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REVIEW

Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia)

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Berridge MJ. Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia). *Am J Physiol Cell Physiol* 314: C135–C151, 2018. First published October 25, 2017; doi:10.1152/ajpcell.00188.2017.—The process of development depends on a number of signaling systems that regulates the progressive sequence of developmental events. Infertility and neurodevelopmental diseases, such as attention deficit hyperactivity disorder, autism spectrum disorders, and schizophrenia, are caused by specific alterations in these signaling processes. Calcium signaling plays a prominent role throughout development beginning at fertilization and continuing through early development, implantation, and organ differentiation such as heart and brain development. Vitamin D plays a major role in regulating these signaling processes that control development. There is an increase in infertility and an onset of neurodevelopmental diseases when vitamin D is deficient. The way in which vitamin D deficiency acts to alter development is a major feature of this review. One of the primary functions of vitamin D is to maintain the phenotypic stability of both the Ca^{2+} and redox signaling pathways that play such a key role throughout development.

attention deficit hyperactivity disorder; autism; schizophrenia

INTRODUCTION

A progressive sequence of events, which are carefully orchestrated by a number of signaling systems, controls the process of development. Infertility and neurodevelopmental diseases such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and schizophrenia, are caused by specific alterations in these signaling events. The calcium (Ca^{2+}) signaling pathway plays a prominent role throughout development beginning at fertilization and continuing through early development, implantation, and organ differentiation such as heart and brain development. Vitamin D deficiency can interfere with these developmental processes, leading to infertility and the onset of the neurodevelopmental diseases (321). The aim of this review is to describe why vitamin D deficiency has such a serious effect on development. The main conclusion is that one of the primary functions of vitamin D is to maintain the phenotypic stability of both the Ca^{2+} and redox signaling pathways that play such a key role throughout development.

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PHENOTYPIC STABILITY HYPOTHESIS OF VITAMIN D ACTION

During development, each cell type has a differentiation program that selects out those genes responsible for its particular function. This differentiation program also determines that each cell type expresses the signaling system that is appropriate for its particular function. It is essential that the transcription of those components that make up the signaling phenotype of each specific cell type be maintained. There are a large number of vitamin D-sensitive target genes that are regulated by vitamin D binding to the vitamin D receptor (VDR), which interacts with the retinoid X receptor before binding to the vitamin D response element (Fig. 1). The action of vitamin D is markedly enhanced by its ability to control the expression of Nrf2 (224) and the anti-aging protein Klotho (102), which are also important regulators of multiple cellular signaling systems that occur in all cells. Many of the genes that are controlled by the vitamin D/Klotho/Nrf2 regulatory network function to maintain both Ca^{2+} and redox homeostasis (252). For example, vitamin D increases the expression of Ca^{2+} pumps, exchangers, and buffers. It also acts to reduce the expression of the L-type Ca^{2+} channel to maintain low levels of Ca^{2+} (47, 48). Similarly, vitamin D together with Klotho and Nrf2 increase cellular antioxidants to maintain the normal reducing environment within the cell thereby preventing oxidative stress by removing reactive oxygen species (ROS). For example, the expression of the γ-glutamyl transpeptidase (γ-GT), glutamate

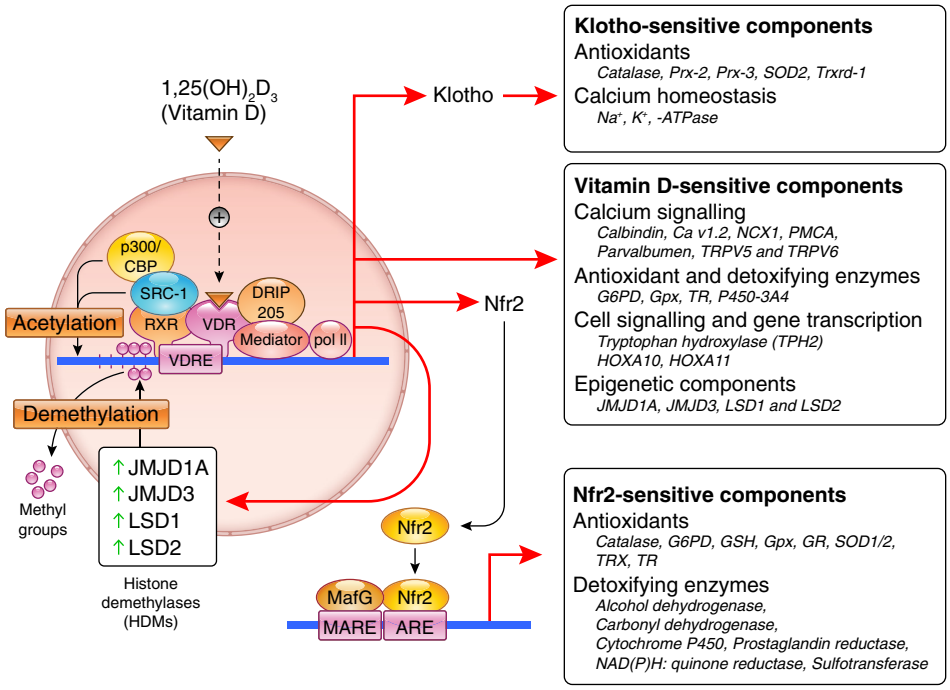

Fig. 1. When vitamin D (1,25-dihydroxyvitamin D_3 [1α,25(OH)2D_3]) binds to the vitamin D receptor (VDR) it then interacts with the retinoid X receptor (RXR) and this complex binds to the vitamin D response element (VDRE) that begins to induce the expression of a number of different genes. Many of these genes act to control many different cellular control mechanisms. In addition, vitamin D controls the expression of both Nrf2 and Klotho that contribute to many of the vitamin D homeostatic functions. [Figure reproduced from Figure 2 in Berridge (28) with permission from Elsevier.]

cysteine ligase, and glutathione reductase, which contribute to the synthesis of the major cellular redox buffer glutathione (GSH), is regulated by vitamin D. Vitamin D also increases the activity of glucose-6-phosphate dehydrogenase (G6PD) to increase the formation of GSH. It downregulates the NADPH oxidase that generates ROS while upregulating the superoxide dismutase that rapidly converts $O_2^{-\cdot}$ to H_2O_2. Vitamin D also upregulates expression of the glutathione peroxidase that drives the conversion of H_2O_2 to water.

