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Vitamin D and Depression: Cellular and Regulatory Mechanisms

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Abstract*——Depression is caused by a change in neural activity resulting from an increase in glutamate that drives excitatory neurons and may be responsible for the decline in the activity and number of the GABAergic inhibitory neurons. This imbalance between the excitatory and inhibitory neurons may contribute to the onset of depression. At the cellular level there is an increase in the concentration of intracellular Ca^{2+} within the inhibitory neurons that is driven by an increase in entry through the NMDA receptors (NMDARs) and through activation of the phosphoinositide signaling pathway that generates inositol trisphosphate ($InsP_3$) that releases Ca^{2+} from the internal stores. The importance of these two pathways in driving the elevation of Ca^{2+} is supported by the fact that depression can be alleviated by ketamine that inhibits the NMDARs and scopolamine that inhibits the M1 receptors that drive $InsP_3/Ca^{2+}$ pathway. This increase in Ca^{2+} not only contributes to depression but it may also explain why individuals with depression have a strong likelihood of developing Alzheimer's disease. The enhanced levels of Ca^{2+} may stimulate the formation of Aβ to initiate the onset and progression of Alzheimer's disease. Just how vitamin D acts to reduce depression is unclear. The phenotypic stability hypothesis argues that vitamin D acts by reducing the increased neuronal levels of Ca^{2+} that are driving depression. This action of vitamin D depends on its function to maintain the expression of the Ca^{2+} pumps and buffers that reduce Ca^{2+} levels, which may explain how it acts to reduce the onset of depression.

I. Introduction

There are two forms of depression, unipolar depression and bipolar depression (BPD). In the case of BPD, there are alternating episodes of depression and mania. The depressive state in BPD resembles that in unipolar depression in that they both respond to antidepressants such as ketamine and the mood-stabilizer lithium (Li^+), but it is still unclear whether they are caused by the same genetic and pathophysiological defects. In this review, it will be assumed that there are similarities in the depressive state that occurs in both BPD and unipolar depression such as major depressive disorder (MDD). Vitamin D deficiency has been linked to both forms of depression but just how this occurs at the cellular level is unclear.

To describe how vitamin D functions, it is necessary to understand the properties of the vitamin D signaling pathway (Fig. 1). The active form of vitamin D is 1α,25-dihydroxy vitamin D_3 [1α,25$(OH)_2D_3$], which is formed by a series of reactions that take place in a number of different tissues. Sunlight acting on the skin initiates the formation of vitamin D_3 (cholecalciferol) through the photolysis of 7-dehydrocholesterol (Holick et al., 1980). The vitamin D_3 enters the blood and is transferred to the liver where a hydroxyl group is added to the C-25 position by a vitamin D-25 hydroxylase (encoded by the *CYP27A1* gene) to form 25-hydroxyvitamin

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D_3 [25(OH)D_3] that is the immediate precursor for active vitamin D. This 25(OH)D_3 is carried in the blood to enter multiple cell types where a 25(OH)D_3-1α-hydroxylase (encoded by the *CYP27B1* gene) adds another hydroxyl group to the 1 position to form the active 1,25$(OH)_2D_3$, which enters the nucleus to activate a large number of genes (Fig. 1). In this review, I will use the term vitamin D with the understanding that it refers to the vitamin D signaling pathway that contains a number of related components.

To understand the pathophysiology of depression and how vitamin D may act to prevent depression, it is necessary to explore what causes the alterations in neural function responsible for the change in mood. To explore how vitamin D might act to prevent depression, it is necessary to formulate a working hypothesis to explain the nature of the dysfunctional intracellular neuronal signaling systems. The hypothesis that is developed in the subsequent sections proposes that an increase in neuronal Ca^{2+} levels is a major factor responsible for driving the onset of depression. Vitamin D normally acts to maintain Ca^{2+} homeostasis (Berridge, 2015a,b), which suggest that the persistent increase in Ca^{2+} caused by vitamin D deficiency may contribute to the onset of depression.

II. Dysfunctional Neural Circuits in Depression

There is increasing evidence that depression occurs from alterations in the way different brain regions communicate with each other (Fitzgerald et al., 2008). Individuals with depression have a decline in neural activity in the frontal and temporal cortex and the insula. In addition, there is a decrease in activity in the cerebellum, subcortical, and limbic regions. This communication between brain regions is very dependent on the fact that neurons oscillate in synchrony with each other. An example of such oscillatory activity is the fast gamma oscillations (20–80 Hz). Such synchronous brain rhythms depend on an intimate mutual interaction between the excitatory and inhibitory neurons. Excitatory neurons release glutamate that not only excites its target neuron, but they also have collateral endings that activate the local inhibitory neurons, which release γ-aminobutyric acid (GABA) that then feeds back to inhibit the excitatory neurons. These tightly regulated feedback interactions between the excitatory and inhibitory neurons is an essential feature of neuronal communication within the brain, which may be altered in depression as a result of a change in the contribution of the inhibitory neurons. In individuals with depression, there is a decline in GABA levels (Sanacora et al., 2004, Hasler et al., 2007) and this may be explained by the fact that the size and the number of inhibitory GABAergic neurons is reduced in the dorsal prefrontal cortex (Rajkowska et al., 2007) and in the occipital cortex (Maciag et al., 2010). These GABAergic inhibitory interneurons, which have an important role in coordinating the activity of the pyramidal neurons to generate brain rhythms (Klausberger et al., 2003) are altered in depression (Croarkin et al., 2011; Luscher et al., 2011; Ren et al., 2016). Such a deficit in the GABA-dependent inhibitory pathway may be responsible for the onset of major depressive disorder (MDD) (Levinson et al., 2010). The decline in the GABAergic neurons may be driven by an increase in the activity of the glutamatergic signaling pathway that occurs in depression (Deutschenbaur et al., 2016; Zhang et al., 2016a). For example, there is an increase in glutamate levels in various brain areas such as the anterior cingulate/medial prefrontal cortical region in patients with BPD (Paul and Skolnick 2003; Frye et al., 2007; Hashimoto et al., 2007; Gigante et al., 2012; Niciu et al., 2014; Zhang et al., 2016a). In individuals with depression, there is a decline in GABA levels (Sanacora et al., 2004; Hasler et al., 2007), and this may be explained by the fact that the size and the number of GABAergic neurons is reduced in the dorsal prefrontal cortex (Rajkowska et al., 2007) and in the occipital cortex (Maciag et al., 2010). High levels of glutamate will increase the intracellular level of Ca^{2+}, resulting in two consequences. First, it will enhance the tonic excitatory drive responsible for regulating neuronal activity. Second, the elevated levels of Ca^{2+} reduce protein synthesis, which may account for the decline in the function and number of GABAergic neurons as described later. There is increasing evidence that the onset and progression of depression may depend on an increase in Ca^{2+} in neuronal cells.

