Title: Tryptophan and Inflammatory markers from the Kynurenine Pathway in mental health.

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Proposal:

Introduction: Emerging evidence suggests that the kynurenine pathway is essential for the modulation of immune and inflammatory responses. During inflammation, the cytokine interferon-γ (IFN-γ) stimulates IDO activity and thereby degradation of tryptophan to kynurenine, leading to an increased kynurenine to tryptophan ratio (KTR) and altered concentrations of other kynurenines. Studies suggest that especially a neuro-inflammatory response induced by e.g. IFN-γ is likely to be the initial factor in the onset and development of cognitive impairment and depression. Dysregulation of the kynurenine pathway - due to IFN-γ induced inflammation or deficiency in vitamins B2 and B6 - results in hyper- or hypofunction of kynurenines, and is associated with neurological disorders. There is a major research gap between animal and pharmacological studies that test efficacy of drugs to manipulate the kynurenine pathway. Furthermore, it is unclear whether the well-known association between diabetes, cognitive performance, and depression is modified by (or perhaps even mediated by) aberrant concentrations of kynurenines.

Hypothesis and Objectives:

Hypotheses:
1. Aberrant concentrations of metabolites from the kynurenine pathway are involved in the development and progression of cognitive impairment and depression.
2. Kynurenines explain the association of depression and cognitive impairment with diabetes.

Specific research questions:
1. Are plasma concentrations of kynurenines associated with indicators of depression/ cognitive impairment?
2. Do plasma kynurenines affect the association between diabetes, cognitive impairment and depression?

Setting and Methods:
The proposed study among 1,500 non-diabetics and 1,000 diabetics from the Maastricht Study will integrate methods that enable us to investigate the role of kynurenines in depression, cognitive impairment, brain structure, and diabetes by also addressing the network of inflammatory markers, B-vitamins and lifestyle which are all liked to both the kynurenine pathway and mental health.

Impact: This research will give insight in 1) the kynurenine pathway as a neurobiological mechanism explaining the development of depression and cognitive impairment in diabetes, and 2) kynurenines as biological and diagnostic markers, which will contribute to 3) formulating dietary guidelines to prevent cognitive impairment and depression, and 4) current attempts to modify the kynurenine pathway as a drug target to combat cognitive impairment and depression.

Requirements candidate: Background in Medicine, Biology, or Immunology/Imflammation

Keywords:
Inflammation, diet, diabetes, mental health, cognitive impairment, depression, magnetic resonance imaging, cardiovascular disease (CVD), epidemiology, statistics

Selected publications: