International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 02-02-2024, Accepted: 25-02-2024, Published: 19-03-2024
Volume 9, Issue 1, 2024, Page No. 15-21

Calcium signaling: A pharmacological approach in remote ischemic preconditioning against cerebral vascular dementia

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Abstract
Dementia is the world's most prevalent neurodegenerative disease, affecting over 50 million people worldwide and estimated to rise affect upto 152 million people by 2050. vascular dementia (VD) is the second most prominent form of dementia. Vascular dementia (VD), in which cognitive decline is attributed to some form of vascular injury, typically ischaemic, is the second most common cause of dementia in Western societies. It is believed that vascular dementia is a distinct clinical and pathological entity from Alzheimer's dementia, Lewy body dementia, or frontotemporal dementia, even if aspects of vascular disease may be present in these conditions. Vascular dementia is caused by ischaemic insults such as haemorrhage and hyperfusion that trigger neurodegeneration by depriving nerve cells of oxygen and glucose. There are two types of vascular dementia. Multi-infarct dementia (MID) and small vessel dementia SVD). MID is considered the most common form of vascular dementia (VD), a primary cause of dementia second to Alzheimer's disease (AD). That is characterized by multiple lesions and infarction of small arteries in the cerebral gray-white matter. SVD primarily distresses the small perforating arteries, being defined as vessels with less than 50 μm diameters, also defined as "all the vessels within the brain parenchyma plus the vessels with a diameter less than 500 μm in the leptomeningeal space" supplying the deep brain structures, general increased arterial stiffness is associated with an increased white matter lesion burden. Ischemia/reperfusion (I/R, restoration of blood flow) injury is a major consequence of cardiac arrest period and resuscitation. However, short duration of cerebral ischemia (less than 10 min) can lead to neuronal death within the brain especially in the hippocampus and causes learning and memory deficits. Following I/R, there are three important threats: excitotoxicity, oxidative/nitrosative stress and neuroinflammation. Under normal physiological conditions, integrate neural signals, inhibit Ca^{2+}-mediated excitation, contribute to information processing, and structurally and functionally bridge neurons and vascular endothelial cells. Incase of I/R injury, due to oxidative stress and mitochondrial dysfunction, the calcium influx increases and thereby calcium overload to activate the caspases and downregulation of eNOS to produce endothelial dysfunction and vascular dementia. Remote ischemic pre-conditioning (RIPC) work by reduced the oxidative stress and regulating the various transduction pathways such as PI3K/Akt pathway, PKC pathway, TLR- 4 pathway. The mechanism involves in pre-conditioning also include inhibition of autophagy and apoptosis, improvement of mitochondrial permeability transition, and attenuation of endoplasmic reticulum stress and also the activation of opioid receptors prevent endothelial dysfunction. Literature survey suggests the role of calcium signalling in I/R, IPC and RIPC. NCX plays an important role in the maintenance of Ca^{2+} homeostasis and is detected in the plasma membrane of most cells, including neurons and glia. Na^{+}/Ca^{2+} exchanger (Sodium/calcium exchanger or NCX) by regulating the homeostasis of Na^{+} and Ca^{2+}, plays a key role in the evolution of ischemic neuronal damage. This review suggests that the pivotal role of NCX inhibition in neuroprotection against cerebral ischemia reperfusion injury and thereby vascular dementia.

Keywords: Vascular dementia, calcium, oxidative stress, apoptosis, neuronal death

Introduction

Dementia is a progressive neurodegenerative disorder characterized by decline in memory and cognitive ability which affects day to day activities of an individual (Cerejeira *et al*., 2012) [1]. Dementia is the world's most prevalent neurodegenerative disease, affecting over 50 million people worldwide as of 2018 (World Alzheimer Report, 2018) and estimated to rise affect upto 152million people by 2050 (Patterson, 2018) [2]. Alzheimer's disease (AD) is the most prominent form of dementia followed by, vascular dementia (VD), lewy body disease, and frontotemporal dementia. Around 70% of dementia cases

arise from AD followed by about 20% due to VD in which cognitive decline is attributed to some form of vascular injury, typically ischaemic, is the second most common cause of dementia in Western societies.

