participants on tests measuring several aspects of cognitive function and depression associated with specific VDR polymorphisms (194); *2*) a higher frequency of a VDR polymorphism in Alzheimer patients (n=104) compared to age-matched controls (195); and *3*) a significant positive correlation (P<0.01) between serum 25OHD3 concentrations and scores on the minimental state examination (MMSE) (a performance test assessing cognitive function) in a retrospective chart review of data obtained on 32 older adults referred to a clinic because of symptoms of dementia; the study did not consider potential confounders, such as the possibility that greater degrees of dementia might result in less sun exposure (196).

Rodents

Motor activity and cognitive or behavioral effects were examined using two experimental systems, both designed to impair ability to utilize vitamin D during brain development. One system utilizes Sprague-Dawley rats made vitamin D deficient using dietary and UV radiation restriction (197–203), resulting in a greater than 90% reduction in serum 25OHD3 concentration in neonates (83). The second system uses mice containing defective VDR that bind calcitriol but cannot bind to DNA (43) (VDR-KO mice) (204–212). VDR-KO mice appear normal in growth rate until after weaning, when they develop a phenotype similar to Type II hereditary rickets in humans (28, 42, 213, 214). The animals usually die by 15 wk of age unless they are fed a special diet (215).

In a series of studies, A. V. Kalueff, who has discussed his work in several recent reviews (38, 68, 84), reported that VDR-KO offspring exhibit a variety of behavioral abnormalities, including aberrant grooming (205, 208, 209) and nest-building activities (206, 210), neglectful or cannibalistic maternal behavior, and submissive social behavior (206). Using the dietary restriction model, an Australian group (J. J. McGrath, D. W. Eyles, A. Mackay Sim, and collaborators) reported several other abnormalities, including hyperlocomotion in the hole-board or open-field tests (199, 201), the absence of latent inhibition in a shuttle-box test (197), and less habituation as measured by head-dipping in the hole-board test (197, 198). On the basis of these results, the Australian group recently suggested that the gestational vitamin D dietary restriction design may be a useful model for studying mechanisms of schizophrenia (198, 201).

Although a detailed critical analysis of all of these studies is beyond the scope of this review, we raise several issues below that suggest that further work is needed to definitively establish that effects observed are

TABLE 2. *Activity and cognitive or behavioral tests of vitamin D-restricted rats or VDR knockout mice*

Test	Investigator-reported results[a]	
	Positive	Negative
Exploratory and activity tests[b]	Open field: *less distance traveled and/or less rearing* (203–205)[c] (216); *greater distance traveled and more rearing* (201)	*Stabilimeter* (216)
	Bedding/nest-building tests: impaired digging activity (204); less paper damage and less accurate nests (206, 210)	*Forced swim test* (199)
	Marble burying test: fewer marbles buried (204)	Y-maze: distance traveled, time spent in each arm, arm entries (204)
	Swimming behavior: more immobility, sinking, rotations (207); reduced ability to float (211)	Actometer (205, 207, 208)
	Light-dark box: less exploration of the light area (205)	Food finding (205, 208)
	Holeboard: *fewer head dips at baseline and less habituation*[d] (197, 198); less distance traveled (205, 208); *more distance traveled* (birth group only)[e] (199, 202); fewer head dips (205)	Object finding (205, 207)
	Rotarod: shorter time on the rotarod (204)	Holeboard: *head dips* (199, 202, 208); *distance* (197, 198); weaning and life groups only (199)[e]
Spatial learning	Radial maze: *more time in the maze* (216)	Horizontal bar test (205)
		Radial maze (197)
		T-maze reversal (216)
		Y-maze (212)
Conditioned learning	Shuttle box: *more avoidance reactions in initial training* (197)	
	Brightness discrimination: *fewer errors after 24 h retention interval* (197)	
Anxiety[f]	*Elevated plus maze* (199); birth group only (205)	*Elevated plus maze* (199, 204, 208) weaning and life groups[e]
	Longer latency to eat novel food (212)	
Developmental measures	Shorter gait (204)	Developmental signs: *self-righting reflex, posture* (203), *SHIRPA screen* (204)
	Vertical screen: shorter retention time (207)	
Other behavioral	Grooming behavior: increased grooming activity (205, 208); abnormal grooming sequence (209)	*Grooming activity* (202, 211)
		Social interaction with nonaggressive mice (199, 206)
	Tail suspension (depression test): *longer* latency to immobility (206)	Two-bottle preference gustatory test (212)
	Social confrontation: more submissive (206)	Buried food pellet olfactory test (212)
	Aberrant maternal behavior: neglect, cannibalism (206)	
	Acoustic startle: *impaired PPI at 10 wk*[g] (200); lower PPI scores at long, but not short, prepulse to pulse interval times (204)	Acoustic startle: *n.s. at 5 wk* (200); *n.s. at 10 wk* (199, 202)