III. Tonic Excitatory Drive and Depression

Abnormal activation of the tonic excitatory drive that functions to regulate neuronal activity may contribute to the elevation of Ca^{2+} that occurs in depression. The rhythmical neuronal oscillations that occur synchronously in the brain have varied frequencies during the sleep/wake cycle. During the wake period there are fast gamma (20–80 Hz) and theta (4–10 Hz) oscillations, which then decline to the much slower delta (1–4 Hz) and slow oscillations (<1 Hz) that occur during sleep (Berridge, 2014a,b). This range of frequencies is

ABBREVIATIONS: ACh, acetylcholine; AD, Alzheimer's disease; BPD, bipolar depression; E-I, excitation-inhibition; ER, endoplasmic reticulum; GABA, γ-aminobutyric acid; GSH, glutathione; 5-HT, 5-hydroxytryptamine; $InsP_3$, inositol 1,4,5-trisphosphate; Li^+, lithium; MDD, major depressive disorder; mGluR, metabotropic glutamatergic receptor; M1, muscarinic acetylcholine receptor; NCS-1, neuronal calcium sensor 1; NCX1, $Na^+/Ca2^+$ exchanger 1; NMDAR, NMDA receptor; PMCA, plasma membrane Ca^{2+}-ATPase; PtdIns4,5P_2, phosphatidylinositol 4,5-bisphosphate; ROS, reactive oxygen species; RYRs, ryanodine receptors; TNF-α, tumor necrosis factor-α.

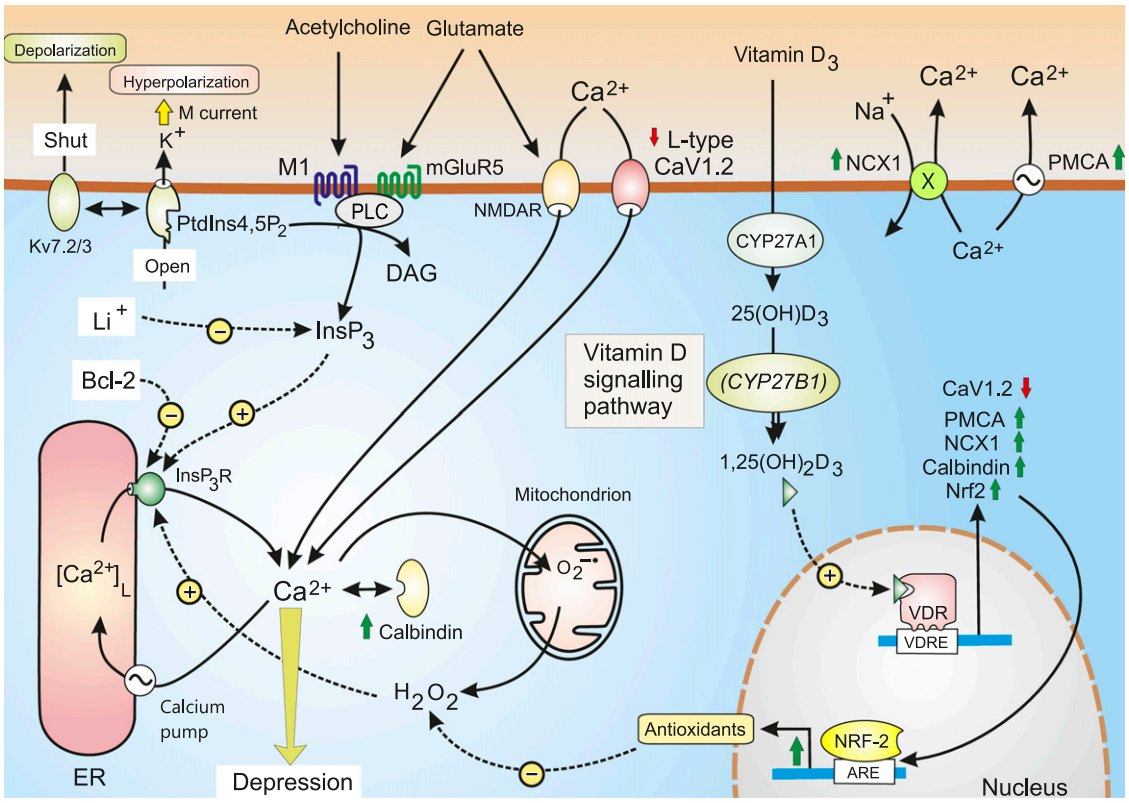

Fig. 1. The role of Ca^{2+} signaling in depression. Increased glutamate that occurs during depression enhances Ca^{2+} through the activation of NMDAR Ca^{2+} channels and by activation of the metabotropic glutamatergic receptor 5 (mGluR5) that is coupled to phospholipase C (PLC) to hydrolyze phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P^2) to form inositol 1,4,5-trisphosphate ($InsP_3$) that releases Ca^{2+} from the endoplasmic reticulum (ER). Acetylcholine acting through the muscarinic 1 (M1) receptor also stimulates the formation of $InsP_3$. The hydrolysis of PIP_2, which normally acts to open the Kv7 2/3 channels that hyperpolarizes the neuronal membrane, acts to close these K^+ channels and the membrane depolarizes, resulting in enhanced neuronal excitability. Vitamin D acts to reduce Ca^{2+} signaling by acting through the vitamin D receptor (VDR) to increase the expression of the Ca^{2+} buffer calbindin and it increases expression of the plasma membrane Ca^{2+} pump (PMCA) and the sodium/Ca^{2+} exchanger 1 (NCX1). Vitamin D also reduces the level of Ca^{2+} by reducing the expression of the L-type CaV1.2 channel.

regulated by the ascending arousal system that consists of a number of different neurons located mainly in the brain stem, midbrain, basal forebrain, and hypothalamus. In addition to arousing the brain from sleep, it also is responsible for maintaining the wake state and can adjust the frequency of the oscillating neural circuits as they participate in different types of behavior. This ascending arousal system regulates the sleep/wake cycle by releasing transmitters such as acetylcholine (ACh), dopamine, histamine, noradrenaline, orexin, and serotonin. Some of these transmitters such as serotonin, dopamine, and acetylcholine feature significantly in depression (Manji et al., 2003).