Vascular Dementia

Vascular dementia is among the most common etiologies of major neurocognitive disorder (MND), affecting primarily older adults (>65), and it is the leading nondegenerative cause of dementia. Vascular dementia (VD), in which cognitive decline is attributed to some form of vascular injury, typically ischaemic, is the second most common cause of dementia in Western societies (Sanders *et al*., 2024) [3]. Developing a valid definition, distinct from AD, has been problematic. It is a heterogeneous condition and clinical manifestations differ depending on the size and location of the cerebrovascular lesions. In autopsy studies, 'mixed' AD and vascular dementia has been reported as accounting for between 0% and 55% of cases of dementia. In addition to co-occurrence due simply to chance, AD and vascular dementia may have aetiological or pathogenetic factors in common (Song *et al*., 2022) [4]. Vascular Dementia (VD) is the second most common type of dementia after Alzheimer's disease (AD). Specifically, it affects approximately 5.6% of people older than 60 years old. Vascular dementia (VD) is less than that of AD, it is still of significance, as it is often associated with a higher mortality rate than AD. VD, recently referred to as vascular cognitive disease includes a variety of cerebrovascular lesions, for which, due to the high variability of morphological findings and multifactorial pathogenesis, no generally accepted morphological criteria are available. Major types of VD are micro-infarcts in functionally important brain areas interrupting major neuronal circuitries (multiple infarct encephalopathy, small-vessel and strategic infarct type dementia), subcortical arteriosclerotic leukoencephalopathy Binswanger (subcortical lacunae mainly involving basal ganglia; white matter lesions and micro-infarcts), large and small cerebral haemorrhages, hippocampal sclerosis; cerebral amyloid angiopathy. Recent guidelines assessing 14 pathologies in 13 brain areas showed reproducible results but need further validation (Skrobot *et al.*, 2016) [5]. Mixed type neuropathology is diagnosed when a combination of various pathologies, in particular AD with cerebrovascular lesions and/or Lewy pathology is present, which occurs in up to 80% of elderly demented patients. Subcortical cerebrovascular lesions are more frequent in AD patients than in non-demented controls (Jellinger, 2013) [6]. Risk factors for VD are multifactorial and include aging, illiteracy, genetic predisposition, abnormal conditions and diseases such as hypertension, stroke, diabetes, obesity, coronary infarction, atrial fibrillation, and atypical biochemical blood parameters such as high cholesterol and homocysteine levels. Various lifestyle factors such as smoking, unhealthy diet and physical inactivity have been associated with an increased risk of VD (Jellinger, 2013) [6]. It is believed that vascular dementia is a distinct clinical and pathological entity from Alzheimer's dementia, Lewy body dementia, or frontotemporal dementia, even if aspects of vascular disease may be present in these conditions. Vascular dementia is caused by ischaemic insults such as haemorrhage and hyperfusion that trigger neurodegeneration by depriving nerve cells of oxygen and glucose.

There are two types of vascular dementia as given below

- *Multi-infract dementia.*
- *Small vassel dementia.*

Multi- Infract Dementia

Multi-infarct dementia (MID) is considered the most common form of vascular dementia (VD), a primary cause of dementia second to Alzheimer's disease (AD) (Thal *et al.*, 2012) [7]. That is characterized by multiple lesions and infarction of small arteries in the cerebral gray-white matter (Iadecola, 2013) [8]. The brain is an organ that consumes a high amount of energy and requires stable blood flow to deliver a sufficient amount of energy to maintain synaptic activity (Iadecola, 2004) [9]. A number of studies have reported that cerebral hypoperfusion is caused by cardiac arrest, arrhythmia and heart failure, decreased cerebral blood flow induced by hyperlipidemia, atherosclerosis and diabetes (de la Torre, 2012) [10], as well as ageing and the apolipoprotein E gene (Qian *et al.,* 2017) [11], which are major risk factors for cognitive impairment. Insufficient or low cerebral blood flow, especially acute cerebral ischemia, can cause insufficient glucose uptake, significantly reduced ATP content and the accumulation of lactic acid in the brain (Feng *et al.*, 1999) [12]. The mitochondria is the main site of ATP synthesis (van der Bliek *et al.,* 2017) [13] and an excessive accumulation of lactic acid can cause mitochondrial dysfunction, inducing oxidative stress, mitochondrial autophagy and apoptosis (Chao *et al*., 2020) [14]. which in turn exacerbate MID lesions and cognitive decline. Therefore, regulating energy metabolism in the brain may be an effective strategy to improve cognitive impairment in MID.

