Chapter 1
Metal Ions in Stroke Pathophysiology

Yang V. Li and John H. Zhang

Abstract Metal ions are used in biology in many ways and are integrated parts of numerous enzymes and proteins. They function as cofactors in cellular and genetic signaling and, therefore, have important roles in biochemistry ranging from essential to toxic. Perturbed homeostasis of metal ions in stroke has been well recognized for several decades. In cellular and biochemical responses following stroke, metal ion imbalance in neurons is in the center of these cellular events, which is immediate results of stroke and, in turn, leads to the overactivation of several deleterious enzymes and signaling process that impairs neuronal function or lead to cell death. The most studies and well-characterized metal ion in stroke-associated ionic imbalance is calcium (Ca). Almost as soon as Ca was recognized as a factor in the ischemic cell death, considerable evidence has emerged regarding the role of iron (Fe), zinc (Zn), potassium (K), sodium (Na), magnesium (Mg), copper (Cu), manganese (Mn), or selenium (Se) in neurotoxicity as well as neuroprotection after stroke. Several exogenous metal ions such as cadmium (Cd), nickel (Ni), arsenic (As), mercury (Hg), and aluminum (Al) are also linked to stroke pathophysiology. For the first time, the dyshomeostasis and pathophysiological actions of these metals in stroke are discussed systematically in one volume.

Keywords Metal ion • Stroke • Ischemia • Cell death • Brain • Calcium • Zinc • Iron • Potassium • Magnesium • Cadmium

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Introduction

Stroke is currently the second or third leading cause of death in the Western world, ranking after heart disease and before cancer (WHO 2004; Donnan et al. 2008). Although the mortality rate decline, the incidence of transient ischemic attach increases especially in elder (Heron and Tejada-Vera 2009). It is the leading cause of adult disability, ranging from motor control and urinary incontinence to depression and memory loss (Heron and Tejada-Vera 2009; NINDS 2011). Over two-thirds of stroke deaths worldwide are in developing countries where some of higher stroke mortality rates are reported recently (WHO 2004). For example, countries like India and China have experienced a rapid economic development; the number of elderly people is rising, life expectancy will increase, and, over the time, the number of stroke victims and disabled stroke survivors will continue to rise (Banerjee et al. 2005; Liu et al. 2007; Das and Banerjee 2008).

Strokes can be classified into two major categories: ischemic and hemorrhagic. About 87% of strokes are caused by ischemia due to the interruption and obstruction of the blood supply, while hemorrhagic strokes (13%) result from rupture of a blood vessel or an abnormal vascular structure causing compression of tissue from an expanding hematoma or hematomas (NINDS 2011). The brain is about 2% of the total body mass, yet 15–20% of blood flow travels from the heart to the brain and the brain accounts for 20% of total oxygen consumption (Kandel et al. 2000). Due to its high metabolic demand, brain cells are extremely sensitive to oxygen deprivation and will suffer irreversible injury possibly leading to death of the tissue, i.e., infarction (Deb et al. 2010). As oxygen and glucose becomes depleted in ischemic brain tissue, the production of high-energy phosphate compounds such as adenosine triphosphate (ATP) fails, leading to failure of energy-dependent processes (such as ion pumping) necessary for tissue cell survival (Annunziato 2009; Bendok 2011). These react with and damage a number of cellular and extracellular elements. The molecular biology of stroke injury is a rapidly growing field of research, which may lead to the identification of novel stroke targets and directed therapies. However, despite clear demonstration of numerous agents that can prevent the cascade of events leading to ischemic neuronal death in animal models, there is no obvious neuroprotective agent that has been shown to conclusively improve stroke outcome in humans (White et al. 1996; O'Collins et al. 2006; Marler 2007; Saver et al. 2009) (also see Report of the Stroke Progress Review Group, NIH 2002, 2006).

