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Abstract

Aim of review: Ganglioside GM1 is a major ganglioside component, which has been shown to potentiate the action of neurotrophins and display a wide variety of CNS functions amongst many neurologic conditions including cerebral ischemic injury. This mini-review aims to summarize the latest knowledge of the possible neuro-reparative properties of GM1 in ischemic stroke in the past ten years.

Method: The literature was searched using Medline between 2005 and the present using search terms including “Ganglioside GM1”, “ischemic stroke”, “ischemic brain injury” and “stroke”. The search terms were cross-referenced and the search was limited to English language articles. All of the articles, found including those associated with the initial search results, were evaluated for methodology and results, and were included if deemed applicable to this review. Recent findings: GM1 treatment has been shown robust and reproducible neuroprotective effects both in the neonatal and adult ischemic brain insult, however, the clinical efficacy of GM1 in stroke patients remains uncertain. The issues exist in the present clinical trials may account for some of the failure.

Summary: More well-designed clinical trials are necessary to re-assess the potential efficacy of GM1 in stroke patients.

Introduction

There is considerable research interest in Ganglioside GM1, a major ganglioside component. This pattern began in reports published in the early 1970s covering its role as a receptor for the bacterial toxin responsible for the cholera pathogenesis [1]. At that time, gangliosides were a relatively hot topic and the subject of many international meetings. Soon afterwards it was also found to be able to potentiate the action of neurotrophins and display a wide variety of central nervous system (CNS) functions including promoting survival, differentiation [2], neurodegeneration [3-5], axon stability, and regeneration [6]. Although the development of the acute inflammatory polyneuropathy Guillain-Barre syndrome (GBS) after intravenous ganglioside treatment resulted in the withdrawal of GM1 from the European market [7], this adverse effect was shown to be rare [8]. These drugs are still available and have been extensively prescribed in other markets, including in China, where a multitude of neurological maladies are treated with gangliosides in the absence of resultant GBS or other severe adverse events [9-12]. Recently, a plethora of studies have suggested that GM1 may be involved in the stroke process, specifically orchestration of cell death and subsequent neurological dysfunctions [13].

GM1 in neonatal ischemic brain injury

White matter injury is the predominant form of brain damage in neonatal hypoxic-ischemic (HI). The concentration of GM1 has been found to undergo a significant decrease in this process [14]. Exogenous GM1 injection has been shown to reduce the damage of myelin sheaths, the primary characteristic of white matter injury, and eventually prevent brain injury. The neuroprotective effect of GM1 might involve promoting the association of neurofascin 155 (or other important proteins) with lipid rafts, increasing the expression of myelin basic protein, and subsequent stabilizing the structure of paranodes [13,14]. In a recent study by Whitehead et al. [15], middle cerebral artery occlusion (MCAO) resulted in a transient induction of GM1 at the border of the infarcted tissue in adult mice. Consistent with this finding, another adult rat experimental study performed by Kwak et al. [16] demonstrated an increase in the mRNA for GM1 synthase and an obvious increase of GM1 expression to protect the cerebral cortex from ischemic damage. One possible explanation is that there may be a self-protection mechanism through which adult animals can avoid suffering from stroke under ischemic condition. However, this self-protection mechanism may not yet have been sufficiently developed in the neonates.

GM1 in adult ischemic brain injury

N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor, and it is extensively distributed in the central nervous system, playing prominent roles in the pathophysiologic process associated with cerebral ischemia [17,18]. Liu et al. reported that GM1 could inhibit both the high expression of NMDAR1 (a NMDAR subunit) in the early stage of focal cerebral ischemia/reperfusion in rats, which caused greater NMDA receptor-related neurotoxicity, but also the overly low level of NMDAR1 during the late stage to maintain the normal neural function [19]. In this study GM1 was found to reduce the infarct volume in a time-dependent manner. That is, GM1 administered 5 min or 1 h after MCAO could significantly decrease...
the infarct volume while GM1 administered at 2 h after surgery could not. The authors concluded that early usage of GM1 may provide better protection for cerebral ischemia.

In the present study, which was performed using a rat MCAO model, GM1 (50 mg/kg) treatment significantly reduced the enhanced conversion of LC3-I into LC3-II, P62 degradation, and high levels of Beclin-1 after ischemic insult. Improved neurobehavioral performance, decreased infarction volume (from 26.3% to 19.5%) and a lower mortality rate were also observed in the study after GM1 administration, without causing significant adverse side effects. GM1 showed safe and robust neuroprotective effects associated with the inhibition of autophagy following experimental stroke.

GM1 in clinical trials

After showing robust and reproducible neuroprotective effects in experimental studies, doctors began to use GM1 in patients with acute ischemic stroke and other neurological disorders [12,20,21]. Although it has demonstrated clinical benefits in patients with Parkinson’s Disease (PD) and Alzheimer disease (AD), the potential efficacy of GM1 in stroke remains uncertain [10,22,23]. As summarized by Candelise and Ciccone [8], in which twelve trials, a total of 2265 cases were included in that research survey, no significant differences in reducing disability and fatality rate were observed between the treatment and control group at the end of follow up. The conclusion is that the use of GM1 in ischemic stroke should be avoided because of the absence of therapeutic benefit and possible cause of GBS. In fact, the clinical trials covering GM1 for stroke treatment have been under way for a long time, but there have been very few reports in the past ten years.

Conclusion

Although GM1 has shown beneficial effects in animal cerebral ischemia, the clinical trials have been disappointing. However, these trials have many noticeable issues, like a large number of excluded cases; incomplete follow-up information; poorly designed of randomization procedures; small sample size; and attrition among the study cohort. They also included strokes whose type and level of severity may have procedures; small sample size; and attrition among the study cohort.

References

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