Pulmonary and Critical Care Medicine

open access text

Mini Review

Ganglioside GM1 for ischemic stroke: An update (2005-2015)

Li Li* and Tianlong Wang*

Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China

Abstract

Aim of review: Ganglioside GM1is 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] emonstrated 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 ionotrophic 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 NMDAR1during 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

Correspondence to: Li Li, Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China, **E-mail:** lili2009kaoyan@163.com

Tianlong Wang, Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China, **E-mail:** w_tl5595@hotmail.com

Received: February 28, 2016; **Accepted:** March 21, 2016; **Published:** March 24, 2016

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 made it hard to obtain a beneficial effect. This may account for some of the failure to demonstrate its therapeutic efficacy. With respect to the associated GBS, it has been reported that this is a rare event and the correlation between the use of GM1and the development of GBS remains controversial.

References

1. Holmgren J, Lönnroth I, Svennerholm L (1973) Tissue receptor for cholera exotoxin: postulated structure from studies with GM1 ganglioside and related glycolipids. *Infect Immun* 8: 208-214. [Crossref]
2. Yu RK, Suzuki Y, Yanagisawa M (2010) Membrane glycolipids in stem cells. *FEBS Lett* 584: 1694-1699. [Crossref]
3. Haughey NJ, Bandaru VV, Bae M, Mattson MP (2010) Roles for dysfunctional sphingolipid metabolism in Alzheimer's disease neuropathogenesis. *Biochim Biophys Acta* 1801: 878-886. [Crossref]
4. Ohmi Y1, Tajima O, Ohkawa Y, Mori A, Sugiura Y, et al. (2009) Gangliosides play pivotal roles in the regulation of complement systems and in the maintenance of integrity in nerve tissues. *Proc Natl Acad Sci USA* 106: 22405-22410. [Crossref]
5. Posse de Chaves E, Sipione S (2010) Sphingolipids and gangliosides of the nervous system in membrane function and dysfunction. *FEBS Lett* 584: 1748-1759. [Crossref]
6. Schnaar RL (2010) Brain gangliosides in axon-myelin stability and axon regeneration. *FEBS Lett* 584: 1741-1747. [Crossref]
7. Figueras A, Morales-Olivas FJ, Capellà D, Palop V, Laporte JR (1992) Bovine gangliosides and acute motor polyneuropathy. *BMJ* 305: 1330-1331. [Crossref]
8. Candelise L, Ciccone A (2001) Gangliosides for acute ischaemic stroke. *Cochrane Database Syst Rev* CD000094. [Crossref]
9. Zhu Y, Yang J, Jiao S, Ji T (2013) Ganglioside-monosialic acid (GM1) prevents oxaliplatin-induced peripheral neurotoxicity in patients with gastrointestinal tumors. *World J Surg Oncol* 11: 19. [Crossref]
10. Schneider JS, Sendek S, Daskalakis C, Cambi F (2010) GM1 ganglioside in Parkinson's disease: Results of a five year open study. *J Neurol Sci* 292: 45-51. [Crossref]
11. McDonald JW, Sadowsky C (2002) Spinal-cord injury. Lancet 359: 417-425. [Crossref]
12. [No authors listed] (1994) Ganglioside GM1 in acute ischemic stroke. The SASS Trial. *Stroke* 25: 1141-1148. [Crossref]
13. Rong X, Zhou W, Xiao-Wen C, Tao L, Tang J (2013) Ganglioside GM1 reduces white matter damage in neonatal rats. *Acta Neurobiol Exp (Wars)* 73: 379-386. [Crossref]
14. Zhang YP, Huang QL, Zhao CM, Tang JL, Wang YL (2011) GM1 improves neurofascin155 association with lipid rafts and prevents rat brain myelin injury after hypoxia-ischemia. *Braz J Med Biol Res* 44: 553-561. [Crossref]
15. Whitehead SN, Chan KH, Gangaraju S, Slinn J, Li J, et al. (2011) Imaging mass spectrometry detection of gangliosides species in the mouse brain following transient focal cerebral ischemia and long-term recovery. *PLoS One* 6: e20808. [Crossref]
16. Kwak DH, Kim SM, Lee DH, Kim JS, Lee SU, et al. (2005) Differential expression patterns of gangliosides in the ischemic cerebral cortex produced by middle cerebral artery occlusion. *Mol Cells*. 20: 354-360.
17. Monaghan DT, Bridges RJ, Cotman CW (1989) The excitatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annu Rev Pharmacol Toxicol.* 29: 365-402.
18. Collingridge GL, Singer W (1990) Excitatory amino acid receptors and synaptic plasticity. *Trends Pharmacol Sci* 11: 290-296. [Crossref]
19. Liu JR, Ding MP, Wei EQ, Luo JH, Song Y, et al. (2005) GM1 stabilizes expression of NMDA receptor subunit 1 in the ischemic hemisphere of MCAo/reperfusion rat. *J Zhejiang Univ Sci* B 6: 254-258. [Crossref]
20. Favaron M, Manev H, Alho H, Bertolino M, Ferret B, et al. (1988) Gangliosides prevent glutamate and kainate neurotoxicity in primary neuronal cultures of neonatal rat cerebellum and cortex. *Proc Natl Acad Sci U S A* 85: 7351-7355. [Crossref]
21. Ledeen RW (1984) Biology of gangliosides: neuritogenic and neuronotrophic properties. *J Neurosci Res* 12: 147-159. [Crossref]
22. Schneider JS, Gollomp SM, Sendek S, Colcher A, Cambi F, et al. (2013) A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients. *J Neurol Sci* 324: 140-148. [Crossref]
23. Svennerholm L, Brane G, Karlsson I, Lekman A, Ramstrom I, et al. (2002) Alzheimer disease - effect of continuous intracerebroventricular treatment with GM1 ganglioside and a systematic activation programme. *Dement Geriatr Cogn Disord* 14: 128-136.