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Role for calcium signaling in manganese neurotoxicity

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ABSTRACT

Background: Calcium is an essential macronutrient that is involved in many cellular processes. Homeostatic control of intracellular levels of calcium ions [Ca^{2+}] is vital to maintaining cellular structure and function. Several signaling molecules are involved in regulating Ca^{2+} levels in cells and perturbation of calcium signaling processes is implicated in several neurodegenerative and neurologic conditions. Manganese [Mn] is a metal which is essential for basic physiological functions. However, overexposure to Mn from environmental contamination and workplace hazards is a global concern. Mn overexposure leads to its accumulation in several human organs particularly the brain. Mn accumulation in the brain results in a manganism, a Parkinsonian-like syndrome. Additionally, Mn is a risk factor for several neurodegenerative diseases including Parkinson's disease and Alzheimer's disease. Mn neurotoxicity also affects several neurotransmitter systems including dopaminergic, cholinergic and GABAergic. The mechanisms of Mn neurotoxicity are still being elucidated.

Aim: The review will highlight a potential role for calcium signaling molecules in the mechanisms of Mn neurotoxicity.

Conclusion: Ca^{2+} regulation influences the neurodegenerative process and there is possible role for perturbed calcium signaling in Mn neurotoxicity. Mechanisms implicated in Mn-induced neurodegeneration include oxidative stress, generation of free radicals, and apoptosis. These are influenced by mitochondrial integrity which can be dependent on intracellular Ca^{2+} homeostasis. Nevertheless, further elucidation of the direct effects of calcium signaling dysfunction and calcium-binding proteins activities in Mn neurotoxicity is required.

1. Introduction

Biological systems require the presence of certain minerals for the maintenance of a constant homeostatic environment. These are termed either "macro" or "essential" minerals which include; calcium, magnesium, phosphorus, chloride, sodium, iron, zinc, potassium, copper amongst others. These perform many physiological functions as coenzymes in various pathways to modulate signal transduction [1,2]. Calcium in its ionic form [Ca^{2+}] plays a vital role in neuronal excitation especially at neuromuscular junctions [3,4]. It is the most abundant mineral in the body which has numerous food sources [5,6].

Several signaling processes are involved in Ca^{2+} regulation, however, ultimate goal is homeostatic intracellular Ca^{2+}concentration [7,8]. Alterations in Ca^{2+} levels have been associated with several diseases, some of which are neurodegenerative, including Alzheimer's disease [AD], psychiatric, as well as disorders of metabolism [1,9–12]. Earlier studies on the mechanisms of Ca^{2+} signaling have shown the extent of its complex pathways, which involve its interaction at multiple activation sites including acting as specialized receptors, Ca^{2+} binding proteins, and ion exchangers at both the cell plasma and intracellular organelle [endoplasmic reticulum and mitochondria] membranes. This makes Ca^{2+} signaling pathways targets for a cascade of pathological events which disrupt the homeostatic state of the cellular environment [12]. Metals such as cadmium and lead are known to mimic the activities of Ca^{2+} at its various binding sites, but fail to elicit its essential roles.

Manganese [Mn] is a metal which is essential for basic physiological functions when in the adequate minute amounts as acquired from dietary sources. Unfortunately, it is also a neurotoxicant at high concentrations, capable of damaging neurons and distorting cognitive behaviors [13–15]. Reports have indicated that Mn transport into neuronal cells may be influenced by Ca^{2+}activities on several fronts including its functions as transporters [16] and signaling molecules [7]. There is a rapid distribution, accumulation but slow elimination rate of Mn within the central nervous system [CNS]. However, the route of exposure and adequate channels of excretion are required to maintain a steady physiological balance [14,17]. The competitive nature of Mn with Ca^{2+} and its high affinity for binding to certain chemical compounds within the CNS and other body systems poses the possibility of interference of Ca^{2+} uptake [18,19].

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The focus of this review is to highlight a potential role for calcium signaling dysfunction in mechanisms of Mn neurotoxicity. Additionally, this review will highlight the role of calcium-binding proteins [CaBPs] in neurodegenerative processes as well as in Mn neurotoxicity.

2. Neurotoxicity of manganese

Manganese is a cofactor for numerous enzymes that are required to support normal physiological activities in cells. These enzymes are essential for normal brain function since they are required for glial and neuronal cell function and contribute in neurotransmitter metabolism and syntheses such as glutamine synthetase, pyruvate carboxylase, acetylcholine esterase [AChE] and Mn-superoxide dismutase [Mn-SOD] [18]. However, overexposure to Mn can induce accumulation of this metal in the brain and result in neurotoxicity to multiple brain regions including the frontal cortex, hippocampus, striatum, substantia nigra [20–22]. The accumulation of Mn can affect the brain microenvironment homeostasis and has been linked to developmental disorders, progressive cognitive impairment and neurodegenerative disease [23,24].

Studies suggest that elevated Mn in the brain could have a correlation with neurological disease such as AD. Besides, AD patients show higher Mn concentration and were correlated with the Mini-Mental State Examination score and Clinical Dementia Rating Scale score, suggesting that high Mn levels are a risk for AD [25]. Indeed, chronic metal exposure produces changes in the aggregation of amyloid-β in the frontal cortex in the non-human primate brain, suggesting that Mn overexposure could be related to cognitive and memory deficits [26].