It turns out that vitamin D working together with Nrf2 and Klotho plays an essential role in maintaining the phenotypic stability of many of these cell signaling pathways and particularly the Ca^{2+} and redox signaling systems (27, 28). In conclusion, the vitamin D/Klotho/Nrf2 trio are the major custodians of such phenotypic stability and this may explain why a deficiency in vitamin D seems to affect so many of the processes that occur during development and could explain the problem of infertility and the onset of the neurodevelopmental diseases such as ADHD, autism, and schizophrenia.

To maintain the gene transcription necessary for phenotypic stability, vitamin D also controls the epigenetic landscape of its multiple gene promoters (136) (Fig. 1). Both the acetylation and methylation states of its promotor regions are maintained by vitamin D. With regard to acetylation, the VDR complex recruits histone acetylases such as p300/CBP and SRC-1. Perhaps its most significant action is to increase the expression of a number of DNA demethylases. Control of demethylation is critical because many of the genes regulated by vitamin D are silenced by methylation of the CpG islands located in their promotor regions. Such hypermethylation can account for a decline in the expression of klotho that occurs during aging (151). Such age-dependent hypermethylation is also evident in many diseases (cancer, cardiovascular and neurodegenerative diseases) (310). The phenotypic remodeling that causes schizophrenia and bipolar disorder may be caused by hypermethylation of the GABAergic neurons (122). This hypermethylation that occurs through vitamin D deficiency can be explained by the fact that vitamin D acts to control the epigenetic landscape by inducing the expression of a number of key DNA demethylases [e.g., Jumonji C domain-containing demethylases 1A (JMJD1A), JMJD3, lysine-specific demethylase 1 (LSD1), and LSD2 (247)] (Fig. 1).

There is now considerable evidence to show that the epigenetic landscape is of critical importance during neural development and function (60, 228, 276). For example, a deficiency in the epigenetic factor euchromatin histone methyltransferase 1 results in an alteration in brain wiring during development (188). The ability of vitamin D to modulate the epigenetic landscape may thus maintain the processes of development through its ability to control phenotypic stability so that the right genes are activated to control each phase of development. Such a view is supported by the fact that the most important signaling pathways that are maintained by vitamin D are the Ca^{2+} and redox signaling pathways, both of which feature significantly particularly during the sequential events that occur during development as described in the following sections.

VITAMIN D DEFICIENCY AND INFERTILITY

There is increasing evidence that vitamin D plays an important role in regulating both male and female fertility (6, 41, 75, 119, 120, 136, 166, 167, 169, 170, 183, 219, 222, 241, 282, 285, 297, 300, 331). The vitamin D status can influence reproductive processes throughout development. For example, it influences gametogenesis, fertilization, the preimplantation phase, and the final phases of organ development (103). It also

plays a role in promoting the function of the endometrium during implantation (311). Low vitamin D levels have been linked to preeclampsia, pregnancy loss (137), and infants who are small for gestational age (109). Preeclampsia, which is characterized by hypertension and proteinuria, occurs in up to 8% of all first-time pregnant women. There is evidence that the onset of preeclampsia may be linked to vitamin D deficiency (2, 138, 207, 295, 296). Vitamin D continues to influence some of the later developmental events in that it regulates the expression of the Homeobox (*Hox*) genes that control body axis programming during embryogenesis (76). It continues to operate at birth in that it has been shown that women with low vitamin D levels are more likely to have caesarean sections, which may be caused by muscle weakness resulting from vitamin D deficiency (202). Vitamin D deficiency can also result in miscarriage, which is also known as spontaneous pregnancy loss (335).

In individuals with vitamin D deficiency, there is a marked reduction in pregnancy rates (1, 18, 64, 75, 134, 219, 241, 256, 265, 266, 323). Low fertility rates have also been attributed to low vitamin D levels in the serum of males (297). There was a large decrease in fertility when female rats were inseminated by sperm taken from males that were deficient in vitamin D (158). A deficiency in vitamin D has also been linked to the infertility that is associated with polycystic ovary syndrome (140, 166, 222, 226, 282). Vitamin D may also contribute to various pregnancy-related disorders such as preeclampsia and gestational and diabetes mellitus and endometriosis (130, 149, 166, 282, 296, 299, 309). The ability of vitamin D to prevent endometriosis may depend on its ability to prevent inflammation (222). Vitamin D deficiency may also be responsible for early-onset neonatal sepsis in term infants (58).There is evidence that vitamin D deficiency reduces the chances of success when undergoing assisted reproductive technology (239, 240, 282).