Small Vassel Dementia

Small vessel disease (SVD) primarily distresses the small perforating arteries, being defined as vessels with less than 50 μm diameters, also defined as "all the vessels within the brain parenchyma plus the vessels with a diameter less than 500 μm in the leptomeningeal space" supplying the deep brain structures (Zanon *et al*., 2021) [15]. Nevertheless, general increased arterial stiffness is associated with an increased white matter lesion burden. SVD is the most important and common cause of vascular dementia, leading to 45% of dementia, and it accounts for about 20–30% of all strokes worldwide, 25% of ischemic (or lacunar strokes). Moreover, it significantly increases the risk of future stroke. Often, SVD lesions are clinically insidious and they act as

"silent" lesions. Thus, SVD is a dynamic pathology, lesions progress over time, and the long-term outcome and impact on brain damage vary. In sporadic cerebral SVD, sporadic aging and hypertension are listed as the most critical risk factors. However, different hereditary forms of SVD have also been described (Haffner *et al.*, 2015) [16]. In the latter forms, several pathological changes to the vasculature in small arterioles (like vascular muscle dysfunction, lipohyalinosis, vascular remodeling, and the deposition of fibrotic material) have been identified. Venous structures are also affected.

Risk Factors of Vascular Dementia

Vascular dementia (VD) is a common form of dementia which is caused by problems with the blood supply to the brain. VD is the most severe form of VCI characterized by the presence in vascular brain injury as well as cognitive impairment. Risk factors for VD are multifactorial and include aging, illiteracy, genetic predisposition, abnormal conditions and diseases such as hypertension, stroke, diabetes, obesity, coronary infarction, atrial fibrillation, and atypical biochemical blood parameters such as high cholesterol and homocysteine levels. Various lifestyle factors such as smoking, unhealthy diet and physical inactivity have been associated with an increased risk of VD (Jellinger, 2013) [6]. In consequence, reducing or avoiding such risk factors, if possible, is strongly recommended for the prevention of VD. These include maintenance of healthy blood pressure, prevention or control of diabetes, smoking cessation, maintaining physical fitness and controlling blood cholesterol levels. The rapid increase in cerebrovascular diseases including stroke worldwide suggests that the currently used primary preventive actions against stroke and cardiovascular diseases have very limited efficacy, most likely due to the fact that they function on a voluntary basis with limited self-motivation (Feigin *et al.*, 2016) [17]. In addition, several monogenic forms of cerebrovascular disease have been identified. The two best studied of these are cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL: a subcortical small vessel disease accompanied by lacunar strokes, migraine, and dementia) and hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D).

Cerebral Ischemia/Reperfusion Injury

Ischemia/reperfusion (I/R, restoration of blood flow) injury is a major consequence of cardiac arrest period and resuscitation (Bellanti, 2016) [18]. However, short duration of cerebral ischemia (less than 10 min) can lead to neuronal death within the brain especially in the hippocampus and causes learning and memory deficits (Bacigaluppi *et al.*, 2010) [19]. Following I/R, there are three important threats for neuronal function in the brain:

a. First excitotoxicity as a result of energy and oxygen depletion which causes the overload of calcium ions inside neurons and released glutamate excitatory neurotransmitter into the extracellular space (Forrest *et al.*, 2023) [20].
b. Second, oxidative and nitrosative stress in which free radicals are continuously produced as a result of oxidative phosphorylation in the mitochondria, although under physio-logical concentrations they serve important functions. The level of free radicals is regulated by an enzymatic antioxidant like as superoxide dismutase (SOD) and non-enzymatic components including glutathione. It is shown that in the ischemic stroke the ratio between oxidants and antioxidants factors collapse which leads to oxidative stress. Neuronal cells have a high oxygen consumption and metabolic demand, therefore, they are very sensitive cell population and are more at risk for ischemic cell death. In this regard, drugs acting as free-radical scavengers or inducers of endogenous antioxidant enzymes are suitable candidates for stroke therapy (Cheon *et al*., 2023) [21].
c. The third important threats following I/R for the neuronal function is neuroinflammation which plays a significant role in the pathogenesis of stroke. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1ß (IL-1ß) are the main cytokines which initiate inflammatory reactions following brain stroke and lead to brain damages (Anrather and Iadecola, 2016) [22].

