Editorial

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Hypoxanthine of Ischemic Brain Edema Modified by Glibenclamide

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Introduction

The development of malignant brain edema is a leading cause of early clinical deterioration and death after ischemic stroke. Lesional swelling exacerbates tissue injury and portends poor long-term functional outcome after stroke. Malignant brain edema [1], the rapid clinical decline in the first 24–72 h after stroke due to mass-occupying tissue swelling, is a highly morbid sequela of large hemispheric stroke. Limited therapies exist for the treatment of brain edema.

The Glyburide Advantage in Malignant Edema and Stroke (GAMES)-RP trial (ClinicalTrials.gov: NCT01794182) evaluated the safety and efficacy of intravenous glibenclamide (glyburide; BIIB093) to mitigate brain edema in patients suffering large hemispheric infarction and demonstrated a reduction in midline shift (MLS) and the plasma matrix metalloproteinase-9 (MMP-9) level in glibenclamide-treated patients. Preclinical data have suggested that glibenclamide binds the sulfonylurea-1 receptor-transient receptor potential melastatin 4 channels (SUR1-TRPM4) and may mitigate brain edema by blocking non-specific ion influx into ischemic cells; however, the exact mechanism of glibenclamide in patients is not fully understood [2].

Metabolomics measures circulating metabolites, the level of which represents an integrated view of metabolism. For example, metabolite levels may directly reflect metabolic disturbances from ischemia or indirectly relate to changes in the metabolic programs that mediate the post-ischemic inflammatory response. Therefore, changes in metabolite levels may reflect underlying pathophysiologic mechanisms and can provide insight into disease mechanisms.

In this study, we investigated potential mechanisms of malignant edema by identifying metabolomic markers that were also modified by i.v. glibenclamide treatment [3]. To address this objective, we first identified candidates associated with MLS and the MMP-9 level, two markers of malignant brain edema that have been shown to be attenuated by i.v. glibenclamide in GAMES-RP. Second, leading candidates were then evaluated as potential pharmacodynamic markers of i.v. glibenclamide treatment. We hypothesized that a marker associated with these criteria would provide insight into the mechanisms of malignant edema after stroke [4].

Discussion

In this study, we identified plasma hypoxanthine as a marker of brain edema after ischemic stroke. This association was independent of age, gender, NIHSS, DWI lesion volume, tPA treatment, decompressive hemicraniectomy, and recanalization status [5,6]. Further, we demonstrate that among 152 metabolites analyzed, hypoxanthine was the only candidate that was associated with MMP-9 and MLS and modified by glibenclamide treatment. Elevated plasma hypoxanthine was associated with increased MMP-9 and greater MLS, whereas treatment with i.v. glibenclamide significantly reduced plasma hypoxanthine. We also demonstrate that the hypoxanthine level acts as a mediator of the effect of glibenclamide on MMP-9 and MLS [7]. Together, these findings broaden our understanding of the mechanism of glibenclamide beyond its effect on the SUR1-TRPM4 channel, raising the possibility that glibenclamide also acts to attenuate brain edema by reducing hypoxanthine.

Hypoxanthine is a reaction intermediate in the purine-degradation pathway. It is

catabolized into xanthine and uric acid by xanthine oxidase (XO). In states of hypoxia, the degradation of adenine nucleotides to hypoxanthine accelerates, and the rate of conversion to xanthine and uric acid by XO is slowed because O2 is a required cofactor [8]. As such, elevated hypoxanthine has been demonstrated to be a marker of hypoxia in several disease states. Interestingly, the oxidation of hypoxanthine and xanthine by XO also produces reactive oxygen species (ROS) and triggers cytotoxicity. In healthy non-ischemic cells, XO exists predominantly as xanthine dehydrogenase (XD), which uses NAD+ instead of O2 as a cofactor. In ischemia, however, XD is rapidly converted to XO. When oxygen becomes available again during tissue reperfusion, XO, with its required cofactor O_2, then oxidizes hypoxanthine and xanthine, generating abundant ROS in the process. Several studies have linked hypoxanthine to the formation of free radicals and ROS. Accordingly, hypoxanthine has been implicated in ischemia-reperfusion injury [9].

In large stroke, edema due to blood-brain-barrier breakdown contributes to mass effect, MLS, and poor functional outcome. Elevated plasma hypoxanthine can amplify ROS production and induce endothelial cell dysfunction in vitro. Further, it is known that oxidative stress induces MMP-9, which mediates degradation of the tight junctions that make up the blood-brain barrier (BBB). Taken together, it is a plausible hypothesis that elevated hypoxanthine promotes increased ROS, which in turn causes an increase in MMP-9, further compromising the BBB and leading to increased brain edema. Previous analysis of the GAMES-RP trial has demonstrated that the MMP-9 level peaks within hours after acute stroke then decreases over time and that i.v. glibenclamide treatment attenuates the MMP-9 level for up to 72 h after stroke [10]. Considering the current literature on hypoxanthine and MMP-9, we posit that i.v. glibenclamide may attenuate the overall severity of ischemic insult by reducing the amount of swelling and/or by reducing oxidative injury. That said, our study does not clarify the precise mechanism of hypoxanthine; rather, our data support a role for hypoxanthine as a pharmacodynamic marker, which can serve as a serial marker of treatment effect. Further study is needed to validate our findings and explore the underlying mechanistic link between hypoxanthine, edema, and i.v. glibenclamide.

Conclusion

Taken together, our findings demonstrate that i.v. glibenclamide acts to reduce plasma hypoxanthine. Our results raise the possibility that i.v. glibenclamide reduces MMP-9 and MLS in patients via a reduction in hypoxanthine level. As a mediator of ROS generation following ischemia, hypoxanthine may be a candidate biomarker for brain-edema formation after acute stroke.

Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

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