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Review

Vitamin D cell signalling in health and disease

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ABSTRACT

Vitamin D deficiency has been linked to many human diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), hypertension and cardiovascular disease. A Vitamin D phenotypic stability hypothesis, which is developed in this review, attempts to describe how this vital hormone acts to maintain healthy cellular functions. This role of Vitamin D as a guardian of phenotypic stability seems to depend on its ability to maintain the redox and Ca^{2+} signalling systems. It is argued that its primary action is to maintain the expression of those signalling components responsible for stabilizing the low resting state of these two signalling pathways. This phenotypic stability role is facilitated through the ability of vitamin D to increase the expression of both Nrf2 and the anti-ageing protein Klotho, which are also major regulators of Ca^{2+} and redox signalling. A decline in Vitamin D levels will lead to a decline in the stability of this regulatory signalling network and may account for why so many of the major diseases in man, which have been linked to vitamin D deficiency, are associated with a dysregulation in both ROS and Ca^{2+} signalling.

1. Introduction

Vitamin D deficiency is a major world pandemic [1,2]. The first clear indication that such a deficiency can cause disease emerged when rickets was found to result from a decline in calcium (Ca^{2+}) uptake across the intestine caused by low levels in Vitamin D. Subsequently, such Vitamin D deficiencies have been linked to many other human diseases such as Alzheimer's disease (AD), cancer, cardiovascular disease, hypertension, type II diabetes, multiple sclerosis (MS), Parkinson's disease (PD) and various inflammatory disorders such as tuberculosis [3]. The role of vitamin D in preventing rickets depends on its ability to increasing the expression of Ca^{2+} pumps and buffers to facilitate the uptake of Ca^{2+} across the intestine as part of vitamin D's role in regulating whole body Ca^{2+} homoeostasis. In the case of all the other diseases mentioned above, there is no general consensus as to how Vitamin D might function despite the overwhelming evidence of its important health benefits.

In this review, I will develop the concept that Vitamin D may act by maintaining the stability of intracellular signalling pathways. This Vitamin D phenotypic stability hypothesis will be illustrated through its role in regulating the cellular mechanisms responsible for maintaining the Ca^{2+} and redox signalling pathways.

2. Vitamin D biosynthesis, metabolism and mode of action

The active component of vitamin D is 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$] that is formed by a series of reactions that take place in a number of different tissues (Fig. 1). The first reaction is driven by sunlight acting on the skin [4] to photolyze 7-dehydrocholesterol to vitamin D_3 (cholecalciferol), which 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 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 hormone 1,25$(OH)_2D_3$, which will be referred to as Vitamin D that functions to regulate many different cellular processes [5].

Vitamin D has both genomic and non-genomic actions. In the case of the latter, Vitamin D may act through a membrane-associated receptor, such as the rapid-response steroid-binding protein (1,25D_3-MARRS) receptor, to directly influence various signalling pathways such as those operating through the phosphoinositides, Ca^{2+}, cyclic GMP and MAP kinase [6–8]. The genomic action, which is responsible for phenotypic stability, depends on Vitamin D binding to the vitamin D receptor (VDR) to regulate gene transcription (Fig. 2). The VDR is a member of the nuclear receptor family and is widely distributed in many different

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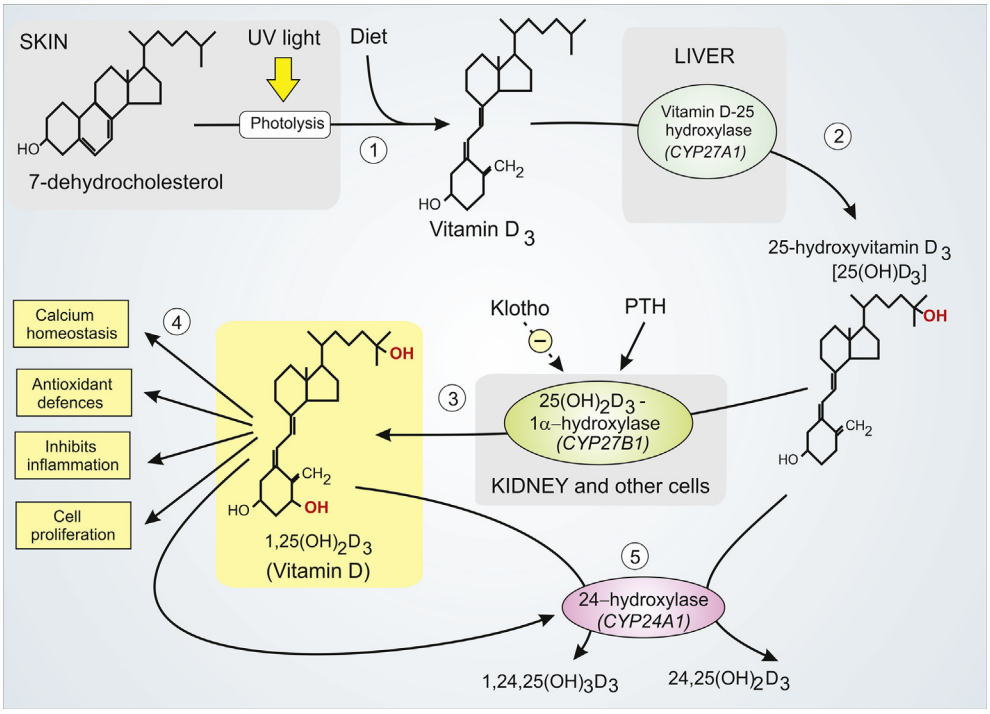

Fig. 1. Vitamin D formation and metabolism. Synthesis of 1,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$] occurs through three steps carried out in separate tissues. 1. The sequence begins in the skin with the UV-dependent photolysis of 7-dehydrocholesterol to Vitamin D3, which can also be obtained from the diet. 2. The next step occurs in the liver, where a vitamin D-25 hydroxylase adds a hydroxyl group to Vitamin D3 to form 25$(OH)D_3$. 3. The final reaction occurs in the kidney and many other cell types where a 1α-hydroxylase adds another hydroxyl group to form 1,25$(OH)_2D_3$. 4. The 1,α25$(OH)_2D_3$ is the active hormone that has multiple signalling functions. 5. Both 1,25$(OH)_2D_3$ and its precursor 25$(OH)D_3$ is metabolized by a 24-hydroxylation step carried out by 1α,25-$(OH)_2$D 24-hydroxylase (encoded by the *CYP24A1*) that convert them to 1,24,25$(OH)_2D_3$ and 24,25$(OH)_2D_3$ respectively. Expression of *CYP24A1* is enhanced by 1,25$(OH)_2D_3$ thus providing a negative feedback loop that regulates the level of this hormone.

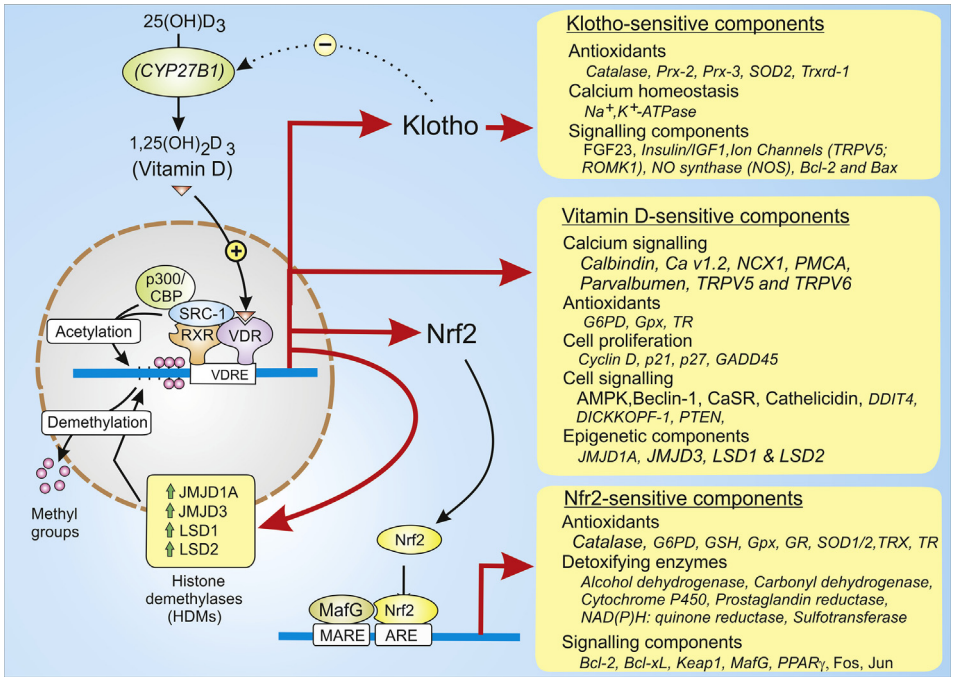

Fig. 2. Vitamin D receptor (VDR) activation. The vitamin D hormone 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] binds to the vitamin D receptor (VDR) that interacts with the retinoid X receptor (RXR) to form the VDR/RXR heterodimer that binds to the vitamin D response element (VDRE). Once in place, the VDR initiates the expression of a large number of genes located in many different cell types to express proteins that function in a number of cellular processes. Vitamin D also increases the expression of both Klotho and Nrf2 that carry out many of its homoeostatic functions.

cell types [9]. The VDR interacts with the retinoid X receptor (RXR) to form a heterodimer that binds to the vitamin D response element (VDRE). There are a large number of vitamin D-sensitive target genes most of which are activated by Vitamin D, but there are some that are repressed. The transcription of these genes contributes to the control of many different cellular processes.

2.1. Vitamin D regulation of epigenetic mechanism

In keeping with its proposed role as a custodian of phenotypic stability, Vitamin D regulates epigenetic mechanisms that maintain the transcription of its target genes that contribute to its regulatory network (Fig. 2) [10]. For example, the VDR/RXR dimer recruits histone acetyltransferases (HATs) such as p300/CBP and steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) that carry out the acetylation reactions that opens up the chromatin structure to facilitate transcription.

Vitamin D also regulates the methylation state of its gene promotors. Methylation of the CpG islands located in such promotor regions can silence many of the genes that are regulated by Vitamin D. For example, the decline in SERCA2a activity in cardiovascular disease may be caused by hypermethylation of its promotor region [11]. Another example is the expression of Klotho, which is another significant custodian of phenotypic stability that is silenced by methylation [12,13]. In cervical cancer, such epigenetic silencing enhances tumorigenesis due to the activation of Wnt signalling that is normally inhibited by Klotho [13]. Such hypermethylation of promotor regions increases during ageing and has been linked to the onset of many diseases such as cancer, cardiovascular and neurodegenerative diseases [14]. For example, hypermethylation of promotors in GABAergic neurons may contribute to the phenotypic remodelling responsible for schizophrenia and bipolar disorder [15]. Given that many of these diseases have also been linked to Vitamin D deficiency, it is not surprising to find that Vitamin D can modulate the epigenetic landscape and this may contribute to its ability to maintain phenotypic stability. This regulation of the epigenome by Vitamin D depends on its ability to induce the expression of a number of key DNA demethylases such as JMJD3, LSD1 and LSD2 [16].

3. Vitamin D a guardian of signalling phenotypic stability

When cells differentiate, they usually stop proliferating and begin to express cell-type-specific signalling mechanisms appropriate to control their designated function. It is essential that such signalling systems are maintained so that they can continue to deliver the signals appropriate for their particular function. There is increasing evidence that vitamin D regulates the expression of many components of different signalling pathways, such as those activated by insulin, ETS, tumour necrosis factor (TNF), ErB, cytokines, TGFβ1, Hedgehog, Notch and Wnt [8,17–19]. In addition, vitamin D can regulate the expression of components that operate in processes such as the cell cycle, autophagy, apoptosis, actin remodelling, cell adhesion, axon guidance and endocytosis [17,20]. Such a role as a custodian of phenotypic stability will be developed further by considering how it regulates the closely related Ca^{2+} and redox signalling pathways.

The first recognized homoeostatic function of Vitamin D was its regulation of whole body Ca^{2+} homoeostasis by promoting Ca^{2+} absorption by the kidney and the intestine. Vitamin D acts by increasing the expression of the main components responsible for epithelial Ca^{2+} transport such as TRPV5, TRPV6, calbindin D-9k, calbindin D-28k, Na^+/Ca^{2+} exchanger (NCX) and plasma membrane Ca^{2+}-ATPase 1b (PMCA1b) [21–25]. A defect in these Vitamin D-dependent Ca^{2+} homoeostatic mechanisms causes rickets in infants and osteomalacia in adults [26,27]. Vitamin D deficiency is now recognized as a major risk factor in many other human diseases. However, there is no explanation as to why Vitamin D deficiency contributes to so many diseases. The primary focus of this review is to develop the hypothesis that Vitamin D acts as a custodian of phenotypic stability by maintaining the integrity of cell signalling pathways. It will be argued that a decline in the stability of signalling systems, such as the Ca^{2+} and redox pathways, may explain why Vitamin deficiency is such a major risk factor in the development of so many diseases.

When considering this custodial action of vitamin D, it is important to include the activity of the nuclear factor-erythroid-2-related factor 2 (Nrf2) and Klotho, because their expression is regulated by Vitamin D (Fig. 2). Both Klotho, which has been implicated in ageing and Nrf2 are included in the hypothesis because they also function to maintain the stability of cell signalling pathways. The vitamin D signalling stability hypothesis proposes that Vitamin D, working in conjunction with Klotho and Nrf2, creates an extensive regulatory network that acts as a custodian to ensure the normal function of both the ROS and Ca^{2+} signalling pathways.

3.1. Vitamin D and the nuclear factor-erythroid-2-related factor 2 (Nrf2)

Vitamin D controls the expression of Nrf2 [28,29], which is a redox-sensitive transcription factor that activates many genes that encode antioxidant and detoxifying enzymes [30–32] (Fig. 2). The transcriptional activity of Nrf-2 is regulated by a number of mechanisms that determines its nuclear import/export balance and its degradation [33–35] (Fig. 3). In the absence of cell stress and reactive oxygen species (ROS), the Nrf2 binds to Kelch-like ECH-associated protein 1 (Keap1), which represses Nrf2 activity and is associated with the ubiquitin ligase Cullin 3 that ubiquitinates Nrf2 resulting in its degradation by the proteasome. When ROS levels rise in response to cell stress, the Keap1 is oxidized and is no longer capable of binding Nrf2, which allows the free Nrf2 to enter the nucleus to increase the expression of many different genes. The release of Nrf2 from Keap-1 can also be induced by a number of agents such as carnosic acid (CA) (derived from the herb rosemary), curcumin (derived from turmeric), dimethyl fumarate (DMF), quercetin (fruits and vegetables), resveratrol (red grapes) and sulforaphane (contained in broccoli, Brussel sprouts and cabbage) [36–38]. This nuclear entry of Nrf2 can also be enhanced following its phosphorylation by a number of protein kinases such as casein kinase II, the MAP kinases (ERK1/2, JNK and p38) and protein kinase C (PKC).

Nrf2 acts by binding to the antioxidant response element (ARE) to enhance the expression of a large number of genes. Nrf2 can increase the expression of Fos and JUN, which then increase the expression of both VDR and RXRα that enhances the ability of cells to respond to low levels of vitamin D [30]. Nrf2 also increases the expression of many antioxidant and detoxifying enzymes such as catalase, glutamate cysteine ligase (GCL) that synthesizes the redox buffer GSH, glutathione S-transferase, haemoxygenase 1 (HO1), NAD(P)H quinone oxidase 1 (NQO1), peroxyredoxins, SOD1, SOD2 and thioredoxin (TRX). Nrf2 also acts to increase the expression of sulfiredoxins that act to reduce the oxidized peroxyredoxins [39,40]. Nrf2 can also influence Ca^{2+} signalling by regulating the expression of Bcl-2 [40,41], which acts by inhibiting the activity of the $InsP_3R$ [42].

The transcriptional activity of Nrf2 can be enhanced by valproate (VPA) and lithium (Li^+) [43–45], which are highly effective in treating bipolar disorder. Valproate acts by inhibiting histone deacetylase (HDAC), which suggests that histone acetylation has an important role in maintaining cellular antioxidant levels in line with the role of Vitamin D in regulating the epigenetic landscape as described earlier (Fig. 2). The export of Nrf2 from the nucleus, which thus terminates its transcriptional activity, is regulated by glycogen synthase kinase-3β (GSK-3β) [46]. VPA and Li^+ were found to act synergistically in

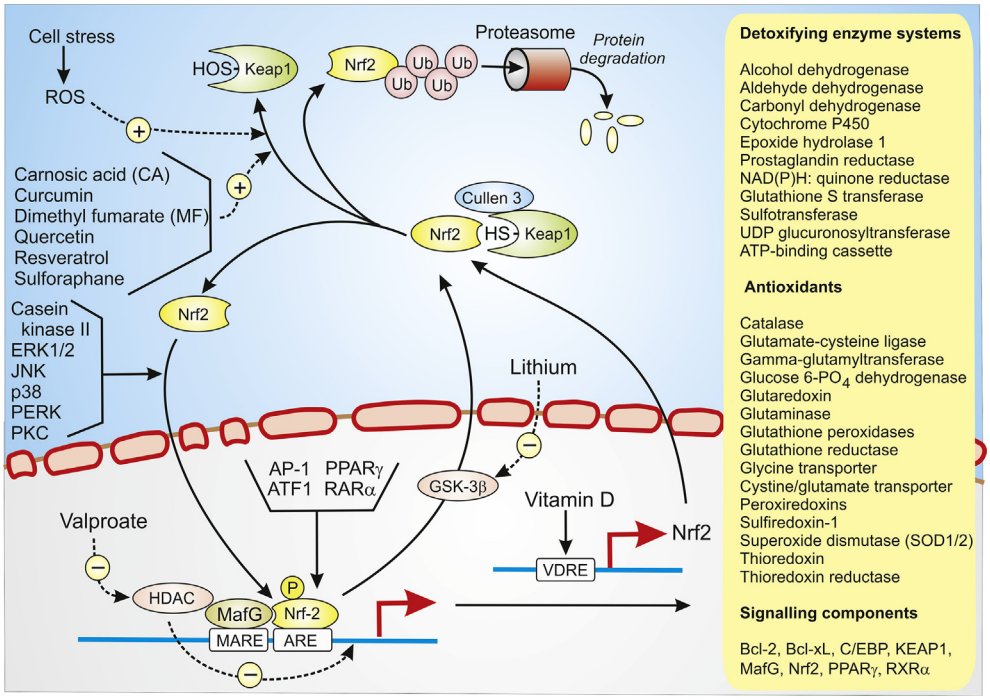

Fig. 3. Regulation of nuclear factor erythroid 2 related factor 2 (Nrf2) function. Vitamin D acts to increase the expression of Nrf2, which is a stress-sensing transcription factor that responds to reactive oxygen species (ROS). In the absence of cell stress and ROS, Nrf-2 binds to Kelch-like ECH-associated protein 1 (Keap1), which is associated with the ubiquitin ligase Cullin 3 that ubiquitinylates Nrf-2 resulting in its degradation by the proteasome. When ROS levels rise, the Keap1 is oxidized and no longer binds to Nrf-2, which then enters the nucleus where it binds to the antioxidant response element (ARE) to enhance the expression of a large number of antioxidants, detoxifying enzymes and various signalling components. See text for further information.

providing a neuroprotective affect and this is of considerable interest as these two drugs are often used in combination to treat bipolar patients that are resistant to either drug alone [44].

