Soluble guanylate cyclase as a novel target for cognition enhancement

Impact

Acknowledgements

Curriculum Vitae

List of publications

Ellis Nelissen

Approximately 50 million people suffer from dementia worldwide, and nearly 10 million new cases are diagnosed each year. By 2050, the number of dementia cases is expected to triple, leading to $4 trillion in estimated costs worldwide. Indeed, in the US alone the economic costs of dementia rose from $279.6 billion to $984 billion between the years 2000 and 2016, while the highest economic burden can be found in Europe [1]. Out of all these dementia cases, 20% is diagnosed with pure vascular dementia, making it the second most common form of dementia, after Alzheimer's disease in Caucasian populations [2]. However, the broader term of vascular cognitive impairment (VCI) also describes mixed pathologies, including contributing factors of VCI within Alzheimer's disease. Therefore, the actual prevalence of VCI is difficult to estimate, yet is much higher than the 20% of pure vascular dementia cases. Symptoms of VCI include memory loss, confusion, disorientation, and symptoms of stroke.

So far, no treatments have been approved for vascular dementia. Preventative measures such as lifestyle interventions and blood pressure medication, but also symptomatic treatment with cognitive enhancers designed specifically for Alzheimer's disease have not proven clear efficacy. The life expectancy of people diagnosed with vascular dementia was found to be on average five years from the moment of diagnosis. In essence, this implies that a vascular dementia diagnosis means a 60% chance of death within five years while slowly losing more cognitive functions which significantly impairs daily living, with no treatments available whatsoever. Indeed, vascular dementia causes the most substantial loss in quality of life out of all dementia types [3]. Furthermore, it is defined by the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guideline as "clinically significant deficits of sufficient severity in at least 1 cognitive domain (deficits may be present in multiple domains) and severe disruption to activities of daily living" [4]. Together this implies that currently a VCI diagnosis is a verdict of a lower quality of life with a reduced life expectancy. This emphasizes the emotional burden of a VCI diagnosis, and that a treatment for VCI is truly needed.

Both the worldwide economic burden and the emotional burden for the patient really emphasize the need for treatments, yet there are none available. The results from this thesis provide mechanistic insights into the enzyme sGC and its potential as a pharmacological target for cognition enhancement (scientific utilization). As

illustrated in chapter 2, sGC is also a target for cardiovascular disease. This suggests that due to the memory enhancing effects of sGC stimulators and activators, targeting sGC with sGC modulators may in the future provide to be a promising treatment for VCI (commercial utilization), which patients are in dire need for (socio-economic utilization). Especially the effects on hippocampal plasticity of brain-penetrant sGC modulators in combination with potential vascular effects may help repair both the brain and the vasculature synergistically. Therefore, sGC modulators may not only provide a symptomatic treatment, i.e. cognition enhancement, but may also repair/prevent damage and treat VCI at the core of its processes. Many of the research described in this thesis was performed in collaboration with pharmaceutical companies (e.g. BAYER and Merck) that have a strong interest in sGC as a target, both as a treatment for cardiovascular disease and neurodegenerative disorders such as vascular dementia. In fact, the research performed with vericiguat was a successful collaboration between us at Maastricht University, researchers from BAYER, and researchers from Merck [5]. Additionally, the experiments performed with BAY-747 and runcaciguat were all in collaboration with BAYER. The promising memory enhancing effects of BAY-747 and runcaciguat have convinced BAYER to continue the collaboration and provide resources for further research into the development for these sGC modulators as a treatment for VCI. Therefore, the results within this thesis may provide the solid basis for future research which has all the elements that can actually help to reach the patient in the end.

References

[1] J. Xu, Y. Zhang, C. Qiu, F. Cheng, Global and regional economic costs of dementia: a systematic review, The Lancet 390 (2017) S47.

[2] F.J. Wolters, M.A. Ikram, Epidemiology of Vascular Dementia, Arteriosclerosis, Thrombosis, and Vascular Biology 39 (2019) 1542-1549.

[3] W. Moon, Quality of life and disease burden in patients with MCI and dementia, Alzheimer's & Dementia 16 (2020) e039199.

[4] O.A. Skrobot, S.E. Black, C. Chen, C. DeCarli, T. Erkinjuntti, G.A. Ford, R.N. Kalaria, J. O'Brien, L. Pantoni, F. Pasquier, G.C. Roman, A. Wallin, P. Sachdev, I. Skoog, V. group, Y. Ben-Shlomo, A.P. Passmore, S. Love, P.G. Kehoe, Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study, Alzheimers Dement 14 (2018) 280-292.

[5] E. Nelissen, E.K. Argyrousi, N.P. Van Goethem, F. Zhao, C.D.G. Hines, G. Swaminath, M. Gerisch, J. Hueser, P. Sandner, J. Prickaerts, Soluble Guanylate Cyclase Stimulator Vericiguat Enhances Long-Term Memory in Rats without Altering Cerebral Blood Volume, Biomedicines 9 (2021) 1047.