[a]Results obtained using a UV radiation and dietary vitamin D restriction model are in italics, and results obtained using VDR-KO mice are underscored. Note that results that are in italics and underscored were obtained using both systems. [b]Open field, light-dark box, and holeboard tests are usually considered to have an anxiety component, but they also have significant exploratory and activity components, and for those reasons are listed in that section of the table, but cross-referenced in the Anxiety section. [c]O'Loan *et al.* (203) was primarily aimed at examining effects of MK-801 on activity. Examination of Fig. 2 in that article suggests that, among controls not injected with MK-801, the vitamin D-restricted group traveled less distance than nonrestricted animals, though investigators do not discuss this finding. [d]Investigators reported that the vitamin D-restricted group demonstrated less habituation than controls because head-dipping decreased over time in controls, but remained relatively constant in the test group. We note that, in both experiments (197, 198), the restricted group had fewer head dips than controls at all time points examined, which could suggest a more complex interpretation. [e]Groups in this study were birth group, deprived of dietary vitamin D from prior to gestation to birth; weaning group, deprived of vitamin D prior to gestation through PND21; and life group, deprived of vitamin D from prior to gestation to PND70. [f]See also results for the holeboard, open field, and light-dark box tests in the Exploratory and Activity Tests section above. [g]Positive result only in the life group; other groups were negative.

independently reproducible and that they are directly related to brain development. Results reported for all of the activity or behavioral endpoints examined using both models are summarized in **Table 2**. Experiments using the dietary restriction and VDR-KO models cannot, strictly speaking, be directly compared because of obvious species and protocol differences. However, since both models severely limit the ability of the organism to utilize vitamin D during brain development, it is useful to consider whether similar performance endpoints are affected. Therefore, Table 2 is organized by type of test rather than experimental system. For clarity, experiments using the dietary restriction model are in italics, and those using VDR-KO

mice are underscored. Several observations are apparent from an examination of Table 2.

First, some results appear to have been inconsistently observed. *1*) Hyperlocomotion, measured as "distance traveled" in holeboard or open-field tests, was inconsistently observed using the gestational dietary restriction protocol, as also noted by investigators (202). Specifically, greater distance traveled was reported in several studies (199, 201, 202) but not observed in other studies from the same laboratory using the same gestational dietary restriction protocol (197, 198). Furthermore, less distance traveled was observed in an older dietary restriction study involving adult rats (216), and no differences were observed if the period of dietary restriction was extended beyond birth (199). Using VDR-KO mice, less distance traveled was observed in all three experiments from both laboratories that examined this endpoint (204, 205, 208). *2*) Several reports of altered grooming activity in VDR-KO mice from the Kalueff group (205, 208, 209) are in apparent contrast to reports of normal grooming activity from the Australian group using the same VDR-KO mutant (204, 211). The two experiments were not identical, and the different results could be due to a variety of factors, including the somewhat larger group sizes in the positive study; its use of only males (*vs.* mixed sex groups), animals with an isogenic (*vs.* mixed) genetic background, and use of different dietary methods to rescue VDR-KO offspring. *3*) Other differences in results obtained using the dietary restriction and VDR-KO systems are also evident in Table 2. These differences could be due to many factors, including differential effects in the two models on ability to utilize vitamin D, differences between rats and mice, or other methodological differences. However, since all protocols (with one exception (216)) should have resulted in vitamin D inadequacy during development, the lack of consistency makes it difficult to conclude there is a clear effect on these endpoints.