There is considerable evidence to suggest that alterations in Nrf2 activity may contribute to numerous diseases [37] many of which have been linked to Vitamin D deficiency, which further emphasizes the importance of considering Nrf2 as it is a key component of the Vitamin D regulatory network.

3.2. Klotho

The expression of Klotho, which is an anti-ageing gene, is regulated by Vitamin D [47,48]. Disruption of the *Klotho* gene in mice induces premature ageing associated with multiple defects such as growth retardation, osteoporosis, cognitive defects, skin atrophy, osteopenia, hyperphosphatemia, endothelial dysfunction, Parkinsonian gait and impaired hearing [49–52]. These ageing-like symptoms displayed by Klotho$^{-/-}$ mice were reversed when Klotho expression was re-induced [53]. A variant of Klotho, known as KL-VS, has also been associated with human ageing. Individuals that are homozygous for the KL-VS alleles have a reduced life span [54]. However, those individuals with the heterozygous genotype have enhanced longevity [54,55]. This human KL-VS variant also has an effect on coronary artery disease [56], hypertension [57] and osteoporosis [58]. Further support for a link to human ageing is the observation that the plasma level of Klotho decreases with age after 40 years [59].

Klotho is a transmembrane protein that contains a large extracellular domain and a much smaller cytosolic domain. Following its cleavage by ADAM 10 and ADAM17, the external domain is shed and functions as a humoral factor to influence a number of signalling pathways and cellular processes (Fig. 2):

- It can inhibit the insulin/IGF1 [50] and Wnt signalling pathways [60]. The ability of Klotho to suppress ageing and oxidative stress may depend on the inhibition of insulin/IGF1 that results in the activation of FOXO that up-regulates the expression of antioxidant enzymes such as mitochondrial manganese-superoxide dismutase (SOD2) and catalase [61].
- Klotho can influence a number of intracellular signalling pathways such as the p53/p21, cyclic AMP and protein kinase C (PKC) pathways [52].
- In the kidney, Klotho facilitates the action of FGF23 by acting as a coreceptor with the FGF receptor [62].
- It acts as a glycosidase to regulate the activity of ion channels such as the TRPV5 channel (Fig. 2) [63,64] and the renal outer medullary potassium channel 1 (ROMK1) [65].
- Klotho may act to protect the cardiovascular system by regulating the NO synthase [66] responsible for generating endothelium-derived nitric oxide (NO) [66,67], which acts to regulates vasomotor tone.
- Klotho can suppress ageing and oxidative stress by increasing the expression of peroxiredoxins (Prx-2 and Prx-3) and thioredoxin reductase 1 (Trxrd-1) that act together to reduce ROS [68]. In Klotho mutant mice, there is a severe decline in cognition and this was associated with an increase in oxidative stress [69]. In addition, there was a decline in the expression of Bcl-2, which would act to enhance the release of internal Ca^{2+} [42]. By contrast, Individuals heterozygous for the KL-VS genetic variant were found to have enhanced cognition and this was associated with increased serum levels of Klotho [70].
- Klotho acts to regulate the communication between neurons and oligodendrites during myelin formation and may thus have important implications for understanding multiple sclerosis [71].

When considering the action of Vitamin D, therefore, it is essential to include the role of Klotho and Nrf2 that carry out many of the actions that have been attributed to Vitamin D. The

importance of considering these three regulators together is emphasized by their close inter-relatedness. In addition to the role of Vitamin D in controlling the expression of Klotho and Nrf2, Klotho feeds back to inhibit the 25(OH)D_3-1α-hydroxylase responsible for the synthesis of Vitamin D (Fig. 2) [47,72], whereas Nrf2 increase the expression of Fos and Jun that feedback to increase the expression of both the VDR and the RXR that mediate Vitamin D's transcriptional activity [73].

3.3. Vitamin D and redox signalling

The internal environment of cells is normally highly reduced, which is critical for normal cell function and survival. Any shift from a reduced to an oxidized state leads to oxidative stress and dysfunction of multiple cellular processes. A large number of proteins, which are sensitive to oxidation, have been referred to as the redox proteome [74]. Cells have evolved a sophisticated mechanism of intracellular signalling that is based on a localized formation of reactive oxygen species (ROS) [75,76], which is a collective term that refers to those oxygen species such as superoxide ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) that act to modify members of the redox proteome, in the same way that protein functions are altered through reversible phosphorylation–dephosphorylation reactions.

There are two main sites of ROS formation: the plasma membrane and the mitochondria (Fig. 4). External signals such as cytokines, growth factors and hormones activate receptors coupled to PtdIns 3-kinase (PI 3-K) to produces PtdIns3,4,5P_3 (PIP_3) that then stimulates NADPH oxidase (NOX) to generate $O_2^{-\bullet}$, which is transformed to H_2O_2 by superoxide dismutase (SOD).

Another important activator of NOX is the receptor for advanced glycation end-product (RAGE), which senses signalling molecules such as the advanced glycation end products (AGEs), high mobility group box 1 (HMGB1), amyloid beta (Aβ), lysophosphatidic acid (LPA), phosphatidylserine, C3a and S100 Ca^{2+}-binding proteins (Fig. 4). RAGE levels are enhanced in a number of diseases states such as cardiovascular disease, Alzheimer's diseases (AD), diabetes, osteoarthritis, and various tumours [77,78]. Many of these diseases are associated with RAGE-induced inflammation so it is significant that Vitamin D may act to modulate RAGE expression [79].

Formation of ROS by the mitochondria is a consequence of its role in energy metabolism. Most of the electrons that enter the electron transport chain are transferred to oxygen in an orderly manner, but there is always a 1–2% leakage during which an electron is transferred directly to oxygen to form $O_2^{-\bullet}$, which is then converted to H_2O_2 by SOD (Fig. 4). Opening of the mitochondrial K_{ATP} channels by diazoxide reduces ROS formation [80,81]. The resulting hyperpolarization of the mitochondrial membrane potential will reduce both mitochondrial Ca^{2+} uptake and the resulting increase in ROS production and this may explain the beneficial effects of diazoxide in neurodegenerative diseases such as AD [81] and multiple sclerosis (MS) [80].

A key element of the normal ROS signalling pathway is its reversibility [82]. Once an oxidized protein has carried out its signalling function, it has to be rapidly reduced to switch it back into an inactive state (Fig. 4). Vitamin D acting in conjunction with Klotho and Nrf2 regulates expression of many of the antioxidant systems that prevent oxidative stress by removing ROS and also by reversing the oxidative changes that occur during normal ROS signalling. Vitamin D regulates expression of the γ-glutamyl transpeptidase (γ-GT), which contributes to the synthesis of GSH

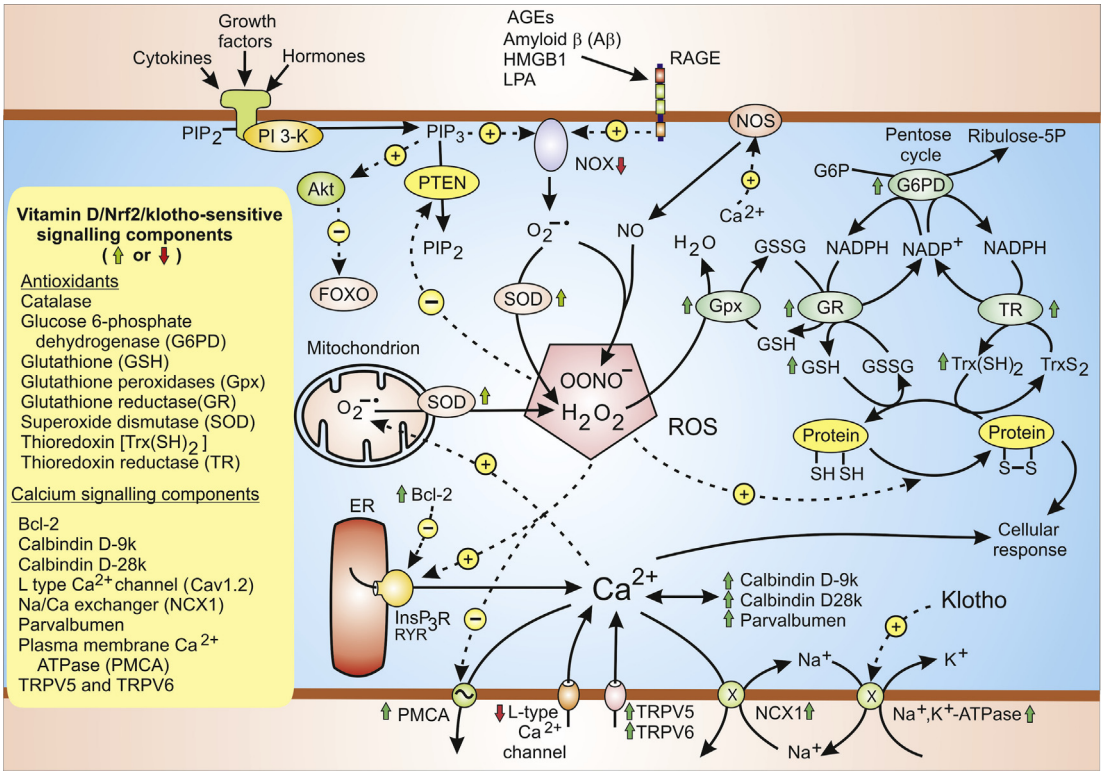

Fig. 4. Vitamin D regulation of Ca^{2+} and redox signalling stability. The arrows represent those signalling components that are either enhanced (green arrows) or reduced (red arrows) by Vitamin D and Nrf-2. The main reactive oxygen species (ROS) in cells are superoxide ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$). The dashed lines represent the many interactions that operate between the Ca^{2+} and redox signalling pathways. The yellow box summarizes some of the redox and Ca^{2+} signalling components that are controlled by the Vitamin D/Nrf2/klotho regulatory system.

[83]. It down-regulates the NOX that generates ROS [84] while upregulating the SOD that rapidly converts $O_2^{-\bullet}$ to H_2O_2 [85]. Vitamin D also increases the activity of G6PD, glutamate cysteine ligase (GCLC) and glutathione reductase (GR) to increase the formation of the major redox buffer GSH [86,87]. Up-regulating the expression of the glutathione peroxidase (Gpx) drives the conversion of H_2O_2 to water [85].

3.4. Vitamin D and Ca^{2+} signalling

Vitamin D may play an important role in maintaining intracellular Ca^{2+} homoeostasis by regulating the expression of many of the Ca^{2+} signalling components that act to reduce the level of Ca^{2+} (Fig. 4) [88]. For example, Vitamin D can reduce the expression of the L-type $Ca_V1.2$ and $Ca_V1.3$ channels [89] and can increase expression of the PMCA and NCX1 that extrude Ca^{2+} and the calbindin D-9k, calbindin D-28k and parvalbumen that buffer Ca^{2+} [21,23,24,90]. In dendritic cells, administering vitamin D acts to increase the expression of NCX that extrudes Ca^{2+} from the cell [91]. Expression of the entry channels TRPV5 and TRPV6 is increased and this has a specific role in promoting the trans-epithelial flux of Ca^{2+} in the kidney and intestine.

A significant feature of redox and Ca^{2+} signalling is the reciprocal interaction that occurs between these two systems (Fig. 4). For example, H_2O_2 can enhance the sensitivity of Ca^{2+} release by inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) [92–96] and ryanodine receptors (RYRs) [97,98] to increase the release of Ca^{2+} from the endoplasmic reticulum (ER). In addition, oxidation can induce an elevation in cytosolic Ca^{2+} by inhibiting the PMCA pumps [99]. In contrast, ROS acts to inhibit Ca^{2+} entry through voltage-operated Ca^{2+} channels such as the T-type channels [100].

Just as redox signalling amplifies Ca^{2+} signalling, an elevation of Ca^{2+} can enhance redox signalling. For example, a persistent elevation in Ca^{2+} can strongly promote mitochondrial ROS formation. When Ca^{2+} builds up within the mitochondrion, it increases mitochondrial metabolism resulting in an increased formation of $O_2^{-\bullet}$ and H_2O_2. In addition, $O_2^{-\bullet}$ formation within the mitochondria can act synergistically with Ca^{2+} to open the mitochondrial permeability transition pore (mPTP) to trigger apoptosis. Another action of Ca^{2+} is to stimulate NOS to increase the formation of NO that contributes to the generation of $ONOO^-$ (Fig. 4).

In summary, guardianship of the redox and Ca^{2+} signalling phenotypes by vitamin D, working together with Nrf2 and Klotho, seems to depend on expression of those components that maintain the low resting state of these two signalling pathways. It will be argued below that dysregulation of these two signalling pathways may play a major role in both ageing and in many of the diseases linked to Vitamin D deficiency.

4. Vitamin D deficiency in ageing and human disease

A deficiency in Vitamin D has been linked to many human diseases [3,22,101–103]. There are multiple polymorphisms of the VDR gene and some of these have been associated with various disorders including autoimmune diseases and cancer. A characteristic of many of these diseases is that they are age-related in that they begin to emerge later in life. The ageing process, which is still not properly understood, seems to be driven by a number of processes that result in a gradual decline in the transcriptional mechanisms responsible for maintaining the cellular processes and signalling mechanisms that constitute each specific cellular phenotype [104]. The fact that this gradual phenotypic erosion occurs simultaneously in cells within different tissues suggests that there may be some commonality in the mechanism driving the ageing process.

An important consequence of the changes in gene transcription and phenotypic stability that occurs during ageing is a decline in the maintenance of mitochondrial energy metabolism and antioxidant defences [105]. Ernesto Carafoli and his colleagues have stressed how mitochondria play a very significant role in the dysregulation of Ca^{2+} signalling that occurs in a number of human diseases [106,107]. Alterations in mitochondrial energy metabolism coupled to a reduction of oxidant defences that occur during Vitamin D deficiency may act together to increase ROS formation and may be one of the universal drivers of age-related diseases. The way in which Vitamin D deficiency and a concomitant decline in both Klotho and Nrf2 function contributes to many diseases may be explained through the ability of these custodial systems to maintain the stability of the ROS and Ca^{2+} signalling systems described earlier.

There is a decline in the level of Vitamin D and Klotho during ageing and this may be related to the age-related decline in the ability of human skin to synthesize Vitamin D [108]. Vitamin D deficiency may contribute to the ageing process through dysregulation of cell signalling pathways such as those regulated by mTORC1 and the Ca^{2+} and redox cell signalling pathways. Dysregulation of Ca^{2+} signalling, which is closely linked to mitochondrial dysfunction and ROS formation, has been implicated in ageing [109].

4.1. Vitamin D and mTOR

One of the proteins that have been linked to ageing and the diseases associated with ageing is the mechanistic target of rapamycin (mTOR) [110–112]. The catalytic mTOR subunit interacts with different subunits to form two separate complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Most information is available for mTORC1 that can be activated by a number of signalling pathways such as growth factors (e.g. insulin/IGF-1), nutrients (e.g. amino acids) and the cellular energy status that is reflected through the ATP/AMP ratio acting through AMPK. These input signals act through the TSC1/TSC2 dimer, which functions as a GTPase activating protein (GAP), to inhibit the GTPase Rheb. When bound to GTP, the Rheb activates mTOR1 that has multiple output signals that regulate protein and lipid synthesis, autophagy, inflammation and glycolysis. Dysregulation of this mTORC1 signalling pathway resulting in enhanced mTORC1 activity has been associated with ageing and many diseases such as Alzheimer's disease, cancer, obesity and type II diabetes [110,113]. Since the same diseases have been linked to Vitamin D deficiency, it is not surprising to find that another significant custodial role of Vitamin D and Klotho is to regulate the activity of the PI3K/Akt/mTOR pathway.

Klotho may reduce ageing by inhibiting the insulin/IGF-1 signalling pathway that is one of the major mechanisms for stimulating mTORC1 activity (Fig. 2). Similarly, Vitamin D also can reduce the activity of the PI3K/Akt/mTOR components of this pathway [114]. For example, a Vitamin D analog 1,25-dihydroxyvitamin D_3-3-bromoacetate (BE) exerts a marked immunosuppressive effect on T cells taken from patients with psoriasis or rheumatoid arthritis (RA) by decreasing the phosphorylation of both Akt and mTOR [115]. This inhibitory activity of Vitamin D depends on two mechanisms. Firstly, Vitamin D acts to increase the expression of PTEN, which functions as a tumour suppressor to inhibit the PI3K/Akt/mTOR pathway [114–116]. Secondly, Vitamin D increases the expression of DNA-damage-inducible transcript 4 (DDIT4), which acts to inhibit the activity of mTORC1 [117].

Regulation of the PI3K/Akt/mTOR pathway by Vitamin D will also have an impact on autophagy. There is increasing evidence that Vitamin D can enhance autophagy [20,118]. In addition to its

regulation of mTORC1 as outlined above, Vitamin D can also enhance autophagy by increasing the expression of AMPK and Beclin-1 that regulate autophagy independently of mTOR [119]. Vitamin D can also modulate autophagy through its regulation of ROS, which can influence many of the autophagic regulatory pathways [120,121]. For example, the ROS that develops during hepatic ischaemia-reperfusion injury induces autophagy that can be reversed by treatment with N-acetylcysteine (NAC) [122]. The autophagic pathway is altered in Parkinson's disease (PD) and this may result from an accumulation of abnormal proteins, because one of the functions of autophagy is to remove damaged molecules such as those that have been oxidized [120].

4.2. Vitamin D deficiency in the age-related decline of cognition

The role of Ca^{2+} dysregulation in ageing, which has long been recognized especially in neurons [123,124], is illustrated by the gradual decline in cognition that occurs in hippocampal neurons [125]. Memory formation depends on the process of long-term potentiation (LTP) driven by local elevations of Ca^{2+} within the dendritic spines that arise from trains of action potentials. In ageing, these action potential trains are terminated prematurely by the development of a slow after hyperpolarization (sAHP) that depend on a build-up of Ca^{2+} that activates SK potassium channels [125] (Fig. 5). This inactivating Ca^{2+} signal, which depends on the opening of L-type voltage-dependent Ca^{2+} channels that provides trigger Ca^{2+} to activate ryanodine receptors (RYRs), inhibits memory in two ways: the sAHP curtails spiking activity necessary for LTP, whereas the increase in Ca^{2+} stimulates calcineurin to induce the long-term depolarization (LTD) that erases memories [125,126]. The development of this sAHP during ageing depend on alterations in both Ca^{2+} and ROS signalling that can be directly attributed to Vitamin D deficiency. An increase in ROS signalling accounts for sensitization of the RYRs that can be reversed by treating neurons with the antioxidant dithiothreitol (DTT) [127]. The onset of the sAHP is also driven by an increase in the expression of L-type channels, which is normally suppressed by Vitamin D [89], and the decrease in the PMA Ca^{2+} pump [128] and buffers, all of which are associated with Vitamin D deficiency. The central role of vitamin D deficiency in this neuronal dysregulation of Ca^{2+} can be reversed by treating neurons with vitamin D that dramatically reduces the sAHP [129]. When tested on ageing rats, Vitamin D was found to enhance hippocampal synaptic function and, more significantly, it could prevent the decline in cognition [130]. Such observations are consistent with the finding that a deficiency in Vitamin D predicts a decline in human cognition that occurs with ageing [131].

