Methylglyoxal and the brain microcirculation

Scientific and societal impact

Cerebral small vessel disease (CSVD) is an umbrella term that covers all pathologies of the small vessels of the brain. This thesis focussed on one of the most prevalent CSVD forms, the age and vascular risk factors associated type. Age is a major risk factor, and it was shown that almost all people of 80 years and older have white matter hyperintensities, with nearly 40% having cerebral microbleeds [1, 2]. Considering our ageing society, the prevalence of CSVD and its impact on society will only increase with time, especially due to its progressive nature [3]. Current predictions from the World Health Organization estimate the number of people over the age of 80 to triple between 2020 and 2050 [4]. Furthermore, diabetes mellitus, a risk factor in CSVD, is also increasing in prevalence [5]. Currently, an estimated 10% of the world's population has a form of diabetes. By 2045 it is estimated that the absolute number of people with diabetes will increase by 46% [5]. Taking into consideration the growing size and age of the world's population and the increasing prevalence of diabetes in societies around the world, it seems likely the prevalence of CSVD will also rapidly increase until an effective treatment or preventative strategy becomes available.

In this thesis, we investigated the effect of MGO on the brain microcirculation, attempting to elucidate the relevance of the highly reactive compound in brain microvascular dysfunction. Methylglyoxal (MGO), a reactive dicarbonyl compound and byproduct of glycolysis, is known to play a role in microvascular function in diabetes and age-related disease [6], and in this thesis we show that MGO formation might also play a role in microvascular dysfunction in the brain.

Scientific relevance; the source matters

The results of this thesis emphasise the importance of defining a relevant research context depending on the research question. Our findings point out that the effect of MGO on the brain microvasculature depends on the source, location, and concentration of MGO. We showed that endogenous formation within cells has detrimental effects on the brain microcirculation and cognitive function, whereas an increase of MGO in the plasma compartment by itself is seemingly harmless in young and healthy mice. Additionally, the findings presented and discussed in this thesis further point out that for experimental studies, we need to use MGO from a purified source in order to investigate its effect.

Furthermore, MGO might play a different role in different neurological disorders. We found endogenous formation of MGO as a consequence of hyperglycaemia to be detrimental for the neurovasculature and cognitive function. However, when (neuro)inflammation is involved in the disease aetiology, MGO could serve as an inflammatory regulator molecule and exert beneficial effects [7]. The findings of this thesis expand the knowledge of the putative role of MGO in neurological disorders including CSVD. We thereby hope to

contribute to the awareness of the importance of the source and location and concentration of MGO in experimental conditions in order to study its role in neurological diseases and in particular CSVD.

Last, the findings presented in this thesis also highlight the importance of causality when it comes to MGO and AGEs and their relation to CSVD and neurological disorders. We found that MGO in plasma is most likely a symptom of increased MGO formation intracellularly and plasma MGO is unlikely to directly affect the brain. Therefore, future research into therapeutic targets should consider the source of MGO causing neurological disease in order to increase treatment efficiency (targeting the source, i.e., MGO formation and intracellular accumulation).

Societal relevance; the possibilities of MGO as a therapeutic target

There are several existing treatment strategies to directly or indirectly target MGO. Based on our findings, it would be most effective to tackle the cause of the problem by reducing formation and/or accumulation of MGO in CSVD. As described in chapter 1, there are several effective antidiabetic drugs that have shown to effectively reduce risk of cognitive impairment. Targeting glucose metabolism in order to prevent MGO formation would be an obvious therapeutic target for people with diabetes. Whether antidiabetic drugs can be effective in people with CSVD but without type 2 diabetes is unclear.

There are several compounds that are able to scavenge MGO and/or enhance MGO detoxification, these include, but are not limited to aminoguanidine/pimagedine [8], pyridoxamine [9], trans-resveratrol [10], and flavonoids such as quercetin [11] and hesperidin [12]. Based on this thesis, a compound which would be able to enhance MGO detoxification or significantly scavenge intracellular levels of MGO, would be most efficient. In particular, hesperidin has been shown promising preclinical results when it comes to neurodegenerative disease and is known to be able to cross the blood-brain barrier [13] and resveratrol might have beneficial effect in cerebrovascular disease [14]. Moreover, trans-resveratrol and hesperidin combination has been shown to also improve glycaemic control in people with type 2 diabetes [15]. The combination treatment of trans-resveratrol and hesperidin might therefore be an interesting future treatment strategy to be investigated in targeting MGO in CSVD.

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