An organ-agnostic drug repurposing strategy for dementia: Pre-clinical validation of network pharmacology to treat cerebrovascular dysfunction and cognitive impairment

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Abstract

Age-related loss of cognitive capacity and neurodegeneration have a great socioeconomical impact on our rapidly aging population. Despite numerous hypotheses, the causes for phenotypes currently termed as vascular dementia (VaD) and Alzheimer’s disease (AD) remain largely unknown. Currently approved drugs for dementias do not target causative mechanisms and only offer symptomatic relief with mild efficacy. Therefore, the identification of dementia causal mechanisms and the development of mechanism-based curative strategies are urgently needed. One common causal disease mechanism recently identified among dementias, cardiovascular, metabolic, respiratory, and other neurological conditions is related to reactive oxygen species (ROS) and cyclic GMP signaling (ROCG) dysfunction [1,2]. In patients with both VaD and AD, the impairment of this signaling pathway plays a crucial role in endothelial dysfunction, leading to reduced cerebral blood flow (CBF), impaired blood brain barrier (BBB), vascular lesions, and to AD-associated pathology amyloid-beta plaques and hyperphosphorylation of tau [3-6]. Here, our aim is to validate the efficacy of a network pharmacology approach, using repurposed drugs targeting the ROCG signaling module, to treat cerebrovascular dysfunction and cognitive impairment in a clinically relevant animal model. Specifically, we will use the transgenic NADPH oxidase 5 (NOX5) KI/apolipoprotein E (ApoE) KO mouse fed with a sodium-rich diet. Rodents lack the NOX5 gene, thus its insertion in the mouse is key due to its major role in the ROCG signaling and its association with disrupted BBB integrity and memory loss [7,8]. ApoE is a positive modulator of endothelial nitric oxide (NO) production and, functionally, loss of ApoE in mice results in attenuation of NO-cGMP dependent endothelial relaxation and reduction of CBF [9-11]. The inclusion of a diet rich in sodium, which in humans is a life-style factor shown to negatively impact cognition, is relevant as this diet impacts endothelial function via increased NOX-derived ROS and decreased endothelial NO synthase activity, leading to attenuated NO-dependent vasodilation [12-14]. By combining the genetic insertion of NOX5, deletion of ApoE and a specific diet, we aim to model ROCG dysfunction and its associated dementia-relevant pathophysiological features. Our purpose is to set the basis for a subsequent phase IIa clinical trial based on this first-in-class mechanism-based treatment for a mechanism-based subgroup of MCI and dementia. Through this proof-of-concept pre-clinical study we aim to acquire the necessary scientific data for the delivery of an innovative drug repurposing strategy with strong potential for clinical application and rapid translation. If demonstrated to be effective, this approach could benefit a subset of patients with ROCG signaling dysfunction, most likely with symptoms beyond cognitive impairment and in other organs, to improve with high precision their quality of life.
Keywords

Dementia, network pharmacology, drug repurposing, pre-clinical validation

References


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