Metal ion dyshomeostasis is a well-recognized cofactor in several neurodegenerative disorders, as presented in this book (Metal ions in stroke, eds: Li and Zhang). Examples of metal ions include calcium (Ca), potassium (K), sodium (Na), magnesium (Mg), copper (Cu), iron (Fe), zinc (Zn), manganese (Mn), and selenium (Se). These metal ions are essential nutrients in brain development and function. Na and K are essential for the generation of electrical potentials or action potentials; Ca, K, Mg, Zn, Cu, and Fe play an important role in regulating brain excitability and neuronal plasticity through their action in neurotransmission or function as second messengers

(Kandel et al. 2000; Silva and Williams 2001). The metal ions (Ca, Mg, Zn, Fe, Cu, Cd, and Se) are bound up in metal–protein complexes or metalloproteins, such as enzymes, transport, and storage proteins, in which metals ion are critical in proper protein folding, structural stability, or enzymatic catalysis (Hanna and Doudna 2000; Silva and Williams 2001). Therefore, they have a central role in many biochemical pathways. Perturbed homeostasis of metal ions in stroke has been well recognized for several decades (Farber 1981; Raichle 1983). The most studied and well-characterized metal ion in stroke-associated ionic imbalance is Ca. Almost as soon as Ca was recognized as the factor in the ischemic cell death, considerable evidence has emerged regarding the role of Fe, Zn, Mg, Cu, Mn, or Se in neurotoxicity as well as neuroprotection following stroke. Among them, the overloads of Ca, Zn, Fe, Zn, or Cu has been associated with the brain injury following a stroke, and the administration of Mg, Se, or K may benefit early recovery or reduce risk of stroke. Several exogenous metal ions such as cadmium (Cd), nickel (Ni), arsenic (As), mercury (Hg), and aluminum (Al) are also linked to stroke pathophysiology. Environmental exposures of these exogenous metal ions are associated with significantly increased risk of stroke.

Metal Ion Dyshomeostasis in Stroke

It has been extensively studied and well recognized that a significant portion of ischemic stroke-induced neuron damage is mediated by excessive accumulation of excitatory amino acids, leading to toxic increases in intracellular Ca, which can in turn lead to an overload of cellular Ca (Berridge 1998; MacDonald et al. 2006). Ca enters the cell through Ca permeable glutamatergic receptors or voltage-dependent ion channels. Toxic cytoplasmic Ca concentrations can also occur due to Ca releases from its internal stores, either through physical damage to mitochondria and the endoplasmic reticulum, or a malfunction of receptors and channels present in their membranes. Such increases of cytoplasmic Ca concentrations can trigger a range of downstream signaling pathways, ultimately leading to cell death (Zipfel et al. 2000). For example, Ca overload can also lead to the failure of mitochondria, which can lead further toward energy depletion and may trigger cell death due to apoptosis (MacDonald et al. 2006). Ca channel antagonists may act as neuroprotective drugs by diminishing the influx of Ca ions through voltage-sensitive Ca channels (Inzitari and Poggesi 2005; Szydlowska and Tymianski 2010). Increased global cytosolic Ca concentration in cerebral artery myocytes contribute to decreased cerebral blood flow and the accompanying neurological deficits associated with subarachnoid hemorrhage (SAH) (Wellman 2006; Brown et al. 2008). Excessive elevation of the cytosolic concentration of Ca can be lethal to white matter glia, as in neurons, and directly disrupt axon function and structure, contributing to the severity of ischemic brain damages (Matute 2010).

Zn and Cu imbalance have been proposed as another cause for neurotoxicity (Bush 2003; Frederickson et al. 2005; Sensi et al. 2009). Particularly, considerable