In the acute (minutes to hours) and late phases (hours to days) of I/R, elevation in the level of reactive oxygen species (ROS), nitrate/nitrite, cytokines and chemokines trigger immune responses and results in the activation of a variety of inflammatory cells (Chamorro *et al.*, 2016) [23].

Pathophysiology

Under normal physiological conditions, integrate neural signals, inhibit Ca^{2+} - mediated excitation, contribute to information processing, and structurally and functionally bridge neurons and vascular endothelial cells. It also protect neurons by producing various regulatory signals, synthesizing neurotrophic mediators, and reactivating or metabolizing Glutamate (Song *et al.*, 2017) [24]. Furthermore, secrete factors that control the formation, maintenance, function, and repair of the BBB (Brambilla, 2019) [25], all of which contribute to regulating local cerebral blood flow. Excessive release of Glutamate leads to hyperexcitability of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors expressed in neurons, causing Na^+, K^+, and Ca^{2+} influx into neurons. Important, excessive Na^+ influx destroys the osmotic pressure between cells, causing dysfunction of cellular metabolism that leads to cytolysis and release of intracellular contents. Ca^{2+} influx further causes calcium overload, resulting in cellular swelling and activation of proteases and phospholipids that produces free radicals, triggering an adaptive immune response (Lamar *et al*., 2022) [26], ultimately leading to neuronal death. Catalases and related proteins and nutritional factors to clear excessive ROS during cerebral

ischemia, thereby reduced neuronal damage induce by hydrogen peroxide and nitric oxide.