The serotonergic neurons in the dorsal raphe, which synthesize serotonin [5-hydroxytryptamine (5-HT)], extend throughout the brain to release serotonin in the hippocampus, prefrontal cortex, substantia nigra, nucleus accumbens, amygdala, and lateral habenula. The serotonin hypothesis, which was one of the first attempts to explain depression, proposed that depression may result from a deficiency in serotonin (Schildkraut 1965; Jacobsen et al., 2012). The selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, and citalopram, relieve the symptoms of depression by bringing about an increase in serotonin levels that have two important actions in the brain (Kobayashi et al., 2008; Thompson et al., 2015). First, the elevated serotonin activates neurogenesis by increasing the proliferation of progenitor cells in the hippocampal dentate gyrus (Malberg et al., 2000) and is the basis of the neurogenesis hypothesis that proposes that a decrease in neurogenesis causes the onset of depression (Jacobs et al., 2000; Miller and Hen, 2015).

Neurogenesis is a process whereby new functional neurons are generated from precursor cells (Ming and Song 2011; Kempermann et al., 2015). Second, serotonin controls excitatory synaptic transmission in the hippocampus and prefrontal cortex (Cai et al., 2013; Thompson et al., 2015), perhaps operating through the tonic excitatory drive. The decline in serotonin may be caused by inflammation that is associated with depression as described later. A reduction in serotonin levels thus seems to be one of the causes of depression as described later.

The transmitters, such as serotonin and acetylcholine (ACh) discussed above, are released globally and are responsible for activating the tonic excitatory drive using a variety of signaling mechanisms to control the

activity of the excitatory and inhibitory neurons that interact with each other to generate the synchronous brain rhythms (Berridge, 2014a,b). For example, ACh acts through M1 receptors to stimulate phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P_2) hydrolysis, which contributes to depolarization by decreasing the permeability of K_v7.2 and K_v7.3 that are delayed rectifier potassium channels that regulate neuronal excitability by controlling the M current (Fig. 1). In addition, the inositol 1,4,5-trisphosphate ($InsP_3$) released after the hydrolysis of PtdIns4,5P_2 promotes the release of Ca^{2+} that stimulates the Ca^{2+}-activated nonselective cation current. The importance of ACh has been highlighted by the fact that scopolamine, which inhibits muscarinic receptors, functions as an antidepressant (Furey and Drevets, 2006; Drevets et al., 2013; Navarria et al., 2015). In the hippocampal CA1 region, the GABAergic interneurons respond to serotonin through 5-HT_{2A} receptors (5-HT_{2A}Rs) that stimulate phospholipase Cβ that hydrolyzes PtdIns4,5P_2, resulting in closure of the hyperpolarizing M current. Serotonin also induces membrane depolarization by producing $InsP_3$ to increase Ca^{2+} that stimulates the Ca^{2+}-activated nonselective cation current, resulting in membrane excitability (Wyskiel and Andrade, 2016). Dopamine acts through both the D1 and D2 receptors to regulate the formation of cyclic AMP, which also regulates neuronal excitability. Inactivation of the D2 receptors in the dorsolateral prefrontal cortex is prevented by neuronal calcium sensor 1 (NCS-1). It is of interest, therefore, to find that the levels of NCS-1 are markedly elevated in BPD (Koh et al., 2003). It is also of interest that NCS-1 enhances the release of Ca^{2+} by the $InsP_3$ receptor 1 ($InsP_3$R1), which explains how NCS-1 may contribute to the elevation in Ca^{2+} that occurs in depression (Schlecker et al., 2006). The antimanic drug lithium (Li^+) inhibits this stimulatory action of NCS-1, further supporting the concept that an elevation in the $InsP_3$/Ca^{2+} signaling pathway contributes to depression pathology (Schlecker et al., 2006).

Another reason for considering a possible role for changes in the tonic excitatory drive in BPD, is the finding that two of the genes that have consistently been linked to BPD play a role in regulating neuronal activity. One of these genes is *CACNA1C*, which encodes the α subunit of the Ca_V1.2 L-type voltage-sensitive Ca^{2+} channels (Ferreira et al., 2008; Tesli et al., 2013; Heyes et al., 2015; Kabir et al., 2016). Opening of this channel generates a Ca^{2+} signal that contributes to the tonic excitatory drive by activating the HCN channel. Neuronal Ca^{2+} levels are enhanced by an increase in the activity of this CaV1.2 L-type voltage-sensitive Ca^{2+} channel, which is encoded by the *CACNA1C* gene. Polymorphisms located within the *CACNA1C* gene, which is associated with both depression and bipolar disorder (Zhang et al., 2013), result in an increase in the level of Ca^{2+} (Perrier et al., 2011; Ou et al., 2015; Uemura et al., 2015; Harrison 2016). Such an increase in the activity of the CaV1.2 L-type channels is of interest because it may help to explain the relationship between vitamin D deficiency and depression as described later. This role of enhanced Ca_V1.2 L-type Ca^{2+} channels causing depression has led to a proposal that the inhibition of these channels may act to improve mood disorders (Boal et al., 2016). Such a possibility is supported by the observation that the Ca^{2+} channel blocker isradipine is able to treat bipolar depression (Ostacher et al., 2014). The other gene is *ANK3* that encodes ankyrin-G, which plays a role in positioning the K_V7.2/K_V7.3 channels to the correct location in the neuronal membrane. K_v7.2 and K_v7.3 are delayed rectifier channels that contribute to the regulation of neuronal excitability by controlling the M current (Fig. 1).