Chronic occupational exposure to high levels of Mn by welding, mining, dry cell battery manufacturing, and Mn-rich agrochemicals is known to cause parkinsonism [specifically called manganism] [27]. The occupational Mn exposure occurs mainly by inhalation of fume, dust and Mn small particles [< 1.0 μm], which can be absorbed in the lungs and transported to the brain [. Regulatory agencies such as Agency for Toxic Substances and Disease Registry [ATSDR] recommend 60 μg/m^3 for no observed effect level [NOAEL] for neurological effects. Also, American Conference of Governmental Industrial Hygienists' [ACGIH] determined the threshold limit value [TLV] for 20 μg/m^3 and 8-h time-weighted average threshold limit value [TLV-TWA] to 200 μg/m^3. Indeed, a recent study that calculated Mn occupational exposure level [OEL] suggests a possible OEL of 100–140 μg/m^3 for Mn inhalation [28]. Previous studies reported that occupational exposure to Mn had been shown to cause neurotoxicity. Racette et al. [29] demonstrated in an American welding cohort study that Mn exposure generated a dose-dependent progression of parkinsonism. Recently, Criswell et al. [30] observed a positive dose-response to occupational Mn exposure and severity of parkinsonism. This syndrome presents features that resemble Parkinson's disease [PD], which is characterized by motor and sensory disturbances, tremors, rigidity, bradykinesia, cognitive deficits [31,32]. The similarities between manganism and PD could be partially explained by the excessive Mn accumulation in the basal ganglia of the brain; the region that is involved in the control of motor and non-motor functions, hence causing progressive neuronal degeneration [27]. However, manganism is distinguishable from PD mostly by the absence of Lewy bodies [another hallmark of PD] [33].

The overexposure to Mn leads to disruption of dopaminergic neurotransmission. It was demonstrated in non-human primate [*Cynomolgus macaques*] and mice that Mn exposure inhibits dopaminergic neurotransmission and depletes striatal dopamine, which is responsible for the motor deficits [34,35]. In addition, reduction of dopaminergic neurons in the substantia par compacta and tyrosine hydroxylase protein, as well as a down-regulation of dopamine levels and D1 dopamine receptor expression has been demonstrated in Mn neurotoxicity [36]. Dopaminergic neurodegeneration and perturbed dopaminergic control of behaviors have been demonstrated in a C. elegans model on Mn neurotoxicity [14,37]. Additionally, in vitro studies demonstrate that metal exposure causes a significant concentration-dependent decrease in cellular dopamine concentrations [38].

Mn also has been shown to interfere with GABAergic transmissions in the globus pallidus, a region that is rich in GABA projections [39]. It was reported that Mn reduces GABA uptake by downregulating the expression and function of glutamine transporters [40,41]. On the other hand, some studies did not find an alteration in brain GABA concentration after Mn exposure [42,43]. Therefore, given these divergent findings, additional studies are required to address the role of GABAergic transmissions in the neurotoxic effects of Mn.

The cholinergic system could be perturbed by Mn exposure. In this regard, studies reported increased acetylcholine esterase [AChE] activity in rat brain extracts under Mn exposure [44]. Likewise, Fernsebner and colleagues observed an enhanced of AChE activity in brain samples of Mn-supplemented rats. Moreover, the increase in AChE activity was correlated with markers of oxidative stress in the brain tissue [45].

The neurotoxicity induced by Mn overexposure includes the formation of reactive oxygen species [ROS], and the promotion of oxidative stress in both neurons and glia, specifically astrocytes [46]. The capacity of Mn promotes oxidative stress is due to the transition of its oxidative state Mn^{2+} to Mn^{3+}, once Mn^{2+} may be oxidized to the active pro-oxidizing agent, Mn^{3+} [47,48]. The superoxide radical formed in the mitochondrial electron transport chain can result in superoxide dismutase [SOD]-dependent hydrogen peroxide [H_2O_2] formation, which via Fenton reaction generates toxic hydroxyl radicals [48]. Moreover, Mn can directly impair mitochondrial function by binding Mn^{2+} to substrates for mitochondrial respiration [succinate, malate, and glutamate] resulting in impairment of mitochondrial electron transport chain [49]. Likewise, the metal impairs normal mitochondrial function and leads to decreased energy production, once the organelle is a susceptible target of Mn-induced toxicity. The mitochondrial dysfunction induced by Mn is reflected by impairment of oxidative respiration, leading to excessive production of ROS and inhibiting the antioxidant system such as glutathione and glutathione peroxidase [50]. Importantly, Mn-induced oxidative stress interferes with Ca^{2+} homeostasis in mitochondria, leading to the accumulation of intramitochondrial Ca^{2+} by inhibiting its efflux [51]. This impairs Ca^{2+} homeostasis, resulting in the opening of the mitochondrial permeability pore, loss of the mitochondrial inner membrane potential, mitochondrial swelling, impairment of oxidative phosphorylation and ATP synthesis [49,52]. Taken together, these findings suggest that Mn-induced oxidative stress promotes mitochondrial dysfunction by impairing Ca^{2+} homeostasis, and therefore this may be a potential mechanism underlying Mn neurotoxicity.

