IS PD A FERRINOPATHY?

D. Berg

Center of Neurology, Dept of Neurodegeneration and Hertie-Institute of Clinical Brain Research, Tübingen, Germany

Iron is increasingly being implicated to play a role in the pathogenesis of Parkinson's disease (PD). The content of iron is under physiologic conditions higher in the basal ganglia and substantia nigra (SN) than in most other regions of the brain. In PD, however, iron content of the SN pars compacta is about 35% elevated. Moreover, an increase of the Fe(III)/Fe(II)-ratio has been found. Increased levels of iron and Fe(II) enhance the conversion of H_2O_2 to $^{\bullet}OH$, contributing to free radical induced cell damage, known as oxidative stress (OS). On the other hand, OS may increase the levels of free iron. Mechanisms include the release of iron from ferritin by $(O_2)^{\bullet-}$, from haem proteins like hemoglobin and cytochrome c by peroxides and from iron-sulphur proteins by $ONOO^{\bullet-}$. Besides the contribution to the formation of highly reactive oxygen species iron has been shown to interact with α–synuclein, enhancing the conversion of unfolded or α-helical conformation of α–synuclein to β-pleated sheet conformation.

It is not clear yet, at what time in the pathophysiological cascade of PD iron accumulation occurs. Epidemiological studies, investigation of dietary compounds, a possible disturbance of the blood brain barrier, an association of sequence variations in some genes encoding for iron metabolizing proteins within the brain and raised iron levels in individual dopaminergic neurons indicate a possibly primary role of iron in idiopathic PD. Also, data from recent transcranial ultrasound studies imply iron accumulation to occur very early in the disease process. There also seems to be a link between increased iron content and mitochondrial dysfunction, i.e. a dysfunction of complex I, induced by endogenous neurotoxins, including iron and exotoxins. Concerning monogenetic PD, a number of studies provide evidence for a disease promoting link of genes involved in monogenetic PD and oxidative stress, which may at least in part result from increased iron levels. It may therefore well be, that altered activity of proteins involved in monogenetic PD like parkin, UCH-L1 and DJ1 as well as increased fibrillation and aggregation of e.g. α-synuclein induced by OS may be critically involved in the etiology of also sporadic PD.