

● LETTER

Neuroprotective effects of monosialotetrahexosylganglioside

Monosialotetrahexosylganglioside (GM1) is a type of glycosphingolipid containing sialic acid that is closely related to cell-cell recognition, adhesion and signal conduction. GM1 is mainly composed of ceramide and oligosaccharide chains, and it is the only ganglioside that can permeate the blood-brain barrier.

Sialic acid is a generic term for the N- or O-substituted derivatives of neuraminic acid. It contains nine carbon atoms as a backbone, and is an acidic amino sugar with a pyranose structure. Different groups can be connected on carbon number 5, leading to various sialic acid derivatives. Sialic acid is widely found in the tissues of vertebrates, mammals, and various plants. It is an important part of glycoconjugates that are located on the cell surface. Sialic acid exists in the form of glycoside at the ends of the structures of glycoproteins and glycolipids, and has a variety of physiological functions. In animals, sialic acid mainly exists in the forms of N-acetyl-neuraminic acid and N-glycoloyl-neuraminic acid.

Sialic acid is also an important sugar component on erythrocyte membrane surfaces, as a terminal sugar residue in glycoproteins. In these functions, sialic acid participates in cell recognition, adhesion and contact inhibition. Sialic acid is a major determining factor in the survival of erythrocytes in the circulatory system, and exerts a crucial effect on the senescence of erythrocytes and the removal of senescent cells. Sialic acid content alters over the life-span of erythrocytes. The amount of sialic acid in young erythrocytes is higher than that in senescent erythrocytes. Sialic acid is a widely accepted marker of senescence of erythrocytes. Geng et al. (2008) investigated the protective effect of salidoside on erythrocytes in rat models after exhaustive swimming exercise. In his study, 32 male rats were randomly divided into blank control and experimental groups treated by salidoside at 100 mg/kg (low-dose group), 200 mg/kg (moderate-dose group) and 300 mg/kg (high-dose group). The results showed that the content of sialic acid in rat erythrocyte membranes was remarkably reduced, suggesting that exercise could accelerate the senescence of erythrocytes. Thus, erythrocytes could be easily identified and phagocytized. The reduction in sialic acid content in rat erythrocyte membranes is probably associated with nonspecific loss of membrane components, and probably induced by the direct reactions of free radicals with ends of glycoprotein sugar chains. The content of sialic acid in rat erythrocyte membranes was evidently elevated in the salidoside group, and sialic acid content was obviously higher in the high-dose group than in the low- and moderate-dose groups. These results indicate that salidoside could increase the sialic acid content in rat erythrocyte membranes after exercise, and reduce the changes in rat erythrocyte membrane components. Moreover, this

increase may be positively correlated with dose.

In recent studies, Li et al. (2015) demonstrated that sialic acid content was increased on neuronal membranes in the sciatic nerve following chronic constriction injury, which increased the electrophoretic velocity in dorsal root ganglion neurons and this led to neuropathic pain.

Peripheral nerve injury can lead to ectopic spontaneous electrical activity of the soma and axon injury of the primary sensory neurons, which can cause neuropathic pain. Ectopic electrical activity resulted from membrane remodeling that occurred following an increase in the number of functional proteins on the membranes of injured neurons, and their ectopic accumulation. Therefore, Li et al. (2015) presumed that, with the increase in protein expression on the surfaces of neuronal membranes in the injured dorsal root ganglion, the amount of sialic acid, the negative charge, and the excitability of injured neurons would be increased. Thus, hyperalgesia and allodynia would appear.

Li et al. (2015) assumed that the increased sialic acid content in injured neurons would increase the negative charge, and that the electrophoretic towards the anode would be faster than that towards normal neurons in cell electrophoresis. The mobility of dorsal root ganglion neurons is consistent with the electrical activity of neurons and animal pain behavior. This suggests that drugs for treating pathological pain following peripheral nerve injury could be selected according to the changes in mobility in the hypersensitive dorsal root ganglion neurons in pathological pain models.