evidence has emerged regarding the role of Zn neurotoxicity following ischemic stroke. These studies demonstrate that neurons give rise to accumulation of intracellular Zn in focal brain ischemia (Galasso and Dyck 2007), with highest accumulation in the CA1 region of hippocampus, the region most vulnerable to excitotoxic damage (Wei et al. 2004; Stork and Li 2006, 2009).The contribution of Zn to ischemic damage has been further clarified that Zn increase is associated with a loss of plasma membrane permeability and with mitochondrial Zn uptake and depolarization. Ischemia-driven Zn rises are the result of a combined process of Zn influx and Zn release from intracellular stores, and synaptically released Zn permeates postsynaptic neurons through NMDAR-associated channels and VGCCs (Frederickson et al. 2005; Sensi et al. 2009). Neurons possess a pool of intracellularly releasable Zn that is bound by cytosolic metallothioneins or contained within intracellular organelles such as mitochondria, vesicles, and lysosomes (Colvin et al. 2010; Hwang et al. 2008). Recent study suggests that Zn is sequestered into thapsigargin/IP3-sensitive stores and is released upon agonist stimulation (Stork and Li 2010). Zn overload induces neuronal death by physical injury to the mitochondria (Medvedeva et al. 2009; Sensi et al. 2009).

Changes in Fe metabolism in the brain have long been associated with neurodegenerative diseases (Zecca et al. 2004). Fe homeostasis is involved in many metabolic processes, including the storage and transport of oxygen, electron transport and oxidation–reduction reactions, as well as DNA synthesis. Experimental and clinical data implicate Fe in brain injury after stroke (Selim and Ratan 2004; Carbonell and Rama 2007). The application of MRI to estimate Fe content within the hematoma found that hematoma Fe content correlates with the relative perihematoma edema volume (Lou et al. 2009). Ferritin-bound ferric iron is released after being reduced to ferrous iron, a process that is facilitated by superoxide, acidosis, and nitric oxide (Galaris et al. 2008; Kurz et al. 2008), which are abundant during cerebral ischemia. As unbound Fe gains access to the extracellular space, its uptake by neuronal cells is paradoxically enhanced by increased level of intracellular Fe (Perez de la Ossa et al. 2010). Fe-dependent oxidative stress in the penumbra can lead to necrosis and further neurological deterioration following ischemic stroke. Therefore, the excess of Fe should be considered pathological in the ischemic brain (Selim and Ratan 2004). Aneurysmal subarachnoid hemorrhage (SAH) is a serious disease causing high morbidity and mortality during early and delayed period. Increased brain Fe levels or Fe overload contribute to brain edema, oxidative injury, and brain atrophy after SAH (Gu et al. 2009). Increased body Fe stores are associated with poor outcome after thrombolytic treatment in acute stroke (Millan et al. 2007). The administration of appropriate “labile Fe” chelating agents, preferentially prior to reperfusion, might improve the efficacy of any therapeutic strategy (Galaris et al. 2008).

The concentration of glutamate outside the cells of the nervous system is normally kept low by uptake carriers, which are powered by the concentration gradients of ions, mainly Na, across the cell membrane. However, stroke cuts off the supply of oxygen and glucose which powers the ion pumps (Na/K-ATPase) maintaining these gradients. This results in cellular swelling and depolarization.

As a result, the transmembrane ion gradients run down, and glutamate transporters reverse their direction, releasing glutamate into the extracellular space. The activity of NCX, ASICs, NHE, and NKCC, a group of ion channels and transporters, could represent a preferential Na influx or efflux route in ischemic neurons (Pignataro et al. 2004; Cuomo et al. 2008) and a new potential target to be investigated in the study of the molecular mechanisms involved in cerebral ischemia. Recent studies suggest that a linear increase in intracellular Na observed during evolution of cerebral ischemia could be used as a marker of sodium-MRI for determining the onset or duration of a ischemic attach (Yushmanov et al. 2009).

K is important in brain function, and the flux of K ions is crucial to maintain the electrolytic balance and neuron membrane potentials. The highly selective K ion channels are responsible for the hyperpolarization of the neuronal membrane and for the depolarization of the inner mitochondrial membrane. In the parenchyma, extracellular K exhibits massive shifts (such as spreading depression waves) which are indicative of the health of the ischemic tissue (Leis et al. 2005). Unlike other metal ions, no data demonstrate direct cytotoxic role of K, but it is involved in the expansion of the stroke volume and is an indicator of the state of health of the neurons (Leis et al. 2005; Yushmanov et al. 2009). K is important in regulating cerebrovascular tone or blood pressure (Gebremedhin et al. 2008; Houston and Harper 2008). Hypoxia enhances the activities of Ca^{2+}-activated K currents (Gebremedhin et al. 2008). Furthermore, the large-conductance Ca-regulated K channel has also been found in the inner mitochondrial membrane (Bednarczyk et al. 2010), which is important for optimal operation of oxidative phosphorylation and may also regulate reactive oxygen species concentration. The activation of mitochondrial K channels protects against both necrotic and apoptotic cell death during myocardial infarction or cerebral hypoxia (Bednarczyk et al. 2010).