Second, only a few tests were specifically targeted at learning. Results in several spatial learning tests were predominantly negative (197, 212, 216). A brightness discrimination test suggested that vitamin D-restricted animals performed *better* than controls in a relearning task (197), and a test for latent inhibition in a shuttle box test was positive (197).

Third, potential confounders were not, in general, assessed in the studies reviewed. For example, VDR-KO offspring appear normal in growth rate and behavior until after weaning, when they develop a phenotype similar to Type II hereditary rickets in humans (28, 42, 213, 214). The animals usually die by 15 wk of age unless they are fed a special diet supplemented with calcium, phosphorus, and lactose (215). In studies from A.V. Kalueff and colleagues, this antirachitic diet was used (*e.g.*, ref. 207); in studies from J. J. McGrath, D. W. Eyles, A. Mackay-Sim, and colleagues, a normal diet supplemented with calcium was used (*e.g.*, ref. 204). Since virtually all performance tests required movement and since it is not clear to what degree these diets attenuated the rachitic phenotype, conclusions of effects on brain function based on tests requiring movement must be considered uncertain, as has been pointed out (211). In addition, the VDR-KO phenotype is characterized by alopecia, which, in the absence of information on effects of nonvitamin D related alopecia on grooming, must be considered a potential confounder.

ARE CAUSAL CRITERIA SATISFIED?

We have previously used five causal criteria (slightly adapted from the original formulation; ref. 217) to evaluate the strength of evidence linking the availability of a micronutrient to cognitive or behavioral function (2–4). These criteria are: *1*) a plausible biological rationale, *2*) a consistent association, *3*) specificity of cause and effect, *4*) a dose-response relationship (*i.e.*, demonstrating that the intensity of effect depends on the degree of deficiency or supplementation), and *5*) ability to experimentally manipulate the effect (*e.g.*, reversibility of effects).

On the basis of the experiments reviewed above, the criterion most convincingly satisfied is a *plausible biological rationale.* Evidence includes the widespread presence of VDR and 1,α-hydroxylase (the terminal rate-limiting enzyme in the synthesis of calcitriol) in the developing and adult brain, and the known involvement of some calcitriol target gene products (*e.g.*, the neurotrophins NGF, NT-3, and NT4/5; GDNF; and the calcium-binding proteins calbindin-D28k, parvalbumin, calretinin, and possibly calmodulin) and calcitriol-regulated processes (*i.e.*, L-type voltage-gated calcium channels) in critical functions required for cognition and behavior.

Among the studies that examined possible *associations* between vitamin D inadequacy or treatment and cognitive or behavioral performance in humans or rodents, some evidence of association is provided, but, as discussed above, effects are subtle and some results have not yet been replicated, suggesting more work is needed (see Discussion and Conclusions). *Specificities of cause and effect* pertain to potential confounding in experiments that measure disease or performance outcomes, which has not been sufficiently accounted for in the studies reviewed. For example, as investigators point out, the consistent associations of schizophrenia or SAD with winter or northern latitude could obviously be due to many factors other than to lower serum concentrations of $25OHD_3$. And, altered motor activity of VDR-KO mice, or rats whose dams were subjected to dietary and UV radiation restriction during pregnancy, could be due to effects of vitamin D inadequacy on bone and muscle development (218) rather than to effects in the brain. The evidence base is not yet extensive enough to permit a discussion of the other two causal criteria.

PROINFLAMMATORY CYTOKINE-INDUCED COGNITIVE/BEHAVIORAL DYSFUNCTION: COULD LOW 25OHD3 STATUS BE AN EXACERBATING FACTOR?

As discussed in many reviews, a significant body of evidence suggests that elevated levels of proinflammatory cytokines in the brain can play a causal role in depression (219–234). Cytokines are small proteins synthesized by cells directly involved in immune function, such as macrophages and their counterparts in the brain, microglia, and also by many other nucleated cells in the body. Among a range of functions (*e.g.*, ref. 235), cytokines play a key role in the inflammatory process (236). There are many cytokines; at least 30 interleukins (IL-1, IL-2, etc), and others such as TNF-α, TGF-β, and the interferons (*e.g.*, IFN-γ). Most cytokines can be classified as either proinflammatory or antiinflammatory.