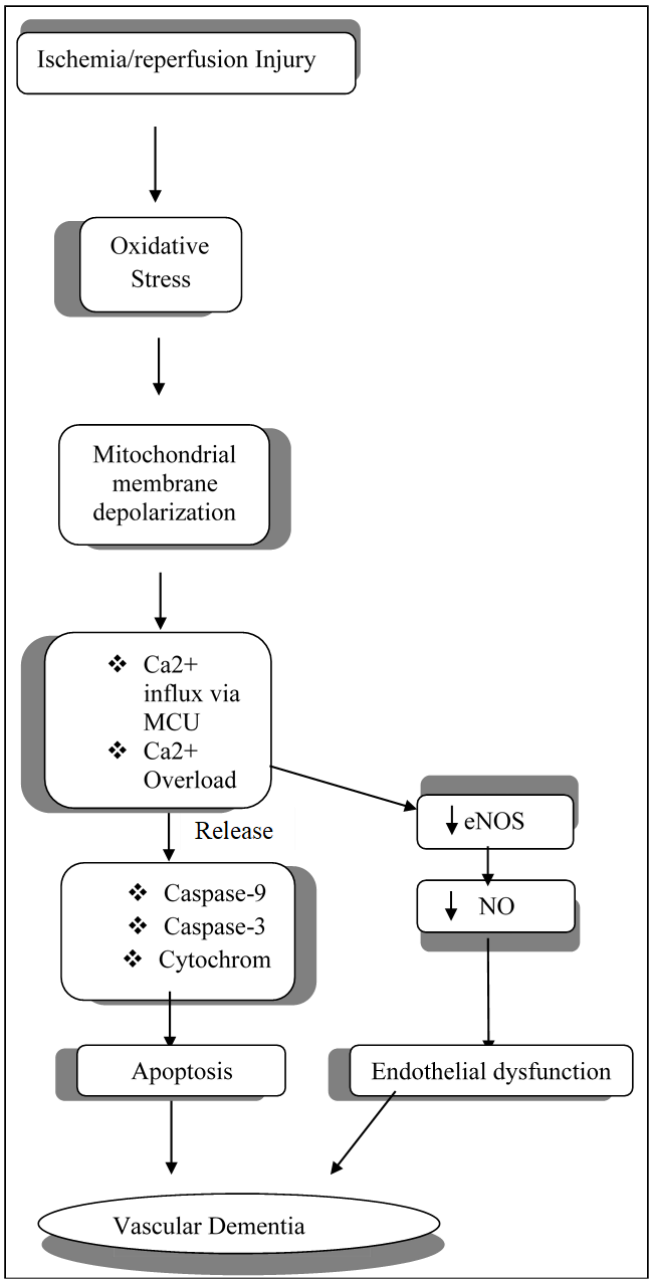

Fig 1: Mechanism of I/R Injury induced vascular dementia

Concept of Ischemic Pre-Conditioning & Remote Ischemic Pre-Conditioning

This term refers to the cell/tissue adaptation to ischemic conditions after being exposed to ‘‘subtoxic’’ doses of stressors, such as hypo-/hyperoxic pre-conditioning, hypo-/hyperthermia, OGD or pharmacological pre-conditioning. Pre-conditioning results in a transient protective phenotype called ischemic tolerance, in which the tissue is more resistant to a subsequent more severe ischemic event. In the neural tissue, this phenomenon was first described in 1990 and co-authors in several different areas of the gerbil brain. Since then, many investigators have been engaged in finding molecular mechanisms that lie beneath the minimization of neuronal damage and the facilitation of regenerative processes. These mechanisms include complex biological cascades that are specific to the applied stimulus and employ both neuronal as well as glial pathways (Thushara *et al.*, 2016) [27]. These are mainly the immune response that involves the microglial activation of the pro-inflammatory cytokines, such as interleukins 1b and 6 (IL-1b, IL-6), and TNFa the nitric oxide synthase (NOS) cascade or the activation of certain enzymes, such as stress-activated kinases, cyclooxygenase-2 or COX-2; or sphingosine kinase 2 (SPK-2). Pre-conditioning is suggested to activate changes at the gene level, which involves activation of molecules, such as transcription factors, transducers, sensors, and effectors, as well as numerous post-translational modifications (Krzy *et al.*, 2014) [28]. NMDA activation is reported to mediate neuroprotection by inhibition of stress-activated c-Jun N terminal kinase (JNK), activation of extracellular signal-regulated kinase (ERK1/2) and protein kinase B (Akt1), and regulation of normal cAMP-responsive element-binding (CREB). In neuronal cortical cultures, tolerance was achieved with glutamate pre-conditioning and blocked by NMDA and AMPA receptor antagonists. Other studies have documented the decreased expression of glutamate receptors, in particular NMDA and AMPA, which reduced the excitotoxicity after ischemic pre-conditioning. Similarly, changes in the expression of glial GLT-1 have been also proposed as key mechanisms of ischemic pre-conditioning. Moreover, OGD pre-conditioning performed in neuron/astrocyte co-culture revealed that the reversed operation of astrocytic GLT-1 was crucial to the development of neuronal ischemic tolerance (Kawahara *et al.*, 2005) [30]. Recent studies show that GLT-1 expression and function of glutamine synthetase during pre-conditioning can be maintained via mechanisms including upregulation of Cx43 and inhibition of cellular kinase Src. Another study suggests that p38mitogen-activated protein kinase (MAPK) participates in the mediation of astrocytic GLT-1 upregulation during the induction of brain ischemic tolerance after ischemic pre-conditioning (Zhang *et al.*, 2017) [24].

A special subtype of ischemic pre-conditioning (IPC) was demonstrated in the early 1990s with the concept of RIPC i.e, REMOTE ISCHEMIC PRE-CONDITIONING (Przyklenk *et al.*, 1993) [31]. Remote ischemic pre-conditioning induced brief ischemia of the circumflex artery. This procedure then provided protection to a region of myocardium that is supplied by a different artery–the left anterior descending. Hence, the circumflex artery served as a remote pre-conditioning stimulus. The remote pre-conditioning concept was extended further as it became obvious that the size of a myocardial infarct could be remarkably decreased by short prior episodes of ischemia and reperfusion in an organ or tissue far from heart.