3. Overview of calcium signaling in neurons

Ca^{2+} are second messenger molecules that relay extracellular cell signals received by receptors to effector proteins within the cell [53]. Signal transmission via Ca^{2+} is induced by either change in cytosolic concentration or direct binding to the target protein. When neuronal cells are in a state of rest, a low intracellular free Ca^{2+} [0.1-0.5 μM] and high extracellular Ca^{2+} [˜1 mM] concentration is maintained [54]. The properties of the various Ca^{2+} channels provide a coordinated interactive environment that promotes steady Ca^{2+} diffusion across varying electrochemical gradients. The importance of Ca^{2+} signaling is reflected by its active role in neuronal growth, plasticity, survival and synaptic transmission [12,55]. The use of optical probes for monitoring intracellular Ca^{2+} imaging has provided a medium for an in-depth understanding of the mechanism by which calcium signals are transmitted. These also enable a broader and more sensitive detection of Ca^{2+} activity at a high spatial resolution [56,57]. The source of Ca^{2+} for signaling is either from the extracellular environment or internal Ca^{2+} stores located in the endoplasmic reticulum [ER]. Both Inositol-

1,4,5-triphosphate [IP_3] and Ryanodine [Ry] receptors found on the ER regulate the release of Ca^{2+} from this store, whereas entry of Ca^{2+} into this store is via the Stromal Interacting Molecule [STIM] and sarcoplasmic/endoplasmic reticulum Ca^{2+} [SERCA] ATPase pump [58,59]. However, maintenance of a balanced concentration is required to avoid toxicity. Ca^{2+} is therefore extruded out of the cell by specialized Ca^{2+} pumps and exchangers to regulate the duration of its elevated concentration. Notwithstanding, the role of Ca^{2+} sensors and buffers are key factors to physiological concentration regulation [60,61].

3.1. Calcium signaling channels

As earlier mentioned, intracellular Ca^{2+} changes are coordinated by the activation of different protein subunits which form channels for the flow of Ca^{2+}. In neuronal cells, there are two basic plasma membrane Ca^{2+} channels; voltage-gated [dependent] channels and receptor-operated channels [54,62].

3.1.1. Voltage-Gated Ca^{2+} Channels [VGCC]

VGCCs are mostly found on excitable cells where they function to initiate Ca^{2+} cellular influx by translating surface electrical signals and mediating a rapid increase in intracellular Ca^{2+}concentration [63]. There are two major categories of VGCCs; high and low voltage-activated. These open to large and small membrane activated depolarizations respectively [64,65].

3.1.2. Receptor-operated Ca^{2+} channels [ROCC]

These channels function only in response to specific ligands binding to the extracellular domain of the receptor. It then undergoes a conformational change that causes it to open for the passage of Ca^{2+} into the intracellular environment [54]. They are also called ionotropic receptors and may include the use of neurotransmitter ligands as; N-methyl-D-aspartate, acetylcholine, γ-aminobutyric acid receptors and the ATP-gated P2X receptor [12,66,67].

3.2. Monitoring Ca^{2+} signaling in vivo and in vitro

The versatile nature with which Ca^{2+} expresses its action in biological tissues makes monitoring its pathway essential. There are two main types of calcium indicators; chemical and genetically encoded calcium indicators, that detect cytoplasmic changes in concentration [68]. While the former has an *in vitro* application, the later *in vivo* studies, both can be used interchangeably in combination with other techniques aid in achieving optimal results in Ca^{2+} measurements [69,70]. These indicators employ the use of fluorescent molecules that respond to the binding of Ca^{2+} within the intracellular environment, by relaying corresponding changes in fluorescent intensity. Imaging devices combined with the above indicators are the diminutive confocal and two-photon microscopy [71,72].

4. Functions of CaBPs in the central nervous system

CaBPs within the CNS is part of the large EF-hand family. One class of these proteins act majorly as buffers which modulate transient spatiotemporal intracellular Ca^{2+} signals and regulate the pathway in order to maintain equilibrium. All of the EF-hand proteins are in a more stable form when bound to Ca^{2+} [73]. The other class of CaBPs acts majorly as a sensor; a predominant example is calmodulin. This class act primarily as effector proteins that decipher encoded information transmitted through the calcium signaling pathway, as they contain calcium-binding motifs. Sensors at suitable high concentrations also function as buffers [74,75]. Parameters that influence the activities of Ca^{2+} binding proteins depend on intracellular Ca^{2+} concentration, an affinity for either Ca^{2+} and other metals, intracellular interaction with ligands and kinetics of Ca^{2+} binding and release [75]. Generally, these CaBPs modulate the kinetics of intracellular Ca^{2+} [76]. Increased vulnerability of neuronal cells to neurodegenerative diseases have been associated with decreased expression of CaBPs [75,77,78]. Here, we highlight four major CaBPs, including parvalbumin, calretinin, calbindin D28k and calmodulin.