Mg is a cofactor in many enzymatic reactions and it functions in a large number of normal cellular processes, in particular, in energy production, protein synthesis, and maintenance of ionic gradients. In the event of a stroke, there are marked declines in intracellular- and extracellular-free Mg concentrations in ischemic brain tissue, resulting in reducing the antioxidant capacity and, subsequently, excessive production of free radicals and inflammation. The therapeutic administration of Mg is considered to normalize serum magnesium after a stroke, by reducing ischemic neurological deficit (Meloni et al. 2006; Hoane et al. 2008; Vink et al. 2009) and improving outcomes after subarachnoid hemorrhage (Wong et al. 2009). The therapeutic Mg may give additional benefits: reducing synaptic glutamate release, decreasing Ca influx via voltage-gated Ca channels, minimizing NMDA-induced excitotoxicity, stabilize mitochondria, increasing cerebral blood flow, and helping to maintain tissue oxygenation.

Se is an essential micronutrient. The physiological role of Se remained unraveled, but selenoproteins or enzymes playing important roles in various processes of redox signaling (Savaskan et al. 2003). Se deficiency is detrimental to cellular functions mediated by these protein/enzymes, leading to increased oxidative stress and adversely affecting neuronal cell survival. Early administration of selenium may improve neurological outcome after ischemic stroke (Reisinger et al. 2009).

Mn is an essential trace element, exerting important functions in metabolic and redox homeostasis. However, increasingly concerns are rising about the Mn exposure of humans and related neurotoxic effects (Erikson et al. 2007; Michalke et al. 2007). There are similarities between Mn exposure and ischemia-induced glutamate excitotoxicity in increased extracellular glutamate levels and depletion of cellular ATP (Erikson et al. 2007).

Action of Exogenous Metal Ions

Exogenous metal dyshomeostasis, although generally no clear physiological role associated with them, has attracted the interest of researchers investigating the etiology of a variety of neurological conditions. Chronic heavy metal (Hg, Al, Cd, and As) contaminations are becoming an emerging epidemic and pose a major worldwide health problem. Cd is also recognized as a neurotoxin and exerts its toxic effects by the perturbation of cellular redox balance and subsequent reduction of the total brain antioxidant status (Leal et al. 2007; Modi and Katyare 2009). Environmental exposure to cadmium was associated with significantly increased stroke and heart failure prevalence (Peters et al. 2010). The clinical consequences of Hg toxicity include hypertension, coronary heart disease, myocardial infarction, cardiac arrhythmias, and cerebrovascular accident, with decreased oxidant defense and increased oxidative stress, mitochondrial dysfunction, and increased lipid peroxidation (Houston 2011b). As (arsenic) contamination of drinking water is becoming a major worldwide public health problem such as hypertension, diabetes mellitus, carotid atherosclerosis, and ischemic stroke (Wang et al. 2007). Ni may be as injurious as lead; exposure to Ni has been related to a variety of neurological symptoms that may attribute to its action in glutamatergic receptors such as NMDA receptor channels (Gavazzo et al. 2011). While the presence of Al in the human body is unwanted, with increasing use of Al materials, the chance of Al cytotoxicity is also rising, which may make the brain much vulnerable to ischemic stroke (Nayak et al. 2011).

