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From blood to brain

Sorgdrager, Freek Jan Hubert

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Promotores

Prof. dr. P.P. De Deyn
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Arend Overeem

Edwin Slingerland

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Human lifespan is rapidly increasing. In the Netherlands, the number of persons aged 80 years or older is projected to double within the next 20 years. As a result, age-related neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) will affect an increasing number of people and severely burden our healthcare systems. A better understanding of the age-related processes that underlie these debilitating diseases is crucial for the development of preventive strategies.

Studies in animal models and humans have shown that ageing causes increased metabolism of the amino acid tryptophan along the kynurenine pathway. Age-related activation of the kynurenine pathway could contribute to AD and PD pathophysiology because it produces neurotoxic kynurenine metabolites. Measuring kynurenine pathway activity can be a potential tool to predict age-related vulnerability to AD and PD or to track disease progression. The analysis of tryptophan and kynurenine concentrations in blood is the most common way to assess kynurenine pathway activity but the interpretation of these values can be challenging; tryptophan metabolism takes place in many organs and is regulated by immune factors and hormones such as the stress hormone cortisol.

Aiming to enhance the understanding of factors that influence blood-based measures of kynurenine pathway activity we studied the relationship between cortisol and tryptophan metabolism in blood within observational and experimentally controlled human cohorts. Next, to further establish the diagnostic potential of systemic kynurenine pathway activity in ageing and neurodegenerative diseases, we analysed kynurenine metabolites in blood and cerebrospinal fluid of aged individuals and persons suffering from AD and PD. Finally, to investigate the therapeutic potential of the kynurenine pathway, we tested whether inhibition of kynurenine pathway activity could improve cognitive function in a mouse model of AD.