Evidence from a variety of systems supports the proinflammatory cytokine theory of depression, first proposed some 25 years ago (237). In humans, support is provided from studies of clinical depression, sickness behavior resulting from infection, illnesses accompanied by inflammation (*e.g.*, autoimmune diseases, heart disease, osteoporosis), chemotherapy, or experimental treatments with endotoxin. Supporting studies in animals involve treatment with proinflammatory cytokines or use of rodent models of human inflammatory diseases (*e.g.*, experimental immune encephalitis, a model of MS, or the streptozotocin model of type 1 diabetes).

Primary evidence (see reviews cited above for specific references) includes *1*) associations or correlations between the severity of depression and increased concentrations of inflammatory markers; *2*) several plausible mechanisms based on observations that proinflammatory cytokines alter neurotransmitters, neuropeptides, and the HPA axis, which are also altered in depression; *3*) evidence that depression is induced in patients with cancer or infectious diseases by cytokine therapy with IFN-α, which induces other proinflammatory cytokines; *4*) evidence that psychological stress, known to be strongly associated with depression, induces proinflammatory cytokines; *5*) evidence that antidepressants and some other treatments for depression are anti-inflammatory; *6*) controlled experiments in humans treated with endotoxin that demonstrate cognitive/behavioral effects; and *7*) experiments in rodents demonstrating that cognitive dysfunction or depressive-like behavior can be elicited by treatment with proinflammatory cytokines such as IL-1β and prevented by antagonists (*e.g.*, refs. 238–241).

Calcitriol's complex, and still incompletely understood, interactions with the immune system have been discussed in many expert reviews (*e.g.*, refs. 31, 36, 242–244). Discussion of these interactions is beyond the scope of this review. However, important elements in calcitriol's spectrum of function appear to be the modulation of enhanced cellular immune response pathways (Th1) or autoimmune (loss of tolerance) responses. Thus, calcitriol appears to participate in regulating Th1:Th2 balance by down-regulating the Th1 pathway, promoting the Th2 pathway, and promoting tolerance by enhancing the production of T regulatory cells. These regulatory shifts are accomplished in part by decreasing the production of proinflammatory cytokines and increasing the production of antiinflammatory cytokines.

There is considerable direct evidence for a modulatory effect of calcitriol treatment on proinflammatory cytokines both *in vitro* and *in vivo*. A few examples are listed: *1*) decreased production of proinflammatory cytokines (or increased production of anti-inflammatory cytokines) in a variety of cell types; examples include monocytes (245–247), microglia (an important source of proinflammatory cytokines in the brain) (248), keratinocytes (249, 250), endothelial cells (251), and human benign prostatic hyperplastic cells (252); *2*) decreased serum concentrations of the proinflammatory cytokine TNF-α and increased concentrations of the antiinflammatory cytokine IL-10 in a recent randomized controlled trial (RCT) involving vitamin D3 supplementation of congestive heart failure patients (253); *3*) decreased TNF-α levels and suppressed disease symptoms in a rodent model of inflammatory bowel disease (IBD) after treatment with calcitriol and calcium (254); *4*) higher levels of proinflammatory cytokines in VDR-KO mice, which are more susceptible to induced IBD (255); and *5*) an inverse correlation of 25OHD3 status with inflammation markers in a study of 171 healthy adults (256) and a positive correlation with IL-10 (an antiinflammatory cytokine) concentrations in cord blood (257).

The down-regulation by calcitriol of NF-κB, a central mediator of inflammation, (see reviews cited above) (258) is also consistent with calcitriol's modulatory effect on proinflammatory states. NF-κB is induced in the brain following treatment with the proinflammatory cytokine IL-1 and is believed to mediate its adverse behavioral effects (259). Increased concentrations of NF-κB are also linked to increased stress in humans (260) and to stress-induced neuronal cell loss in rodents (261).

While cytokine signals from the periphery can be transmitted to the brain *via* the circumventricular organs or vagal afferents (262, 263), a key question is whether calcitriol can also directly modulate proinflammatory cytokine production in the brain. Calcitriol is known to be synthesized by microglial cells (264), which are the primary mediators of proinflammatory immune responses in the brain (265–267). Calcitriol has been observed to inhibit the synthesis of proinflammatory cytokines in a microglial cell line (248). In addition, oral treatment with 25OHD3 reduced IL-1β production in the rat hippocampus (268).