Such activation of the RYRs by L-type Ca^{2+} channels, which is responsible for this age-related decline in cognition, is a significant feature of Alzheimer's disease (AD) as discussed later (Fig. 6) [132].

4.3. Vitamin D control of cell proliferation and cancer.

There is strong evidence linking Vitamin D deficiency to many different cancers [3, 102,103,133–135]. Mortality rates from a variety of cancers (colon, breast and prostate) are higher in regions where there is less UV irradiation [22]. In addition, Vitamin D can have anticancer effects in model systems of breast, ovary, lung and prostate cancers [133,136–138]. Vitamin D together with Klotho and Nrf2 seem to act by reducing cell proliferation, angiogenesis and metastasis.

4.3.1. Cell proliferation

There is increasing evidence that a dysregulation of Ca^{2+} signalling contributes to both the proliferation and subsequent metastasis of cancer cells [139–143]. The increase in cancer that occurs during Vitamin D deficiency would be consistent with its role in maintaining Ca^{2+} homoeostasis. Vitamin D can also inhibit cell proliferation by reducing the expression of cyclin D and by promoting the expression of the CDK inhibitors such as p21 and

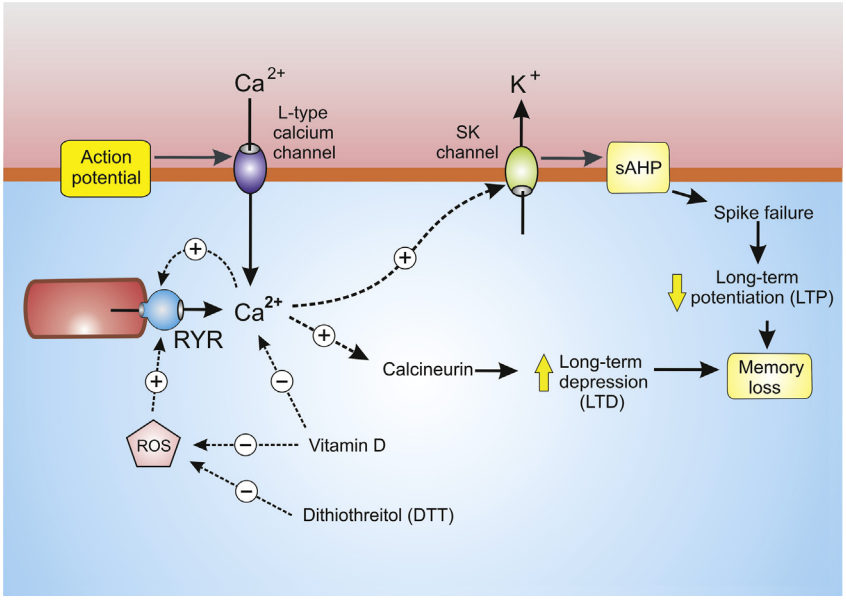

Fig. 5. Age-related memory loss. During ageing, there is a gradual decline in memory associated with an increase in the amplitude of the slow after hyperpolarization (sAHP). During action potentials, the L-type Ca^{2+} channel opens and the entry of external Ca^{2+} is amplified by Ca^{2+} release from the ryanodine receptors (RYRs). The increase in Ca^{2+} causes memory loss through two effects. 1. It acts to open SK K^+ channels to induce the sAHP that results in spike failure and a decline in long-term potentiation (LTP) resulting in memory loss. 2. It activates calcineurin to induce long-term depression (LTD) and memory loss. The dysregulation that occurs with ageing seems to depend on an enhanced sensitivity of the RYR resulting from an increase in ROS because the memory loss can be reversed by treatment with the antioxidant dithiothreitol (DTT) (Bodhinathan et al. [127]) or vitamin D (Brewer et al. [129]).

p27 (Fig. 2) [144,145]. In certain cancers (colon, ovarian and leukaemia), Vitamin D can also induce the expression of growth-arrest and DNA-damage-inducible protein 45 (GADD45) that suppresses cell proliferation during periods of DNA repair [146].

Vitamin D can induce the differentiation of a wide range of cancer cells such as colon, breast, prostate, squamous cell carcinoma, osteosarcoma, and acute myeloid leukaemia (AML) cancer cells [138]. The ability of Vitamin D operating together with carnosic acid to enhance the differentiation of AML cancer cells depends upon the activation of Nrf2 [30]. The ability of curcumin to inhibit the proliferation of breast cancer cells may depend on its activation of Nrf2 (Fig. 3) [147]. Vitamin D and Nrf2 acted together to stimulate γ-glutamylcysteine synthetase (γGCSh) to produce a large increase in the level of the antioxidant GSH. Such suppression of ROS signalling by Vitamin D [86] is significant because many growth factors increase the production of H_2O_2 that facilitates growth factor signalling by inhibiting PTEN that inhibits the hydrolysis of PIP_3 thereby setting up a positive-feedback loop, since the formation of PIP_3 is responsible for stimulating the production of H_2O_2 (Fig. 4). Excess ROS levels may also enhance the ERK/MAPK signalling pathway because the tyrosine protein phosphatases that reverse these pathways are also inhibited by H_2O_2.

The anti-proliferative action of Vitamin D also depends on its suppression of the Wnt/β-catenin signalling pathway [60,148]. Klotho also acts as a tumour suppressor through its ability to inhibit the IGF-1 [149] and Wnt pathways [13,60]. In colon cancer cells, Vitamin D induces the expression of DICKKOPF-1 (DKK-1), which inhibits the Wnt pathway [150], and it reduces the expression of the transcription factor β-catenin [151]. The inhibition of colon cancer cell proliferation by Vitamin D also depends on the activity of the calcium sensing receptor (CaSR) [152], which functions as a tumour suppressor. Expression of the CaSR is enhanced by Vitamin D [153–155]. As described earlier, Vitamin D can also reduce cell proliferation by inhibiting the PI3K/Akt/mTOR signalling pathway [114–117].

4.3.2. Angiogenesis

Tumour growth is very dependent on angiogenesis to provide the blood supply to the developing tumour. Vitamin D may act to reduce the proliferation of the endothelial cells required to form new blood vessels [22,133]. In animal models, the growth of solid tumours is suppressed by vitamin D [156,157]. Vitamin D reduces the expression of the vascular endothelial growth factor (VEGF), which is essential to drive endothelial cell proliferation [137].

4.3.3. Metastasis

During metastasis, degradation of the extracellular matrix enables cancer cells to break away from the original tumour to invade secondary sites. In animal models, vitamin D significantly inhibits prostate cancer metastasis [136]. Vitamin D plays an essential role in maintaining the cell–cell adhesion system by controlling the expression of E-cadherin and some of the other adhesion components such as *Zonula occludens -1 (*ZO-1), ZO-2 and vinculin. The stability of the E-cadherin depends on its interaction with β-catenin, which has dual functions in that it not only acts as a transcription factor to drive proliferation (as described above) but it also acts to stabilize E-cadherin. Vitamin D also reduces the ability of migrating cells to invade and develop a secondary tumour by inhibiting secretion of the matrix metalloproteinase 2 and 9 (MMP-2 and MMP-9), that degrade components of the extracellular matrix such as collagen [137]. The migration of tumour cells is driven by an increase in Ca^{2+} signalling [142]. The ability of Vitamin D to maintain normal Ca^{2+} homoeostasis may explain how it can prevent metastasis.

5. Vitamin D and neurodegenerative diseases

There are an increasing number of studies indicating that a deficiency in vitamin D may contribute to the onset of neurodegenerative diseases such as Alzheimer's disease (AD), autism, depression, Parkinson's disease (PD), schizophrenia and multiple sclerosis (MS) [158,159]. Neurons strongly express the vitamin D receptor (VDR) and VDR polymorphisms have been associated with PD [160], AD [161–164] and have been linked to an age-related decline in cognition. Increased Ca^{2+} and redox signalling, which is a feature of these neurodegenerative diseases [159,165], may reflect a decline in the proposed role of Vitamin D as a guardian of these signalling pathways.

5.1. Vitamin D and Alzheimer's disease (AD)

Alzheimer disease (AD) is a progressive neurodegenerative disorder caused by an initial period of memory loss followed by neuronal cell death and dementia. These changes are induced by extracellular β-amyloid (Aβ) deposits that disrupt neuronal signalling pathways to reduce cognition. The Ca^{2+} hypothesis considers that the loss of memory depends on an upregulation of neuronal Ca^{2+} signalling [166–171]. One of the fascinating aspects of this relationship between Aβ and Ca^{2+} is its reciprocity-as outlined below Aβ acts to increase the level of Ca^{2+}, which then feedsback to increase the formation of Aβ [170,172–175]. Inhibiting the RYR2 with dantrolene that reduces their contribution to the Ca^{2+} signal was found to markedly reduce the formation of AD [175]. The existence of this positive feedback loop offers a possible explanation to account for the onset of AD, which is still a mystery. On the basis of the phenotypic stability hypothesis developed earlier, it is conceivable that the sporadic onset of AD may depend on Vitamin D deficiency that leads to the initial dysregulation of Ca^{2+} that then triggers this positive feedback loop to drive the progression of the disease process. Evidence for such a dysregulation of Ca^{2+} is evident from the studies on age-dependent memory loss described earlier (Fig. 5). The marked elevation in the sAHP, which is driven by an abnormal elevation of Ca^{2+} that is reduced by Vitamin D treatment, is an example of the sort of Ca^{2+} signal that might explain the onset of AD.

The Aβ protein can elevate intracellular Ca^{2+} levels through different mechanisms [176,177]. It can bind to the cellular prion protein (PrP^C), which is coupled to mGluR5 to increase the formation of $InsP_3$ to release internal Ca^{2+} [178]. Aβ can also activate the calcium-sensing receptor (CaSR) on the plasma membrane to increase the formation of $InsP_3$ (Fig. 6) [179–181]. An important role for $InsP_3Rs$ in the pathogenesis of AD has also emerged from studies on the effects of presenilin mutations in familial Alzheimer's disease (FAD). Such presenilin mutations enhance the activity of $InsP_3Rs$ resulting in an increase in Ca^{2+} signalling in both human cells and mouse neurons [182]. This proposed contribution of the $InsP_3R$ in the Ca^{2+} dysregulation is consistent with the observation that caffeine can protect against the cognitive decline in AD. There is increasing evidence that caffeine can reduce the risk of developing AD in studies on both humans and transgenic mice [183,184]. This protective action of caffeine may depend on its ability to markedly inhibit Ca^{2+} release by the $InsP_3R$ (Fig. 6) [185,186].

The Aβ-induced elevation in Ca^{2+} may contribute to AD pathogenesis by activating the mitochondria to increase the generation of ROS [187–192]. A decline in the NADH-dependent regulation of GSH levels accounts for the age-dependent elevation of ROS especially in diseases such as AD [193]. The enhanced ROS formation would further increase Ca^{2+} signalling through the sensitization of both the $InsP_3Rs$ and RYRs (Fig. 6) [194]. ROS-

dependent dysregulation of Ca^{2+} release by neuronal RYRs, which is triggered by entry of Ca^{2+} through the L-type Ca^{2+} channels, is a feature of age-related memory loss as described earlier (Fig. 5) [127]. Such L type Ca^{2+} channel activation of Ca^{2+} release from RYRs also plays a significant role in AD pathology [132,175]. In addition, ROS inhibits the activity of the NMDARs that are responsible for the pulses of Ca^{2+} that initiate memory formation [195,196]. ROS formation may also depend on Aβ activating the RAGE receptor to induce the neuroinflammation that is a significant factor in the neurodegeneration resulting in memory loss [197,198]. The expression of RAGE is markedly enhanced in the brain of AD patients. The G82S polymorphism of RAGE has been linked to AD and results in a faster deterioration in the decline of cognition [199]. The RAGE receptors will increase oxidative stress by activating the NADPH oxidase (NOX) that induces ROS formation (Fig. 6) [200,201].

This dysregulation of both the Ca^{2+} and ROS signalling pathways as a result of the Aβ oligomers acting on both the neurons and microglia (Fig. 6) may result in the persistent elevation in the resting level of Ca^{2+} into the 300 nM range. When Ca^{2+} is measured in the spines and dendrites of cortical pyramidal neurons of transgenic mice, there was a higher than normal resting level in those neurons located close to amyloid deposits [202]. Similarly, the resting level of Ca^{2+} in the cortical neurons of 3xTg-AD animals was 247 nmol/L, which was twice that found in the non-Tg controls (110 nmol/L) [203]. This persistent elevation in the resting level of Ca^{2+} may act to induce long-term depression (LTD) to continuously erase memories shortly after they are formed during the wake period [194,204]. A persistent elevation of Ca^{2+} may also influence cognition by activating the protein phosphatase 1 (PP1) to enhance the activity of striatal-enriched protein tyrosine phosphatase (STEP), which reduces the activity of the MAPK signalling pathway responsible for memory consolidation [205].

There are an increasing number of studies indicating that a deficiency in Vitamin D may contribute to the onset of Alzheimer's disease (AD) [163,206–208]. The decline in cognition that occurs normally in older adults may also be linked to Vitamin D deficiency [164,210–212]. The level of Vitamin D in AD patients is lower than that in controls and enhanced dietary Vitamin D intake lowers the risk of developing AD in a study of older women [213,214]. A clinical trial is in progress to test whether Vitamin D can alleviate some of the degenerative processes associated with AD [215]. Since AD seem to be caused by abnormal elevations in Ca^{2+}, I shall develop the idea that the deleterious effect of Vitamin D deficiency may be explained by a decrease in its normal role as a custodian of Ca^{2+} and ROS homoeostasis (Fig. 4).

The enzymes responsible for both vitamin D formation and degradation are present in the brain and neurons also express the vitamin D receptor (VDR) [158,209]. VDR polymorphisms have been associated with age-related decline in cognition and are also a risk factor for AD [161,163,216]. Vitamin D may protect the brain by regulating the expression of those toolkit components responsible for maintain ROS and Ca^{2+} levels (Fig. 6). For example, vitamin D stimulates the expression of Ca^{2+} pumps (PMCA and NCX) and Ca^{2+} buffers such as CB and parvalbumin [21,23,24]. Neuronal levels of CB are known to be reduced in AD [217]. Mice expressing mutant APP also display a decline in the level of CB especially in the dentate gyrus region of the hippocampus, which functions in learning and memory [218]. While these proposed Vitamin D mechanisms for lowering the level of Ca^{2+} remain to be determined, it is clear that Vitamin D can curb the influx of external Ca^{2+} by reducing the expression of L-type voltage-sensitive channels, which are markedly elevated in rat hippocampal neurons [89].

The deleterious effect of vitamin D deficiency in AD is enhanced by a decline in the expression of its two collaborators Nrf2 and Klotho. The level of Nrf2 is markedly reduced in the brain of patient with AD [219]. Cognition in AD transgenic mice was markedly improved following vector-mediated expression of Nrf2 in the hippocampus [220]. Nrf2 may act to reduce the symptoms of AD by maintaining the cellular level of the redox buffer GSH, which is a critical factor in preventing AD [221]. Nrf2 and Klotho also act to maintain the level of Bcl-2 that inhibits the ability of $InsP_3$ to activate the $InsP_3$ receptors (Fig. 4) thereby reducing the level of Ca^{2+} [42]. Klotho may also play a role in AD. The levels of Klotho in the CSF of patients with AD are lower than those in age-matched controls [222]. In the senescence-accelerated mouse prone-8 (SAMP8) mouse, a decline in the expression of Klotho has been linked to symptoms of AD, including a decline in cognition and an accumulation of amyloid-β_{1-42} [223]. Compounds that enhance the expression of Klotho have been developed as possible therapies for AD [224].

In summary, any reduction in vitamin D, Nrf2 and Klotho levels will result in a decline in the phenotypic stability of signalling systems resulting in elevated neuronal Ca^{2+} and ROS levels and this could contribute to the onset of AD. It is conceivable that this dysregulation of Ca^{2+} initiates the formation of the pathological Aβ oligomers to trigger the Aβ/Ca^{2+} positive feedback loop responsible for the onset of AD. Such a scenario is entirely consistent with the fact the Vitamin D deficiency is such a strong risk factor for AD.

5.2. Vitamin D and Parkinson's disease (PD)

Parkinson's disease (PD) is a neurodegenerative disease characterized by degeneration and death of the dopaminergic (DA) neurons located in the substantia nigra pars compacta (SNc). The single most important risk factor for PD is ageing. There is increasing evidence that PD is linked to a deficiency in vitamin D [208,225,226]. The VDR is strongly expressed in the dopaminergic neurons and VDR polymorphisms have been associated with PD [160,227,228].

The SNc neurons are particularly vulnerable to Ca^{2+} and oxidative stress that arise from the repetitive surges in Ca^{2+} that occur every few seconds during the operation of the dopaminergic neuronal pacemaker mechanism. Oxidative stress in the locus coeruleus and substantia nigra is reduced by a local infusion of Vitamin D [229,230], which may alleviate the deleterious effects of ROS by increasing expression of γ-glutamyl transpeptidase that synthesizes the redox buffer glutathione (GSH) [83]. This is another example of how Vitamin D may protect neurons by maintaining the ROS and Ca^{2+} signalling pathways. The pacemaker activity of these neurons results in the repetitive activation of the Ca_V 1.3 L-type channels that generate regular pulses of Ca^{2+} every second that are amplified by release of internal Ca^{2+} from the ryanodine receptors (RYR) [231,232] (Fig. 7). During Vitamin D deficiency, the Ca_V 1.3 L-type channels will be particularly active because the expression of this channel is reduced by Vitamin D [89]. During the course of each transient, Ca^{2+} is handled by the plasma membrane Ca^{2+} pump (PMCA), the Na^+/Ca^{2+} exchanger (NCX), the cytosolic buffers such as calbindin and mitochondria. These buffers play a relatively minor role because their concentration in these SNc neurons is very low relative to other neurons [232]. Consequently, the mitochondria are under particular pressure because they have to deal with the constant uptake of Ca^{2+} and the associated increase in mitochondrial ROS formation. When vitamin D levels are low, the Ca^{2+} and ROS levels begin to rise and will contribute to the death of these SNc neurons.

Support for this calcium and ROS hypothesis of PD has emerged from the finding that many PD susceptibility genes (*PINK1*, *Parkin* and *DJ-1*) [233,234] function to regulate mitochondrial Ca^{2+} and ROS dynamics. The redox-sensitive protein DJ-1 induces the

migration of Nrf2 into the nucleus where it activates the expression of many antioxidant and detoxifying enzymes [235] (Fig. 7). Another redox-sensitive protein that is mutated in AD is the E3 ubiquitin ligase Parkin, which is a neuroprotective protein that is crucial for the survival of SNc neurons. One of the functions of Parkin is to ubiquitinate Parkin interacting substrate (PARIS) that is then subjected to proteasomal degradation. The activity of Parkin is reduced by ROS allowing PARIS to accumulate and enter the nucleus where it acts as a potent repressor of peroxisome-proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α), which can regulate a number of different processes. One of the actions of PGC-1α is to stimulate the expression of proteins involved in mitochondrial biogenesis and respiration. A decrease in the activity of this system will contribute to oxidative stress and the onset of neuronal cell death. Another action of PGC-1α is to stimulate the expression of both Nrf1 and Nrf2 that maintain the levels of both antioxidants and detoxifying enzymes to protect against the deleterious effects of ROS. A decrease in the activity of these systems, which can be traced back to a ROS-dependent decline in the activity of Parkin and DJ-1, will contribute to the onset of the neuronal cell death that occurs during PD. Vitamin D may act to reduce the onset of PD by maintaining the normal low resting levels of ROS and Ca^{2+} thus reducing the pressure on the mitochondria.