An important feature of this tonic excitatory drive is that it normally is applied equally to both the excitatory and inhibitory neurons and this excitation-inhibition (E-I) balance is essential for proper brain function (Tao et al., 2014). Through a process of homeostatic plasticity, the excitatory and inhibitory neurons adjust their synaptic strength so as to maintain this E-I balance (McClung and Nestler, 2008; Turrigiano 2008; Ren et al., 2016). The idea that depression may be caused by an E-I imbalance is supported by the observation that depression is associated with a decline in the number of the GABAergic inhibitory interneurons (Klausberger et al., 2003), which may be driven by the increase in the glutamatergic signaling pathway that occurs in BPD (Paul and Skolnick, 2003; Frye et al., 2007; Gigante et al., 2012). For example, there is an increase in glutamate levels in various brain areas such as the anterior cingulate/medial prefrontal cortical region in patients with depression (Frye et al., 2007; Gigante et al., 2012). In addition to distorting the E-I balance, this increase in glutamate levels could also contribute to the increase in the levels of both Ca^{2+} and reactive oxygen species (ROS) levels that are associated with depression as described below.

Depression seems to occur as a result of a decline in both the number and connectivity of spine synapses particularly in the GABAergic neurons (Duman and Duman, 2015; Calabrese et al., 2016). Ketamine, which inhibits the Ca^{2+} entry through the NMDARs, and scopolamine that inhibits muscarinic receptors can restore this decline in synaptogenesis that occurs during depression (Duman and Aghajanian, 2012; Raab-Graham et al., 2016; Ren et al., 2016; Wohleb et al., 2017). This restoration of normal synaptic connections may be mediated through the ability of ketamine to reduce the elevated levels of Ca^{2+} that are a feature of depression. Similarly, the antidepressant action of scopolamine (Furey and Drevets, 2006; Drevets et al., 2013; Navarria et al., 2015) may depend on its ability to reduce Ca^{2+} levels by inhibiting the

muscarinic receptors that act through the $InsP_3/Ca^{2+}$ signaling pathway. This may explain why the activation of KCNQ channels, which will hyperpolarize the membrane to reduce neuronal hyperactivity and intracellular Ca^{2+} levels, can also alleviate depression (Friedman et al., 2016). High levels of calcium that occur in depression activate eukaryotic elongation factor 2 kinase, which phosphorylates and inhibits eukaryotic elongation factor 2, resulting in less dendritic protein synthesis and negatively affecting synapse formation (Sutton et al., 2007). The persistent elevation in Ca^{2+} may thus be a key pathologic factor responsible for the decline is synapses that occur during depression.

IV. Enhanced Neuronal Ca^{2+} Signaling in Depression

A number of mechanisms contribute to the abnormal elevation of neuronal Ca^{2+} that seems to be responsible for the onset of depression (Berridge. 2012; 2014b). Again a key aspect of depression appears to be an elevation in glutamate that will elevate Ca^{2+} by acting on both ionotropic and metabotropic receptors (Fig. 1). For example, the NMDA receptor (NMDAR) is an ionotropic channel that responds to glutamate by increasing the entry of external Ca^{2+}. The antidepressant drug ketamine acts by inhibiting the NMDARs, thus reducing the influx of external Ca^{2+} (Miller et al., 2014). One of the consequences of ketamine acting to reduce the intracellular level of Ca^{2+} is to promote the protein synthesis necessary to restore the synaptic connections that are reduced in depression as described above (Sutton et al., 2007).

The enhanced glutamate levels may also contribute to the elevation in Ca^{2+} by activating metabotropic glutamatergic receptors such as the mGluR2/3 and mGluR5 (Chaki et al., 2013; Pałucha-Poniewiera et al., 2013; Newell and Matosin, 2014). The function of mGluR5 is facilitated by the protein S100A10 (p11) that binds to the cytoplasmic tail of this receptor (Lee et al., 2015). Knockout of p11 in GABAergic neurons has an antidepressant effect supporting the idea that the function of the mGluR5s is closely related to p11. The significance of the mGluRs is also supported by studies on the scaffolding protein Homer, which has three members Homer1, Homer2, and Homer3. An alteration in the function of these Homer proteins has been implicated in a number of neurologic diseases (Szumlinski et al., 2006; Luo et al., 2012). Genome-wide association studies have established that single nucleotide polymorphisms in Homer1 are linked to major depression (Rietschel et al., 2010). In the medial prefrontal cortex, the expression of Homer1a is increased by various antidepressant treatments, whereas a decrease in its expression increased depressive-like behavior (Serchov et al., 2015; 2016).

One of the primary locations of Homer1 is in the postsynaptic density where it acts as an adaptor protein to regulate a number of Ca^{2+} signaling components (Serchov et al., 2016). For example, Homer1 functions to link the NMDA receptor (NMDAR) to the metabotropic receptors (mGluR1 and mGluR5) (Bertaso et al., 2010). The interaction between these two receptors is functionally important in that there is a reciprocal inhibition operating between the NMDAR and mGluR5 receptors (Perroy et al., 2008). This would imply that if Homer1 is defective then the two receptors would separate and would become more active to enhance Ca^{2+} signaling. This is of interest in that the mGluR5 and NMDARs have been implicated in the pathophysiology of depression (Newell and Matosin 2014). The significance of NMDARs in depression is evident by the fact that ketamine, which is a potent inhibitor of this receptor, has antidepressant effects (Miller et al., 2014). Homer proteins also provide a link between metabotropic glutamate receptors (mGluRs), which generate $InsP_3$, and the underlying $InsP_3Rs$ (Tu et al., 1998). Antidepressant responses have been observed after inhibition of metabotropic glutamate receptors (mGluRs) such as mGluR2 and mGluR5 (Krystal et al., 2010). Homer can also provide a link between the $InsP_3Rs$ in the endoplasmic reticulum (ER) and the TRPC1 Ca^{2+} channels in the plasma membrane, thereby promoting an increase in the entry of external Ca^{2+} (Yuan et al., 2003). The activity of ryanodine receptors (RYRs), which can contribute to depression by releasing Ca^{2+} from the internal stores (Galeotti et al., 2008a,b), can also be regulated by Homer proteins (Feng et al., 2002; Hwang et al., 2003; Pouliquin and Dulhunty, 2009).