The possible relationship of low 25OHD3 status to disease-associated depression has, so far as we are aware, only been examined in one small study of anxiety and depression in fibromyalgia patients (269), which observed a significant relationship. It is well known that poor 25OHD3 status is common in many

human diseases associated with inflammation, including infection, autoimmune diseases, obesity and metabolic syndrome, type 2 diabetes, osteoporosis, cancer, and cardiovascular diseases (33, 35, 41, 193, 269–293). Depression is not uncommon in these diseases, which is the subject of a very large experimental literature; a few recent examples are cited: multiple sclerosis (294–297), type 1 diabetes (298–301), rheumatoid arthritis (221, 302), lupus erythrematosus (303, 304), inflammatory bowel disease (IBD) (305–308), obesity and metabolic syndrome (309–311), type 2 diabetes (312–314), osteoporosis (315–317), cancer (318, 319), cardiovascular disease (320), infection (321), and fibromyalgia (269, 322). In this literature, the possible involvement vitamin D has not been discussed, so far as we are aware.

DISCUSSION

The primary goal of this review is to provide an overview of evidence relevant as to whether vitamin D availability affects cognition or behavior. As summarized in the body of the review, evidence that calcitriol is involved in both brain development and function is strong, on the basis of studies involving biochemical or other biological endpoints, as also reviewed by others (30, 37–39). Evidence from studies directly measuring cognitive or behavioral endpoints is suggestive, but less clear-cut, as summarized in **Fig. 1**. As we discuss, a number of studies in humans and rodents that directly examined effects of vitamin D inadequacy or supplementation on cognitive or behavioral performance individually suggest subtle cognitive and/or behavioral changes (179, 188–190, 193, 194, 196–199, 201–212, 216). However, examination of these latter studies as a group using several causal criteria suggests that the evidence base does not yet appear to be sufficient to conclude with certainty that there is a causal connection.

The inconclusiveness of the human studies is not particularly surprising, given their small number and the many difficulties involved in conducting human trials. However, it is curious that results of rodent studies are not stronger and more consistent, since rodents afford the opportunity for more flexibility in design and ability to control experimental variables than can be achieved in human studies. If calcitriol plays an important role in brain development and function, one might have predicted that performance deficits would be more obvious, particularly in the studies using a severe dietary restriction model or VDR-KO mice (see Table 2 and text).