5.3. Vitamin D and schizophrenia

Schizophrenia is a severe psychiatric condition brought about by changes in brain rhythms that drive processes such as perception, memory and consciousness. These changes in brain rhythms are caused by defects in fast-spiking parvalbumin-expressing GABAergic inhibitory interneurons, which often occur during development [236] that results in a decline in the brain rhythm synchronization that is a feature of schizophrenia.

One of the causes of the alterations in neural circuitry seems to be the inflammation resulting from viral infections during pregnancy. Such neuroinflammation induces oxidative stress, which has been implicated in schizophrenia [236–239]. This increase in oxidation reduces the activity of NMDA receptors (NMDARs) and is the basis of the NMDAR hypofunction hypothesis of schizophrenia [240–243]. The ROS responsible for oxidizing the NMDARs depends on the formation of both $O_2^{-\bullet}$ and nitric oxide (NO). The generation of NO by nitric oxide synthase (NOS) is facilitated by the nitric oxide synthase 1 adaptor protein (NOS1AP). The *NOS1AP gene* has been identified as a schizophrenia susceptibility gene [244]. The NO and $O_2^{-\bullet}$ then interact to form peroxynitrite ($ONOO^-$), which is much more reactive than the two parent molecules [245]. The $ONOO^-$ nitrosylates the NMDAR to reduce channel open probability resulting in a decline in the gating of Ca^{2+}. Another cause of NMDAR hypofunction in schizophrenia is a decline in the level of D-serine, which is a co-agonist that acts together with glutamate to open NMDAR channels. The decline in D-serine is also caused by ROS that reduces the activity of the serine racemase (SR) responsible for generating D-serine [246,247]. The expression of D-amino acid oxidase (DAAO) is markedly increased in the brains of patients with schizophrenia, which will also contribute to the decline in D-serine. During inflammation, the excessive $O_2^{-\bullet}$ formation in these inhibitory neurons results in NMDAR hypofunction, which is responsible for the onset of schizophrenia [236,245,248].

There are a number of epidemiological studies that have linked low vitamin D levels to schizophrenia [249] and this association has been supported by a number of studies on animal models [250,251]. Low maternal Vitamin D levels in rats impair brain development resulting in large scale structural changes that resemble those seen in schizophrenia [159,252]. In schizophrenia, gene polymorphisms have been described in the enzymes responsible for the synthesis of GSH [253,254]. Such defects in GSH synthesis may explain the decreased GSH levels found in the prefrontal cortex from patients with schizophrenia and other psychiatric diseases such as major depressive disorder and bipolar disorder [255,256]. The denitrosylation reaction, which functions to reverse the nitrosylation reaction that reduces the activity of the NMDAR, depends on the antioxidants GSH and TRX. The hypothesis of vitamin D acting as a guardian of the ROS signalling pathways is thus entirely consistent with what is known about the signalling defects responsible for schizophrenia [204,257]. Antioxidants such as GSH and NAC, which act to reduce ROS activity, offer a novel pharmacological approach to controlling schizophrenia and other psychiatric conditions such as bipolar disorder (BPD) [253,258,259].

6. Vitamin D and cardiovascular disease

Hypertension and cardiovascular diseases have been linked to vitamin D deficiency [102,103,260–264]. Protection of the cardiovascular system by vitamin D occurs at multiple levels and is highlighted by its role in guarding the stability of the ROS and Ca^{2+} signalling systems that are dysregulated in hypertension, cardiac hypertrophy, congestive heart failure (CHF) and atrial arrhythmias.

6.1. Hypertension

The renin–angiotensin system (RAS) plays a major role in regulating blood pressure. One of the primary actions of vitamin D is to curb the renin-angiotensin system to prevent the hypertension that is a major risk factor for heart disease. In patients with type 2 diabetes, the associated hypertension was improved following vitamin D supplementation [265].

Secretion of renin by renin-producing granular cells is controlled by the cyclic AMP signalling pathway and Vitamin D acts by preventing the cyclic AMP response element-binding protein (CREB) from binding to the renin gene promotor [266]. In mice, deletion of either the enzyme $25(OH)_2D_3$ 1α-hydroxylase (step 3 in Fig. 1) or the VDR resulted in an increase in the renin-angotensin system, hypertension and the onset of cardiac hypertrophy [267–269]. These abnormalities could be corrected by treating the knockout mice with Vitamin D [269] and vitamin D supplementation markedly increased the survival of patients suffering from cardiovascular diseases [263].

The excessive release of renin and the resulting increase in angiotensin II can have multiple effects on some of the key components of the cardiovascular system. One of the actions of angiotensin II is to increase the formation of endothelin-1 (ET-1), which is a potent vasoconstrictor and thus contributes to angiotensin II-induced hypertension [270,271]. This vasoconstrictor action of angiotensin II is markedly enhanced by the fact that it activates the surface NOX1 that increases ROS formation (Fig. 4) [270,272], which would stimulate Ca^{2+} signalling and the subsequent smooth muscle contraction enhances hypertension. Such a mechanism is supported by the observation that vitamin D can reduce enhanced ROS levels in the renal arteries of hypertensive patients by inhibiting the NOX enzyme that generates ROS and by increasing the SOD-1 enzyme that metabolizes ROS [84].

Smooth muscle tone, which determines blood pressure, is also regulated by the endothelial cells that release both relaxing and contracting factors. In hypertension, the release of contracting factors is increased due to an up-regulation of endothelial Ca^{2+} signalling. In the arteries of Vitamin D deficient rats, there is an increase in the basal tone of the mesenteric arteries. In addition, dilation of the arteries by endothelial-derived NO was greatly reduced, which would further contribute to the elevation of blood

pressure [273]. Vitamin D can normalize smooth muscle tone by reducing the entry of the Ca^{2+} that is driving the excessive release of contracting factors [274]. Klotho may also play a role, because its expression is markedly reduced in the spontaneously hypertensive rat (SHR) [275]. A role for Klotho in regulating hypertension was confirmed by the observation that the gene delivery of Klotho stopped the progression of hypertension. Klotho increases the formation of the relaxing factor nitric oxide (NO), [66,67,276]. Klotho also protects endothelial cells against angiotensin-induced ROS formation by increasing the activity of manganese superoxide dismutase (Mn-SOD) [276].

6.2. Cardiac hypertrophy and congestive heart failure (CHF)

The hypertension associated with vitamin D deficiency is driven by an increase in the levels of angiotensin II and ET-1, which are responsible for activating cardiac hypertrophy and congestive heart failure (CHF) [277]. In the presence of these two hormones, which operate through the $InsP_3/Ca^{2+}$ signalling system, there are subtle changes in the spatial and temporal properties of the individual Ca^{2+} transients that drive contraction. The idea is that perinuclear $InsP_3Rs$ function as coincident detectors that respond to both $InsP_3$ and the brief Ca^{2+} transients that induce contraction to create a nuclear Ca^{2+} microdomain responsible for driving the transcriptional processes that initiate hypertrophy [278,279] (Fig. 8). There is now considerable experimental evidence to show that $InsP_3Rs$ can indeed function to enhance nuclear Ca^{2+} transients to control hypertrophy [280–285].

Vitamin D deficiency will promote hypertrophy by increasing Ca^{2+}signalling at a number of levels. In particularly, there is a decrease in the expression of both SERCA and phospholamban (PLN) that contributes to an increased Ca^{2+} transient amplitude and a decline in the recovery phase [286]. Some of these changes are brought about by an increased formation of angiotensin II and ET-1 and increased activity of the ROS/Ca^{2+} duo that then enhances the Ca^{2+} signalling events that initiate the processes of hypertrophy that results in CHF [287,288]. The angiotensin II and ET-1 not only act to increase Ca^{2+}, but they also increase ROS levels by stimulating NOX at the plasma membrane [289–291] (Fig. 8). ROS acts by increasing the activity of the ion channels ($Na_V1.5$ sodium channel, $Ca_V1.2$ channels and RYR2) and pumps (SERCA) that contribute to the Ca^{2+}cycling events that occur during each heartbeat. In addition, ROS can also act indirectly by increasing the activity of protein kinases such as PKA and CaMKIIδ_c that act normally to regulate cardiac activity [291]. These increased ROS and Ca^{2+} signalling processes contribute to the alterations in gene transcription that result in hypertrophy [288]. The cardiac hypertrophy in spontaneously hypertensive rats is reduced by Vitamin D [292] and Vitamin D supplementation can also markedly improve the outcome of patients suffering from heart failure [293].

6.3. Atrial arrhythmias

There is a relationship between vitamin D deficiency and atrial fibrillation (AF) [294–296]. There are indications that excessive activation of type 2 $InsP_3Rs$ may account for the onset of AF. The $InsP_3/Ca^{2+}$ signalling pathway has a major role in modulating the contraction of atrial cells [297–300]. Under normal conditions, these $InsP_3R2s$ play little role in the activation process, but if these atrial cells are stimulated in the presence of ET-1, which is increased during vitamin D deficiency, there is an increase in atrial arrhythmias [298]. Increases in $InsP_3$ are also responsible for the arrhythmogenic action of ET-1 in ventricular cardiac myocytes [301].

Klotho, which is strongly expressed within the sinoatrial (SA) node, may also play an important role in maintaining the rhythmical activity of the heart [302]. In mice that lack Klotho, there is an

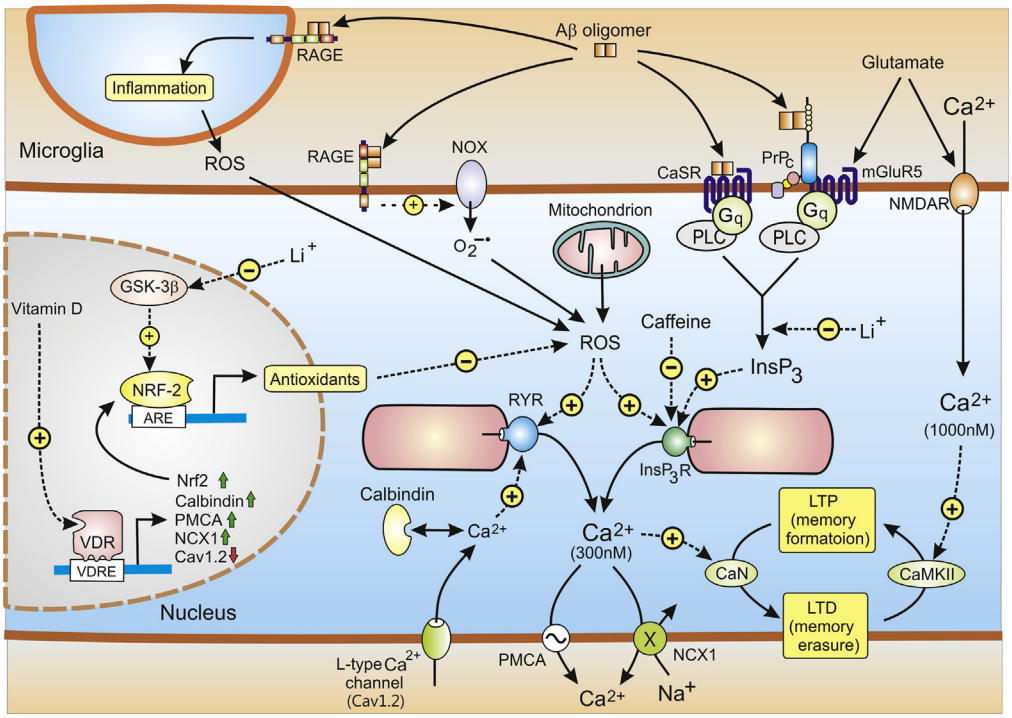

Fig. 6. Dysregulation of Ca^{2+} and redox signalling in Alzheimer's disease (AD). Memories are formed when glutamate initiates brief high concentration Ca^{2+} pulses (1000 nM) to induce memory formation through long-term potentiation (LTP). The calcium hypothesis of AD suggests that the formation of Aβ oligomers brings about an overall increase in Ca^{2+} signalling that results in a permanent elevation in the resting level of Ca^{2+} to 300 nM that then erases memories soon after they are formed by inducing long-term depression (LTD). Aβ oligomers can also enhance the formation of ROS that also acts to increase the level of Ca^{2+}. Vitamin D reduces the risk of AD by acting to maintain Ca^{2+} and redox signalling at its normal low resting levels.

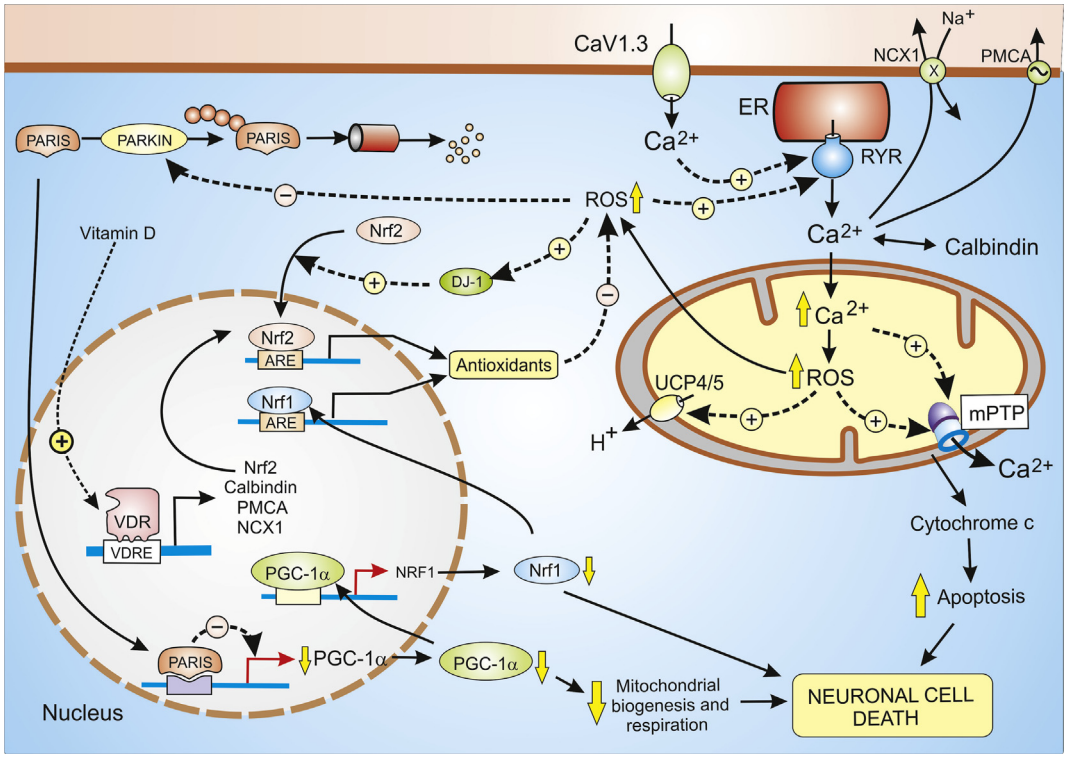

Fig. 7. Redox and Ca^{2+} signalling dysregulation in Parkinson's disease (PD). The redox and Ca^{2+} signalling mechanisms of dopaminergic neurons in the substantia nigra pars compacta (SNc) undergo numerous changes during PD (as illustrated by the yellow arrows). Many of these changes result in elevations of mitochondrial ROS and Ca^{2+} levels that activate the mitochondrial permeability transition pore (mPTP) to induce neuronal cell death. Vitamin D can protect these neurons by increasing the formation of antioxidants and by maintaining the Ca^{2+} pumps and buffers to reduce the pressure of Ca^{2+} on the mitochondria. Vitamin D also acts to reduce expression of the $Ca_V1.3$ L-type channels.

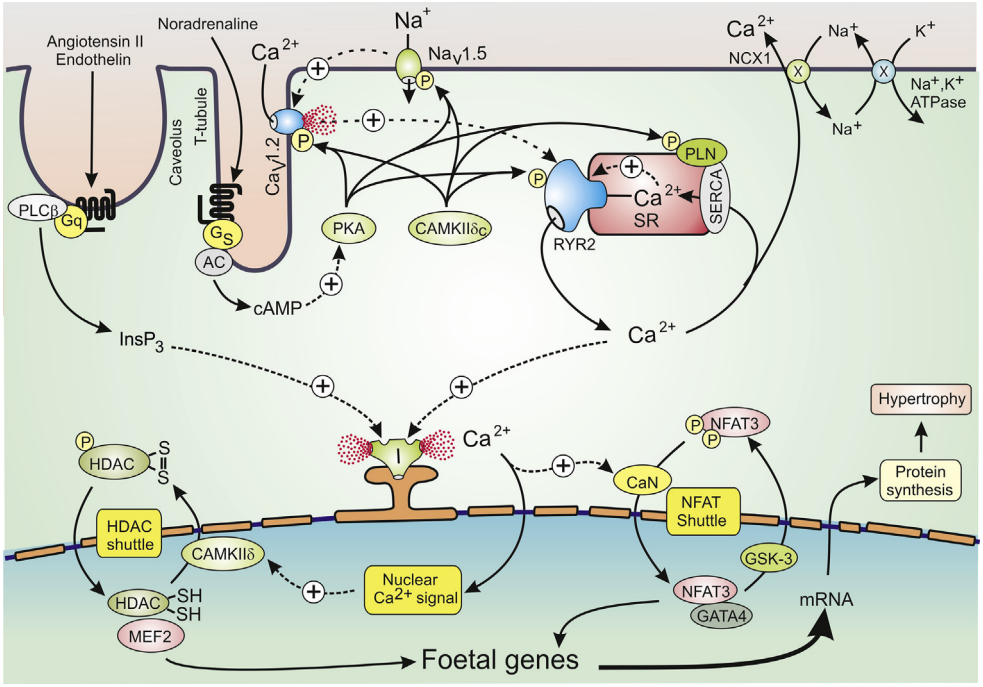

Fig. 8. The role of enhanced Ca^{2+} and ROS levels in cardiac hypertrophy. A number of signalling pathways have been implicated in the activation of hypertrophy. A major pathway is induced by Angiotensin II and endothelin that stimulate the formation of $InsP_3$ that acts together with Ca^{2+} coming from the ryanodine receptor 2 (RYR2) to trigger a nuclear Ca^{2+} signal that activates the HDAC and NFAT shuttles to stimulate the transcription factors responsible for switching on the foetal genes that induce hypertrophy. These hormones also activate NOX to form reactive oxygen species (ROS) that contributes to hypertrophy by altering a number of the Ca^{2+} signalling events.

increased rate of sudden heart death resulting from a dysfunction of the pacemaker activity of the SA node.