THE ROLE OF CALCIUM AND VITAMIN D IN EARLY DEVELOPMENT

Both egg activation and early embryo development is a carefully regulated sequential process that is orchestrated by many different signaling systems. The Ca^{2+} signaling system plays a significant role during many of the processes that occur during development such as fertilization, implantation, and organ development (55, 205, 322, 325). While the embryo is undergoing its early preimplantation phases of development, it participates in a synchronized interaction with the endometrium. For example, the proinflammatory cytokine interleukin-1β (IL-1β) is synthesized by the embryo and acts on the endometrium (175) to induce the expression of the 1α-hydroxylase (1α-OHase) that catalyzes the active form of vitamin D. In a reciprocal way, the uterus produces lysophosphatidic acid (LPA), which regulates the development of the embryo. Just before implantation, the uterus releases calcitonin, which promotes implantation by inducing the embryo to express fibronectin. These interactions ensure that both the embryo and the endometrium are prepared to carry out the complex process of implantation leading on to the formation of the placenta. Many of these processes are regulated by the Ca^{2+} signaling system that plays a prominent role throughout development beginning at gamete formation and continuing through fertilization, cleavage, compaction, cavitation, implantation placenta formation, and organ development (11, 16, 89, 205, 322, 325).

Gamete Formation

One of the actions of vitamin D is to induce the expression of Anti-Müllerian hormone (AMH), which is generated in both the Sertoli cells in the testes and the granulosa cells in the ovaries (79). AMH acts as a paracrine factor to control testicular function in males and fertility in females. The level of AMH is an important predictive marker for the success of in vitro fertilization (IVF) treatment (161).

The quality of spermatozoa is strongly dependent on vitamin D (41). Following ejaculation, the spermatozoa undergo a number of modifications called capacitation including an increase in motility that are driven by Ca^{2+} signals (331). Before sperm can fertilize the oocyte, they have to become hyperactive to enable them both to pass through the mucous layer within the oviduct and to penetrate the zona pellucida to react with the oocyte plasma membrane (8, 290). This hyperactivity is driven by an increase in Ca^{2+} derived from both external and internal sources. Some of the Ca^{2+} enters through the plasma membrane via the TRPV5 channel (291), which is known to be regulated by vitamin D (252). Vitamin D is also responsible for maintaining the extracellular level of Ca^{2+} (291). In addition, Ca^{2+} is also released by inositol 1,4,5-trisphosphate ($InsP_3$) receptors ($InsP_3Rs$) located in the redundant nuclear envelope that surrounds the sperm axoneme (132, 133). Vitamin D is responsible for maintaining sperm motility (Fig. 2) (37). This hyperactive state is triggered by vitamin D acting through a nongenomic mechanism to activate the formation of the $InsP_3$ responsible for the release of Ca^{2+} (35, 36). It has been suggested that these effects of vitamin D may act to select out the best spermatozoa for fertilization (42).

Fertilization

The developmental program begins when the sperm fuses with the egg to introduce phospholipase Cζ (PLCζ), which then diffuses through the cytoplasm where it hydrolyzes the phosphatidylinositol 4,5-bisphosphate ($PtdIns4,5P_2$) located in intracellular membranes to release the second messenger $InsP_3$ (Fig. 2) (152, 184, 230, 277, 292–294). The $InsP_3$ is then responsible for setting up the Ca^{2+} oscillations that initiate the developmental program (Fig. 2) (74, 210, 211, 325, 334). The importance of PLCζ in the process of fertilization is supported by the observation that a mutation of PLCζ has been linked to male infertility (232). The activity of the $InsP_3Rs$, which are responsible for setting up the Ca^{2+} oscillations, is regulated by M-phase kinases such as Cdk1 and ERK (334). This regular pulsing of Ca^{2+} continues for several hours and ends when the pronucleus is formed. During the course of these oscillations, a number of Ca^{2+} homeostasis mechanisms operate to maintain the persistent pulses of Ca^{2+} that occur during fertilization (318). Oscillations are maintained by Ca^{2+} entry across the plasma membrane that refills the stores after each transient. This entry may depend on the store-operated Ca^{2+} entry system that uses STIM1 located in the endoplasmic reticulum (ER) that senses depletion of the store and activates the Orai1 channel in the plasma membrane to activate Ca^{2+} entry. This regular pulsing of Ca^{2+}, which occurs during fertilization,

