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Review

Neurodegenerative diseases and therapeutic strategies using iron chelators

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ABSTRACT

This review will summarise the current state of our knowledge concerning the involvement of iron in various neurological diseases and the potential of therapy with iron chelators to retard the progression of the disease. We first discuss briefly the role of metal ions in brain function before outlining the way by which transition metal ions, such as iron and copper, can initiate neurodegeneration through the generation of reactive oxygen and nitrogen species. This results in protein misfolding, amyloid production and formation of insoluble protein aggregates which are contained within inclusion bodies. This will activate microglia leading to neuroinflammation. Neuroinflammation plays an important role in the progression of the neurodegenerative diseases, with activated microglia releasing pro-inflammatory cytokines leading to cellular cell loss. The evidence for metal involvement in Parkinson's and Alzheimer's disease as well as Friedreich's ataxia and multiple sclerosis will be presented. Preliminary results from trials of iron chelation therapy in these neurodegenerative diseases will be reviewed.

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Introduction

The human brain gives us the power to speak, imagine and problem solve as well as the ability to perform a number of tasks, which include the control of body temperature, blood pressure, heart rate and breathing, accept information from various senses,

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such as visual, auditory and smell, as well as allowing one to think, dream, reason and experience emotions. However, it is difficult to imagine how mental entities such as thoughts and emotions could be implemented by physical entities such as neurons, glial cells and synapses or by any other type of mechanism. For these reasons, the way in which the brain can perform such functions remains one of the greatest scientific challenges of the 21st century. Recently the Human Brain Project has been launched by the European Commission [1], which should go a long way to improving our understanding of brain function in health and disease, as well as the changes which occur with ageing. It has as its goal to lay the technical foundations for a new model of ICT-based brain research, driving integration between data and knowledge from different disciplines, and catalysing a community effort to achieve a new understanding of the brain, new treatments for brain disease and new brain-like computing technologies. Thanks to the progress of modern medicine, and to improved living standards, the life expectancy of the human race continues to increase steadily, unlike other mammals. However, the downside is that as our population ages, the risk of contracting one of a number of neurodegenerative diseases also increases. The most common of these are dementias, characterised by decline in cognitive faculties and the occurrence of behavioural abnormalities which interfere with the capacity of the afflicted individual to carry out normal daily activities. It most often affects elderly individuals and the most common is Alzheimer's disease (AD). Dementia prevalence increases with age; in the USA whereas 5.0% of those aged 71–79 years are affected, this climbs to 37.4% of those aged 90 and older [2].

In this review, we outline some of the mechanisms underlying neurodegenerative diseases which involve the essential metal iron and discuss some of the preliminary results which have used the therapeutic strategy of chelation to remove potentially toxic iron from the brain.

The importance of metals in the brain

A number of important biological functions in the brain require metal ions such as potassium, sodium, calcium and zinc together with the redox-active iron and copper [3]. For example, the fast transmission of electrical impulses between neurons and along their axons to muscles and endocrine tissues, the maintenance of ionic gradients and the synthesis of neurotransmitters require these metal ions. The opening and closing of gated sodium and potassium channels to generate electrochemical gradients across the plasma membranes of neurons allows the transmission of nervous impulses, not only within the brain, but also the transmission of signals from the brain to other parts of the body.

The function of proteins is often dependent on their shape and their charge, and the binding of Ca^{2+} to proteins, just like the phosphorylation of the hydroxyl groups of Ser, Thr or Tyr residues by protein kinases, can trigger changes in both shape and charge. This ability of Ca^{2+} and phosphoryl groups to alter local electrostatic fields and thereby protein conformation and function are the two universal tools of signal transduction in biology. In most cells, including nerve cells, fluxes of Ca^{2+} ions play an important role in signal transduction regulating a wide range of cellular processes through ligand-gated channels, such as the NMDA receptor, activated by the glutamate agonist N-methyl-D-aspartate or voltage-gated Ca^{2+} channels. The transient rise in cytosolic Ca^{2+} levels initiated by extracellular signals, leads to the binding of Ca^{2+} by Ca^{2+}-sensor proteins, like calmodulin and synaptotagmin 1, which in turn activate a great variety of enzymes. Two target proteins for calmodulin in mammalian brain are calcineurin, a heterodimeric phosphatase, which is involved in synaptic plasticity [4], and the Ca^{2+}/calmodulin-dependent protein kinase CaMKII, which plays a central role in Ca^{2+} signal transduction [5], and is the most abundant protein in the postsynaptic density [6], the region of the postsynaptic membrane physically connected to the ion channels which mediate synaptic transmission.

Another metal ion that has been extensively implicated in brain function is Zn^{2+} [7]. The mammalian forebrain contains a subset of glutamatergic neurons that sequester zinc in their synaptic vesicles, which is released into the synaptic cleft during synaptic transmission. Zinc may act as a critical neural messenger through its ability to regulate NMDA receptor activity. Excessive synaptic release of Zn^{2+} followed by entry into vulnerable neurons contributes to severe neuronal cell death.

The redox-active metal ions copper and iron are both essential for normal brain function [8,9]. Deficiency of copper during the foetal or neonatal period will have adverse effects both on the formation and the maintenance of myelin. Excess "free" copper is however also dangerous, due to its capacity, like iron, to participate in redox reactions, generating toxic reactive oxygen and nitrogen species. Copper serves as an essential cofactor for two key proteins involved in neurotransmitter synthesis, dopamine β-hydroxylase, which transforms dopamine to nor-adrenaline, and peptidyl-α-amidating monooxygenase involved in the amidation of neuropeptides. Iron is involved in many fundamental biological processes in the brain, including oxygen transport, DNA synthesis, nitric oxide metabolism and mitochondrial respiration, as well as for several specific neuronal functions in myelin synthesis and neurotransmitter synthesis and metabolism [9]. Since iron is involved in many central nervous system processes [9] which might affect infant behaviour and development, iron deficiency has adverse effects on pre- and post-natal brain development. With ageing, there is an elevation of brain iron (within ferritin and neuromelanin) in specific brain regions, i.e. frontal cortex, caudate nucleus, putamen, substantia nigra and globus pallidus, with no apparent adverse effect. However, ill-placed excessive amounts of iron in specific intracellular compartments or in specific regions of the brain lead to neurodegenerative diseases [10,11] through mechanisms described in the next section.

Metal-based neurodegeneration

Over the last decade, it has become more and more widely accepted that inflammation, associated with dysfunction of metal ion homeostasis (Fe, Cu, Zn) resulting in concomitant oxidative stress, are key factors in a large number of neurodegenerative diseases [10,11]. Support comes from the observation that AD, PD and many other neurodegenerative diseases are characterised by increased levels of these metal ions in specific regions of the brain.

The '*metal-based neurodegeneration hypothesis*' is briefly outlined here [10,11]. Redox-active metal ions (Fe, Cu), present within specific brain regions, can generate oxidative stress by production of reactive oxygen and nitrogen species (ROS, RNS). The chemistry of iron with oxygen and its two-electron reduction product, hydrogen peroxide, has been reviewed [12,13]. The one-electron reduction of H_2O_2, the well-known Fenton reaction gives the hydroxyl radical, $OH^{\bullet}$ (Eq. (1)), one of the most reactive free radical species known, which can react with a wide number of cellular constituents.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-} \quad (1)$$

When ROS are generated by redox metals in proximity to membrane phospholipids they initiate peroxidation of polyunsaturated fatty acids in the phospholipids, and the lipid hydroperoxides which are generated will break down to form a variety of lipid-derived α,β-unsaturated 4-hydroxyaldehydes [14,15], of which the