Role of iron in neurodegenerations

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Progressive atrophy of brain structure is referred to as neurodegeneration. The mechanisms of this process, leading to several neurological diseases of older age, are not well known. Among several causes the oxidative stress injury is taken into account. It is known that the oxidative stress may be triggered by an excess of divalent iron, which can initiate Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}$$

The possible role of iron in neurodegeneration was studied by various techniques: Mössbauer spectroscopy (MS), electron microscopy, enzyme-linked immuno-sorbent assay (ELISA), atomic absorption, ultrasonography and magnetic resonance imaging (MRI). The measurements were made on human tissues extracted from liver and from brain structures involved in diseases of the human brain: substantia nigra (Parkinson disease, PD), hippocampal cortex (Alzheimer disease, AD) and globus pallidus (progressive supranuclear palsy, PSP). Mössbauer spectroscopy of all these structures has shown that most of iron is ferritin-like iron [1]. Ferritin is the main iron-storage compound in human body [2]. Ferritin is composed of the protein shell and inner cavity filled with iron. The protein shell is build of 24 ferritin H and L chains. H and L ferritins play various roles: H ferritin is mostly related to an absorption of iron into the protein shell of ferritin, while L ferritin is involved in the safe storage of iron within the protein shell. The sizes of the iron cores of ferritin assessed with the use of electron microscopy were found to be smaller in brain than in liver – 3.5 nm vs. 6.5 nm [3]. These values correlate well with the blocking temperatures determined by Mössbauer spectroscopy [4]. Brain ferritin has a higher proportion of H to L chains compared to liver (H/L in hippocampus – 14, in globus pallidus – 5, in substantia nigra – 4, in liver – 0.4) [5]. With the use of ELISA a significant decrease of the concentration of L chains in PD compared to control was found – 98 ng/mg wet tissue vs. 52 ng/mg wet tissue [6].

No increase in the concentration of iron in PD vs. control was detected, however there was an increase of labile iron, which constitutes only 2‰ of brain iron [7]. In AD an increase in the concentration of ferritin was noticed, without a significant increase in iron concentration [8]. In PSP an increase of total iron was observed [9].

Although the post mortem studies add a lot to the understanding of the mechanisms of neurodegeneration, the possibility to assess iron in vivo in patients with neurodegenerative diseases would be of ultimate importance. The discovery of hyperechogenicity of parkinsonian SN by TCS was originally interpreted as the result of a higher concentration of iron in the tissues [10]. It was shown however, that insertion of iron-loaded ferritin to the animal brain does not produce hyperechogenicity. On the other hand, insertion of glial tissue to the same animal brain, gives a hyperechogenic signal similar to the one found in PD. One may suspect therefore that the hyperechogenicity is not the result of higher iron concentrations in the tissues, but of higher proportions of glial cells, which replace dying nervous cells [11].

MRI was also used in studies of the possible role of iron in the pathogenesis of PD. The published studies gave, however, controversial results. As in some studies the change of the T2 MRI signal in PD patients was attributed to an increase of the concentration of iron in parkinsonian SN [12] and our MS studies did not confirm such an increase, we tried to assess, how much iron loaded ferritin and/or non-ferritin iron is needed to cause the change of the MRI signal. In this study, phantoms containing a one liter water solution of five metabolites present in the human brain grey matter tissue were used [13]. This experiment showed that the change of the T2 signal appears only when the ratio of ferrous/ferritin iron is bigger than one. As such high concentration of ferrous, non-ferritin bound iron was excluded by our MS studies there must be another cause for the change observed by MRI.

Our findings suggest that the mechanisms leading to nervous cells death in these three, investigated by us, diseases may be different, although all may be related to iron mediated oxidative stress.

[1] Galazka-Friedman J, Hyperfine Interactions, 182, (2008), 31-44
[2] Harrison PM, Arosio P, Biochim Biophys Acta 1275 (1996), 161-203
[3] Galazka-Friedman J, Bauminger ER, Tymosz T, Friedman A. Hyperfine Interactions (C), 3, (1998), 49-52
[4] Galazka-Friedman J, Bauminger ER, Friedman A, Koziorowski D, Szlachta K, Hyperfine Interactions 165, (2005), 285-288
[5] Galazka-Friedman J, Bauminger ER, Koziorowski D, Friedman A. Biochim. Biophys. Acta 1688, (2004), 130-136
[6] Koziorowski D, Friedman A, Arosio P, Santambrogio P, Dziewulska D. Park Rel Disord 13, (2007), 214-218
[7] Wypijewska A, Galazka-Friedman J, Bauminger ER, Wszolek ZK, Schweitzer KJ, Dickson DW, Jaklewicz A, Elbaum D, Friedman A. Park Rel Disord 16, (2010), 329-333
[8]Gałązka-Friedman J, Bauminger ER, Szlachta K, Koziorowski D, Tomasiuk R, Jaklewicz A, Wszolek ZK, Dickson D, Kaplinska K, Friedman A. Acta Phys Pol 119, (2011), 81-83
[9] Galazka-Friedman J, Bauminger ER, Szlachta K, Schweitzer K, Wszolek Z, Dickson D, Friedman A. Acta Phys Pol 115, (2009), 431-433
[10] Berg D, Roggendorf W, Schröder U, Klein R, Tatschner T, Benz P et al. Arch Neurol 59, (2002), 999-1005
[11] Sadowski K, Szlachta K, Serafin-Król M, Galazka-Friedman J, Friedman A. J Neural Trasm, (2011) doi.org/10.1007/s00702-011-0707-5
[12] Antonini A, Leenders KL, Meier D, Oertel WH, Boesiger P, Anliker M. Neurology 43, (1993), 697-700
[13] Szlachta K, Sadowski K, Kuliński R, Galazka-Friedman J, Friedman A. Acta Phys Pol (in press)