The mGluRs act by stimulating the phosphoinositide signaling pathway, which generates the $InsP_3$ that releases Ca^{2+} from internal stores and thus contributes to the increase in neuronal Ca^{2+} levels. Such a mechanism could account for the elevated levels of Ca^{2+} that have been described in a large number of cell types taken from patients with BPD (Dubovsky et al., 1992; Warsh et al., 2004). Lithium (Li^+) reduces this increase in phosphoinositide signaling by reducing the supply of inositol as described in the inositol depletion hypothesis (Berridge et al., 1989). This inositol depletion hypothesis is based on the idea that depression arises through overactive phosphoinositide signaling pathways (as described above) that can be corrected by drugs such as Li^+ and valproate. The excessive phosphoinositide signaling may contribute to depression by increasing the intracellular level of Ca^{2+} by altering the tonic excitatory drive that alters the E-I balance within the central nervous system. The inositol depletion hypothesis emerged from the observation that Li^+ is a potent inhibitor of the inositol monophosphatase responsible for hydrolyzing inositol monophosphates (Ins1P, Ins3P, and Ins4P) to free inositol. By inhibiting the formation

of inositol, Li^+ reduces the supply of the free inositol required to resynthesize the PtdIns necessary to provide the PtdIns4,5P_2 required for this signaling pathway. There is now considerable support for this inositol depletion hypothesis (Lubrich and van Calker, 1999; Harwood, 2005; Deranieh and Greenberg, 2009; Kim and Thayer, 2009). Further support for the hypothesis comes from the observation that Li^+ can inhibit the sodium *myo*-inositol transporter-1 (SMIT1) responsible for taking up inositol from the plasma (Lubrich and van Calker, 1999). This inositol depletion hypothesis was strengthened further when it was discovered that valproate has a similar action in that it too will deplete internal inositol (Eickholt et al., 2005) by inhibiting both the uptake of external inositol by SMIT and by inhibiting the inositol synthase responsible for the de novo synthesis of inositol from glucose 6-phosphate.

The inositol depletion hypothesis suggests that depression may arise through excessive elevation of the neuronal phosphoinositide signaling pathway that alters the tonic excitatory drive. Such a conclusion is supported by the observation that the levels of G alpha q/11 and phospholipase C (PLC)-beta 1, which are key components of the phosphoinositide signaling pathway, are elevated in the occipital cortex from patients with BPD (Mathews et al., 1997). The consequence of this change will depend on whether this increase in signaling is functionally important in either the excitatory or inhibitory neurons. Changes in the activity of either the excitatory or inhibitory neurons result in subtle alterations in the neuronal circuits that control behavior. The basic idea is that the periodic switching between depression and mania, which is a characteristic feature of BPD (Salvadore et al., 2010), is caused by an alteration in the E-I balance that controls neuronal activity. During the generation of brain rhythms, it is essential for the excitatory and inhibitory neurons to be activated equally.

The onset of both BPD and major depressive disorder (MDD) has also been linked to dysfunction of the mitochondria (Kato, 2007; Andreazza et al., 2010;2013; Jou et al., 2009; Clay et al., 2011; Callaly et al., 2015; Morris and Berk, 2015; Bansal and Kuhad, 2016). There is a decline in the nuclear mRNA molecules and proteins that contribute to mitochondrial respiration (Scaini et al., 2016; Kim et al., 2014). In particular, there is a decline in the function of complex I of the electron transport chain responsible for ATP formation. A decline in the efficiency of this electron transport chain also results in an increase in the formation of reactive oxygen species (ROS) that induces oxidative stress. Such oxidative stress arising from increased levels of ROS plays an important role in the pathophysiology of BPD (Steckert et al., 2010; Andreazza et al., 2013; Brown et al., 2014; Callaly et al., 2015). The elevation of ROS is enhanced by the fact that neurons from patients with depression have much reduced antioxidants such as glutathione (GSH) (Gawryluk et al., 2011; Kulak et al., 2013). The Ca^{2+} buffering role of the mitochondria is also compromised, resulting in an increase in the intracellular level of Ca^{2+}, which is a feature of neurons in both BPD and MDD.

A particularly interesting aspect of this decrease in mitochondrial function in depression is that it may result from a decline in vitamin D. Vitamin D acts to maintain the normal mitochondrial control of cellular bioenergetics (Calton et al., 2015). Vitamin D regulates the activity of the mitochondrial respiratory chain (Consiglio et al., 2015). In skeletal muscle, fatigue and a decline in muscle strength are alleviated by vitamin D acting to enhance mitochondrial respiration and oxidative phosphorylation, thereby increasing the formation of ATP (Bouillon and Verstuyf, 2013; Sinha et al., 2013; Ryan et al., 2016). Vitamin D regulates mitochondrial function through two actions. First, it acts on the nucleus to increase the expression of many of the components responsible for mitochondrial function. Second, the VDR enters the mitochondrion where it may act directly to regulate mitochondrial function, but exactly what it does is still not clear. In human platelets, the VDR is located in the mitochondria (Silvagno et al., 2010). In keratinocytes, the VDR enters the mitochondria through the permeability transition pore (Silvagno et al., 2013). The role of vitamin D in maintaining normal mitochondria may be one explanation for the link between vitamin D deficiency and depression. When vitamin D is low, mitochondrial function will be compromised, resulting in an elevation of ROS and a reduction in the formation of ATP, which will have a major impact on Ca^{2+} homeostasis. The formation of ROS facilitates the release of Ca^{2+} from the ER by the $InsP_3$Rs and the RYRs, whereas the decline in ATP will reduce the ability of neurons to extrude Ca^{2+} from the cell. Both these effects will contribute to the abnormal elevation in neuronal Ca^{2+} levels that have been linked to the onset of depression as described earlier.

