



# The Contribution of Iron to Protein Aggregation Disorders in the Central Nervous System

Karina Joppe<sup>1\*</sup>, Anna-Elisa Roser<sup>1</sup>, Fabian Maass<sup>1</sup> and Paul Lingor<sup>1,2,3,4\*</sup>

<sup>1</sup> Department of Neurology, University Medical Center Göttingen, Göttingen, Germany, <sup>2</sup> Center for Biostructural Imaging of Neurodegeneration, Göttingen, Germany, <sup>3</sup> German Center for Neurodegenerative Diseases, Göttingen, Germany, <sup>4</sup> Rechts der Isar Hospital, Technical University of Munich, Munich, Germany

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### \*Correspondence:

Karina Joppe  
Karina.Joppe@med.uni-goettingen.de  
Paul Lingor  
p.lingor@gwdg.de

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The homeostasis of iron is of fundamental importance in the central nervous system (CNS) to ensure biological processes such as oxygen transport, mitochondrial respiration or myelin synthesis. Dyshomeostasis and accumulation of iron can be observed during aging and both are shared characteristics of several neurodegenerative diseases. Iron-mediated generation of reactive oxygen species (ROS) may lead to protein aggregation and cellular toxicity. The process of misfolding and aggregation of neuronal proteins such as  $\alpha$ -synuclein, Tau, amyloid beta (A $\beta$ ), TDP-43 or SOD1 is a common hallmark of many neurodegenerative disorders and iron has been shown to facilitate protein aggregation. Thus, both, iron and aggregating proteins are proposed to amplify their detrimental effects in the disease state. In this review, we give an overview on effects of iron on aggregation of different proteins involved in neurodegeneration. Furthermore, we discuss the proposed mechanisms of iron-mediated toxicity and protein aggregation emphasizing the red-ox chemistry and protein-binding properties of iron. Finally, we address current therapeutic approaches harnessing iron chelation as a disease-modifying intervention in neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.

**Keywords:** iron, protein aggregation, neurodegeneration, disease mechanism, iron chelator

## INTRODUCTION

Neurodegenerative disorders (NDDs) rapidly gain importance due to their age-related prevalence and the resulting socio-economic burden (Hindle, 2010; Abbott, 2011). Aging is one of the main risk factors for NDDs (Ashraf et al., 2018) and the constantly growing life expectancy will result in their increased prevalence (Oeppen and Vaupel, 2002). Although different NDDs present a variety of symptoms ranging from cognitive, motor, sensory and/or autonomic failure, neuronal loss is the shared characteristic. Therefore, it is of great relevance to identify common pathophysiological features that are present in multiple NDDs to elucidate general mechanisms of neurodegeneration and potential pathways for intervention.

Iron does not only play a main role in cellular senescence but also in NDDs such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) or prion diseases (PrD) (Ashraf et al., 2018). As protein aggregation is another shared hallmark among many NDDs

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**Reginald Robert Hawkins**



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United States. Congress,1975      *Sleisenger and Fordtran's Gastrointestinal and Liver Disease E-Book* Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt, 2010-05-03 Make optimal use of the newest techniques technologies and treatments with Sleisenger and Fordtran's Gastrointestinal and Liver Disease the indispensable information source in this broad field Edited by Mark Feldman MD Lawrence S Friedman MD and Lawrence J Brandt MD this 9th Edition equips you with the amassed knowledge of hundreds of respected authorities from around the world helping you to overcome all of your most complex clinical challenges and make the most effective use of the newest techniques technologies and treatments Significant updates on bariatric surgery Barrett's esophagus and many other evolving areas keep your practice current Full text online access includes downloadable illustrations and links to reference abstracts The result remains the indispensable core reference in gastroenterology and hepatology World renowned experts provide reliable guidance on every area of your field A consistent full color chapter design lets you find information quickly Significant updates on bariatric surgery Barrett's esophagus endoscopic ultrasound endosonography treatment of liver disease and much more keep you current on the latest advances Many new contributors from all over the world provide you with fresh insights on all areas of gastroenterology and hepatology Full text online access via Expert Consult includes downloadable illustrations and links to reference abstracts

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