Role of Metal Ions in Stroke Pathophysiology

The pathophysiology of stroke is complex and involves numerous processes, including: energy failure, loss of cell ion homeostasis, acidosis, excitotoxicity, free radical-mediated toxicity, generation of arachidonic acid products, activation of glial cells, and disruption of the blood–brain barrier (BBB) (Woodruff et al. 2011). These are interrelated and coordinated events, which can lead to ischemic apoptosis or neuronal death. Over the past few decades, experimental studies have provided considerable information on the role of metal ions in apoptotic processes occurring after ischemic stroke.

Glutamate excitotoxicity. Excessive stimulation of glutamatergic receptors induces alterations in the concentration of ions, most notably Ca and Na. Elevations of intracellular Na can be detrimental to neuronal survival at earlier time points after ischemia, while glutamate excitotoxicity is primarily dependent on Ca influx. K conductance affects excitotoxicity as well. During cerebral ischemia, the opening of neuronal ATP-sensitive K channels (K_{ATP} channels) affords intrinsic protection by regulating membrane potential (Bednarczyk et al. 2010). There is a negative relationship between Cu or Zn homeostasis and NMDA receptor activity. Potentially paradoxical actions of Cu or Zn are that both ions also block GABA(A) receptor-mediated current. Adding to already "touchy" situation, most of the glutamatergic synapses in the cerebral cortex co-release Zn (may be Cu too) along with glutamate (Bush 2003; Frederickson et al. 2005; Sensi et al. 2009). Mn may exert its neurotoxic effects by facilitating the release of excessive amounts of glutamate into the extracellular space (Erikson et al. 2007)**.** Methylmercury (MeHg) has been shown to preferentially accumulate in astrocytes, produce astrocytic swelling both in vitro and in vivo, inhibit astrocytic glutamate uptake, and stimulate the efflux of excitatory amino acids (Aschner et al. 2007).

Oxidative stress. Ca overload is detrimental to mitochondrial function and may present as an important cause of mitochondrial ROS generation. The accumulation of other metal ions (Zn, Fe, and Cu) is associated with oxidative stress. Energy failure and initial oxidative stress such as nitric oxide production may elicit the dysregulation homeostasis of metal ions, which in turn exert its toxic effects by the perturbation of cellular redox balance, inhibition of oxidative DNA repair systems, alteration in signal transduction, further stimulation in the production of ROS. These ions may accumulate in or be taken up by mitochondria, produce mitochondrial membrane permeability transition, inhibit respiratory complex I, and cause cytochrome *c* release following stroke (Bush 2003; Frederickson et al. 2005; MacDonald et al. 2006; Galaris et al. 2008). Exogenous heavy metal ions (Hg, Cd, Ni, etc.) are also linked with oxidative and mitochondrial dysfunction (Finney and O'Halloran 2003; Modi and Katyare 2009; Houston 2011b). Se may act as an antioxidant either after incorporation into selenoproteins or directly as in the case of selenite (Savaskan et al. 2003; Reisinger et al. 2009). In the case of Zn, Cu, or Mn, they are intrinsic factors for neuron survival and, in low amounts, are an active neuroprotectant against neurotoxic cell death. This protective effect is assumed to be mediated in part through antioxidant enzymes of superoxide dismutase (SOD; Zn, Cu, or Mn are cofactors) and the antagonism of glutamatergic receptor (NMDA receptor by Zn) activation (Frederickson et al. 2005; Erikson et al. 2007). In general, it is widely accepted that excessive increases of these metal ions after ischemic stroke is detrimental.

Blood–brain barrier (BBB) dysfunction. Ischemic stroke and hypoxic stress disrupt the BBB, which subsequently aggravate brain tissue damage. Many studies have reported an important role of Fe in supporting the generation of reactive oxygen species that affect BBB permeability by the activation of matrix metalloproteinases, particularly matrix metalloproteinase-9, leading to degradation of vascular basement membrane collagen and modulation of tight junction protein complexes

(Perez de la Ossa et al. 2010; Selim and Ratan 2004). Following BBB disruption, the ferritin and the free Fe can enter the penumbra, leading to necrosis and further neurological deterioration following ischemic stroke. Al and Mn exposures are associated with the loss of BBB integrity (Erikson et al. 2007; Nayak et al. 2011). Ca is also critical to normal BBB function. BBB endothelial cells express a number of Ca permeable channels (Brown et al. 2008), which is linked to the disruption of the BBB in stroke. Ca dyshomeostasis is also a major event in the pathophysiology of white matter disorders of the brain (Matute 2010). Ca signaling mechanisms are crucial for proper regulation of vascular smooth muscle contractility and vessel diameter (Wellman 2006).