Hyperactivity of the $InsP_3/Ca^{2+}$ pathway contributes to BPD. This is supported by studies showing that depression is associated with single nucleotide polymorphisms in the Bcl-2 gene, which reduce Bcl-2 expression that results in an increase in $InsP_3$-induced Ca^{2+} release (Machado-Vieira et al., 2011; Uemura et al., 2011;2015; Soeiro-de-Souza et al., 2013). This Ca^{2+} release by $InsP_3$ is normally suppressed by Bcl-2 (Fig. 1) (Distelhorst and Bootman, 2011). One of the actions of the antidepressant drug Li^+ is to increase the expression of Bcl-2 (Chen et al., 1999; Manji et al., 2000; Corson et al., 2004). Studies on mice have revealed that the blockade of both $InsP_3$Rs and RyRs, through inhibition or deletion, induces an antidepressant-like effect (Galeotti et al., 2006). An antidepressive state in mice was obtained by either inhibiting the RYRs or by deleting them (Galeotti et al., 2008a). A similar decline in depression was observed when the $InsP_3$Rs were

either inhibited or deleted (Galeotti et al., 2008b). On the other hand, depressant-like responses were observed upon stimulation of these Ca^{2+}-mobilizing channels, thus confirming the hypothesis outlined earlier that an elevation of Ca^{2+} plays a role in depression. An increase in the activity of the CaV1.2 L-type Ca^{2+} channel also contributes to this dysregulation of Ca^{2+} as described earlier (section III).

All this evidence suggests that an increase in neuronal Ca^{2+} may be a primary driver of depression. This conclusion may also explain the close relationship between inflammation and depression as described below.

V. Inflammation and Depression

There is a close association between inflammation and depression (Maes, 1995; 2011; Dantzer et al., 2008; Miller et al., 2009; Barbosa et al., 2014a,b; Swardfager et al., 2016; Berk et al., 2013b; Najjar et al., 2013; Brites and Fernandes, 2015; Wohleb et al., 2016). The bidirectional link between inflammation and depression has emerged from studies showing that major depressive disorders are associated with individuals with chronic inflammation and with diseases such as cardiovascular diseases, type 2 diabetes, and rheumatoid arthritis. The proinflammatory cytokines interleukin-1α and β , tumor necrosis factor-α (TNF-α), and interleukin-6 have been implicated in the onset of depression (Maes, 2011; Dantzer et al., 2008; Najjar et al., 2013; Swardfager et al., 2016; Zhang et al., 2016b). The TNF-α protein levels were significantly increased in those areas of the brain such as the dorsolateral prefrontal and anterior cingulate cortex that play a significant role in regulating both mood and cognition (Dean et al., 2013). The microglia plays a major role in releasing these cytokines within the brain (Barbosa et al., 2014b). A part of the therapeutic action of Li^+, which is used to treat BPD, is to reduce inflammation by altering the expression of a number of cytokines (Nassar and Azab, 2014).

One of the consequences of inflammation is a decline in the plasma level of tryptophan, which is an essential amino acid that is transported into the brain where it functions in the synthesis of serotonin (Catena-Dell'Osso et al., 2011). Depression is associated with a decline in the level of serotonin. Interleukin-6 appears to be one of the major cytokines associated with depression (Sukoff Rizzo et al., 2012; Money et al., 2016). Depression induced by cytokines may also result from changes in the activity of the hippocampus, extended amygdala, and hypothalamus. In patients suffering from depression, there is an increased activation of microglia in the anterior cingulate cortex, prefrontal cortex, and insula (Swardfager et al., 2016). The alterations in neural function during depression are also reflected in alterations in sleep patterns (Turek, 2005; Franzen and Buysse, 2008; Bower et al., 2010).

There are a number of ways whereby inflammation might act to alter the neural activity responsible for depression. An increase in the formation of reactive oxygen species (ROS), which can exert a profound effect on neuronal function, has been observed in depression (Kunz et al., 2008; Wang et al., 2009; Leonard and Maes 2012; Berk et al., 2013b; Najjar et al., 2013; Barbosa et al., 2014b). Much of the ROS is generated by mitochondria (Zorov et al., 2014) and there is evidence that depression is associated with an increase in mitochondrial function (Berk et al., 2013b). This evidence is supported by the fact that mood disorders have been linked to genetically mediated alterations in mitochondrial function (Anglin et al., 2012). A role for ROS is supported by the observation that the level of glutathione (GSH), which is one of the major antioxidants in neurons (Dean et al., 2009), is depleted in depression (Gawryluk et al., 2011; Berk et al., 2013a). The mood-stabilizing drug Li^+ may reduce oxidative damage by increasing the expression of genes (*GCL* and *GST*) that are responsible for generating GSH (Cui et al., 2007; Shao et al., 2008). In addition, treatment with *N*-acetylcysteine, which acts to restore neuronal GSH levels, is also proving to be an effective treatment of depression (Dean et al., 2011; Berk et al., 2013a).

The increase in ROS that occurs during inflammation may induce depression through a number of mechanisms such as an alteration in the formation of key transmitters such as serotonin and an increase in Ca^{2+} signaling. One of the actions of cytokines and the associated increase in ROS formation is inhibition of serotonin synthesis (Catena-Dell'Osso et al., 2011; Leonard and Maes, 2012), which is a component of the serotonin hypothesis of depression described earlier. Tumor necrosis factor α (TNF-α), which is one of the cytokines, that contributes to depression, acts through the specificity protein 1 to increase the transcription of $InsP_3Rs$ that will enhance Ca^{2+} signaling (Park et al., 2009; Xia et al., 2012). There is a crosstalk between Ca^{2+} and redox signaling in that ROS enhances Ca^{2+}, which then feeds back to enhance ROS (Hidalgo and Donoso, 2008; Paula-Lima et al., 2014: Berridge 2015b). An important action of ROS is to enhance Ca^{2+} signaling by increasing the sensitivity of the inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) (Fig. 1) (Missiaen et al., 1991; Bootman et al., 1992; Bird et al., 1993; Bánsághi et al., 2014) and ryanodine receptors (RYRs) (Terentyev et al., 2008; Donoso et al., 2011) 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 PMCA pump on the plasma membrane (Lock et al., 2011).