Accordingly, remote IPC confers neuroprotection against stroke by priming the peripheral immune system prior to a subsequent ischemic attack by enhancing host defenses (Liu *et al.*, 2016) [32]. Emerging clinical trials are also demonstrating that remote pre-conditioning may be cardioprotective and neuroprotective.

With regard to the remote pre-conditioning stimulus, it is important to identify the most effective remote tissue. Skeletal muscle ischemia has been shown to be a powerful remote pre-conditioning stimulus in larger animals and humans (Kharbanda *et al.*, 2002) [33]. For example, inflating a blood-pressure cuff to induce four episodes of 5-min limb ischemia prevented ischemic endothelial dysfunction in the forearm of normal volunteers and decreased infarct size in an animal model of myocardial infarction. This same

stimulus, applied to the recipient in a cardiac transplant model, prevented I/R injury to the donor and regulated expression of pro-inflammatory genes in circulating human neutrophils. In a porcine model of cardiopulmonary bypass (CPB), re-IPC provided myocardial and pulmonary protection (Kharbanda *et al.,* 2002; 2006) [33, 34]. Therefore, skeletal muscle provides an effective target for pre-conditioning. However, there is no conclusive evidence regarding.

Mechanism of Remote Ischemic Pre-Conditioning (RIPC)

Remote ischemic pre-conditioning (RIPC) work by reduced the oxidative stress and regulating the various transduction pathways such as PI3K/Akt pathway, PKC pathway, TLR 4 pathway. The mechanism involves in pre-conditioning also include inhibition of autophagy and apoptosis, improvement of mitochondrial permeability transition, and attenuation of endoplasmic reticulum stress and also the activation of opioid receptors prevent endothelial dysfunction. Literature survey suggests the role of calcium signalling in I/R, IPC and RIPC.

Calcium Signalling & RIPC

Ca^{2+} signaling plays a crucial role in mediating numerous cellular processes in plants and animals. Ca^{2+} enters the cell through a number of finely regulated plasma membrane channels and binds to a multiplicity of sensor proteins, which decode the Ca^{2+} signal to activate specific effector pathways. Subsequent Ca^{2+} extrusion is mediated by membrane transporter systems (Carafoli, 2002; Berridge *et al*., 2003) [35, 36]. Ca^{2+} signaling is a prerequisite of many cellular physiological activities. Precise control of intracellular Ca^{2+} ($Ca^{2+}{}_i$) is therefore critical for proper regulation of cellular functions. Intracellular organelles, including endoplasmic reticulum, mitochondria, and secretory vesicles have Ca^{2+} uptake mechanisms to remove Ca^{2+} from the cytosol and bring $Ca^{2+}{}_i$ concentration back to the resting level. In the plasma membrane, the Ca^{2+} pump and the Na^+/Ca^{2+} exchanger (NCX) are the two main mechanisms for exporting Ca^{2+} out of the cell. Using these mechanisms, Ca^{2+} concentration in various regions of the cell may be differentially modulated (Rizzuto R and Pozzan, 2006;) [37]. The idea of NCX dates back to the 1960s, when investigators identified a counter transport mechanism between Na^+ and Ca^{2+} across the plasma membrane (Annunziato *et al.,* 2004). NCX plays an important role in the maintenance of Ca^{2+} homeostasis and is detected in the plasma membrane of most cells, including neurons and glia (Annunziato *et al*., 2004; Blaustein and Lederer, 1999) [42].