4.1. Parvalbumin [PV]

PV is distributed in a few cell types like the skeletal and heart muscles, teeth, skin, seminal vesicles, parathyroid glands, kidney, and brain. It maintains and synchronizes cortical neuronal activity via GABAergic synapses. The expression of PV in inhibitory GABAergic interneurons is found in varying brain regions like hippocampus, cerebellum, cortex, thalamus, and striatum [79]. During development, changes occur in PV distribution that influences neuronal cell synaptic transmission. This distribution for example in the molecular layer interneurons of the cerebellum is further expressed by the inhibitory synapses between the cellular components, thereby emphasizing on the slow acting effect following Ca^{2+} binding [80]. Deficiency in this protein has been associated with neuronal alteration leading to epileptic seizures and several psychotic disorders [81,82]. This atypical EP-hand protein has three domains; the Ca^{2+}-binding site which is Ca^{2+}/Mg^{2+} mixed, the second and third are C-terminal domains [CD and EF domains] for metal binding. It consists of two isoforms α and β; both enable the PV molecule to function not only as a buffer but also as a sensor [75].

4.2. Calretinin [CR]

Unlike the PV molecule, calretinin consists of six EF-hand domains, of which Ca^{2+} readily binds to five. The first two domains are arranged in pairs, giving rise to a non-linear modulation of intracellular Ca^{2+} signals. CR has the capacity to undergo Ca^{2+} conformational changes, making it behave like a sensor though it originally possesses a slow onset buffer property [83]. There is tentative evidence that it provides neuroprotection against excitotoxicity from glutamate and impairment in motor coordination [75]. It is differentially distributed in the cerebellum, auditory neurons, and olfactory bulb, amongst other regions and cells during development. The neuroprotective role of CR is channeled towards suppressing high concentrations of the Ca^{2+} that could be harmful to cell viability. Also, it is crucial in the induction of long-term potentiation [84,85]. There are reports indicating a loss in the proliferation of cells within the subgranular zone neurogenic niche of the dentate gyrus, due to CR deficiency. This cell loss could be carried into adult life depending affecting survival and migration of newly formed granule cells [86]. It is also a good anatomical marker for spinal motoneuron as a fast buffer when compared to PV, aiding fast locomotion activities such as swimming, in which any CR pattern irregularity could lead to the generation of continuous spike discharge [87].

4.3. Calbindin D28k [CB]

The CB binding protein consists of six EF-hands; four are mixed metal binding sites with high Ca^{2+} affinity and two non-functional metal binding sites. Its binding kinetics to Ca^{2+} is quantified to be from rapid to the intermediate rate of affinity, giving it a major role as a determinant of Ca^{2+} kinetics. It is the main calcium buffer that prevents calcium neurotoxicity [88]. The coupling of short thick-necked dendritic spines is mediated majorly by CB, a mechanism crucial for brain neurotransmission function [89]. Absence of CB protein in cerebellar Purkinje cells results in neuronal behavioral alteration and cognitive deficits, whereas, the excitotoxic activity of excess intracellular Ca^{2+} may lead to a selective neuronal cell degeneration [90,91]. Though it is abundant in the entire central nervous system [0.1–1.5% total soluble protein], it is mostly distributed in the hippocampus where it is expressed by pyramidal, granule, and mossy cells. Deficiency in these cells is linked to impairment in long term potentiation [92–94]. Other

known tissues for CB expression apart from the brain include kidneys and mineralized tissues where it could be a vitamin-D dependent endogenous calcium protein and exhibit some tissue-specific protective activity [95,96].

4.4. Calmodulin [CaM]

CaM is a calcium sensor binding protein that is found abundant in the CNS. It is composed of two EF-hand motifs each located in its N and C-domains [97]. The binding of calcium to this protein results in a conformational change that forms the Ca^{2+}/CaM complex. This complex regulates a host of other proteins including the CaM-kinase [CaMK] family, particularly the CaMKII which regulates numerous neuronal activities like neurodevelopment and plasticity [98]. The CaMK plays a major role is establishing long term potentiation in the hippocampus for memory enhancement [99]. Two classes of the CaMK are known based on the number of substrate binding targets; dedicated [substrate specific] kinases and multifunctional kinases [100,101]. Furthermore, the CaMK is involved in the phosphorylation and activation of the transcription factor, CREB which is involved in neuronal protection against neurodegeneration [102,103]. This multiprotein signaling complex also targets some subcellular organelles like the nucleus, mitochondrial and endoplasmic reticulum thereby regulating the functional dynamics of the cell [104–106].

5. Calcium signaling in neurodegeneration

Ca^{2+} performs a crucial part in the physiologic functioning of a healthy brain, and thus highlights its importance for neurodegeneration and neurotoxicity. The perturbation of Ca^{2+} homeostasis has been implicated in various mechanisms underlying the development and complications of several neurodegenerative diseases such as AD, PD, amyotrophic lateral sclerosis [ALS], Huntington's disease [HD], amongst others. Although each of these diseases has established specific pathogenic hypotheses in relation to Ca^{2+} signaling dysfunction, these are not yet sufficient for providing therapeutic strategies (Fig. 1).