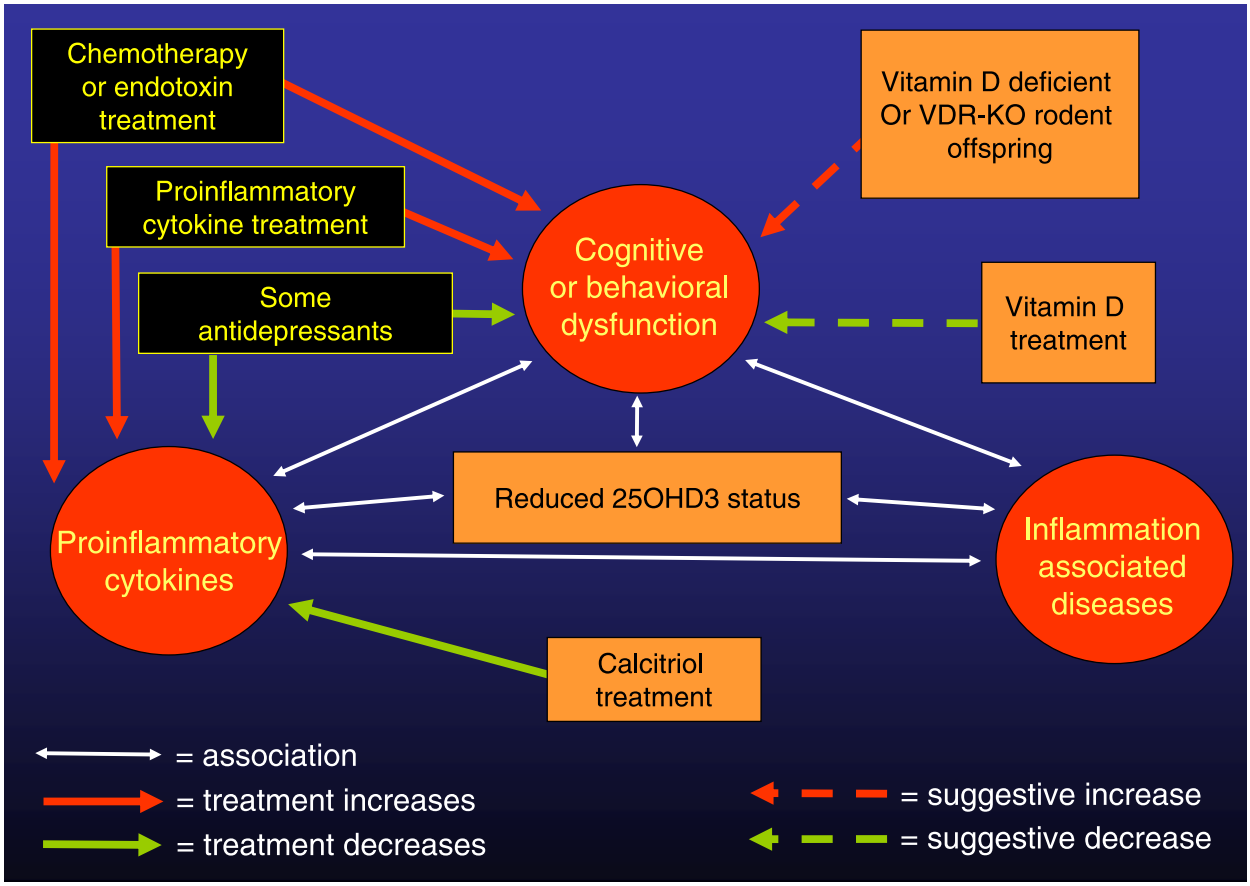

Figure 1. Vitamin D, proinflammatory cytokines, and cognitive or behavioral dysfunction. Types of evidence from human or rodent studies that link cognitive and behavioral performance to vitamin D adequacy, proinflammatory cytokine status, and inflammation-associated diseases. See text for discussion and citations.

Several observations suggest that additional research may help to explain this apparent paradox. First, a relatively small number of cognitive/behavioral tests have been conducted. If individual neural systems are affected by vitamin D inadequacy, tests specifically targeted at those systems may be required to achieve sufficient sensitivity to detect an effect (323, 324). Second, it is possible, given the importance of vitamin D in so many aspects of mammalian biology, that there are homeostatic and/or back-up mechanisms that protect vital organs, such as the brain, from loss of calcitriol-regulated functions. This may be particularly true in rodents, who are covered with fur and primarily nocturnal. In this regard, the recent observation that lithocholic acid can substitute for vitamin D under deficiency conditions in rodents is potentially relevant (53). Third, effects observed in all *in vivo* rodent studies that demonstrated effects of calcitriol treatment on gene expression in the brain used relatively high doses of calcitriol (69, 73, 76, 77, 107, 111); some of these studies injected calcitriol directly into the brain (69, 76, 77). The only study that used vitamin D_3 instead of calcitriol (111) treated animals by gastric cannulation with 20,000 IU/kg/day for 4 mo. It is possible that effects resulting from these high-dose treatments do not occur under physiological conditions. However, calcitriol is believed to exert its effects in an autocrine or paracrine manner, even within tiny "nanodomains" within the cell (23, 25). Hence, the classical concept of "concentration" may not apply, and very high concentrations of calcitriol may be delivered subcellularly under normal physiological conditions. Fourth, there are very few studies that examined effects of vitamin D deficiency on gene expression (21, 82). And, we are also not aware of any studies in rodents that examined effects of calcitriol treatment on cognitive or behavioral performance. These experiments seem important to do. And fifth, with respect to use of VDR-KO strains, some critical vitamin D-regulated functions during fetal and neonatal brain development could involve non-VDR-mediated mechanisms (22). Also, other VDR knockout strains are available (28, 213), as are 1,α-hydroxylase-knockout strains (325–327), which might be productive to explore as alternative models.