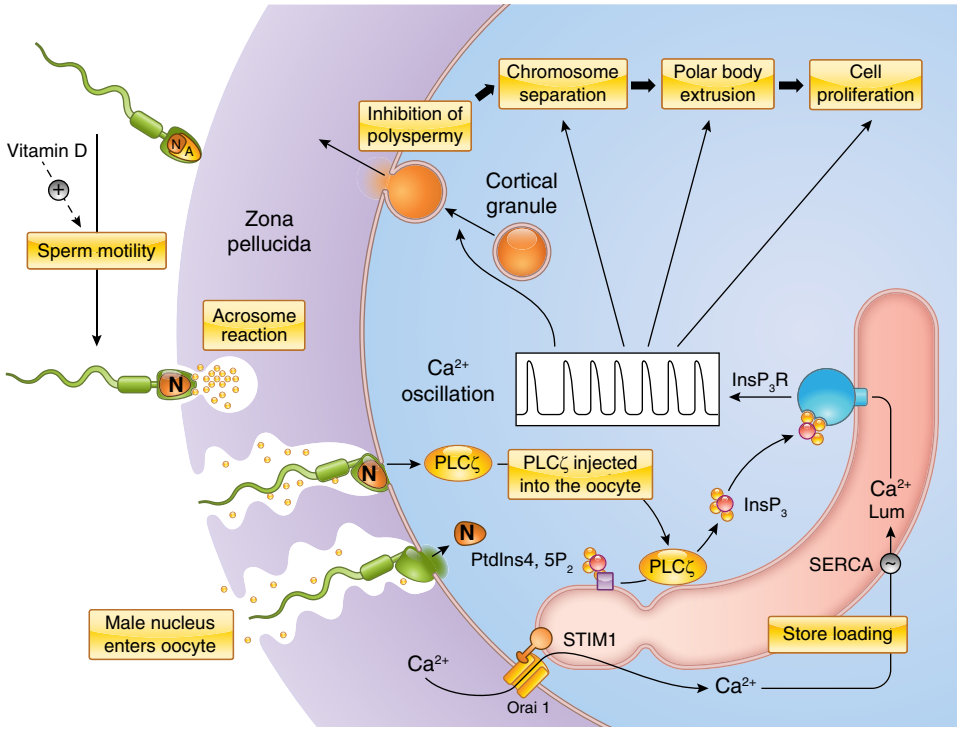

Fig. 2. The role of Ca^{2+} signaling in fertilization. Vitamin D plays an important role in maintaining sperm motility that enables the sperm to approach the oocyte to initiate fertilization. When the sperm head fuses with the oocyte, it injects phospholipase Cζ (PLCζ) that begins to hydrolyze phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P_2) to release inositol 1,4,5-trisphosphate ($InsP_3$) that then acts on the $InsP_3$ receptors ($InsP_3$Rs) to release pulses of Ca^{2+} that generate a Ca^{2+} oscillation that is responsible for activating the sequence of events that initiate the developmental process.

drives egg activation responsible for orchestrating the early events of development such as the release of cortical granules that prevents polyspermy by altering the zona pellucida, activation of the cell cycle to complete meiosis, induction of the gene transcription responsible for the embryonic genome activation that initiates the early developmental program that ends with the first cleavage (Fig. 2) (11, 231, 277, 292).

A significant aspect of how the Ca^{2+} oscillation drives these early development events is the observation that the onset of these sequential events is tightly related to the number of oscillations (85). For example, the exocytosis of the cortical granules occurs after two transients, the resumption of the cell cycle occurs after four transients, polar body extrusion requires eight transients and twenty-four transients are required for pronuclear formation (Fig. 2). In effect, the prolonged oscillation functions as a molecular clock to ensure the sequential activation of each developmental event (86).

One way in which vitamin D deficiency might induce infertility is by altering the properties of this Ca^{2+} oscillation that orchestrates the precise onset of all these developmental events. The phenotypic stability hypothesis discussed earlier suggest that the main function of vitamin D is to maintain low resting levels of both the Ca^{2+} and the ROS signaling pathways (27, 28). When vitamin D levels are low, both signaling systems become more active and this could markedly increase the frequency of the Ca^{2+} oscillations and could seriously interfere with the orderly progression of these early developmental events.

The subsequent events in embryogenesis such as cleavage, compaction, cavitation, and implantation are also regulated by Ca^{2+} as described below (11, 16).

Cleavage

The next step in development after fertilization is a sequence of cleavage events whereby the zygote divides to form blastomeres that aggregate together surrounded by the zona pellucida. Autocrine factors such as platelet-activating factor (PAF) released by the zygote (236, 237) and lysophosphatidic acid (LPA) released from the uterus function to maintain survival and drive further development and cell cleavage by generating periodic pulses of Ca^{2+} (181). These Ca^{2+} pulses, which are mediated by PAF and LPA, then activate the formation of $InsP_3$ that releases Ca^{2+} from the ER (11, 90, 286, 287).

At the 8 cell stage, the blastomeres begin to form gap junctions that enables them to coordinate the subsequent developmental events. After the next round of mitoses, the 16 cells called the morula begin to bind firmly to each other through a process known as compaction, which is the next stage of the developmental process.

Compaction

When the embryo reaches the 8–16 cell stage it begins a process of compaction as the blastomeres adhere to each other to form a tight cluster during which they begin to exchange signals that promotes the emergence of a distinct epithelial polar morphology. There is an inner cell mass that will form the embryonic ectoderm/endoderm cells. The cells on the outside form the trophoectoderm, which will go on to form the placenta, which is the first evidence of embryonic differentiation that continues during cavitation. There are indications that this process of compaction may be driven by Ca^{2+} (205, 251) that is released from internal stores by $InsP_3$ (287).

Cavitation

The blastocyst differentiates into the outer trophoectoderm epithelium (TE) that surrounds the blastocoelic cavity that contains the inner cell mass. The latter then differentiates into the epiblast, which separates during blastocyst

expansion into the epiblast that lies adjacent to the TE and will develop into the main components of the embryo and the endoderm that faces the blastocoel cavity and is the precursor of the extraembryonic tissues. The calcitonin released from the uterus promotes implantation by inducing the embryo to express fibronectin that contributes to the interaction between the trophoblast and the uterus, which is the first step in the implantation process that is driven by Ca^{2+} signaling (11, 12, 319). Towards the end of the differentiation process, the TE develops long villi that are responsible for interacting and invading the endometrial tissues during implantation. The Ca^{2+} signaling responsible for the cavitation that forms the blastocyst is dependent on $InsP_3$-induced Ca^{2+} transients (11, 286, 287).

Approximately half of the embryos produced by IVF fail to reach the blastocyst stage (330). The demise of these early embryos seems to be mediated by embryo arrest or apoptosis that appears to be driven by an increase in ROS (29, 30). The p66Shc protein plays a significant role in the ROS production in embryos (18, 98, 99). Blastocyst survival is markedly improved following the addition of antioxidants (17, 100, 238). Such observations are consistent with the notion that vulnerability of blastocysts may arise due to low levels of antioxidants that result in the increase in ROS levels. Such low antioxidant levels are a feature of vitamin D deficiency, because an important role for vitamin D is to main the expression of a wide range of cellular antioxidants (Fig. 1).

There also is increasing evidence that maternal obesity can result in reduced fertility as a result of a decline in embryo viability at the blastocyst stage (117, 139, 186, 203, 258). Obesity may influence blastocyst survival as a result of an increase in nutrients within the follicular fluid that enhances mitochondrial metabolism and ROS formation. There is evidence for such an increase in oxidative stress as enhanced by a decline in GSH levels and a concomitant increase in reactive oxygen species (ROS) (139). The enhanced ROS levels induce both molecular and cellular damage (164) that contributes to developmental arrest and apoptosis. Some of these metabolic changes, particularly the increase in ROS levels, may be related to the fact that there is a close association between obesity and vitamin D deficiency (80, 126, 235, 248, 283, 303, 312).