7. Vitamin D in adaptive immunity and autoimmune diseases

Vitamin D can modulate both adaptive and innate immunity. A deficiency in Vitamin D has been linked to a number of autoimmune diseases such as rheumatoid arthritis, autoimmune diabetes, multiple sclerosis (MS) and inflammatory bowel disease [303]. In animal models, many of these diseases can be prevented by administering Vitamin D [304,305]. Autoimmunity arises when T helper-1 (Th1) cells are misdirected against self-proteins [303]. Vitamin D acts to represses the proliferation of these Th1 cells and also reduced the secretion of IL-2 and IFNγ [306,307]. It can also reduce B cell proliferation and their differentiation to plasma cells [308]. Vitamin D also acts to increase the activity of the regulatory T cells (Tregs), which play an important role in maintaining immunological self-tolerance [303].

Vitamin D regulates immunity by inhibiting differentiation of the antigen-presenting dendritic cells (DCs) and their ability to stimulate T cells [309–311]. One of the actions of Vitamin D is to inhibit IL-12 [309,312], which helps to promote the development of the Th1 cells described earlier. Vitamin D may also reduce macrophage-mediated inflammatory processes by repressing the expression of cyclooxygenase-2 (COX-2) and increasing expression of thioesterase superfamily member 4 (THEM4), which is a negative regulator of Akt [313]. Just how Vitamin D acts to maintain the normal function of the dendritic cells is not clear, but there are indications that it may depend on its role as a guardian of the Ca^{2+} and ROS signalling pathways. The fact that the antioxidant NAC, which can act to elevate GSH levels, can inhibit dendritic cells is consistent with the fact that there may be an elevation of ROS when Vitamin D levels are low [314]. The Ca^{2+} signalling pathway plays a role in regulating the response of dendritic cells to antigens [91,315] and to ligands that activate the TLRs [316]. The TLR-induced Ca^{2+} signal in dendritic cells was markedly reduced by administering Vitamin D, which acted by increasing the expression of NCX that extrudes Ca^{2+} from the cell [91]. This increase in the expression of a Ca^{2+} extrusion mechanism is an example of how Vitamin D prevents excessive Ca^{2+} signalling. Through this ability to maintain Ca^{2+} homoeostasis, Vitamin D exerts a strong immunosuppressive effect and this could explain how it acts to reduce a number of autoimmune diseases such as multiple sclerosis (MS).

7.1. Vitamin D and multiple sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory demyelinating disease that affects the central nervous system (CNS). The cause of MS is not known, but it has all the hallmarks of an autoimmune disease that results in damage to the oligodendrocytes that are responsible for forming the myelin sheath, which enables neurons to conduct action potentials.

This active demyelination and neurodegeneration in MS is exacerbated by oxidative stress [317,318] resulting from NOX activation, which generate ROS (Fig. 4) [319]. The increase in ROS will result in damage of the mitochondria to generate further ROS [318,320]. This buildup of ROS can reduce the efficiency of glutamate transporters, resulting in raised glutamate concentrations that enhances excitotoxic damage [321] and the inevitable increase in Ca^{2+} will combine to activate the permeability transition pore (PTP) resulting in apoptosis [320].

There is increasing evidence that decreased exposure to light is an important risk factor in MS [322,323]. The incidence of MS is lowest at the equator and increases progressively as one moves towards the poles. High circulating levels of vitamin D have been shown to lower the risk of MS [324]. In mesencephalic dopaminergic neurons, ROS-induced neurotoxicity can be alleviated by vitamin D that acts by increasing the level of GSH [325].

There is increasing genetic evidence to suggest that a decline in Vitamin D activity is linked to MS [326,327] through its immunoregulatory function [249,328,329]. In a mouse model of MS [autoimmune encephalomyelitis (EAE)], administration of Vitamin D was found to improve the inflammatory symptoms typical of MS [330–332].

An exception to the inverse relationship between exposure to sunlight and the incidence of MS has been uncovered in Sardinia. A large proportion of the population in this Mediterranean island suffer from MS. Furthermore, they have normal high levels of Vitamin D, which thus challenged the hypothesis of a link between sunlight exposure and MS. However, subsequent studies revealed that the MS patients in Sardinia have reduced expression of the *Ifng* gene that encodes Interferon-γ (IFN-γ) [333]. The action of Vitamin D is markedly affected by this reduction in *Ifng* gene activity, because IFN-γ plays a role in the expression of the VDR.

All the above evidence suggests that MS may be caused by inflammation and oxidative stress and the latter may be exacerbated by low levels of vitamin D and Nrf2. With regard to the latter, it has been argued that the symptoms of MS might be reduced by using fumaric acid esters such as dimethyl fumarate (DMF) [36,318], which act to stimulate the Nrf2 antioxidant pathway (Fig. 3). In German-speaking countries, fumaric acid esters (FAEs) are already in use to treat psoriasis [318].

8. Vitamin D in innate immunity and infectious disease

Vitamin D has an important role in the innate immune response and its deficiency is linked to a number of infectious diseases such as tuberculosis, septicaemia, influenza, pneumonia and periodontal disease [3,334,335]. Adequate levels of vitamin D are required to initiate antimicrobial responses [336,337]. Indeed, one of the initial responses is to increase the expression of both $25(OH)_2D_3$-1α-hydroxylase (encoded by the *CYP27B1* gene) and the VDR [337]. The former enhances the local production of vitamin D (Fig. 1) that then acts in an autocrine/paracrine manner through the VDR to increase the formation of antimicrobial peptides such as cathelicidin and defensin beta 4 (DEFB4) that act to facilitate the killing of mycobacteria.

8.1. Tuberculosis

Tuberculosis, which is a classic example of how a deficiency in vitamin D can reduce the host's defense to a microbial infection, is an infectious disease caused by *Mycobacterium tuberculosis.* A component of innate immunity is the phagocytosis and elimination of invading organisms by the phagolysosome [338]. For example, the *M. tuberculosis*, which is responsible for tuberculosis, interfers with the membrane trafficking processes responsible for converting the maturing phagosome into the phagolysosome. This “phagosme maturation arrest” enables *M. tuberculosis* to survive and accounts for its persistence in the human population [338].

Patients with tuberculosis have low serum levels of Vitamin D when compared to healthy controls [339] and Vitamin D supplementation can have therapeutic benefits [340,341] in that it can increase macrophage phagocytosis of *M. tuberculosis* and it can increase expression of the antimicrobial peptide cathelicidin [342]. Susceptibility to tuberculosis has been linked to single nucleotide polymorphisms in the VDR thus emphasizing the role of Vitamin D in maintaining an effective immune defence against *M. tuberculosis* [343].

9. Conclusion

The Vitamin D phenotypic stability hypothesis attempts to explain why its deficiency contributes to the development of so many chronic disease states. Many of these diseases are often associated with alterations in both Ca^{2+} and redox signalling, both of which are regulated by Vitamin D operating together with Klotho and Nrf2. The basis of this stability hypothesis, therefore, is that any reduction in Vitamin D levels will contribute to the development of these disease states as a result of elevated Ca^{2+} and redox levels. It is conceivable that the elevation of Ca^{2+} caused by Vitamin D deficiency may be responsible for the onset of many of these diseases. For example, such a mechanism may explain the onset of sporadic Alzheimer's disease where a reciprocal feedback loop exists between the generation of Ca^{2+} and the amyloid proteins. The studies on age-dependent memory loss, which is driven by an elevation in Ca^{2+} caused by Vitamin D deficiency, provides evidence of how such Ca^{2+} dysregulation could trigger the onset of AD. This relationship between Vitamin D deficiency and the decline in memory raises the interesting possibility that Vitamin D deficiency may be a significant determinant in driving the ageing process. There is every reason to suspect that maintaining normal Vitamin D levels could prove efficacious in reducing the rate of aging and the onset of these diseases by preventing the dysregulation of the Ca^{2+} and redox signalling pathways.

Conflict of interest

None declared.

References

[1] M.F. Holick, The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action, Mol. Asp. Med. 29 (2008) 361–368.
[2] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (2011) 1911–1930.
[3] W.R. Grant, The health benefits of solar irradiance and Vitamin D and the consequences of their deprivation, Clinic. Rev. Bone Miner. Metab. 7 (2009) 134–146.
[4] H.F. Holick, J.A. MacLaughlin, M.B. Clark, et al., Photosynthesis of previtamin D3 in human skin and the physiologic consequences, Science 210 (1980) 203–205.
[5] A.S. Dusso, Update on the biologic role of vitamin D on the endocrine system, Curr. Vasc. Pharmacol. 12 (2014) 272–277.
[6] A.S. Dusso, A.J. Brown, E. Slatopolsky, Vitamin D, Am. J. Physiol. Renal Physiol. 289 (2005) F8–F28.
[7] M.R. Haussler, P.W. Jurutka, M. Mizwicki, et al., Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)vitamin D: genomic and non-genomic mechanisms, Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 543–559.
[8] M.J. Larriba, J.M. González-Sancho, F. Bonilla, A. Muñoz, Interaction of vitamin with membrane-based signaling pathways, Front. Physiol. 5 (2014) 60.
[9] J.W. Pike, M.B. Meyer, The Vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-Dihydroxyvitamin D_3, Endocrinol. Metab. Clin. North Am. 39 (2010) 255–269.
[10] I.S. Fetahu, J. Höbaus, E. Kállay, Vitamin D and the epigenome, Front. Physiol. 5 (2014) 164.
[11] Y.H. Kao, C.C. Cheng, Y.C. Chen, et al., Hydralazine-induced promoter demethylation enhances sarcoplasmic reticulum Ca^{2+} -ATPase and calcium homeostasis in cardiac myocytes, Lab. Invest 91 (2011) 1291–1297.
[12] G.D. King, D.L. Rosene, C.R. Abraham, Promoter methylation and age-related downregulation of Klotho in rhesus monkey, Age 34 (2011) 1405–1419.
[13] J. Lee, D.-J. Jeong, J. Kim, et al., Theranti-aging gene *KLOTHO* is a novel target for epigenetic silencing in human cervical carcinoma, Mol. Cancer 9 (2010) 109.
[14] S.D. van Otterdijk, J.C. Mathers, G. Strathdee, Do age-related changes in DNA methylation play a role in the development of age-related diseases? Biochem. Soc. Trans. 41 (2013) 803–807.
[15] A. Guidotti, J. Auta, Y. Chen, et al., Epigenetic GABAergic targets in schizophrenia and bipolar disorder, Neuropharmacology 60 (2011) 1007–1016.
[16] F. Pereira, A. Barbáchano, P.K. Singh, et al., Vitamin D has wide regulatory effects on histone demethylase genes, Cell. Cycle 11 (2012) 1081–1089.
[17] F. Goeman, F. De Nicola, P.D. Meo, et al., VDR primary targets by genome-wide transcriptional profiling, J. Steroid Biochem. Mol. Biol. 143 (2014) 348–356.
[18] N. Ding, R.T. Yu, N. Subramaniam, et al., A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response, Cell 153 (2013) 601–613.
[19] X. Zhang, P. Li, J. Bao, et al., Suppression of death receptor-mediated apoptosis by 1,25-dihydroxyvitamin D3 revealed by microarray analysis, J. Biol. Chem. 280 (2005) 35458–35468.
[20] S. Wu, J. Sun, Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection, Discov. Med. 11 (2011) 325–335.
[21] P.A. de Viragh, K.G. Haglid, M.R. Celio, Parvalbumin increases in the caudate putamen of rats with vitamin D hypervitaminosis, Proc. Natl. Acad. Sci. U S A 86 (1989) 3887–3890.
[22] R. Bouillon, G. Carmeliet, L. Verlinden, et al., Vitamin D and human health: lessons from Vitamin D receptor null mice, Endocr. Rev. 29 (2008) 726–776.
[23] R.H. Wasserman, Vitamin D and the dual processes of intestinal calcium absorption, J. Nutr. 134 (2004) 3137–3139.
[24] A.V. Pérez, G. Picotto, A.R. Carpentieri, et al., Minireview on regulation of intestinal calcium absorption. Emphasis on molecular mechanisms of transcellular pathway, Digestion 77 (2008) 22–34.
[25] M.R. Haussler, G.K. Whitfield, I. Kaneko, et al., Molecular mechanisms of Vitamin D action, Calcif. Tissue Int. 92 (2013) 77–98.
[26] K. Rajakumar, Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective, Pediatrics 112 (2003) e132–e135.
[27] J.Y. Lee, T.V. So, J.A. Thackray, A review on Vitamin D deficiency treatment in pediatric patients, J. Pediatr. Pharmacol. Ther. 18 (2013) 277–291.
[28] R. Lin, Y. Nagai, R. Sladek, et al., Expression profiling in squamous carcinoma cells reveals pleiotropic effects of vitamin D3 analog EB1089 signaling on cell proliferation, differentiation, and immune system regulation, Mol. Endocrinol. 16 (2002) 1243–1256.
[29] K. Nakai, H. Fujii, K.Kono, et al., Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats, Am. J. Hypertens. 27 (2014) 586–595.
[30] L. Bobilev, V. Novik, L. Levi, et al., The Nrf2 transcription factor is a positive regulator of myeloid differentiation of acute myeloid leukemia cells, Cancer Biol. Ther. 11 (2011) 317–329.
[31] M.C. Jaramillo, D.D. Zhang, The emerging role of the Nrf2-Keap1 signaling pathway in cancer, Genes. Dev. 27 (2013) 2179–2191.
[32] J.D. Hayes, A.T. Dinkova-Kostova, The Nrf2 regulatory network provides an interface between redox and intermediary metabolism, Trends Biochem. Sci. 39 (2014) 199–218.
[33] J.W. Kaspar, S.K. Niture, A.K. Jaiswal, Nrf2:INrf2 (Keap1) signaling in oxidative stress, Free Radic. Biol. Med. 47 (2009) 1304–1309.
[34] Y. Mitsuishi, H. Motohashi, M. Yamamoto, The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism, Front. Oncol 2 (2012) 200.
[35] H. Saito, Toxico-pharmacological perspective of the Nrf2-Keap1 defense system against oxidative stress in kidney diseases, Biochem. Pharmacol. 85 (2013) 865–872.
[36] D.H. Lee, R. Gold, R.A. Linker, Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters, Int. J. Mol. Sci. 13 (2012) 11783–11803.
[37] S. Magesh, Y. Chen, L. Hu, Small molecule modulators of Keap1-Nrf2-ARE pathway as potential preventive and therapeutic agents, Med. Res. Rev. 32 (2012) 687–726.
[38] C.-W. Tsai, C.-Y. Lin, Y.-J. Wang, Carnosic acid induces the NAD(P)H: quinone oxidoreductase 1 expression in rat clone 9 cells through the p38/Nuclear factor erythroid-2 related factor 2 pathway, J. Nutr. 141 (2011) 2119–2125.
[39] W. Jeong, S.H. Bae, M.B. Toledano, S.G. Rhee, Role of sulfiredoxin as a regulator of peroxiredoxin function and regulation of its expression, Free Radic. Biol. Med. 53 (2012) 447–456.
[40] Y.-O. Son, P. Pratheeshkumar, R.V. Roy, et al., Carcinogenesis and its role in cadmium-induced Nrf2/p62 signaling in apoptosis resistance, J. Biol. Chem. 289 (2014) 28660–28675.
[41] S.K. Niture, A.K. Jaiswal, Nrf2 protein up-regulates antiapoptotic protein Bcl-2 and prevents cellular apoptosis, J. Biol. Chem. 287 (2012) 9873–9886.
[42] Y.P. Rong, C.W. Distelhorst, Bcl-2 protein family: versatile regulators of calcium signaling in cell survival and apoptosis, Annu. Rev. Physiol. 70 (2008) 73–91.
[43] F. Correa, C. Mallard, M. Nilsson, M. Sandberg, Activated microglia decrease histone acetylation and Nrf2-inducible anti-oxidant defence in astrocytes: restoring effects of inhibitors of HDACs, p38 MAPK and GSK3β, Neurobiol. Dis. 44 (2011) 142–151.
[44] Y. Leng, M.H. Liang, M. Ren, et al., Synergistic neuroprotective effects of lithium and valproic acid or other histone deacetylase inhibitors in neurons: roles of glycogen synthase kinase-3 inhibition, J. Neurosci. 28 (2008) 2576–2588.
[45] A.L. Rojo, P. Rada, J. Egea, et al., Functional interference between glycogen synthase kinase-3 beta and the transcription factor Nrf2 in protection against kainite-induced hippocampal cell death, Mol. Cell. Neurosci. 39 (2008) 125–132.
[46] M. Salazar, A.L. Rojo, D. Velasco, et al., Glycogen synthase kinase-3beta inhibits the xenobiotic and antioxidant cell response by direct phosphorylation and nuclear exclusion of the transcription factor Nrf2, J. Biol. Chem. 281 (2006) 14841–14851.
[47] H. Tsujikawa, Y. Kurotaki, T. Fujimori, K. Fukuda, Y. Nabeshima, Klotho, a gene related to a syndrome resembling human premature aging, functions in