Ganglioside is glycosphingolipid containing sialic acid, and is strongly associated with intercellular adhesion and signal transduction. In particular, GM1 plays an important role in repair and regeneration following nerve injury. GM1 was first identified by Kroenke in 1935. GM1 is a component of normal cell membranes and accounts for 5% of cell membrane lipids. Its molecular formula is $C_{73}H_{130}N_3NaO_{51}$ or $C_{75}H_{134}N_3NaO_{51}$, and its molecular weight is 1,568.84 or 1,597.18. The concentration of GM1 is highest in the cerebral gray matter, making up approximately 730 nmol/g of brain tissue. GM1 is mainly located in the myelin sheath, neuronal cell membrane and axons. A previous study (Cotman et al., 1981) showed that the ganglioside content levels differed among 102 people, aged 20–102 years. Ganglioside content was low in aged patients, and dropped to 60% in those with the minimum content. This means that ganglioside is continuously lost during aging. The loss of ganglioside is also very apparent in patients with brain injury. Following nerve injury, exogenous GM1 in the blood binds to lipoprotein, enters the nervous system through the blood-brain barrier, becomes highly localized to the injury zone, and exerts neuroprotective effects through a variety of functions. Some of these functions include: neural remodeling in nerve cell membranes, enhancing nerve growth factor function, participating in the interactions between the nervous system and the environment and in nerve signal transmission, inhibiting lipid peroxidation, reducing the release of excitatory amino acids, and improving cerebral blood supply (Yu et al., 2012). Scientists found that ganglioside could remodel



nerves, repair injured nerves by promoting dendritic growth, and maintain the normal operation of nerve networks in the brain (Garofalo, et al. 1992; Takebayashi et al. 2004). Ganglioside effectively regulated ion channels and stabilized the open times and probabilities of ion channels in the brain, ensured information transfer among neural networks, and contributed to nerve growth and development (Bremer et al., 1984; Brunda et al., 1993; Harder et al., 1998).

To assess the effects of exogenous ganglioside on acute ischemic stroke, Candelise and Ciccone (2001) performed a systematic analysis of the results of clinical studies in the Cochrane Stroke Group Trials Register. Specifically, they reviewed 12 clinical trials involving 2,265 patients. Three trials described how randomization procedure was used, and follow up time was 15–180 days. At the end of follow up, no significant difference in the number of deaths was detected (odds ratio [OR] 0.91, 95% confidence intervals (CI) 0.73 to 1.13). The results did not suggest that injection of ganglioside within 48 hours could obtain better clinical effects compared with delayed treatment. Three trials also revealed that ganglioside did not improve Barthel index scores (weighted mean difference 2.1; 95% CI –4.8 to 8.9). In two trials, eight patients had adverse reactions and treatment was withdrawn. Seven patients suffered from skin reactions. One patient experienced Guillain-Barre syndrome. The authors considered that the evidence was not sufficient to verify the beneficial effect of ganglioside on acute ischemic stroke. They also suggested that we should pay close attention to adverse reactions after treatment with ganglioside.

In the North American Clinical Trial Registry, there were 21 registered projects related to ganglioside. Only one project addressing ganglioside for the clinical treatment of nervous system diseases has been finished. In that study (NCT00037830), Schneider et al. (2013) performed a randomized, controlled, delayed-start trial of GM1 for Parkinson's disease. Seventy-seven subjects with Parkinson's disease aged 39–85 years were randomly assigned to an early-start group (GM1 for 120 weeks) or a delayed-start group (placebo for 24 weeks followed by GM1 for 96 weeks). At 1 and 2 years after treatment, washout evaluations were conducted. Seventeen additional subjects who received the standard of care were followed for comparative information about disease progression. The primary outcome was the change from baseline in the Unified Parkinson's Disease Rating Scale motor scores. The results showed that, at 24 weeks, Unified Parkinson's Disease Rating Scale motor scores were lower in the early-start group than in the delayed-start group. At 72 and 120 weeks, a sustained improvement was found in the early-start group. Symptoms were evidently worsened in both groups during washout. GM1 use for 24 weeks was superior to placebo for improving motor symptoms, and extended GM1 use (for up to 120 weeks) resulted in a lower than expected rate of symptom progression. The data from this study suggest that GM1 may have symptomatic and potentially disease-modifying effects on Parkinson's disease. The mechanisms of action underlying the nerve protection and nerve repair effects of ganglioside remain poorly under-