In AD pathogenesis, the Ca^{2+} hypothesis indicates that an increase in the level of phosphatidylserine on neuronal surfaces heightens the development of Ca^{2+}-permeable channels by the accumulated Aβ oligomers [107,108]. Aβ oligomers also induce Ca^{2+} dysregulation via its modulatory effect on the NMDA and AMPA receptors, as well as P/Q-type calcium currents [109–113]. Likewise, a mutation of calcium homeostasis modulator 1 which is a novel Ca^{2+}-influx channel, has been identified to increase susceptibility to late-onset AD [114,115]. Also, neuronal cells of the frontal, parietal and temporal cortices of AD brains were found to contain significantly decreased levels of CaBPs including calmodulin and calbindin-D28 K [77].

Just as the Aβ oligomers aggregation, the alpha-synuclein toxicity theory of PD brains has been attributed to an increased level of neuronal Ca^{2+} influx [116,117], and the vulnerability of the dopaminergic neurons in the substantia nigra pars compacta to mitochondrial damage due to continuous Ca^{2+} influx [118,119]. Similarly, some regions of PD brains such as the hippocampus, substantia nigra, and nucleus raphe dorsalis were observed to be intensely deficient in calbindin-D28 K mRNA and related proteins [77]. The Ca^{2+}-mediated excitotoxicity of glutamatergic NMDA receptors has been reported to cause overstimulation of dopaminergic neuronal projections, impairments of NMDA receptor-binding ligands, as well as changes in gene expression, phosphorylation, and protein profusion of NMDA receptors and its subunits [77,120].

Confirmation of the imperative roles of Ca^{2+} signaling in ALS pathogenesis have been repeatedly documented and includes disproportionate mitochondrial engorgement and Ca^{2+} accretion in motor nerve endings, activation of calpain proteins in motor neurons, as well as truncated levels of Ca^{2+}-binding proteins in the hypoglossal and spinal motor neurons [121–123]. Reports also show that there is higher susceptibility of motor neurons to Ca^{2+}-induced excitotoxicity of glutamatergic AMPA receptors in ALS brains [124–127].

The role of Ca^{2+} in HD pathologies is similar to other neurodegenerative disorders described above. There are also documentation of mitochondrial Ca^{2+} accumulation, activation of Ca^{2+} binding proteins such as calpains, and deteriorated Ca^{2+} buffering ability of affected neurons of HD patients and animal models [122,128,129].

6. CaBPs in neurodegeneration

PV regulates cortical and spinal motor neurons. Its deficiency has been shown to result in neuronal loss as seen in patients with ALS [130]. PV, as well as CB, have been found to be deficient in the majority of motor neurons such as lower cranial nerve, spinal and cranial motor neurons, which are lost during the early stage of ALS [77,131]. A study carried out using a schizophrenic rat model showed a reduction and apparent shift in the distribution of PV interneurons [132].

A substantial decrease in expression of other CaBPs in the CNS has been noted in neurodegeneration, and consequent neurologic disorders [75,77,78]. However, reports given for CR propose that its neuroprotective role may provide possible shielding against any deleterious/deteriorating effect from degenerative mechanisms; hence it usually appears unaffected [133]. A previous report suggests that CR expressing neurons may be resistant to neurodegeneration [134]. Nonetheless, AD has been associated with impairment in PV and CR [135]. Early onset of accumulation of Aβ deposits in the hippocampus was found to correlate with a corresponding selective reduction in the population of CR-positive interneurons particularly in the hippocampal CA1-3 fields of PS1/AβPP mice model of AD [136]. Also, the involvement of the periglomerular cells in regulating the synapses from the sensory neuron of the olfactory epithelium to the glomeruli of the olfactory bulb implicates a possible role of CR expressing cells in the neural basis of hyposmia in AD. This may be due to the adequate expression of CR in these periglomerular cells [137]. There is a modulatory effect of dopamine on CR cells in large cholinergic neurons of the striatum, in which an adaptation to dopamine denervation has been postulated to be the cause of the increased expression of CR interneurons in these cholinergic neuronal cells in MPTP primate model of PD [138].

Age-related decrease in CB expression in cortical neurons has been demonstrated in some neurodegenerative cases. Such decrease in CB expression is a feature that could heighten the vulnerability to age-related AD deficits. However, resistance to AD pathogenic process has been seen to be exhibited by CB expressing cells [10,139]. CB has been shown to modulate apoptosis possibly by binding with caspase-3, and this interaction is of interest in the onset of AD and Huntington's disease [HD] [92]. Additionally, loss of CB-containing neurons has been documented in HD pathologies [129]. Increase in tyrosine hydroxylase and CB induced by estrogen provided protection against neurodegenerative changes in PD [140]. This portrays a keen relationship between dopamine production and CB.

Several CaM-binding proteins have been associated with the formation of amyloid β plaques enhanced by the hyperactivation of the CaMKII complex [141,142]. Impairments of the T286-autophosphorylation of α-CaMKII shows significant deterioration at reinforcing synapses and possibly result in memory loss seen in AD patients [143].