Vitamin D deficiency could have a marked effect on this preimplantation phase because there is increasing evidence that this developmental stage is particularly sensitive to oxidative stress. Embryonic mitochondrial function seems particularly sensitive to such oxidative stress (88). Effective regulation of the redox state of embryos is critical during early development (87). Vitamin D supports such redox control by maintaining mitochondrial function (44, 267). In addition, one of the main functions of vitamin D is to maintain low resting levels of both the Ca^{2+} and the ROS signaling pathways as described in the phenotypic stability hypothesis (26, 27).

A significant feature of obesity is that there is a decline in vitamin D levels (80, 84, 126, 176, 248, 312) and this deficiency could account for the increase in oxidative stress that reduces fertility. Because vitamin D plays a major role in maintaining the expression of cellular antioxidants, as described in the phenotypic stability hypothesis, it is reasonable to speculate that this may explain why vitamin D is so important in maintaining normal development. There is now evidence that such a decrease of vitamin D in follicular fluid reduces the reproductive success following in vitro fertilization (97, 239, 241, 266).

Implantation and Placenta Formation

While passing along the oviduct and uterus, the developing embryo is supported by nutrients and a variety of signaling molecules such as growth factors, hormones and cytokines. In the preimplantation phase, the blastocyst within the uterine lumen begins to receive paracrine signals such as PAF, lysophosphatidic acid (LPA) and other factors from the uterine epithelium that act through phospholipase C (PLC) to release $InsP_3$ that then mobilizes Ca^{2+} to drive the embryonic developmental program (180, 205). Later in development, the blastocyst emerges from the zona pellucida thus enabling the trophoectoderm epithelium (TE) to interact with the uterine endometrium to initiate the process of implantation. Some of the processes that mediate implantation through the interaction between the TE and the uterine endothelium is driven by Ca^{2+} signaling (11, 12). For example, the heparin-binding epidermal growth factor-like growth factor located on the surface of the uterus interacts with ERBB1/4 receptors on the blastocyst to induce juxtacrine signaling that facilitates the attachment of the blastocyst through a process of Ca^{2+} signaling, which appears as oscillations that can persist for ~1 h to mediate the early implantation program (11). The subsequent process of placenta formation is also regulated by Ca^{2+} signaling.

The Ca^{2+} signaling program that controls the sequential developmental processes responsible for implantation and placenta formation may be vulnerable to vitamin D deficiency. The vitamin D level in the endometrium is one of the processes that is regulated by signals emanating from the embryo. The embryo releases the cytokine interleukin-1β (IL-1β) that acts on the endometrium (175) to induce the expression of the 1α-hydroxylase (1α-OHase) that catalyzes the active form of vitamin D (311). The vitamin D acts to increase the expression of calbindin and 1α-hydroxylase (1α-OHase), which helps to prepare the endometrium to receive the embryo during implantation. Vitamin D continues to influence some of the later developmental events via regulation of the expression of the Homeobox (*Hox*) genes that control body axis programming during embryogenesis (76, 256).

Following placenta formation there is a large flux of Ca^{2+} from the maternal to the placental circulation to promote bone formation in the developing fetus (16). Vitamin D plays an important role in this process, because it functions to maintain the Ca^{2+} pumps and exchangers responsible for this transfer of Ca^{2+}. Decreased fetal growth and birth size are some of the defects caused by a deficiency in vitamin D (38, 39, 165).

VITAMIN D AND NEURODEVELOPMENTAL DISEASES

There is increasing evidence that maternal vitamin D deficiency may be one of the primary causes of neurodevelopmental diseases as shown below:

1) Autism spectrum disorder (ASD) (52–54, 91, 96, 134, 136, 185, 192, 244, 250, 313, 314, 326, 327).
2) Schizophrenia (96, 147, 197, 198).
3) Attention deficit hyperactivity disorder (ADHD) (216, 217).

A deficiency in vitamin D within the developing brain can influence a number of essential processes such as the synthesis of neurotransmitters, cell differentiation, Ca^{2+} signaling, the activity of antioxidants, and the expression of genes that maintain mitochondrial activity (95). An important consequence of vitamin D deficiency is an alteration in the function of the dopaminergic transmitter signaling pathway (72). There are indications that vitamin D acts to increase the expression of genes that function in the dopaminergic signaling pathway and may thus contribute to neuronal development (249). In a young boy, the core symptoms of ASD were improved following administration of vitamin D (143).