One of the important actions of vitamin D is to reduce inflammation (Hewison, 2010; Berk et al., 2013b) (Fig. 2). One way it does this is to reduce the expression of

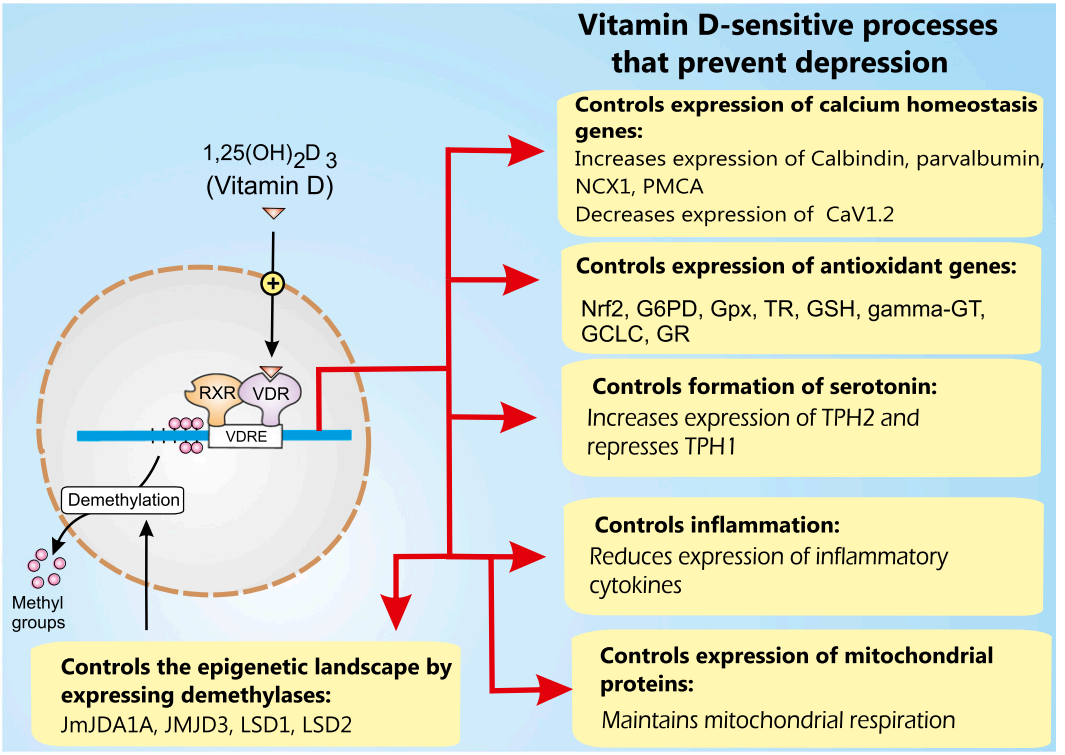

Fig. 2. Vitamin D prevents the onset of depression by activating a number of processes that are critical to maintain normal healthy neurons. Vitamin D enters the nucleus where it associates with the retinoid X receptor (RXR) and then binds to the vitamin D response element (VDRE), which is located on a large number of genes. It maintains Ca^{2+} homeostasis by inducing the expression of calbindin, parvalbumin, Na^{+}/Ca^{2+} exchanger 1 (NCX1), and the plasma membrane Ca^{2+}-ATPase (PMCA) pump. It also regulates Ca^{2+} by reducing the expression of the CaV1.2 calcium channel. It activates expression of many antioxidant genes such as the nuclear factor-erythroid-2-related factor 2 (NRF2), γ-glutamyl transpeptidase (γ-GT), glutamate cysteine ligase (GCLC), glutathione reductase (GR), glutathione peroxidase (Gpx). It controls the formation of serotonin by increasing the level of tryptophan hydroxylase 2 (TPH2) while repressing tryptophan hydroxylase1 (TPH1). It reduces inflammation by reducing the expression of inflammatory cytokines. It regulates the expression of many mitochondrial proteins that maintain normal mitochondrial respiration. Finally, it regulates the epigenetic landscape by promoting the expression of DNA demethylases such as Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) and lysine-specific demethylase 1 and 2 (LSD1, LSD2).

inflammatory cytokines (Beilfuss et al., 2012; Grossmann et al., 2012; Wei and Christakos, 2015), which is a prominent feature of how inflammatory responses lead to depression.

VI. Vitamin D and Depression

There is increasing evidence to show that vitamin D deficiency is associated with depression. Individuals with normal levels of vitamin D have a much lower probability of developing depression (Hoogendijk et al., 2008; Stewart and Hirani, 2010; Chan et al., 2011; Gracious et al., 2012; Anglin et al., 2013; Black et al., 2014; Grudet et al., 2014; von Känel et al., 2015; Kerr et al., 2015; Brouwer-Brolsma et al., 2016; Moy et al., 2016). In patients with heart failure and cancer, depression has been associated with vitamin D deficiency (Björkhem-Bergman and Bergman, 2016; Johansson et al., 2016). Depression in the young has also been linked to vitamin D deficiency (Polak et al., 2014; Kerr et al., 2015). There are indications that depression in younger people has increased in the United Kingdom. Because this may be caused by a deficiency in vitamin D, there is an imperative to measure the levels of vitamin D in school children. A deficiency in vitamin D is also a risk factor for late-life depression (Okereke and Singh, 2016). It has been suggested that vitamin D deficiency may set the stage for both the onset and the progression of depression by acting synergistically with other factors (Cui et al., 2015). The risk of developing depression is reduced in those individuals that have high serum vitamin D levels (Jääskeläinen et al., 2015). Mood symptoms in depression were improved after treatment with vitamin D (Sikoglu et al., 2015; Stokes et al., 2016). There is increasing evidence that one of the main functions of vitamin D is to maintain Ca^{2+} homeostasis as outlined in the phenotypic stability hypothesis (Fig. 2).