7. ROS release in calcium signaling dysfunction

Dysfunctional calcium signaling mechanism may be caused by a number of factors, which include reduced expression of CaBPs, dysregulated channels and disrupted organelle homeostasis [77]. The organelles most affected aside the nucleus are the mitochondria and endoplasmic reticulum, both of which have strong functional and structural networks established through zones called mitochondria-associated endoplasmic reticulum membrane [MAM]. Coordination of Ca^{2+} transport along these zones is crucial to maintain cellular

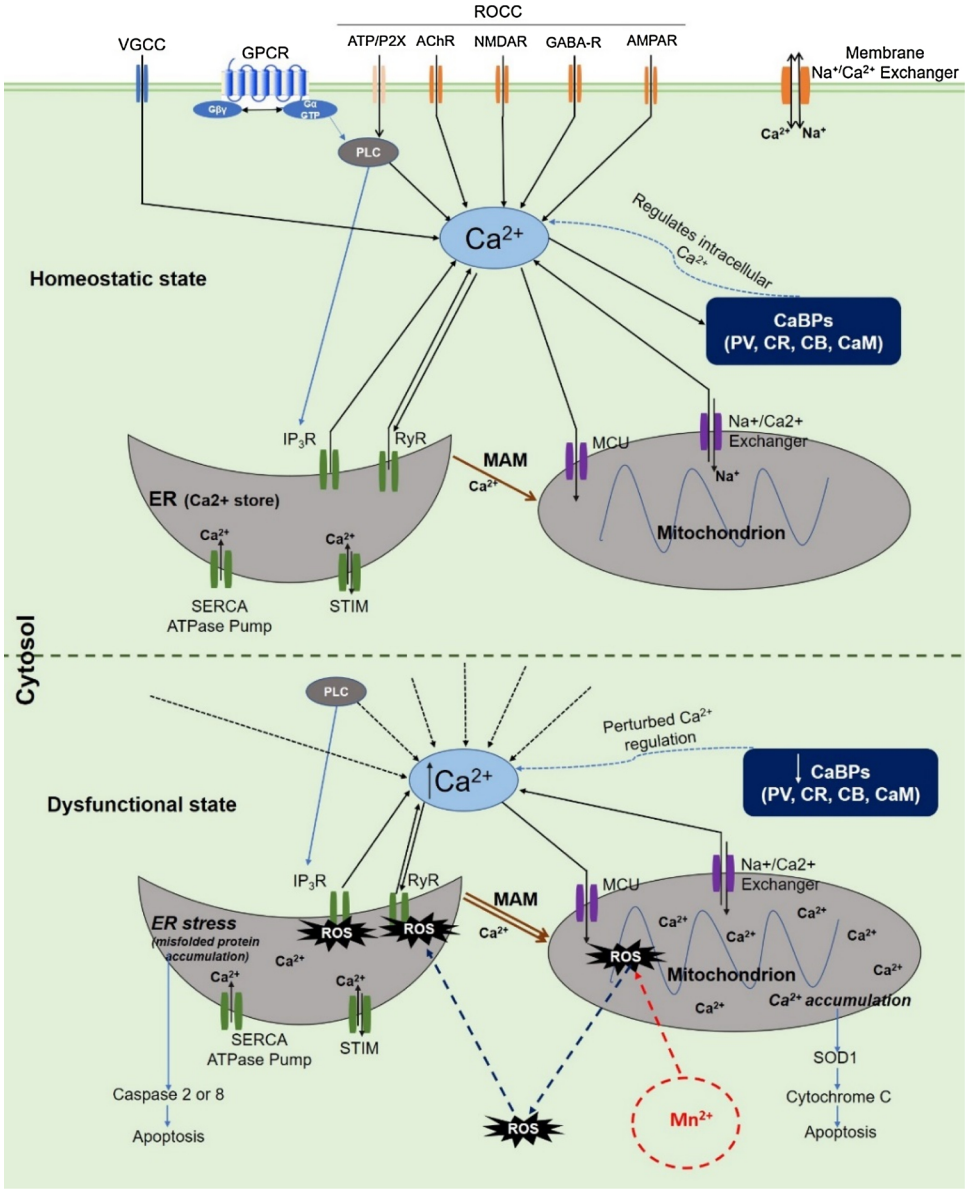

Fig. 1. Calcium signaling in homeostatic [normal] and dysfunction state. In the homeostatic state, Ca^{2+} concentration is delicately balanced by various signaling molecules involved in Ca^{2+} regulation. Perturbation of Ca^{2+} homeostasis is implicated in the neurodegenerative process. Several factors can result in calcium signaling dysfunction; however, the generation of ROS is usually predominant. ROS-mediated perturbed calcium signaling is implicated as an indirect mechanism of Mn neurotoxicity. Nevertheless, it is unclear if Mn accumulation could have a direct influence on several molecules involved in Ca^{2+} homeostasis. VGCC – voltage-gated calcium channels; ROCC – receptor-operated calcium channels; ATP/P2X – ATP-gated P2X receptor; AChR – ACh receptor; NMDAR – NMDA receptor; GABA-R – GABA receptor; AMPAR – AMPA receptor; IP_3R – IP_3 receptors; RyR – Ry receptors; ER – endoplasmic reticulum; SERCA – sarcoplasmic/endoplasmic reticulum Ca^{2+}; STIM – stromal interacting molecule; MAM – mitochondria-associated endoplasmic reticulum membrane; CaBPs – calcium-binding proteins; PV – parvalbumin; CR – calretinin; CB – calbindin D28k; CaM – calmodulin.