Autism Spectrum Disorder

Vitamin D deficiency in women during pregnancy has been linked to the onset of neurodevelopmental diseases such as autism spectrum disorder (ASD) and schizophrenia (10, 61, 153, 313, 314). ASD pathogenesis has been linked to mutations in vitamin D-related genes (172). A number of studies have revealed that providing vitamin D supplementation during pregnancy can markedly reduce the onset of autism (53, 289, 317). The symptoms of autism in children can be improved by providing vitamin D supplementation (53, 143, 268). Such autism spectrum disorders (ASD) result from alterations in neural connectivity during brain development (110). Many cases of ASD have been linked to gene mutations many of which have been shown to alter synapse formation such as SHANK and neuroligin that contribute to alterations in the synaptic plasticity, neuronal connectivity and the excitation-inhibition (E-I) balance (22, 45, 156, 254). One of the important mutations responsible for ASD has been identified in the SHANK proteins, which are significant postsynaptic scaffolding proteins that function normally to bring together a number of important signaling molecules that function in neuronal connectivity (214). One of the consequences of SHANK mutations is to reduce the expression of parvalbumin in GABAergic inhibitory neurons that contributes to the alteration in the E-I balance that is a feature of ASD (101). Such evidence supports the concept that ASD is caused by subtle alterations in neuronal connectivity during the course of brain development. Many of these neuronal changes are also thought to occur as a result of vitamin D deficiency during pregnancy (4, 54, 250, 314, 320). Vitamin D deficiency has also been linked to ASD in adults (91). There is considerable evidence to show that vitamin D has a number of functions in the brain (105) including the control of cognition (48, 49, 160, 271, 326). There also are indications that vitamin D plays a role in controlling brain development (93, 95, 96, 249, 250). Exactly why a deficiency in vitamin D causes the alteration in brain function during development is still not clear but there are a number of possibilities. One suggestion is that developmental disorders may arise as a result of a decline in serotonin levels in the brain that is caused by vitamin D deficiency (244, 245). There is evidence that serotonin plays an important role in modulating different brain developmental processes such as neurogenesis, axon branching and the formation of dendrites (107). Vitamin D acts to promote serotonin synthesis by maintaining the expression of tryptophan hydroxylase 2 (TPH2). There also is evidence that vitamin D may act to maintain the levels of oxytocin and vasopressin that have also been implicated in autism (7, 31, 179, 212).

Another way in which vitamin D might regulate brain function is through its ability to modulate the Wnt/β-catenin signaling pathway. There are indications that this Wnt/β-catenin pathway plays a role in early brain development (62, 78, 221, 234, 333). In keeping with the phenotypic stability hypothesis, one of the functions of vitamin D is to maintain the expression of DICKKOPF-1 (DKK-1), which functions as an inhibitor of the Wnt/β-catenin signaling pathway (3, 246). During vitamin D deficiency, there will be a decline in the expression of DKK-1 and this will result in an increase in the activity of the Wnt/β-catenin signaling pathway that will contribute to ASD by changing the processes responsible for early brain development.

Another possibility is that vitamin D deficiency may give rise to autism through an alteration in the Ca^{2+} signaling processes that control brain development (96). As described above, one of the primary functions of vitamin D is to maintain low resting levels of both Ca^{2+} and ROS (27, 28, 192). There are indications from gene analysis that the Ca^{2+} signaling pathway plays a major role in the development of autism (46, 324). It is well established that brain development is orchestrated through precise Ca^{2+} transients (34, 121, 187, 304). These spontaneous Ca^{2+} transients that occur during brain development may be distorted by subtle alterations in the Ca^{2+} dynamics that results from vitamin D deficiency.

One of the functions of vitamin D is to reduce the expression of the L-type CaV1.2 and CaV1.3 channels (47, 111). If vitamin D is deficient, the expression of the CaV1.2 and CaV1.3 channels will be increased, whereas the Ca^{2+} pumps and buffers will be reduced and these changes may contribute to the elevated levels of Ca^{2+} that act to distort the developmental processes.

One of the consequences of an alteration in the Ca^{2+} dynamics during brain development might be to alter the balance between the excitatory and inhibitory neurons. Such an alteration in the excitatory/inhibitory (E-I) balance may be responsible for ASD (57, 221, 229, 262). Such an E-I imbalance is also consistent with the fact that ASD is associated with a high incidence of epilepsy (5). This high incidence of epilepsy is also consistent with the observation that there is a decline in GABAergic signaling in the brains of individuals with autism (56, 255). This decline in GABAergic signaling is a result of a decrease in the function of parvalbumin-expressing interneurons, which play a major role in maintaining the E-I balance (101, 128).

Alterations in Ca^{2+} signaling appear to play an important role in ASD pathology (106, 182, 221, 242, 272). One of the significant alterations appears to be in the $InsP_3/Ca^{2+}$ signaling pathway that has been linked to ASD (273). One of the genes that is affected by rare copy number variants in ASD is the *ITPR1* gene that encodes the IP_3R1 (113, 273). The significance of Ca^{2+} dysregulation as a cause of autism is supported by observations that genetic alterations of voltage-dependent Ca^{2+} channels result in both autism (46, 106, 131) and schizophrenia (116, 171, 233). For example, autism has been associated with single nucleotide polymorphisms of the *CACNA1C* gene that encodes the α_{1C}-subunit of the voltage-dependent L-type Ca^{2+} channel (170, 171, 182). Similarly, gain-of-function mutations of the *CACNA1D* gene that encodes the CaV1.3

L-type calcium channel have also been linked to autism (174, 253). Such mutations result in an increased activity of the Ca^{2+} channels (174) and are thus consistent with the notion that elevations in Ca^{2+} may be responsible for inducing autism during the early stages of brain development. As described earlier, one of the functions of vitamin D is to reduce the expression of the L-type CaV1.2 and CaV1.3 channels (47, 111).

Individuals with ASD also display oxidative stress (112, 201, 218, 257, 261) in that they have low levels of antioxidants such as glutathione (GSH) and GSH peroxidase, which is another feature of vitamin D deficiency. An important action of ROS is to enhance Ca^{2+} signaling by increasing the sensitivity of both the inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) (20, 33, 43, 208) and the ryanodine receptors (83, 298) to increase the release of Ca^{2+} from the endoplasmic reticulum (ER). The increase of ROS can also elevate intracellular Ca^{2+} levels by inhibiting the plasma membrane calcium-ATPase Ca^{2+} pump on the plasma membrane (177).