Therefore, from the above discussion it may be suggested that sodium/calcium exchanger plays a dominant role in removing Ca^{2+} from the cytosol in cells that require extracellular Ca^{2+} for their physiological activities, such as neurons and cardiac muscle cells (Philipson and Nicoll, 2000; Quednau *et al.,* 2004) [41, 39]. Na^+/Ca^{2+} exchanger (Sodium/calcium exchanger or NCX) by regulating the homeostasis of Na^+ and Ca^{2+}, plays a key role in the evolution of ischemic neuronal damage (Annunziato *et al*., 2004; Anna *et al*., 2020) [40]. NCX is a nine trans-membrane protein that plays an important role in the exchange of sodium and calcium across the cell membrane and is widely distributed in the body. NCX is a bi-directional membrane ion transporter. The direction of transport depends on the prevailing Na^+ and Ca^{2+} electrochemical gradients (Philipson and Nicoll, 2000; Quednau *et al.,* 2004) [41, 39]. Using the energy of the sodium gradient the transporter produces an electrogenic exchange of three sodium ions for one calcium ion. Under normal physiological conditions, sodium is transported into the cell and calcium is extruded from the cytoplasm (Philipson and Nicol, 2002) [38]. When the electrochemical gradient for sodium is reversed, such as during membrane depolarisation or the opening of gated sodium channels, the exchanger transports sodium out of the cell and calcium into the cell (Blaustein *et al.,* 1999) [42]. The calcium exit mode is commonly referred to as the ‘‘forward’’ mode of NCX and the calcium entry mode as the ‘‘reverse’’ mode. NCX contributes to modulate the extent of neuronal damage. In particular, block NCX activity worsens cellular damage induce by ischemia (Secondo *et al.,* 2015) [43].

NCX Subtypes

NCX belongs to a multigene family comprising three isoforms named NCX1, NCX2, and NCX3, which are differentially distributed through the body. NCX1 is ubiquitously expressed in all tissues, NCX2 is mainly restricted to the brain, and NCX3 is expressed exclusively in the brain and the skeletal muscles (Quednau *et al.,* 1997) [44]. Excitatory amino acid transpoters (EAATs) are secondary active, electrogenic transport systems that couple the accumulation of glutamate in the cytoplasm to downhill movement of cotransported ions along their concentration gradient (Divito *et al.,* 2014) [45]. We reported a physical and functional interaction between NCX1 and a member of the EAAT family, EAAT3 (Excitatory Amino-Acid Carrier 1—EAAC1—in rats), at both the plasma membrane and mitochondrial levels. These proteins cooperate to promote glutamate entry into the cytoplasm and then into mitochondria, where glutamate serves as a fuel for ATP synthesis. Two variants of NCX3 exist in mice: NCX-B, existing in the brain and NCX-AC, predominant in the skeletal muscles. NCX3 AC has a higher Na^+ sensitivity (Michel *et al.,* 2014) [46]. Brain expression of the three exchanger genes and of many of their splice variants has been studied (Quednau *et al.,* 1997) [44]. The presence of multiple isoforms underlines the critical role of the exchanger in the control of cytosolic Ca^{2+} concentration in neurons, although the kinetic properties of NCX1, NCX2, and NCX3 activation by Na^+ and Ca^{2+} are apparently similar (Linck *et al.,* 1998) [47]. Although all three members arise from separate genes on different chromosomes, they share high amino acid identity (about 70 %), especially in the hydrophobic regions (Li *et al.,* 1994) [48]. Although NCX subtypes are found in almost every type of cell, the expression profiles of these isoforms vary among different tissues and change during development (Papa *et al.,* 2003) [49].

1. NCX1 is express in multiple organs, include the brain, heart, kidney, skeletal muscle, eye, and blood cells.
2. NCX2 is found only in the brain whereas NCX3 is found in both brain and skeletal muscle (Philipson *et al.,* 1996).

In addition to neurons, NCX is also expressed in glial cells, playing many crucial roles, including the regulation in Na^+ and Ca^{2+} homeostasis in astrocytes, neurotransmitter release, oligodendrocyte maturation, and myelin formation (Boscia

et al., 2012) [50]. NCX can also function in calcium entry mode under pathophysiological conditions such as cerebral ischaemia.

However, after a vast literature survey, it was found that NCX inhibition may play an important role in neuroprotection against cerebral ischemia reperfusion injury. Therefore, it may be concluded that a novel NCX inhibitor as pharmacological intervention may have beneficial role in neuroprotective mechanism of RIPC. Further, it is warranted that experimental studies are required to be conducted to rule out the exact role and mechanism in pathophysiology of cerebral ischemia in near future.

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