homeostasis and prevent cellular death [144,145]. Other functions associated with this inter-organelle junction include; phospholipid exchange, intracellular trafficking, autophagy, ER-stress and unfolded protein response and inflammasome formation [146]. CaBPs are expressed distinctively in different segments of neurons and participate in modulating Ca^{2+} concentration as well as assisting in morphological appearance of the cell [147]. Disturbance of CaBPs activities can drive calcium signaling dysfunction in the neurons and is implicated as a contributor to neurodegenerative changes [148].

The flow of Ca^{2+} into the intracellular environment during the signaling process may cause the generation of ROS. However, inadequate removal of ROS is capable of further deleterious impact on the Ca^{2+} signaling leading to neurodegeneration [149]. Under normal physiological conditions, the mitochondria are the powerhouse for the production of energy. It also acts as a buffer center for Ca^{2+} and the main source of ROS in a stress-related cellular condition.

ROS is formed by oxygen electron transfer into hydrogen peroxide [H_2O_2] sometimes in the presence of superoxide dismutase [SOD]. This reaction can occur at various sites within the mitochondria [150]. Mutations in the SOD1 gene have been found to correlate with damaged mitochondrial function in the neurodegenerative process [151]. Free radicals become more destructive when they exceed the antioxidant scavenging rate [150,152]. There is also the involvement of B-cell lymphoma-2 [Bcl-2] family of proteins which enhance the flow of Ca^{2+} from the endoplasmic reticulum to the mitochondria. This interactive mechanism promotes Ca^{2+} accumulation in the mitochondria leading to excitotoxicity and eventual cell death via apoptosis [153].

8. Calcium signaling in Mn neurotoxicity

In a homeostatic state, whole brain concentrations of Ca^{2+} range between 3.5 and 5 μM/gm [154]. Meanwhile, basal Mn level is elevated in mitochondria loaded tissues like the brain, in a range of 0.3-0.7 μg/g wet weight [155]. As already stated above, Mn is important to the maintenance of biological processes that involve the catalytic action of co-enzymes. However, excessive Mn concentrations result in neurotoxicity that may be capable of modifying intracellular Ca^{2+} homeostasis [156]. The influx of Mn into the brain by crossing the blood-brain barrier [BBB] has been suggested to also occur via Ca^{2+} channels [157]. A proposed mechanism by which toxic metals can interfere with Ca^{2+} homeostasis is by binding directly to the sulfhydryl groups of proteins resulting in functionally impaired channels and pumps [156].

But this may not be the case with Mn^{2+} which does not readily bind to these groups of amines [18].

8.1. Mitochondrial involvement

Particular interest has been channeled into understanding the mitochondrial Ca^{2+} uniporter [MCU] which has an affinity to also transport Mn^{2+} [18]. There are strong indications that the reaction of Mn with this site may be the medium for Mn-induced oxidative stress in neuronal cells [158]. The presence of Mn can cause distortions in the morphology and functional integrity of mitochondria plasma membrane by the activation of cytochrome P450, inhibition of some respiratory enzymes like succinate and blockage of electron transfer. Overall mitochondrial dysfunction and apoptotic cell death have been associated with Mn neurotoxicity [158–160]. Worthy of note is that the homeostatic balance during mitochondrial calcium signaling involves cytosolic Ca^{2+} buffering in cellular processes by actions of the CaBPs [161,162]. In the normal resting stage, the affinity of this mitochondrial channel for Ca^{2+} is low. MCU mediates uptake of Ca^{2+} when it is in high extramitochondrial concentrations [163,164]. Pro-apoptotic stimuli enhance the sensitivity of MCU to apoptotic cell death due to increased Ca^{2+} loading [165]. A pathological mechanism enhanced by Mn^{2+}, which is also capable of initiating and sustaining a resultant accumulation of Ca^{2+} by replacing Mg^{2+} in Ca^{2+}-Mg^{2+} ATPase during mitochondrial ATP synthase [158]. Efflux of Mn^{2+} out of the mitochondria is by the passively active Na^{+}-independent mechanism; the resultant effect of this mechanism is the prolonged difficulty in extruding Mn^{2+} once inside the cell [18]. Thus, a pathologic neurotoxic sequence is induced that disrupts other cellular mechanisms. Generally, mitochondrial dysfunction as a result of a disruption in calcium signaling can lead to degenerative disorders [166].

