Brain iron and neurodegenerative disorders

Farukh Jabeen and Ming Fu*
Cardiovascular and Metabolic Research Unit, Laurentian University, Sudbury, Ontario, Canada

Iron in the brain plays a crucial role in maintaining normal physiological functions through its participation in many cellular activities such as mitochondrial respiration, myelin synthesis, and neurotransmitter synthesis and metabolism, however, excess iron is a potent source of oxidative damage, to neuronal cells through free radical formation, [1]. At the end of last century, abnormally high levels of iron in the brain had been reported in a number of neurodegenerative disorders (NDs), including Hallervorden–Spatz syndrome, Parkinson’s disease (PD) and Alzheimer’s disease (AD) [2-5]. However, it was not known at that time, whether the iron accumulation in the brain was an initial event which leads to neuronal death or it was a consequence of the disease progression. In 2001, Prof. Zhong-Ming Qian [6] in Hong Kong Polytechnic University proposed for the first time that, at least in some neurodegenerative disorders, brain iron misregulation is an initial cause of neuronal death. Two years later, in 2003, Profs. Qian and Ya Ke [7] summarized the evidence that the misregulation in brain iron metabolism is one of the basic causes of neuronal death in some neurodegenerative disorders. Their findings made a great breakthrough in the etiological research of neurodegenerative disorders and also opened a novel avenue for the scientific community to continue studies in this new field.

Today, abnormally increased iron level in the brain has been well-confirmed in various neurodegenerative diseases including neurodegeneration with brain iron accumulation (NBIA). NBIA is a heterogeneous and complex group of inherited neurodegenerative diseases, characterized by excessive iron accumulation in the globus pallidus and other brain regions [8,9]. Clinical features include Parkinsonism and severe dystonia, gait abnormalities, cognitive dysfunction, pyramidal signs, and retinal abnormalities [8,10]. So far, mutations in 10 genes have been identified [11] including ferritin light chain (FTL) and ceruloplasmin (CP), Neuroferritinopathy (NFP) and ceruloplasmnemia (CPM), induced by mutation in FTL and CP respectively, have been demonstrated to be directly caused by iron dysfunction. FTL and C19orf12 (CoASY, PLA2G6, FTL and ceruloplasmin) as a ferrireductase, α-synuclein transcripts, the activity of APP as a neuronal iron export protein is controlled in the brain under physiological circumstances [16]. These findings suggest those autophagy and lipid metabolisms are both associated with iron metabolism.

In several other neurodegenerative diseases including AD, PD, HD, multiple sclerosis, amyotrophic lateral sclerosis and Friedreich’s ataxia, iron dyshomeostasis, oxidative stress and mitochondrial injury have been suggested to constitute a common pathway to cell death [17,18] although the pathological hallmarks of these neurodegenerative diseases vary. Indeed, many proteins initially characterized in those diseases such as amyloid-β protein, α-synuclein, and huntingtin have found to be linked with iron neurochemistry [19,20]. The presence of 5’UTR sequences in the amyloid precursor protein (APP) and α-synuclein transcripts, the activity of APP as a neuronal iron export ferroxidase, α-synuclein and prion protein (PrPSc) as a ferrireductase, the functional role of PrPSc in iron transport, the ability of iron to enhance neurotoxicity of amyloid beta (Aβ) and sequestration of iron in PrPSc-protein complexes [21-23] leaves little doubt that iron plays a significant role in the neurotoxicity associated with AD, PD and HD [19,24,25]. Furthermore, iron chelators have shown their efficacy against neurodegeneration in a series of animal models and been applied in several clinical trials [26]. A novel multimodal brain-permeable iron-chelating compound M30 and HLA20, the were demonstrated to possess neuroprotective/neurorescue activities both in vitro and in vivo against several insults applicable to various neurodegenerative diseases, such as AD and PD [27]. Moreover, three smaller clinical trials targeting metal interactions with Aβ have shown benefit for patients [28,29], while several major clinical trials targeting Aβ by Pfizer, Lilly and Johnson & Johnson have failed [19,30,31]. All of these therapeutic studies provided neuropharmacological evidence to further support a causative interplay between brain iron misregulation and neuronal death.

The new progresses obtained during the past few years strengthen the belief that the brain iron misregulation is one of the initial causes of neuronal death probably in most if not all of the neurodegenerative disorders. However, in order to completely understand the link between iron and neuronal death in neurodegenerative disorders, further studies on how iron homeostasis is maintained in the brain are still needed in spite of the recent studies have greatly improved our knowledge of this topic. How the expression of iron transport proteins is controlled in the brain under physiological circumstances and what are the genetic and non-genetic causes that might lead to misregulation of brain iron metabolism are another two key questions to be considered /worth exploration/ addressed by researchers in detail to entangle/elaborate clearly the significance of role of iron in

Correspondence to: Fu M, Cardiovascular and Metabolic Research Unit, Laurentian University, Sudbury, Ontario, Canada, Tel: 1-705-675-1151, E-mail: MFU@LAURENTIAN.CA

Received: August 06, 2017; Accepted: August 21, 2017; Published: August 23, 2017
neurodegeneration. In addition, iron should be considered as a new target for pharmacological intervention in these diseases. Keeping brain iron at optimum level required for normal brain activities, reduction in high level of iron toward normal levels or hampering increases in iron level in the aging brain may be a promising therapeutic strategy in all iron-associated neurodegenerative disorders. Undoubtedly, intensive studies on the development of specific therapeutic approaches will make key contributions to the prevention and treatment of these disorders at large.

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