a negative regulatory circuit of vitamin D endocrine system, Mol. Endocrinol. 17 (2003) 2393–2403.
[48] R.E. Forster, P.W. Jurutka, J.-C. Hsieh, et al., Vitamin D receptor controls expression of the anti-aging Klotho gene in mouse and human renal cells, Biochem. Biophys. Res. Commun. 414 (2011) 557–562.
[49] M. Kuro-o, Y. Matsumura, H. Aizawa, et al., Mutation of the mouse klotho gene leads to a syndrome resembling ageing, Nature 390 (1997) 45–51.
[50] H. Kurosu, M. Yamamoto, J.D. Clark, et al., Suppression of aging in mice by the hormone Klotho, Science 309 (2005) 1829–1833.
[51] M. Shiozaki, K. Yoshimura, M. Shibata, et al., Morphological and biochemical signs of age-related neurodegenerative changes in Klotho mutant mice, Neuroscience 152 (2008) 924–941.
[52] Y. Wang, Z. Sun, Current understanding of Klotho, Ageing Res. Rev. 8 (2009) 43–51.
[53] H. Masuda, H. Chikuda, R. Suga, et al., Regulation of multiple ageing-like phenotypes by inducible Klotho gene expression in Klotho mutant mice, Mech. Ageing Dev. 126 (2005) 1274–1283.
[54] D.E. Arking, A. Krebsova, M. Macek Sr., et al., Association of human aging with a functional variant of klotho, Proc. Natl. Acad. Sci. U S A. 99 (2002) 856–861.
[55] L. Invidia, S. Salvioli, S. Altilia, et al., The frequency of Klotho KL-VS polymorphism in a large Italian population, from young subjects to centenarians, suggests the presence of specific time windows for its effect, Biogerontology 11 (2010) 67–73.
[56] D.E. Arking, D.M. Becker, L.R. Yanek, et al., KLOTHO allele status and the risk of early-onset occult coronary artery disease, Am. J. Hum. Genet. 72 (2003) 1154–1161.
[57] D.E. Arking, G. Atzmon, A. Arking, et al., Association between a functional variant of the KLOTHO gene and high-density lipoprotein cholesterol, blood pressure, stroke, and longevity, Circ. Res. 96 (2005) 412–418.
[58] Y. Yamada, F. Ando, N. Niino, H. Shimokata, Association of polymorphisms of the androgen receptor and klotho genes with bone mineral density in Japanese women, J. Mol. Med. 83 (2005) 50–57.
[59] N. Xiao, Y. Zhang, Q. Zheng, J. Gu, Klotho is a serum factor related to human aging, Chin. Med. J. 117 (2004) 742–747.
[60] H. Liu, M.M. Fergusson, R.M. Castilho, et al., Augmented Wnt signaling in a mammalian model of accelerated aging, Science 317 (2007) 803–806.
[61] M. Yamamoto, J.D. Clark, J.V. Pastor, et al., Regulation of oxidative stress by the anti-aging hormone klotho, J. Biol. Chem. 280 (2005) 38029–38034.
[62] I. Urakawa, Y. Yamazaki, T. Shimada, et al., Klotho converts canonical FGF receptor into a specific receptor for FGF23, Nature 444 (2006) 770–774.
[63] Q. Chang, S. Hoefs, A.W. van der Kemp, et al., The beta-glucuronidase Klotho hydrolyzes and activates the TRPV5 channel, Science 310 (2005) 490–493.
[64] S.K. Cha, B. Ortega, H. Kurosu, et al., Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1, Proc. Natl. Acad. Sci. U S A. 105 (2010) 9805–9810.
[65] S.K. Cha, M.C. Hu, H. Kurosu, et al., Regulation of renal outer medullary potassium channel and renal K(+) excretion by Klotho, Mol. Pharmacol. 76 (2009) 38–46.
[66] K. Fukino, T. Suzuki, Y. Saito, et al., Regulation of angiogenesis by the aging suppressor gene Klotho, Biochem. Biophys. Res. Commun. 293 (2002) 332–337.
[67] Y. Saito, T. Yamagishi, T. Nakamura, et al., Klotho protein protects against endothelial dysfunction, Biochem. Biophys. Res. Commun. 248 (1998) 324–329.
[68] E. Zeldich, C.-D. Chen, T.A. Colvin, et al., The neuroprotective Effect of Klotho is mediated via regulation of members of the redox system, J. Biol. Chem. 289 (2014) 24700–24715.
[69] T. Nagai, K. Yamada, H.C. Kim, et al., Cognition impairment in the genetic model of aging klotho gene mutant mice: a role of oxidative stress, Faseb. J. 17 (2003) 50–52.
[70] D.B. Dubal, J.S. Yokoyama, L. Zhu, et al., Life extension factor klotho enhances cognition, Cell. Rep. 7 (2014) 1065–1076.
[71] C.D. Chen, J.A. Sloane, H. Li, et al., The antiaging protein Klotho enhances oligodendrocyte maturation and myelination of the CNS, J. Neurosci. 33 (2013) 1927–1939.
[72] T. Yoshida, T. Fujimori, Y. Nabeshima, Mediation of unusually high concentrations of 1,25 dihydroxyvitamin D in homozygous klotho mutant mice by increased expression of renal 1α-hydroxylase gene, Endocrinology 143 (2002) 683–689.
[73] I. Bobilev, V. Novik, I. Levi, et al., The Nrf2 transcription factor is a positive regulator of myeloid differentiation of acute myeloid leukemia cells, Cancer Biol. Ther. 11 (2011) 317–329.
[74] Y.-M. Go, D.P. Jones, The redox proteme, J. Biol. Chem. 288 (2013) 26512–26520.
[75] T. Finkel, Signal transduction by reactive oxygen species, J. Cell. Biol. 194 (2011) 7–15.
[76] H. Sies, Role of metabolic H_2O_2 generation: redox signalling and oxidative stress, J. Biol. Chem. 289 (2014) 8735–8741.
[77] G. Daffu, C.H. del Pozo, K.M. O'Shea, et al., Radical roles for RAGE in the pathogenesis of oxidative stress in cardiovascular diseases and beyond, Int. J. Mol. Sci. 14 (2013) 19891–19910.
[78] J. Xie, J.D. Méndez, V. Méndez-Valenzuela, M.M. Aguilar-Hernández, Cellular signalling of the receptor for advanced glycation end products (RAGE), Cell. Signal 25 (2013) 2185–2197.
[79] T.W. Lee, Y.H. Kao, T.I. Lee, et al., Calcitriol modulates receptor for advanced glycation end products (RAGE) in diabetic hearts, Int. J. Cardiol. 173 (2014) 236–241.
[80] N. Virgili, P. Mancera, B. Wappenhans, et al., K_{ATP} channel opener diazoxide prevents neurodegeneration: a new mechanism of action via antioxidative pathway activation, PLoS One 8 (9) (2013) e75189.
[81] X. Zeng, T. Wang, L. Jiang, et al., Diazoxide and cyclosporin A protect primary cholinergic neurons against beta-amyloid (1-42)-induced cytotoxicity, Neurol. Res. 35 (2013) 529–536.
[82] C.M. Cremers, U. Jakob, Oxidant sensing by reversible disulphide bond formation, J. Biol. Chem. 288 (2013) 26489–26496.
[83] E. Garcion, L. Sindji, G. Leblondel, et al., 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes, J. Neurochem. 73 (1999) 859–866.
[84] J.H. Dong, S.L. Wong, C.W. Lau, et al., Calcitriol protects renovascular function in hypertension by downregulating angiotensin II type 1 receptors and reducing oxidative stress, Eur. Heart J. 33 (2012) 2980–2990.
[85] T.L. Briones, H. Darwish, Decrease in age-related tau hyperphosphorylation and cognitive improvement following vitamin D supplementation are associated with modulation of brain energy metabolism and redox state, Neuroscience 262 (2014) 143–155.
[86] B.-Y. Bao, H.-J. Ting, J.-W. Hsu, Y.-F. Lee, Protective role of 1a, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells, Int. J. Cancer 122 (2008) 2699–2706.
[87] S.K. Jain, D. Micinski, Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes, Biochem. Biophys. Res. Commun. 437 (2013) 7–11.
[88] D.D. Bikle, Vitamin D: an ancient hormone, Expt. Dermatol. 20 (2010) 7–13.
[89] L.D. Brewer, V. Thibault, K.C. Chen, et al., Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type Ca^{2+} channel expression in hippocampal neurons, J. Neurosci. 21 (2001) 98–108.
[90] M.E. Alexianu, E. Robbins, S. Carswell, S.H. Appel, 1 Alpha,25 dihydroxyvitamin D-3-dependent up-regulation of calcium-binding proteins in motoneuron cells, J. Neurosci. Res. 51 (1998) 58–66.
[91] E. Shumilina, N.T. Xuan, N. Matzner, et al., Regulation of calcium signaling in dendritic cells by 1,25-dihydroxyvitamin D3, Faseb. J. 24 (2010) 1989–1996.
[92] L. Missiaen, C.W. Taylor, M.J. Berridge, Spontaneous calcium release from inositol trisphosphate-sensitive calcium stores, Nature 352 (1991) 241–244.
[93] M.D. Bootman, C.W. Taylor, M.J. Berridge, The thiol reagent, thimerosal, evokes Ca^{2+} spikes in HeLa cells by sensitizing the inositol 1,4,5-trisphosphate receptor, J. Biol. Chem. 267 (1992) 25113–25119.
[94] G.S. Bird, G.M. Burgess, J.W. . Putney Jr., Sulfhydryl reagents and cAMP-dependent kinase increase the sensitivity of the inositol 1,4,5-trisphosphate receptor in hepatocytes, J. Biol. Chem. 268 (1993) 17917–17923.
[95] J.T. Lock, W.G. Sinkins, W.P. Schilling, Protein S-glutathionylation enhances Ca^{2+}-induced Ca^{2+} release via the IP_3 receptor in cultured aortic endothelial cells, J. Physiol. 590 (2012) 3431–3447.
[96] S. Bánsághi, T. Golenár, M. Madesh, et al., Isoform- and species-specific control of inositol 1,4,5-trisphosphate (IP_3) receptors by reactive oxygen species, J. Biol. Chem. 289 (2014) 8170–8181.
[97] P. Donoso, G. Sanchez, R. Bull, C. Hidalgo, Modulation of cardiac ryanodine receptor activity by ROS and RNS, Front. Biosci. 16 (2011) 553–567.
[98] B.L. Prosser, R.J. Khairallah, A.P. Ziman, et al., X-ROS signaling in the heart and skeletal muscle: stretch-dependent local ROS regulates $[Ca^{2+}](i)$, J. Mol. Cel.l Cardiol. 58 (2013) 172–181.
[99] J.T. Lock, W.G. Sinkins, W.P. Schilling, Effect of protein S-glutathionylation on Ca^{2+} homeostasis in cultured aortic endothelial cells, Am. J. Physiol. Heart. Circ. Physiol. 300 (2011) H493–H506.
[100] P.M. Joksovic, M.T. Nelson, V. Jevtovic-Todorovic, et al., $Ca_V3.2$ is the major molecular substrate for redox regulation of T-type Ca^{2+} channels in the rat and mouse thalamus, J. Physiol. 574 (2006) 415–430.
[101] S. Nagpal, S. Na, R. Rathnachalam, Noncalcemic actions of vitamin D receptor ligands, Endocr. Rev. 26 (2005) 662–687.
[102] R.H. Heaney, Vitamin D in health and disease Clin, J. Am. Soc. Nephrol. 3 (2008) 1535–1541.
[103] A. Hossein-nezhad, M.F. Holick, Vitamin D for health: a global perspective, Mayo Clin. Proc. 88 (2013) 720–755.
[104] C. López-Otín, M.A. Blasco, L. Partridge, et al., The hallmarks of ageing, Cell 153 (2013) 1194–1217.
[105] K.N. Lewis, J. Mele, J.D. Hayes, R. Buffenstein, Nrf2, a guardian of healthspan and gatekeeper of species longevity, Integr. Comp. Biol. 50 (2010) 829–843.
[106] L. Fedrizzi, E. Carafoli, Ca^{2+} dysfunction in neurodegenerative disorders: Alzheimer's disease, Biofactors 37 (2011) 189–196.
[107] M. Brini, T. Cali, D. Ottolini, E. Carafoli, Neuronal calcium signalling: function in health and disease, Cell. Mol. Life Sci. 71 (2014) 2787–2814.
[108] J. MacLaughlin, M.F. Holick, Aging decreases the capacity of human skin to produce vitamin D3, J. Clin. Invest. 76 (1985) 1536–1538.
[109] J.-P. Decuypere, G. Monaco, L. Missiaen, et al., IP_3 receptors, mitochondria, and Ca^{2+} signaling: implications for aging, J. Aging Res. 2011 (2011) 920178.
[110] M. Laplante, D.S. Sabatini, mTOR signalling in growth control and disease, Cell 149 (2012) 274–293.
[111] S.C. Johnson, P.S. Rabinovitch, M. Kaeberlein, mTOR is a key modulator of ageing and age-related disease, Nature 493 (2013) 338–345.

[112] D. Ehninger, F. Nef, K. Xie, Longevity, aging and repamycin, Cell. Mol. Life Sci. 71 (2014) (2014) 4325–4346.
[113] E. Dazert, M.N. Hall, mTOR signaling in disease, Curr. Opin. Cell Biol. 23 (2011) 744–755.
[114] J. O'Kelly, M. Uskokovic, N. Lemp, J. Vadgamac, H.P. Koeffler, Novel Gemini-vitamin D3 analog inhibits tumor cell growth and modulates the Akt/mTOR signaling pathway, J. Steroid Biochem. Mol. Biol. 100 (2006) 107–116.
[115] A. Datta-Mitra, R. Mitra, S.P. Ray, et al., 1,25-dihydroxyvitamin D3-3-bromoacetate, a novel vitamin D analog induces immunosuppression through PI3K/Akt/mTOR signaling cascade, Int. Immunopharmacol. 17 (2013) 744–751.
[116] J. Hisatake, J. O'Kelly, M.R. Uskokovic, et al., Novel vitamin D(3) analog, 21-(3-methyl-3-hydroxy-butyl)-19-nor D(3), that modulates cell growth, differentiation, apoptosis, cell cycle, and induction of PTEN in leukemic cells, Blood 97 (2001) 2427–2433.
[117] T.S. Lisse, T. Liu, M. Irmler, et al., Gene targeting by the vitamin D response element binding protein reveals a role for vitamin D in osteoblast mTOR signaling, Faseb. J. 25 (2011) 937–947.
[118] J.M. Yuk, D.M. Shin, H.M. Lee, et al., Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin, Cell Host Microbe 6 (2009) 231–243.
[119] W. Jang, H.J. Kim, H. Li, et al., 1,25-Dyhydroxyvitamin D3 attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy, Biochem. Biophys. Res. Commun. 451 (2014) 142–147.
[120] J. Lee, S. Giordano, J. Zhang, Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling, Biochem. J. 441 (2012) 523–540.
[121] G. Filomeni, D. De Zio, F. Cecconi, Oxidative stress and autophagy: the clash between damage and metabolic needs, Cell Death Differ. (2014 Sep 26), http://dx.doi.org/10.1038/cdd.2014.150.
[122] C. Wang, K. Chen, Y. Xia, et al., N-Acetylcysteine attenuates ischemia-reperfusion-induced apoptosis and autophagy in mouse liver via regulation of the ROS/JNK/Bcl-2 pathway, PLoS One 9 (2014) e108855.
[123] Z.S. Khachaturian, Hypothesis on the regulation of cytosol calcium concentration and the aging brain, Neurobiol. Aging 8 (1987) 345–346.
[124] P.W. Landfield, 'Increased calcium-current' hypothesis of brain aging, Neurobiol. Aging 8 (1987) 346–347.
[125] T.C. Foster, Calcium homeostasis and modulation of synaptic plasticity in the aged brain, Aging Cell. 6 (2007) 319–325.
[126] T.C. Foster, K.M. Sharrow, J.R. Masse, et al., Calcineurin links Ca^{2+} dysregulation with brain aging, J. Neurosci. 21 (2001) 4066–4073.
[127] K. Bodhinathan, A. Kumar, T.C. Foster, Redox sensitive calcium stores underlie enhanced after hyperpolarization of aged neurons: role for ryanodine receptor mediated calcium signaling, J. Neurophysiol. 104 (2010) 2586–2593.
[128] A. Zaidi, L. Gao, T.C. Squier, M.L. Michaelis, Age-related decrease in brain synaptic membrane Ca^{2+}-ATPase in F344/BNF1 rats, Neurobiol. Aging 19 (1998) 487–495.
[129] L.D. Brewer, N.M. Porter, D.S. Kerr, P.W. Landfield, O. Thibault, Chronic 1alpha,25-(OH)2 vitamin D3 treatment reduces Ca^{2+} -mediated hippocampal biomarkers of aging, Cell. Calcium 40 (2006) (2006) 277–286.
[130] C.S. Latimera, L.D. Brewer, J.L. Searcy, et al., Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats, Proc. Natl. Acad. Sci. U S A. 111 (2014) E4359–E4366.
[131] E.D. Toffanello, A. Coin, E. Perissinotto, et al., Vitamin D deficiency predicts cognitive decline in older men and women: the Pro.V.A. Study, Neurology 83 (2014) 2292–2298.
[132] M.E. Koran, T.J. Hohman, T.A. Thornton-Wells, Genetic interactions found between calcium channel genes modulate amyloid load measured by positron emission tomography, Hum. Genet. 133 (2014) 85–93.
[133] K.K. Deeb, D.L. Trump, C.S. Johnson, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, Nat. Rev. Cancer 7 (2007) 684–700.
[134] A.E. Gorham, S.B. Mohr, F.C. Garland, C.F. Garland, Vitamin D for cancer prevention and survival, Clinic. Rev. Bone Miner. Metab 7 (2009) 159–175.
[135] D. Feldman, A.V. Krishnan, S. Swami, E. Giovannucci, B.J. Feldman, The role of vitamin D in reducing cancer risk and progression, Nat. Rev. Cancer 14 (2014) 342–357.
[136] B.L. Lokeshwar, G.G. Schwartz, M.G. Selzer, et al., Inhibition of prostate cancer metastasis in vivo: a comparison of 1,25–dihydroxyvitamin D (calcitriol) and EB1089, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 241–248.
[137] K. Nakagawa, A. Kawaura, S. Kato, et al., 1α,25-Dihydroxyvitamin D(3) is a preventive factor in the metastasis of lung cancer, Carcinogenesis 26 (2005) 429–440.
[138] E. Gocek, G.P. Studzinski, Vitamin D and differentiation in cancer, Crit. Rev. Clin. Lab. Sci. 46 (2009) 190–209.
[139] G.R. Monteith, D. McAndrew, H.M. Faddy, et al., Calcium and cancer: targeting Ca^{2+} transport, Nat. Rev. Cancer 7 (2009) 519–530.
[140] H.L. Roderick, S.J. Cook, Ca^{2+} signalling checkpoints in cancer: remodelling Ca^{2+} for cancer cell proliferation and survival, Nat. Rev. 8 (2008) 361–375.
[141] C. Szatkowski, J.B. Parys, H. Ouadid-Ahidouch, F. Matifat, Inositol 1,4,5-trisphosphate-induced Ca^{2+} signalling is involved in estra-diol-induced breast cancer epithelial cell growth, Mol. Cancer 9 (2010) 156.
[142] N. Prevarskaya, R. Skryma, Y. Shuba, Calcium in tumour metastasis: new roles for known actors, Nat. Rev. Cancer 11 (2011) 609–618.
[143] N. Prevarskaya, H. Ouadid-Ahidouch, R. Skryma, Y. Shuba, Remodelling of Ca^{2+} transport in cancer: how it contributes to cancer hallmarks? Philos. Trans. R. Soc. Lond B Biol. Sci. 369 (1638) (2014) 20130097.
[144] L. Verlinden, A. Verstuyf, R. Convents, et al., Action of 1,25(OH)2D3 on the cell cycle genes, cyclin D1, p21 and p27 inMCF-7 cells, Mol. Cell. Endocrinol. 142 (1998) 57–65.
[145] S.S. Jensen, W.S. Madsen, J. Lukas, et al., Inhibitory effects of 1a,25-Dihydroxyvitamin D_3 on the G1–S phase-controlling machinery, Mol. Endocrinol. 15 (2001) 1370–1380.
[146] F. Jiang, P. Li, A.J. Fornace Jr., S.V. Nicosia, W. Bai, G2/M arrest by 1,25-dihydroxyvitamin D3 in ovarian cancer cells mediated through the induction of GADD45 via an exonic enhancer, J. Biol. Chem. 278 (2003) 48030–48040.
[147] B. Chen, Y. Zhang, Y. Wang, et al., Curcumin inhibits proliferation of breast cancer cells through Nrf2-mediated down-regulation of Fen1 expression, J. Steroid Biochem. Mol. Biol 143 (2014) 11–18.
[148] R.E. Stubbins, A. Hakeem, N.P. Nunez, Using components of the Vitamin D pathway to prevent/treat colon cancer, Nutr. Rev. 70 (2012) 721–729.
[149] I. Wolf, S. Levanon-Cohen, S. Bose, et al., Klotho: a tumor suppressor and a modulator of the IGF-1 and FGF pathways in human breast cancer, Oncogene 27 (2008) 7094–7105.
[150] O. Aguilera, C. Peña, J. Garcia, et al., The Wnt antagonist DICKKOPF-1 gene is induced by 1alpha,25-dihydroxyvitamin D3 associated to the differentiation of human colon cancer cells, Carcinogenesis 28 (2007) 1877–1884.
[151] H. Pálmer, J. González-Sancho, J. Espada, et al., Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of β-catenin signaling, J. Cell. Biol. 154 (2001) 369–387.
[152] G. Liu, X. Hu, S. Chakrabarty, Vitamin D mediates its action in human colon carcinoma cells in a calcium-sensing receptor-dependent manner: down-regulates malignant cell behavior and the expression of thymidylate synthase and survivin and promotes cellular sensitivity to 5-FU, Int. J. Cancer 126 (2010) 631–639.
[153] L. Canaff, G.N. Hendy, Human calcium-sensing receptor gene. Vitamin D response elements in promoters P1 and P2 confer transcriptional responsive-ness to 1,25-dihydroxyvitamin D, J. Biol. Chem. 277 (2002) 30337–30350.
[154] S. Chakrabarty, H. Wang, L. Canaff, et al., Calcium sensing receptor in human Colon Carcinoma: interaction with Ca^{2+} and 1,25-Dihydroxyvitamin D_3, Cancer Res. 65 (2005) 493–498.
[155] I.S. Fetahua, D.M. Hummela, T. Manhardta, et al., Regulation of the calcium-sensing receptor expression by1,25-dihydroxyvitamin D3, interleukin-6, and tumor necrosis factor alpha in colon cancer cells, J. Steroid Biochem. Mol. Biol. 144 (2014) 228–231.
[156] J.A. Eisman, D.H. Barkla, P.J.M. Tutton, Suppression of in vivo growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D_3, Cancer Res. 47 (1987) 21–25.
[157] D.J. Mantell, P.E. Owens, N.J. Bundred, et al., 1α,25- dihydroxyvitamin D_3 inhibits angiogenesis in vitro and in vivo, Circ. Res. 87 (2000) 214–220.
[158] E. Garcion, N. Wion-Barbot, C.N. Montero-Menei, et al., New clues about vitamin D functions in the nervous system, Trends Endocrinol. Metab 13 (2002) 100–105.
[159] D.W. Eyles, T.H.J. Burne, J.J. McGrath, Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease, Front. Neuroendocrinol. 34 (2013) 47–64.
[160] M.W. Butler, A. Burt, T.L. Edwards, et al., Vitamin D receptor gene as a candidate gene for Parkinson disease, Ann. Hum. Genet. 75 (2011) 201–210.
[161] D.J. Lehmann, H. Refsum, D.R. Warden, et al., The vitamin D receptor gene is associated with Alzheimer's disease, Neurosci. Lett. 504 (2011) 79–82.
[162] D. Gezen-Ak, E. Dursun, B. Bilgiç, et al., Vitamin D receptor gene hap-lotype is associated with late-onset Alzheimer's disease, Tohoku J. Exp. Med. 228 (2012) 189–196.
[163] L. Wang, K. Hara, J.M. Van Baaren, et al., Vitamin D receptor and Alzheimer's disease: a genetic and functional study, Neurobiol. Aging 33 (2012) 1844.e1–1844.e9.
[164] M. Schlögl, M.F. Holick, Vitamin D and neurocognitive function, Clin. Interv. Aging 9 (2014) 559–568.
[165] G. Zündorf, G. Reiser, Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection, Antioxid. Redox Signal 14 (2011) 1275–1288.
[166] Z.S. Khachaturian. Calcium, membranes, aging, and Alzheimer's disease. Introduction and overview. Ann. N. Y. Acad. Sci. 568(1089) 1–4.
[167] F.M. LaFerla, Calcium dyshomeostasis and intracellular signaling in Alzheimer's disease, Nat. Rev. Neurosci. 3 (2002) 862–872.
[168] G.E. Stutzmann, The pathogenesis of Alzheimer's disease is it a lifelong 'calciumopathy', Neuroscientist 13 (2007) 546–559.
[169] O. Thibault, J.C. Gant, P.W. Landfield, Expansion of the calcium hypothesis of brain ageing and Alzheimer's disease: minding the store, Aging Cell. 6 (2007) 307–317.
[170] I. Bezprozvanny, M.P. Mattson, Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease, Trends Neurosci. 31 (2008) 454–463.
[171] G.E. Stutzmann, M.P. Mattson, Endoplasmic reticulum Ca2+ handling in cells in health and disease, Pharmacol. Rev. 63 (2011) 700–727.
[172] H.K. Querfurth, D.J. Selkoe, Calcium ionophore increases amyloid beta peptide production by cultured cells, Biochemistry 33 (1994) 4550–4561.