The regulators of the MCU are MICU1 and MICU2. While the former being the key regulator of mitochondrial Ca^{2+} uptake elicits a stimulatory effect on MCU, the later stops its activity [163,167,168]. There appears to be an interactive but dependent communicative action between the CaBPs and the MCU, via the properties of the EF-hand domains which control the threshold for calcium uptake. The MICU1 inhibits mitochondrial calcium influx in low cytosolic concentration [169]. If the presence of Mn^{2+} with these EF-hand possessing domain proteins neither replaces nor substitutes the action of Ca^{2+}, it could be extrapolated that it may act as a barrier to impair proper calcium binding at this site or just hinder appropriate response by the proteins leading to a mutated conformational change. If this is the case, it means the sensing and subsequent structural configuration of Ca^{2+} on its binding proteins will be altered. Such alteration would lead to a dysfunctional state in the calcium signaling within the cytoplasm, which would cause a corresponding hypersensitivity but defective response of the MICU1 and vice-versa. If this hypothesis correlates, it goes further to indicate another indirect mechanism of Mn-induced oxidative stress in neuronal cells and the release of endogenous reactive oxygen species [ROS] [158]. Mn-induced cell death can result from mitochondrial and CNS dysfunction via the production of free radicals. This ROS generation contributes a great deal to mitochondrial DNA damage, modification of calcium signaling proteins kinetics and apoptosis, especially at the junction between the mitochondria and endoplasmic reticulum [18,170]. It could also trigger the release of Ca^{2+} from internal stores by activating the RyR receptors of the ER [171]. Such mitochondrial dysfunction and oxidative stress have been implicated in neurodegeneration [172–176].

Additionally, DMT 1 plays a crucial role in Mn influx amongst other divalent cations. Considering most importers of Mn have the capacity to transport other metals, there is an increasingly competitive tendency of these other metals especially with a high Mn concentration and vice-versa [177,178]. Therefore, an increase in Mn could initiate a subsequent rise in other metals that increase toxicity. Such correlating increase has been reported between Mn and Ca^{2+}, in which Mn accumulation leads to a Ca^{2+} dysfunction and depreciation in the mitochondrial energy production [32,179]. The Blood Brain Barrier and Blood Cerebro-spinal Fluid Barrier are mainly responsible for regulating the manganese content of the brain [180]. As earlier stated, the Ca^{2+} uniporter and Na exchanger channel are responsible for maintaining the homeostasis of Mn within the mitochondria [177]. Limited studies have been done to demonstrate the storage of Manganese in neuronal cells, but toxic levels of accumulation have been shown in neurons and astrocytes predominantly within the mitochondria and nucleus. Therefore, harmful levels do not necessarily account for a dysfunctional storage system; the slow efflux of Mn in the mitochondria, for example, has been indicated to cause accumulation [181]. Circulating Mn^{2+} is initially bound to albumin in the plasma; subsequent oxidation occurs that transforms Mn^{2+} into Mn^{3+} which enters the brain. After diffusion into the brain, movement into neuronal cells involves breakage of the Transferrin Manganese [Tf-Mn] complex, which reduces the oxidized Mn. This oxidized Mn^{2+} state is stable in physiological environment and enables efficient metal transport via the DMT1. Areas of adequate expression of DMT1 [Dopamine-rich neurons of the basal ganglia and olfactory epithelium] have been stated as access sites for the influx of environmental Mn into the CNS [157,180].

9. CaBPs in Mn neurotoxicity

Activities of CaBPs may be more implicated in the aforementioned role of mitochondrial calcium signaling process in Mn neurotoxicity than has been investigated. However, there is a dearth of studies to ascertain the specific effects of Mn exposure to the activities of CaBPs. Mn accumulation modifies or suppresses neurotrophins such as Brain-Derived Neurotrophic Factor [BDNF], which influences the maturation of binding proteins interneuron. Additionally, BDNF has a vital role in excitability and neurotransmission and plasticity [78,182]. Reduction of this BDNF has been reported in the striatum of Mn-exposed non-human primates [183]. Whereas reduction in BDNF is correlated reduced or abnormal expression of CaBPs, specifically PV [184]. A common cause of abnormal changes in PV interneuron has been associated with disruptive neurogenesis, which can be caused by developmental Mn neurotoxicity [185]. Another medium for Mn neurotoxicity and distortion of PV expression is directly on alteration of GABAergic neuronal tone marked by its depleting effect on dopamine in manganism [186].

10. Concluding remarks

In the current review, we have highlighted the influence of Ca^{2+} regulation in the neurodegenerative process and a possible role for perturbed calcium signaling in Mn neurotoxicity. Several mechanisms have been implicated in Mn-induced neurodegeneration including oxidative stress, generation of free radicals, and apoptosis. These are greatly influenced by mitochondrial structural and functional integrity which can be dependent on intracellular Ca^{2+} homeostasis as have been severally highlighted in the current review. However, further elucidation of the direct effects of calcium signaling dysfunction and CaBPs activities in Mn neurotoxicity is required. Our ongoing studies are attempting to evaluate protein and mRNA expression of CaBPs in experimental models of Mn neurotoxicity. CaBPs are major contributors in enhancing the neurotoxic cascade and could be a focus for not just regulating the calcium signaling pathway but also curtailing the deleterious actions of neurotoxicants.

Declaration of Competing Interest

None.

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