stood. The future studies should be carried out to investigate whether the neuroprotective mechanisms are associated with the structural and functional regulation of lipid rafts.

The present article summarized the neuroprotective effects of GM1. With further, in-depth study, the molecular mechanisms underlying the neuroprotective effects of ganglioside can be clarified and provide a solid foundation for clinical research. Moreover, well-designed, randomized controlled trials will open up new prospects for the clinical use of ganglioside.

This study was supported by the National Natural Science Foundation of China (General Program), No. 81373095.

Ai-ping Xi, Zhong-xin Xu, Feng-li Liu, Yan-li Xu

The Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China (Xi AP)

School of Medicine, Hebei University of Engineering, Handan, Hebei Province, China (Xu ZX, Liu FL, Xu YL)

*Correspondence to: Yan-li Xu, Ph.D., xuyanli@vip.sina.com.

orcid: 0000-0002-8270-1569 (Ai-ping Xi)

Accepted: 2015-07-23

doi:10.4103/1673-5374.162950 <http://www.nrronline.org/>

Xi AP, Xu ZX, Liu FL, Xu YL (2015) Neuroprotective effects of monosialotetrahexosylganglioside. *Neural Regen Res* 10(8):1343-1344.

References

- Bremer EG, Hakomori S, Bowen-Pope DF, Raines E, Ross R (1984) Ganglioside-mediated modulation of cell growth, growth factor binding, and receptor phosphorylation. *J Biol Chem* 259:6818-6825.
- Brunda MJ, Luistro L, Warriar RR, Wright RB, Hubbard BR, Murphy M, Wolf SF, Gately MK (1993) Antitumor and antimetastatic activity of interleukin 12 against murine tumors. *J Exp Med* 178:1223-1230.
- Candelise L, Ciccone A (2001) Gangliosides for acute ischaemic stroke. *Cochrane Database Syst Rev* CD000094.
- Cotman CW, Nieto-Sampedro M, Harris EW (1981) Synapse replacement in the nervous system of adult vertebrates. *Physiol Rev* 61:684-784.
- Garofalo L, Ribeiro-da-Silva A, Cuello AC (1992) Nerve growth factor-induced synaptogenesis and hypertrophy of cortical cholinergic terminals. *Proc Natl Acad Sci U S A* 89:2639-2643.
- Geng X, Ji CF, Ji YB (2008) Effect of salidroside on erythrocyte membranes in rats with exercise fatigue. *Zhongyao Yaoli Yu Linchuang* 24:49-51.
- Harder T, Scheiffele P, Verkade P, Simons K (1998) Lipid domain structure of the plasma membrane revealed by patching of membrane components. *J Cell Biol* 141:929-942.
- Li CX, Ma GY, Guo MF, Liu Y (2015) Sialic acid accelerates the electrophoretic velocity of injured dorsal root ganglion neurons. *Neural Regen Res* 10:972-975.
- Schneider JS, Gollomp SM, Sendek S, Colcher A, Cambi F, Du W (2013) A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients. *J Neurol Sci* 324:140-148.
- Takebayashi M, Hayashi T, Su TP (2004) Sigma-1 receptors potentiate epidermal growth factor signaling towards neuritegenesis in PC12 cells: potential relation to lipid raft reconstitution. *Synapse* 53:90-103.
- Yu RK, Tsai YT, Ariga T (2012) Functional roles of gangliosides in neurodevelopment: an overview of recent advances. *Neurochem Res* 37:1230-1244.