[173] A. Itkin, V. Dupres, Y.F. Dufrêne, et al., Calcium ions promote formation of amyloid β-peptide (1–40) oligomers causally implicated in neuronal toxicity of Alzheimer's disease, PloS One 6 (2011) e18250.

[174] N. Pierrot, S.F. Santos, C. Feyt, et al., Calcium-mediated transient phosphorylation of tau and amyloid precursor protein followed by intraneuronal amyloid-beta accumulation, J. Biol. Chem. 281 (2006) 39907–39914.

[175] D. Del Prete, F. Checler, M. Chami, Ryanodine receptors: physiological function and deregulation in Alzheimer disease, Mol. Neurodegener. 9 (2014) 21.

[176] L.E. Jensen, G. Bultynck, T. Luyten, et al., Alzheimer's disease-associated peptide Aβ42 mobilizes ER Ca^{2+} via $InsP_3R$-dependent and -independent mechanisms, Front. Mol. Neurosci. 6 (2013) 36.

[177] B. Brawek, O. Garaschuk, Network-wide dysregulation of calcium homeostasis in Alzheimer's disease, Cell. Tissue Res. 357 (2014) 427–438.

[178] J.W. Um, A.C. Kaufman, M. Kostylev, et al., Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer abeta oligomer bound to cellular prion protein, Neuron 79 (2013) 887–902.

[179] C. Ye, C.L. Ho-Pao, M. Kanazirska, et al., Amyloid-beta proteins activate Ca^{2+}-permeable channels through calcium-sensing receptors, J. Neurosci. Res. 47 (1997) 547–554.

[180] A. Chiarini, I. Dal Pra, M. Marconi, et al., Calcium-sensing receptor (CaSR) in human brain's pathophysiology: roles in late-onset Alzheimer's disease (LOAD), Curr. Pharm. Biotechnol. 10 (2009) 317–326.

[181] U. Armato, C. Bonafini, B. Chakravarthy, et al., The calcium-sensing receptor: a novel Alzheimer's disease crucial target? J. Neurol. Sci. 322 (2012) 137–140.

[182] K.H. Cheung, L. Mei, D.O. Mak, et al., Gain-of-function enhancement of IP_3 receptor modal gating by familial Alzheimer's disease-linked presenilin mutants in human cells and mouse neurons, Sci. Signal 3 (2010) ra22.

[183] G.W. Arendasha, C. Cao, Caffeine and coffee as therapeutics against Alzheimer's Disease, J. Alzheimer's Dis. 20 (2010) S117–S126.

[184] M.H. Eskelinena, M. Kivipeltoa, Caffeine as a protective factor in dementia and Alzheimer's Disease, J. Alzheimer's Dis. 20 (2010) S167–S174.

[185] I. Parker, I. Ivorra, Caffeine inhibits inositol trisphosphate-mediated liberation of intracellular calcium in *Xenopus* oocytes, J. Physiol. 433 (1991) 229–240.

[186] G.R. Brown, L.G. Sayers, C.J. Kirk, et al., The opening of the inositol 1,4,5-trisphosphate-sensitive Ca^{2+} channel in rat cerebellum is inhibited by caffeine, Biochem. J. 282 (1992) 309–312.

[187] M. Müller, K.H. Cheung, J.K. Foskett, Enhanced ROS generation mediated by Alzheimer's disease presenilin regulation of $InsP_3R$ Ca^{2+} signaling, Antioxid. Redox Signal 14 (2011) 1225–1235.

[188] M.A. Smith, C.A. Rottkamp, A. Nunomura, A.K. Raina, G. Perry, Oxidative stress in Alzheimer's disease, Biochim. Biophys. Acta 1502 (2000) 139–144.

[189] L.M. Sayre, M.A. Smith, G. Perry, Chemistry and biochemistry of oxidative stress in neurodegenerative disease, Curr. Med. Chem. 8 (2001) 721–738.

[190] D.A. Butterfield, Amyloid b-peptide (1–42)-induced oxidative stress and neurotoxicity: implications for neurodegeneration in Alzheimer's disease brain. A Review, Free Radic. Res. 36 (2002) 1307–1313.

[191] S.J. Texel, M.P. Mattson, Impaired adaptive cellular responses to oxidative stress and the pathogenesis of Alzheimer's disease, Antioxid. Redox Signal 14 (2011) 1519–1534.

[192] D.A. Butterfield, A.M. Swomley, R. Sultana, Amyloid b-Peptide (1–42)-Induced oxidative stress in Alzheimer Disease: importance in disease pathogenesis and progression, Antioxid. Redox Signal 19 (2013) 823–835.

[193] D. Ghosh, K.R. Levault, G.J. Brewer, Relative importance of redox buffers GSH and NAD(P)H in age-related neurodegeneration and Alzheimer disease-like mouse neurons, Aging Cell. 13 (2014) 631–640.

[194] M.J. Berridge, Calcium regulation of neural rhythms, memory and Alzheimer's disease, J. Physiol. 592 (2014) 281–293.

[195] K. Bodhinathan, A. Kumar, T.C. Foster, Intracellular redox state alters NMDA receptor response during aging through Ca^{2+}/calmodulin-dependent protein kinase II, J. Neurosci. 30 (2010) 1914–1924.

[196] A. Kumar, T.C. Foster, Linking redox regulation of NMDAR synaptic function to cognitive decline during aging, J. Neurosci. 33 (2013) 15710–15715.

[197] S.S. Yan, D. Chen, S. Yan, et al., RAGE is a key cellular target for Abeta-induced perturbation in Alzheimer's disease, Front. Biosci (Schol Ed) 4 (2012) 240–250.

[198] F. Fang, L.F. Lue, S. Yan, et al., RAGE-dependent signaling in microglia contributes to neuroinflammation, Abeta accumulation, and impaired learning/memory in a mouse model of Alzheimer's disease, Faseb J. 24 (2010) 1043–1055.

[199] K. Li, D. Dai, B. Zhao, et al., Association between the RAGE G82S polymorphism and Alzheimer's disease, J. Neural. Transm. 117 (2010) 97–104.

[200] E. Borchi, V. Bargelli, V. Guidotti, et al., Mild exposure of RIN-5F β-cells to human islet amyloid polypeptide aggregates upregulates antioxidant enzymes via NADPH oxidase-RAGE: an hormetic stimulus, Redox Biol. 2 (2013) 114–122.

[201] L. Shi, H. Chen, X. Yu, X. Wu, Advanced glycation end products delay corneal epithelial wound healing through reactive oxygen species generation, Mol. Cell. Biochem. 383 (2013) 253–259.

[202] K.V. Kuchibhotla, S.T. Goldman, C.R. Lattarulo, et al., Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks, Neuron 59 (2008) 214–225.

[203] J.R. Lopez, A. Lyckman, S. Oddo, et al., Increased intraneuronal resting $[Ca^{2+}]$ in adult Alzheimer's disease mice, J. Neurochem. 105 (2008) 262–271.

[204] M.J. Berridge, Dysregulation of neural calcium signalling in Alzheimer disease, bipolar disorder and schizophrenia, Prion 6 (2012) 1–12.

[205] J. Xu, M. Chatterjee, T.D. Baguley, et al., Inhibitor of the tyrosine phosphatase STEP reverses cognitive deficits in a mouse model of Alzheimer's disease, PLoS Biol. 12 (2014) e1001923.

[206] P. Tuohimaa, T. Keisala, A. Minasyan, et al., Vitamin D, nervous system and aging, Psychoneuroendocrinology 34 (Suppl. 1) (2009) S278–S286.

[207] C. Annweiler, B. Fantino, D. Le Gall, et al., Severe vitamin D deficiency is associated with advanced-stage dementia in geriatric inpatients, J. Am. Geriatr. Soc. 59 (2011) 169–171.

[208] G.C. DeLuca, S.M. Kimball, J. Kolasinski, S.V. Ramagopalan, G.C. Ebers, Review: the role of vitamin D in nervous system health and disease, Neuropathol. Appl. Neurobiol. 39 (2013) 458–484.

[209] D. Gezen-Ak, S. Yılmazer, E. Dursun, Why vitamin D in Alzheimer's disease? The hypothesis, J. Alzheimers Dis. 40 (2004) 257–269.

[210] R.J. Przybelski, N.C. Binkley, Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function, Arch. Biochem. Biophys. 460 (2007) 202–205.

[211] M. Kuningas, S.P. Mooijaart, J. Jolles, et al., VDR gene variants associate with cognitive function and depressive symptoms in old age, Neurobiol. Aging 30 (2009) 466–473.

[212] M.A. Beydoun, E.L. Ding, H.A. Beydoun, et al., Vitamin D receptor and megalin gene polymorphisms and their associations with longitudinal cognitive change in US adults, Am. J. Clin. Nutr. 95 (2012) 163–178.

[213] C. Annweiler, Y. Rolland, A.M. Schott, et al., Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: a 7-year follow-up, J. Gerontol. A Biol. Sci. Med. Sci. 67 (2012) 1205–1211.

[214] C. Annweiler, D.J. Llewellyn, O. Beauchet, Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis, J. Alzheimers Dis. 33 (2013) 659–674.

[215] C. Annweiler, O. Beauche, Possibility of a new antialzheimer's disease pharmaceutical composition combining memantine and vitamin D, Drugs Aging 29 (2012) 81–91.

[216] D. Gezen-Ak, E. Dursun, T. Ertan, et al., Association between vitamin D receptor gene polymorphism and Alzheimer's disease, Tohoku J. Exp. Med. 212 (2007) 275–282.

[217] M.K. Sutherland, M.J. Somerville, L.K.K. Yoong, et al., Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington hippocampus: correlation with calbindin-28 k mRNA levels, Mol. Brain Res. 13 (1992) 239–250.

[218] J.J. Palop, B. Jones, L. Kekonius, et al., Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits, Proc. Natl. Acad. Sci. U S A 100 (2003) 9572–9577.

[219] C.P. Ramsey, C.A. Glass, M.B. Montgomery, et al., Expression of Nrf2 in neurodegenerative diseases, J. Neuropathol. Exp. Neurol. 66 (2007) 75e85.

[220] K. Kanninen, R. Heikkinen, T. Malm, et al., Intrahippocampal injection of a lentiviral vector expressing Nrf2 improves spatial learning in a mouse model of Alzheimer's disease, Proc. Natl. Acad. Sci.U S A 106 (2009) 16505–16510.

[221] D. Ghosh, K.R. LeVault, G.J. Brewer, Dual-energy precursor and nuclear erythroid-related factor 2 activator treatment additively improve redox glutathione levels and neuron survival in aging and Alzheimer mouse neurons upstream of reactive oxygen species, Neurobiol. Aging 35 (2014) 179–190.

[222] R.D. Semba, A.R. Moghekar, J. Hu, et al., Klotho in the cerebrospinal fluid of adults with and without Alzheimer's disease, Neurosci. Lett. 558 (2014) 37–40.

[223] X. Kuang, Y.S. Chen, L.F. Wang, et al., Klotho upregulation contributes to the neuroprotection of ligustilide in an Alzheimer's disease mouse model, Neurobiol. Aging 35 (2014) 169–178.

[224] C.R. Abraham, C. Chen, G.D. Cuny, et al., Small-molecule Klotho enhancers as novel treatment of neurodegeneration, Future Med. Chem. 4 (2012) 1671–1679.

[225] M.L. Evatt, M.R. Delong, N. Khazai, et al., Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease, Arch. Neurol. 65 (2008) 1348–1352.

[226] P. Knekt, A. Kilkkinen, H. Rissanen, et al., Serum vitamin D and the risk of Parkinson disease, Arch. Neurol. 67 (2010) 808–811.

[227] X. Han, L. Xue, Y. Li, et al., Vitamin D receptor gene poly-morphism and its association with Parkinson's disease in Chinese Han population, Neurosci. Lett. 525 (2012) 29–33.

[228] R. Török, N. Török, L. Szalardy, et al., Association of vitamin D receptor gene polymorphisms and Parkinson's disease in Hungarians, Neurosci. Lett. 551 (2013) 70–74.

[229] K.B. Chen, A.M. Lin, T.H. Chiu, Systemic vitamin D3 attenuated oxidative injuries in the locus coeruleus of rat brain, Ann. N. Y. Acad. Sci. 993 (2003) 313–324.

[230] A.M. Lin, S.F. Fan, D.M. Yang, et al., Zinc-induced apoptosis in substantia nigra of rat brain: neuroprotection by vitamin D3, Free Radic. Biol. Med. 34 (2003) 1416–1425.

[231] T. Calli, D. Ottolini, M. Brini, Calcium signalling in Parkinson's disease, Cell. Tissue Res. 357 (2014) 439–454.