Schizophrenia

Vitamin D deficiency has been associated with the onset of schizophrenia (40, 63, 82, 91, 153, 194, 195, 269, 274, 278, 329, 332, 336). There are indications that vitamin D deficiency in pregnant women causes neurodevelopmental defects during early brain development and this can lead to the onset of schizophrenia in the child (196, 199, 200, 204, 274, 313). There is increasing evidence that vitamin D deficiency alters many of the processes responsible for brain development (63, 93–96, 118, 193, 250). Similar studies in rats have revealed that there are anatomical and histological changes such as narrowing of the anterior and posterior cingulate and the medial and occipital areas of the cortex (227). There is also a shrinkage of the hippocampus and the amygdala (162). For example, a decline in hippocampal gray matter volume has been observed in schizophrenia patients that are deficient in vitamin D (279). Patients with schizophrenia have lower levels of vitamin D (220).

Perception, consciousness, and memory are regulated by the tonic excitatory drive responsible for maintain brain rhythms (26). Many of the symptoms of schizophrenia may depend on alterations in the high-frequency gamma rhythms (163, 305–307). These gamma rhythms are driven by a network oscillator that depends on interactions between the inhibitory GABAergic interneurons and the excitatory pyramidal glutamatergic neurons (73, 168). The susceptibility genes and pharmacological inducers that can induce schizophrenia act by reducing the ability of the GABAergic neurons to respond to glutamate due to a decline in the activity of their *N*-methyl-D-aspartate receptors (NMDARs). This decline in the activity of the NMDARs means that the GABAergic interneurons cannot operate properly in the network oscillator, thus resulting in an alteration of the gamma and theta rhythms that are characteristic of schizophrenia (65, 115). Alterations in the epigenetic landscape may also contribute to the alterations in gene transcription responsible for the onset of schizophrenia (122, 125, 228).

In summary, the reduction in NMDAR function results in a decline in Ca^{2+} signaling that acts to remodel transcription and compensatory events that alter the GABAergic phenotype. This alteration results in a decline in the release of inhibitory transmitter GABA that could explain the change in the gamma rhythm that occurs in schizophrenia. The NMDAR hypofunction hypothesis of schizophrenia can be explained by this decline in the response of the NMDARs to glutamate on the inhibitory interneurons (66, 127, 146, 225, 284). Support for this hypothesis has come from studies showing that schizophrenic symptoms in healthy adults can be induced by ketamine and phencyclidine, which are NMDAR antagonists (142, 308).

There are indications that schizophrenia may arise through an increase in inflammation (63, 91, 127, 223, 288), which is normally suppressed by vitamin D. One of the consequences of inflammation is an increase in the expression of reactive oxygen species (ROS), which play a significant role in altering the neuronal signaling pathways during development to result in schizophrenia (25, 51, 81, 127, 157, 209, 223, 288, 328). An increase in ROS levels in patients with schizophrenia also occurs due to a decline in the level of glutathione (GSH), which is a major antioxidant in cells (25). The significance of GSH is also evident from the fact that polymorphisms in the genes coding for the enzymes responsible for the synthesis of GSH have been identified in individuals with schizophrenia (25, 127, 328). *N*-acetylcysteine, which is a precursor drug for GSH, has been shown to alleviate the symptoms of schizophrenia (24, 25, 51). This has suggested that GSH may be significant target for treatment of schizophrenia (25). Vitamin D prevents oxidative stress by increasing the expression of the γ-glutamyl transpeptidase (γ-GT), which contributes to the synthesis of GSH (104). In addition, vitamin D increases the activity of G6PD, glutamate cysteine ligase, and glutathione reductase, which also contribute to the formation of GSH (21, 141).

Vitamin D deficiency in the developing brain also influences a number of processes such as proliferation, apoptosis, and neurotransmission. The alteration in neurotransmitters responsible for the change in neurotransmission is the cause of the change in brain rhythms described earlier. With regard to this change in neurotransmission, vitamin D plays an important role in controlling a number of transmitters and their downstream signaling pathways such as the development of dopaminergic neurons (70). When vitamin D is deficient, there are alterations in dopamine (DA) metabolism that may reflect the decline in the expression of the DA neurons that are a feature of schizophrenia (69, 96, 148). Such an action may be explained by the fact that vitamin D acts to increase the expression of tyrosine hydroxylase, which is responsible for the synthesis of dopamine (71). There is evidence of a decline in the activity of serotonergic neurons located in the prefrontal cortex of patients with schizophrenia (145, 191). Many of these neurons express the $5\text{-}HT_{2A}$ receptor, which acts to increase $InsP_3/Ca^{2+}$ signaling (77). Alteration in this phosphoinositide signaling pathway plays a role in schizophrenia pathogenesis. The metabotropic glutamate receptor (mGluR5) is linked together to the NMDAR through scaffolding proteins such as Homer, SHANK, guanylate kinase-associated protein, and PSD95. Alterations in some of the proteins in this complex such as the mGluR5 and SHANK are associated with the onset of schizophrenia (108, 123, 190). Schizophrenia has also been associated with a decline in acetylcholine signaling (270). Schizophrenia has also been associated with a decline in the expression of the regulator of G protein signaling 4 (RGS4)

that regulates the activity of the PLC-β1 that mediates the activity of the G protein-coupled receptors (206). In the orbitalfrontal cortex, there is a deletion of PLC-β1 in individuals with schizophrenia (178). In schizophrenia, there also is evidence of an abnormal expression of PLC-β1 (154).

In addition to these alterations in the transducing mechanisms responsible for generating the $InsP_3/Ca^{2+}$ signaling pathway, there also are indications that the function of the $InsP_3R1$ itself is altered. For example, one of the actions of the susceptibility gene disrupted-in-schizophrenia-1 (*DISC1*) is to alter the activity of the $InsP_3R1s$ (243). DISC1 contributes to the transport of the mRNA of the *ITPR1* gene that encodes the $InsP_3R1s$ (302). It attaches the *ITPR1* mRNA to the kinesin-1 molecular motor that then propels it down the microtubules to distribute it throughout the dendritic tree. Once in position, the *ITPR1* mRNA begins to express the $InsP_3R1$ channels, which are key components of neuronal Ca^{2+} signaling mechanisms.