Additional suggested areas for research

The independent associations of inflammation, low 25OHD3 status, and cognitive or behavioral dysfunction in a number of human diseases are intriguing. To our knowledge, a possible relationship between 25OHD3 status and disease-associated depression has only been addressed experimentally in one small study of fibromyalgia patients, with encouraging results (269). We also note that the broad spectrum of calcitriol's functions (*e.g.*, effects on cell proliferation and differentiation) have suggested the use of calcitriol and its analogues to treat cancer and autoimmune diseases (currently the only therapeutically recommended use of calcitriol is for treatment of psoriasis) (328, 329). Some analogues, as well as calcitriol, are effective in treating a variety of cancers and autoimmune diseases in model systems (*e.g.*, refs. 254, 330–332). It would be of interest to include cognitive and behavioral endpoints, in addition to primary disease endpoints, in future human trials and rodent studies using disease models.

Rickets is the only human disease that is known to be caused by vitamin D deficiency during early postnatal life, a critical period of brain development (218). To our knowledge, no studies have examined cognitive or behavioral function in children with rickets. We have also been unable to locate any studies that have measured inflammatory markers in children with rickets. While overt symptoms of mental dysfunction in rickets patients would most likely have been noticed, cognitive or behavioral deficits resulting from nutritional inadequacies are frequently subtle and require focused testing to detect (*e.g.*, refs. 2, 4).

Public health issues

Vitamin D inadequacy is largely based on whether circulating concentrations of 25OHD3 are below certain cutoff levels (14). There is a great deal of discussion and uncertainty as to what cutoff levels should be used (35, 333–336). For example, in surveys of >18,000 individuals in the United States (337) and >7000 individuals in the United Kingdom (338), inadequacy was calculated using several different 25OHD3 cutoff values, resulting in prevalence estimates ranging from 3 to 57% (337) or 15.5 to 87.1% (338) for adult men and women. Prevalence estimates are much higher for some other groups, including the elderly (337, 339) and African-Americans, who are 2–8 times more likely to be insufficient compared to age-matched Caucasians (340–342). The lower end of the prevalence estimate ranges indicate minimum 25OHD3 concentrations required to prevent rickets (14). The higher end of the ranges reflect opinions of a number of experts based on recent data concerning 25OHD3 concentrations required to decrease fracture risk or to prevent or mitigate certain forms of cancer (41, 335, 343), as well as evidence suggesting that vitamin D can be tolerated at higher levels than formerly thought (35, 334–336). It has been suggested that research to determine what concentrations of 25OHD3 are required to optimize these and other functions of calcitriol should be a high priority (*e.g.*, refs. 41, 270, 334).

The involvement of calcitriol in brain function only serves to underline the importance of ensuring an adequate supply of vitamin D, as has been pointed out (*e.g.*, refs. 38, 82). It remains to be seen to what degree evidence for this involvement can be translated into quantitative information relevant to setting adequacy requirements. Clearly relevant, if they can be more consistently replicated, are studies suggesting that depression may be linked to lower concen-

trations of 25OHD3 (183, 188–190, 193, 196, 269). However, in our opinion, it is uncertain whether cognitive/behavioral endpoints, which are inherently difficult to quantify and are often nonspecific (323), are amenable to the level of precision required to optimize 25OHD3 concentrations. Other more readily quantifiable markers of altered brain function would be highly desirable.

CONCLUSIONS

While mechanistic and biological evidence strongly suggests that calcitriol is involved in brain development and critical brain functions, it has proved more difficult experimentally to demonstrate obvious effects of vitamin D inadequacy on cognitive or behavioral endpoints. Although there is some limited evidence for a relationship between vitamin D inadequacy and depression, or possibly schizophrenia, studies are relatively few in number and results are mixed. The evidence base in rodents is larger, with two laboratories providing intriguing and clearly suggestive, though in our opinion not definitive, evidence of subtle behavioral effects of vitamin D inadequacy. Despite residual uncertainty, we believe the evidence overall suggests that supplementation to ensure adequacy is prudent, particularly for groups whose 25OHD3 status is exceptionally low, including nursing infants, the elderly, and African-Americans. Such supplementation is already recommended to protect against rickets, fracture risk, and possibly some forms of cancer. FJ

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