[232] D.J. Surmeier, P.T. Schumacker, Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease, J. Biol. Chem. 288 (2013) 10736–10741.
[233] B. Thomas, M.F. Beal, Parkinson's disease, Hum. Mol. Genet. 16 (2007) R183–R194.
[234] O. Corti, A. Brice, Mitochondrial quality control turns out to be the principal suspect in parkin and PINK1-related autosomal recessive Parkinson's disease, Curr. Opin. Neurobiol. 23 (2013) 100–108.
[235] C.M. Clements, R.S. McNally, B.J. Conti, et al., DJ-1, a cancer- and Parkinson's disease-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2, Proc. Natl. Acad. Sci. U S A. 103 (2006) 15091–15096.
[236] P. Steullet, J.H. Cabungcal, A. . Monina, et al., Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? Schizophrenia Research (2014) http://dx.doi.org/10.1016/j.schres.2014.06.021.
[237] S.J. Wood, M. Yücel, C. Pantelis, M. Berk, Neurobiology of schizophrenia spectrum disorders: the role of oxidative stress, Ann. Acad. Med. Singapore 38 (2009) 396–401.
[238] A. Kulak, P. Steullet, J.-H. Cabungcal, et al., Redox dysregulation in the pathophysiology of schizophrenia and bipolar disorder: insights from animal models, Antioxid. Redox Signal 18 (2013) 1428–1443.
[239] S. Najjar, D.M. Pearlman, K. Alper, et al., Neuroinflammation and psychiatric illness, J. Neuroinflammation 10 (2013) 43–67.
[240] J.T. Coyle, Glutamate and schizophrenia: beyond the dopamine hypothesis, Cell. Mol. Neurobiol. 26 (2006) 363–382.
[241] J.T. Kantrowitz, D.C. Javitt, N-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? Brain Res. Bull. 83 (2010) 108–121.
[242] K. Nakazawa, V. Zsirosa, Z. Jiang, et al., GABAergic interneuron origin of schizophrenia pathophysiology, Neuropharmacology 62 (2012) 1574–1583.
[243] M.A. Snyder, W.-J. Gao, NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia, Front. Cell. Neurosci. 7 (2013) 1–12.
[244] L.M. Brzustowicz, *NOS1AP* in schizophrenia, Curr. Psychiatry Rep. 10 (2008) 158–163.
[245] M.M. Behrens, T.J. Sejnowski, Does schizophrenia arise from oxidativdysregulation of parvalbumin-interneurons in the developing cortex? Neuropharmacology 57 (2009) 193–200.
[246] V. Labrie, A.H.C. Wong, J.C. Roeder, Contributions of the D-serine pathway to schizophrenia, Neuropharmacology 62 (2012) 1484–1503.
[247] J.-M. Billard, Serine racemase as a prime target for age-related memory defecits, Eur. J. Neurosci. 37 (2013) 1931–1938.
[248] K.Q. Do, J.H. Cabungcal, A. Frank, et al., Redox dysregulation neurodevelopment, and schizophrenia, Curr. Opin. Neurobiol. 19 (2009) 220–230.
[249] L.R. Harms, T.H.J. Burne, D.W. Eyles, J.J. McGrath, Vitamin D and the brain, Best Pract. Res. Clin. Endocrinol. Metabolism 25 (2011) 657–669.
[250] T.H.J. Burne, A. Becker, J. Brown, et al., Transient prenatal vitamin D deficiency is associated with hyperlocomotion in adult rats, Behav. Brain Res. 154 (2004) 549–555.
[251] J.P. Kesby, X.Y. Cui, J. O'Loan, et al., Developmental vitamin D deficiency alters dopamine-mediated behaviours and dopamine transporter function in adult female rats, Psychopharmacology (Berlin) 208 (2010) 159–168.
[252] D. Eyles, J. Brown, A. Mackay-Sim, J. McGrath, F. Feron, Vitamin D_3 and brain development, Neuroscience 118 (2003) 641–653.
[253] M. Berk, F. Ng, O. Dean, et al., Glutathione: a novel treatment target in psychiatry, Trends Pharmacol. Sci. 29 (2008) 346–351.
[254] O.M. Dean, M. van den Buuse, A.I. Bush, et al., A role for glutathione in the pathophysiology of bipolar disorder and schizophrenia? Animal models and relevance to clinical practice, Curr. Med. Chem. 16 (2009) 2965–2976.
[255] J.W. Gawryluk, J.F. Wang, A.C. Andreazza, et al., Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders, Int. J. Neuropsychopharmacol. 14 (2011) 123–130.
[256] A. Monin, P.S. Baumann, A. Griffa, et al., Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients, Mol. Psychiatry (2014) 1–12, http://dx.doi.org/10.1038/mp.2014.88.
[257] M.J. Berridge, Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia, Cell. Tissue Res. 357 (2014) 477–492.
[258] M. Bulut, H.A. Savas, A. Altindag, et al., Beneficial effects of nacetylcysteine in treatment resistant schizophrenia, World J. Biol. Psychiatry 10 (2009) 626–628.
[259] M. Berk, G.S. Malhi, L.J. Gray, O.M. Dean, The promise of nacetylcysteine in neuropsychiatry, Trends Pharm. Sci. 34 (2013) 167–177.
[260] R. Scragg, R. Jackso, I.M. Holdaway, et al., Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study, Int. J. Epidemiol. 19 (1990) 559–563.
[261] D.H. Kim, S. Sabour, U.N. Sagar, et al., Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004), Am. J. Cardiol. 102 (2008) 1540–1544.
[262] J.L. Anderson, H.T. May, B.D. Horne, et al., Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population, Am. J. Cardiol. 106 (2010) 963–968.
[263] J.L. Vacek, S.R. Vanga, M. Good, et al., Vitamin D deficiency and supplementation and relation to cardiovascular health, Am. J. Cardiol. 109 (2012) 359–363.
[264] J. Dong, C.W. Lau, S.L. Wong, Y. Huang, Cardiovascular benefits of vitamin D, Acta Physiol. Sin. 66 (2014) 30–36.
[265] H. Nasri, S. Behradmanesh, A. Ahmadi, M. Rafieian-Kopaei, Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, dou-ble-blind, placebo controlled clinical trial, J. Nephropathol. 3 (2014) 29–33.
[266] W. Yuan, W. Pan, J. Kong, et al., 1,25-Dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter, J. Biol. Chem. 282 (2007) 29821–29830.
[267] Y.C. Li, J. Kong, M. Wei, et al., 1, 25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin–angiotensin system, J. Clin. Invest. 110 (2002) 229–238.
[268] W. Xiang, J. Kong, S. Chen, et al., Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin–angiotensin systems, Am. J. Physiol. Endocrinol. Metab. 288 (2005) E125–E132.
[269] C. Zhou, F. Lu, K. Cao, et al., Calcium-independent and $1,25(OH)_2D_3$-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice, Kidney Int. 74 (2008) 170–179.
[270] J.C. Romero, J.F. Reckelhoff, Role of angiotensin and oxidative stress in essential hypertension, Hypertension 34 (1999) 943–949.
[271] M.C. Ortiz, M.C. Manriquez, J.C. Romero, J.A. Juncos, Antioxidants block angiotensin II-induced increases in blood pressure and endothelin, Hypertension 38 (2001) 655–659.
[272] S. Rajagopalan, S. Kurz, T. Munzel, et al., Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations of vasomotor tone, J. Clin. Invest. 97 (1996) 1916–1923.
[273] M. Tare, S.J. Emmett, H.A. Coleman, et al., Vitamin D insufficiency is associated with impaired vascular endothelial and smooth muscle function and hypertension in young rats, J. Physiol. 589 (2011) 4777–4786.
[274] M.S.K.R. Wong, R. Delansorne, R.Y.K. Man, P.M. Vanhoutte, Vitamin D derivatives acutely reduce endothelium-dependent contractions in the aorta of the spontaneously hypertensive rat, Am. J. Physiol. Heart Circ. Physiol. 295 (2008) H289–H296.
[275] Y. Wang, Z. Sun, Klotho gene delivery prevents the progression of spontaneous hypertension and renal damage, Hypertension 54 (2009) 810–817.
[276] H. Rakugi, N. Matsukawa, K. Ishikawa, et al., Anti-oxidative effect of Klotho on endothelial cells through cAMP activation, Endocrine 31 (2007) 82–87.
[277] M.J. Berridge, Calcium signalling remodelling and disease, Biochem. Soc. Trans. 40 (2012) 297–309.
[278] M.J. Berridge, Remodelling Ca^{2+} signalling systems and cardiac hypertrophy, Biochem. Soc. Trans. 34 (2006) 228–231.
[279] M.J. Berridge, Calcium microdomains: organization and function, Cell. Calcium 40 (2006) 405–412.
[280] X. Wu, T. Zhang, J. Bossuyt, et al., Local $InsP_3$-dependent perinuclear Ca^{2+} signaling in cardiac myocyte excitation–transcription coupling, J. Clin. Invest 116 (2006) 675–682.
[281] J.D. Molkentin, Dichotomy of Ca^{2+} in the heart: contraction versus intracellular signaling, J. Clin. Invest 116 (2006) 623–626.
[282] D. Luo, D. Yang, X. Lan, et al., Nuclear Ca^{2+} sparks and waves mediated by inositol 1,4,5-trisphosphate receptors in neonatal rat cardiomyocytes, Cell. Calcium 43 (2008) 165–174.
[283] D. Harzheim, M. Movassagh, R.S. Foo, et al., Increased $InsP_3Rs$ in the junctional sarcoplasmic reticulum augment Ca^{2+} transients and arrhythmias associated with cardiac hypertrophy, Proc. Natl. Acad. Sci. U S A 106 (2009) 11406–11411.
[284] D.R. Higazi, C.J. Fearnley, F.M. Drawnel, et al., Endothelin-1-stimulated $InsP_3$-induced Ca^{2+} release is a nexus for hypertrophic signalling in cardiac myocytes, Mol. Cell. 33 (2009) 472–482.
[285] H. Nakayama, I. Bodi, M. Maillet, et al., The IP_3 receptor regulates cardiac hypertrophy in response to select stimuli, Circ. Res. 107 (2010) 659–666.
[286] S. Choudhury, S. Bae, Q. Ke, J.Y. Lee, S.S. Singh, et al., Abnormal calcium handling and exaggerated cardiac dysfunction in mice with defective Vitamin D signaling, PLoS One 9 (9) (2014) e108382.
[287] C.M. Sag, C.X. Santos, A.M. . Shah, Redox regulation of cardiac hypertrophy, J. Mol. Cell. Cardiol. 73 (2014) 103–111.
[288] A.C. Köhler, C.M. Sag, L.S. Maier, Reactive oxygen species and excitation-contraction coupling in the context of cardiac pathology, J. Mol. Cell. Cardiol. 73 (2014) 92–102.
[289] J.K. Bendall, A.C. Cave, C. Heymes, et al., Pivotal role of a gp91(phox)-containing NADPH oxidase in angiotensin II-induced cardiac hypertrophy in mice, Circulation 105 (2002) 293–296.
[290] J.M. Li, N.P. Gall, D.J. Grieve, et al., Activation of NADPH oxidase during progression of cardiac hypertrophy to failure, Hypertension 40 (2002) 477–484.
[291] J.R. Burgoyne, H. Mongue-Din, P. Eaton, A.J. Shah, Redox signalling in cardiac physiology and pathology, Circ. Res. 111 (2012) 1091–1106.
[292] P. Mancuso, A. Rahman, S.D. Hershey, et al., 1,25-dihydroxyvitamin-D_3 treatment reduces cardiac hypertrophy and left ventricular diameter in spontaneously hypertensive heart failure-prone (cp/+) rats independent of changes in serum leptin, J. Cardiovasc. Pharm. 51 (2008) 559–564.
[293] I. Gotsman, A. Shauer, D.R. Zwas, et al., Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome, Eur. J. Heart Fail 14 (2012) 357–366.

[294] W.R. Chen, Z.Y. Liu, Y. Shi, et al., Relation of low vitamin d to nonvalvular persistent atrial fibrillation in Chinese patients, Ann. Noninvasive Electrocardiol. 19 (2014) 166–173.
[295] M. Demir, U. Uyan, M. Melek, The effects of vitamin D deficiency on atrial fibrillation, Clin. Appl. Thromb. Hemost. 20 (2014) 98–103.
[296] D.A. Hanafy, S.L. Chang, Y.Y. Lu, et al., Electromechanical effects of 1,25-dihydroxyvitamin D with antiatrial fibrillation activities, J. Cardiovasc. Electrophysiol. 25 (2014) 317–323.
[297] L. MacKenzie, M.D. Bootman, M.J. Berridge, P. Lipp, Predetermined recruitment of calcium release sites underlies excitation–contraction coupling in rat atrial myocytes, J. Physiol. 530 (2001) 417–429.
[298] L. MacKenzie, M.D. Bootman, M. Laine, et al., The role of inositol 1,4,5-trisphosphate receptors in Ca2+ signalling and the generation of arrhythmias in rat atrial myocytes, J. Physiol. 541 (2002) 395–409.
[299] L. Mackenzie, H.L. Roderick, M.J. Berridge, S.J. Conway, M.D. Bootman, The spatial pattern of atrial cardiomyocyte calcium signalling modulates contraction, J. Cell. Sci. 117 (2004) 6327–6337.
[300] J. Kockskämper, A.V. Zima, H.L. Roderick, et al., Emerging roles of inositol 1,4,5-trisphosphate signalling in cardiac myocytes, J. Mol. Cell. Cardiol. 45 (2008) 128–147.
[301] A. Proven, H.L. Roderick, S.J. Conway, M.J. Berridge, J.K. Horton, S.J. Capper, M.D. Bootman, Inositol 1,4,5-trisphosphate supports the arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes, J. Cell. Sci. 119 (2006) 3363–3375.
[302] K. Takeshita, T. Fujimori, Y. Kurotaki, et al., Sinoatrial node dysfunction and early unexpected death of mice with a defect of klotho gene expression, Circulation 109 (2004) 1776–1782.
[303] M.T. Cantorna, B.D. Mahon, Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence, Exp. Biol. Med. (Maywood) 229 (2004) 1136–1142.
[304] L. Adorini, Intervention in autoimmunity: the potential of vitamin D receptor agonists, Cell. Immunol. 233 (2005) 115–124.
[305] H.F. Deluca, M.T. Cantorna, Vitamin D: its role and uses in immunology, Faseb. J. 15 (2001) 2579–2585.
[306] I. Alroy, T.L. Towers, L.P. Freedman, Transcriptional repression of the interleukin-2 gene by vitamin D3: direct inhibition of NFATp/AP-1 complex formation by a nuclear hormone receptor, Mol. Cell. Biol. 15 (1995) 5789–5799.
[307] B.D. Mahon, A. Wittke, V. Weaver, M.T. Cantorna, The targets of vitamin D depend on the differentiation and activation status of CD4-positive T cells, J. Cell. Biochem. 89 (2003) 922–932.
[308] S. Chen, G.P. Sims, X.X. Chen, et al., Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation, J. Immunol. 179 (2007) 1634–1647.
[309] G. Penna, L. Adorini, 1 Alpha, 25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation, J. Immunol. 164 (2000) 2405–2411.
[310] L. Piemonti, P. Monti, M. Sironi, et al., Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells, J. Immunol. 164 (2000) 4443–4451.
[311] M.O. Canning, K. Grotenhuis, H. de Wit, et al., 1-alpha,25-Dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes, Eur. J. Endocrinol. 145 (2001) 351–357.
[312] D. D'Ambrosio, M. Cippitelli, M.G. Cocciolo, et al., Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene, J. Clin. Invest 101 (1998) 252–262.
[313] Q. Wang, Y. He, Y. Shen, et al., Vitamin D Inhibits COX-2 expression and inflammatory response by targeting thioesterase superfamily member 4, J. Biol. Chem. 289 (2014) 11681–11694.
[314] V. Verhasselt, W. Vanden Berghe, N. Vanderheyde, et al., N-acetyl-L-cysteine inhibits primary human T cell responses at the dendritic cell level: association with NF-kappaB inhibition, J. Immunol. 162 (1999) 2569–2574.
[315] S.F. Connolly, D.J. Kusner, The regulation of dendritic cell function by calcium-signaling and its inhibition by microbial pathogens, Immunol. Res. 39 (2007) 115–127.
[316] D. Aki, Y. Minoda, H. Yoshida, et al., Peptidoglycan and lipopolysaccharide activate PLCγ2, leading to enhanced cytokine production in macrophages and dendritic cells, Genes. Cells 13 (2008) 199–208.
[317] L. Haider, M.T. Fischer, J.M. Frischer, et al., Oxidative damage in multiple sclerosis lesions, Brain 134 (2011) 1914–1924.
[318] P. Arnold, D. Mojumder, J. DeToledo, et al., Pathophysiological processes in multiple sclerosis: focus on nuclear factor erythroid-2-related factor 2 and emerging pathways, Clin. Pharmacol. Adv. Appl. 6 (2014) 35–42.
[319] M.T. Fischer, R. Sharma, J.L. Lim, et al., NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury, Brain 135 (2012) 886–899.
[320] K. Su, D. Bourdette, M. Forte, Mitochondrial dysfunction and neurodegeneration in multiple sclerosis, Front. Physiol. 4 (2013) 169.
[321] A. Volterra, D. Trotti, C. Tromba, et al., Glutamate uptake inhibition by oxygen free radicals in rat cortical astrocytes, J. Neurosci. 14 (1994) 2924–2932.
[322] E.D. Acheson, C.A. Bachrach, F.M. Wright, Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation and other variables, Acta Psychiatr. Scand. Suppl. 35 (1960) 132–147.
[323] I.A. van der Mei, A.L. Ponsonby, T. Dwyer, et al., Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study, BMJ 327 (2003) 316–321.
[324] K.L. Munger, L.I. Levin, B.W. Hollis, et al., Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis, JAMA 296 (2006) 2832–2838.
[325] K. Shinpo, S. Kikuchi, H. Sasaki, et al., Effect of 1,25-dihydroxyvitamin D(3) on cultured mesencephalic dopaminergic neurons to the combined toxicity caused by L-buthionine sulfoximine and 1-methyl-4-phenylpyridine, J. Neurosci. Res. 62 (2000) 374–382.
[326] A.J. Berlanga-Taylor, G. Disanto, G.C. Ebers, S.V. Ramagopalan, Vitamin D-gene interactions in multiple sclerosis, J. Neurol. Sci. 311 (2011) 32–36.
[327] L. Krizova, B. Kollar, D. Jezova, P. Turcani, Genetic aspects of vitamin D receptor and metabolism in relation to the risk of multiple sclerosis, Gen. Physiol. Biophys. 32 (2013) 459–466.
[328] C.E. Hayes, M.T. Cantorna, H.F. DeLuca, Vitamin D and multiple sclerosis, Proc. Soc. Exp. Biol. Med. 216 (1997) 21–27.
[329] C.E. Hayes, Vitamin D: a natural inhibitor of multiple sclerosis, Proc. Nutr. Soc. 59 (2000) 531–535.
[330] K.M. Spach, C.E. Hayes, Vitamin D3 confers protection from autoimmune encephalomyelitis only in female mice, J. Immunol. 175 (2005) 4119–4126.
[331] C.G. Mayne, J.A. Spanier, L.M. Relland, et al., 1,25-Dihydroxyvitamin D3 acts directly on the T lymphocyte vitamin D receptor to inhibit experimental autoimmune encephalomyelitis, Eur. J. Immunol. 41 (2011) 822–832.
[332] F.E. Nashold, C.D. Nelson, L.M. Brown, C.E. Hayes, One calcitriol dose transiently increases Helios+FoxP3+ T cells and ameliorates autoimmune demyelinating disease, J. Neuroimmunol. 263 (2013) 64–74.
[333] J.A. Spanier, F.E. Nashold, J.K. Olson, C.E. Hayes, The Ifng gene is essential for Vdr gene expression and Vitamin D 3-mediated reduction of the pathogenic T Cell burden in the central nervous system in experimental autoimmune encephalomyelitis, a multiple sclerosis model, J. Immunol. 189 (2012) 3188–3197.
[334] D.D. Bikle, Extra renal synthesis of 1,25-dihydroxyvitamin D and its health implications, Clinic Rev. Bone Miner. Metab 7 (2009) 114–125.
[335] J.S. Adams, M. Hewison, Update on vitamin D, J. Clin. Endocrinol. Metab. 95 (2010) 471–478.
[336] G.A. Rook, J. Steele, L. Fraher, et al., Vitamin D3, gamma interferon, and control of proliferation of Mycobacterium tuberculosis by human monocytes, Immunology 57 (1986) 159–163.
[337] P.T. Liu, S. Stenger, H. Li, et al., Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response, Science 311 (2006) 1770–1773.
[338] I. Vergne, J. Chua, S.B. Singh, V. Deretic, Cell biology of Mycobacterium tuberculosis phagosome, Ann. Rev. Cell Dev. Biol. 20 (2004) 367–394.
[339] K.E. Nnoaham, A. Clarke, Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis, Int. J. Epidemiol. 37 (2008) 113–119.
[340] A.K. Coussens, R.J. Wilkinson, Y. Hanifa, et al., Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment, Proc. Natl. Acad. Sci. U S A. 109 (2012) 15449–15454.
[341] N. Salahuddin, F. Ali, Z. Hasan, et al., Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study [Supplementary Cholecalciferol in recovery from tuberculosis]. A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis', BMC Infect. Dis. 13 (2013) 22.
[342] P. Selvaraj, Vitamin D, vitamin D receptor, and cathelicidin in the treatment of tuberculosis, Vitam. Horm. 86 (2011) 307–325.
[343] P.T. Liu, R.L. Modlin, Human macrophage host defense against Mycobacterium tuberculosis, Curr. Opin. Immunol. 20 (2008) 371–376.