There is increasing evidence that alterations in Ca^{2+} signaling may alter the developmental processes responsible for brain development (59). Mutations of the *CACNA1C* and *CACNB2* genes, which code for the α_{1C}- and β2-subunits of the $Ca_V1.2$ L-type channel, have been linked to psychiatric disorders such as borderline personality disorder and schizophrenia (68, 173). It is evident that these alterations in this Ca^{2+} channel can influence neural activity because it controls both neural gene transcription, excitability, and synaptic plasticity (159, 215). Such actions would explain the changes in brain circuits in the prefrontal cortex and hippocampus that are a feature of schizophrenia (32, 92).

One of the primary functions of vitamin D is to maintain Ca^{2+} homeostasis. One of its functions is to decrease the expression of the L-type voltage-gated Ca^{2+} channels. It also maintains low Ca^{2+} levels by maintaining the Ca^{2+} buffers and the pumps that extrude Ca^{2+} from the cell.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is another example of a neurodevelopmental disorder with symptoms that resemble both ASD and schizophrenia. There is increasing evidence that vitamin D deficiency during pregnancy contributes to the onset of ADHD (216, 217) just as it does for ASD and schizophrenia. Low vitamin D levels have been associated with ADHD in children (15, 19, 114, 144, 275). The symptoms of ADHD, such as attention deficit and hyperactivity, are improved following vitamin D supplementation (263, 264). It is likely that this vitamin D deficiency interferes with brain development as described earlier for ASD and schizophrenia. This possibility is supported by the fact that some individuals show comorbidity between ASD and ADHD (260). For example, individuals with ASD will also display occasional symptoms of ADHD such as attention deficit and hyperactivity. It seems likely that during development the brain changes in certain regions that will lead to ASD and may also change in some other region to induce the episodes of ADHD.

Some of the changes that occur in ADHD resemble those seen in ASD. For example, there is evidence that ADHD may arise as a result of a decline in serotonin levels in the brain that is caused by vitamin D deficiency (244, 245). There is evidence that serotonin plays an important role in modulating different brain developmental processes such as neurogenesis, axon branching, and the formation of dendrites (107). Vitamin D acts to promote serotonin synthesis by maintaining the expression of tryptophan hydroxylase 2 (TPH2). Low levels of serotonin are also a feature of ASD and schizophrenia as described earlier.

Neuropsychiatric diseases such as ASD and ADHD are also induced by a number of other processes such as oxidative stress (257). Such stress is exacerbated by the fact that the brain has a reduced oxidative capacity as described earlier for ASD. Oxidative stress may also contribute to ADHD symptoms in adults (50). Another process that induces ADHD is alcohol intake. Prenatal alcohol exposure (PAE) induces an alcohol-related neurodevelopment disorder (ARND) that displays symptoms that closely resemble those seen in ADHD (259). This similarity seems to depend on the fact that alcohol can influence the developing brain by altering a number of those changes that occur during ADHD. For example, alcohol can alter neurotransmission by influencing a number of transmitter systems such as the cholinergic, glutamatergic, and dopaminergic systems (259). As for ADHD, PAE may also induce epigenetic changes that will reduce the expression of key genes that play a central role in brain development (129, 150, 280).

A decrease in dopamine activity is one of the features of ADHD in children and adults (315). Two of the drugs used to treat ADHD, methylphenidate hydrochloride and amphetamine, act by increasing the activity of the dopamine signaling pathway (315, 316). The effect of methylphenidate in treating ADHD was enhanced by vitamin D supplementation (213). One of the functions of dopamine is to control the tonic excitatory drive that regulates the frequency of brain rhythms (26). It is known that individuals with ADHD display too many slow theta brain waves, which result in relaxation, with a decline in the faster alpha/beta waves responsible for mental focus (23). An increase in the dopamine signaling pathway would contribute to an increase in the higher frequency waves. Some patients with ADHD are treated through neurofeedback whereby they are trained to increase the frequency of their brain waves (13, 135, 189). Another manifestation of the changes in brain rhythms in ADHD is the evidence that patients with this disorder suffer from disturbed sleep (67, 155, 301). It has been suggested that this sleep disorder, particularly the insomnia, may be caused by excessive activation of the tonic excitatory drive through enhanced levels of orexin (155). Such persistent activation may prevent the brain rhythms from declining down to the delta and slow oscillations that characterize sleep (26). There are indications that neurofeedback therapy may help to improve this sleep disorder in ADHD (14).

CONCLUSIONS

Vitamin D is an essential hormone that acts to maintain the phenotypic stability of cell signaling systems, particularly the Ca^{2+} and redox pathways. Alterations in these pathways during the course of development can account for both infertility and neurodevelopmental diseases. Vitamin D deficiency results in an increase in the resting levels of both Ca^{2+} and reactive oxygen species (ROS), which means that the Ca^{2+} signals that are generated during the course of development will be markedly altered and will result in changes in early development and implantation, leading to infertility. Later in development, when organs are differentiating, such Ca^{2+} dysregulation in-

duced by vitamin D deficiency will seriously interfere with how cells organize their relationships to each other; this is particularly relevant to brain development and results in neurodevelopmental diseases such as autism spectrum disorders (ASD), schizophrenia, and attention deficit hyperactivity disorder (ADHD). There is evidence that such changes occur in pregnant women that are deficient in vitamin D and result in the children having these neurodevelopmental diseases.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

M.J.B. prepared figures; drafted, edited and revised manuscript; approved final version of manuscript.

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