The phenotypic stability hypothesis attempts to explain how vitamin D functions to maintain healthy cells to prevent the onset of the many diseases that have been linked to vitamin D deficiency such as depression (Berridge, 2014b; 2015a,b). One of the primary functions of vitamin D is to regulate the expression of those Ca^{2+} signaling toolkit components that function to maintain low cytosolic resting levels of Ca^{2+} (Fig. 2). The phenotypic stability hypothesis explains how vitamin D acts to maintain both Ca^{2+} and redox

homeostasis (Berridge, 2015a,b). For example, vitamin D can increase expression of the plasma membrane Ca^{2+}-ATPase (PMCA) and Na^{+}/Ca^{2+} exchanger 1 (NCX1) that extrude Ca^{2+} and the calbindin D-9k, calbindin D-28k, and parvalbumen that buffer Ca^{2+} (de Viragh et al., 1989; Alexianu et al., 1998; Perez et al., 2008; Wasserman, 2004). Both the calbindins and parvalbumin are significant Ca^{2+} buffers in the cytoplasm of neurons. Vitamin D can also reduce the expression of the L-type CaV1.2 and CaV1.3 channels in hippocampal (Brewer et al., 2001) and cortical neurons (Gezen-Ak et al., 2011). If vitamin D is deficient, the expression of the CaV1.2 and CaV1.3 channels will be increased and the Ca^{2+} pumps and buffers will be reduced and these changes will contribute to the elevated levels of Ca^{2+} that occur in BPD. Ca^{2+} channel blockers can reduce depression (Dubovsky 1993) and there is increasing interest in the possibility that such Ca^{2+} channel antagonists could be developed to treat depression (Cipriani et al., 2016).

Another important function of vitamin D is to control the formation of serotonin and this is another feature of the link between vitamin D deficiency and depression (Patrick and Ames, 2015). It has been shown that one of the actions of vitamin D is to induce the expression of the serotonin-synthesizing gene tryptophan hydroxylase 2 while repressing the expression of tryptophan hydroxylase 1 (Fig. 2). Both tryptophan hydroxylase 1 and tryptophan hydroxylase 2 play a role in serotonin synthesis. Vitamin D may thus prevent depression by maintaining normal serotonin levels.

The basis of the phenotypic stability hypothesis is that vitamin D controls the expression of those genes that are responsible for maintaining both Ca^{2+} and reactive oxygen species (ROS) homeostasis. There is evidence that vitamin D may prevent depression by reducing neural Ca^{2+} levels (Kalueff et al., 2004). The elevation in both Ca^{2+} and ROS levels in neuronal cells that occurs during vitamin D deficiency (Berridge, 2015b) may explain the link to depression. Another important function of vitamin D is to prevent the hypermethylation of gene promotors (Fig. 2). Such epigenetic alterations that lead to a decline in the expression of key signaling proteins are a feature of many neural diseases including depression (Tsankova et al., 2007; Guidotti et al., 2011; Dogra et al., 2016; Saavedra et al., 2016). One of the main functions of vitamin D is to maintain the expression of the DNA demethylases (Fig. 2), such as Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) and lysine-specific demethylase 1 and 2 (LSD1, LSD2) that act to prevent the hypermethylation of promoter regions that are responsible for reducing gene transcription (Pereira et al., 2012). Some of these genes play an important role in the function of GABAergic neurons (Guidotti et al., 2011), which may account for the decline in the size and number of GABAergic neurons that occurs during depression (Rajkowska et al., 2007; Maciag et al., 2010).

VII. Depression and Alzheimer's Disease

Older adults that suffer from depression, especially when associated with mild cognitive impairment, have a strong risk of developing Alzheimer's disease (AD) (Van der Mussele et al., 2014; Mourao et al., 2016; Kaup et al., 2016; Kida et al., 2016; Mirza et al., 2016). What is interesting about both depression and AD is that they both display an increase in Ca^{2+} that has been linked to vitamin D deficiency (Darwish et al., 2015). There also is evidence that a deficiency in vitamin D is linked to a decline in cognition (Annweiler, 2016). Such a decline in cognition is often associated with depression (Dong et al., 2016). Such vitamin D deficiency will result in an elevation of Ca^{2+} that not only induces the decline in cognition and the onset of depression, but it may also set the stage for the initiation of AD. The onset of AD may occur in those individuals who are deficient in vitamin D and thus have abnormally elevated levels of Ca^{2+} that may induce the formation of the pathologic Aβ oligomers that then initiates the onset of AD (Berridge 2016a). Such a possibility is based on the fact that Ca^{2+} acts to stimulate the formation of Aβ (Querfurth and Selkoe, 1994; Green and LaFerla, 2008; Itkin et al., 2011). Such a mechanism would explain how the increase in Ca^{2+} that occurs in depression may trigger the formation of Aβ and thus initiate the onset and progression of AD. In addition to AD, depression may also be associated with the onset of other neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (Réus et al., 2016) that are induced by a dysregulation of Ca^{2+} signaling (Berridge, 2016b).

VIII. Conclusion

Depression arises through a change in neural activity. Normal brain function depends on a fine balance between the activity of the excitatory and inhibitory neurons (E-I balance). There are indications that there is an increase in the levels of glutamate that results in an increase in the activity of the excitatory neurons, whereas there is a decline in the activity and number of the GABAergic inhibitory neurons. This alteration in neural activity is associated with a marked increase in the intracellular level of Ca^{2+}, which may account for the decline in the inhibitory neurons through the inhibition of protein synthesis in the synapses. The increase in glutamate levels may contribute to the increase in Ca^{2+} levels in that glutamate activates both the ionotropic NMDARs that gate Ca^{2+} and the metabotropic glutamatergic receptors such as the mGluR5s and the muscarinic M1 receptors that are coupled to the phosphoinositide signaling pathway that generates

$InsP_3$ that releases Ca^{2+} from the internal stores. The significance of these two pathways is supported by the fact that depression can be alleviated by ketamine that inhibits the NMDARs and scopolamine that inhibits the M1 receptors. The increase in Ca^{2+} may also help to explain why depression is such a strong risk factor for the onset of Alzheimer's disease (AD). It is conceivable that the increase in Ca^{2+} that occurs in depression may act to trigger the activation of amyloid formation that then initiates the onset of AD.

A role for this increase in neuronal Ca^{2+} levels in driving depression may also explain why vitamin D deficiency is a risk factor for depression. Vitamin D functions normally to maintain low intracellular Ca^{2+} levels, but when vitamin D levels decline the levels of Ca^{2+} begin to rise within the cell and this may enhance the onset of depression. This elevation of Ca^{2+} is enhanced by the fact that vitamin D plays an important role in maintain normal mitochondrial respiration. In addition, vitamin D acts to reduce inflammation, it maintains the synthesis of serotonin, and it induces the expression of DNA demethylases that controls the epigenetic landscape, thus enabling gene transcription to continue to maintain normal neuronal activity and to prevent depression.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Berridge.

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