Therapeutic Perspectives

Although metal ion dyshomeostasis is certainly not the only trigger of the disease, therapeutic interventions aimed at restoring metal homeostasis remain strong candidates as disease-modifying strategies for stroke treatment. Evidently, treatments designed to alter Ca influx or Ca homeostasis, based on the understanding of known cell death mechanisms, have been extensively investigated in both animal studies and clinical drug trials (O'Collins et al. 2006; Marler 2007; Saver et al. 2009). What is emerging from literature is that more than one target and strategy should be developed. A change in the brain level of a single metal ion can upset the whole metal pool, resulting in a relevant complex metal imbalance in the brain, but it should also be emphasized that pinpointing a single metal as the major culprit of the disease seems to be less productive. Recent studies suggest that modulating astrocytic Ca signaling may help in the development of new therapeutic means to diminish brain damage after stroke (Matute 2010). Ca channel antagonists may act as neuroprotective drugs by diminishing the influx of Ca ions through voltage-sensitive calcium channels. The most frequent indication for Ca channel blocker is their use as antihypertensive agents for primary or secondary stroke prevention (Inzitari and Poggesi 2005). Recent studies have also focused on identifying novel mechanisms of calcium influx as well as neuroprotection by inhibiting multiple calcium influx pathways (Thompson et al. 2008; Szydlowska and Tymianski 2010).

Since K channels are key players in the control of neuronal excitability, and activation of neuronal K channels decrease excitability and neurotransmitter release, a novel approach for targeting acute ischemic stroke has been to develop openers of neuronal K channels (Leis et al. 2005; Houston 2011a). Ca channel blocker, along with K and Mg, may contribute toward reducing the risk of recurrent stroke in patients who are usually at high risk of recurrence(Hoane et al. 2008; Houston and Harper 2008). Zn may represent an independent risk factor for stroke. A chelator may serve as a protective therapeutic agent for reducing Zn increases that occur following ischemia or other insults (Calderone et al. 2004; Barkalifa et al. 2009). Se is a potent protective agent for neurons through the expression of selenoproteins, which may be a potential therapeutic target of stroke (Savaskan et al. 2003;

Reisinger et al. 2009). There has been mounting interest toward the therapeutic potential of Mg in SAH in recent years (Turner et al. 2004; Wong et al. 2009). The ongoing pre-hospital trials of Mg therapy in the acute stroke phase have shown some promise (Saver 2010). Targeting Fe toxicity as a treatment for stroke is an appealing and promising option. Clinical therapeutic trials of Fe-modifying agents in patients with ischemic and hemorrhagic strokes are currently underway (Selim and Ratan 2004; Gu et al. 2009). Finally, dietary intervention such as increasing dietary K intake has been demonstrated to significantly lower blood pressure in both hypertensive and nonhypertensive patients and may reduce the risks of cardiovascular disease and stroke (Houston 2011a).

In summary, since stroke-induced brain injury results from the interaction of complex pathophysiological processes, the effective protection of brain tissue is not likely to be achieved by a single agent. Despite clear demonstration of numerous agents that can prevent the cascade of events leading to ischemic neuronal death in animal models, there is no obvious neuroprotective agent that has been shown to conclusively improve stroke outcome in humans. Metal ions have unique chemical properties that allow them to play diverse roles in cellular biochemistry of the brain. The metal ion-dependent molecular modification of stroke injury is a rapidly growing field of research, which may lead to the identification of novel stroke targets and directed therapies. The new century will open opportunities for the development of therapies based on more global signaling pathways through manipulating metal ion signals or buffering the labile metal levels after stroke.

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