MONOSIALOGLANGLIOSIDE EFFECTS FOLLOWING CEREBRAL ISCHEMIA: RELATIONSHIP WITH ANTI-NEURONOTOXIC AND PRO-NEURONOTROPHIC EFFECTS

M. LIPARTITI, M. S. SEREN, A. LAZZARO, T. KOGA, S. MAZZARI, L. FACCI, M. FUSCO, G. TOFFANO and A. LEON

CNS Department, Fidia Research Laboratories, Via Ponte della Fabbrica 3/A, 35031 Abano Terme, Italy and Institute of Brain Disease, Kurume University, School of Medicine, Fukuoka, Japan

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Abstract. Increasing evidence is available indicating that systemically administered GM, is able to provide for functional recovery in different experimental models of CNS injury, including cerebral ischemia. Current evidence indicates that the GM, effects are associated, in the acute phase, with attenuation of secondary neuronal damage due to its capability to antagonize excitatory amino acid-related neurotoxicity in vivo as in vitro. Furthermore, the ganglioside is able to facilitate occurrence of long-term reparative processes, an effect most likely reflecting the potentiation of the action of neuronotrophic factors. This bifaceted action of GM, makes the ganglioside ideally suited for clinical treatment of patients afflicted by cerebrovascular insufficiencies.

INTRODUCTION

Although advances have been made in identifying predisposing risk factors, stroke and CNS trauma are still among the leading causes of death and/or disability. Both clinical situations are accompanied by evolving neuronal cell damage and death. As the latter is presumably due to overstimulation of excitatory amino acid (EAA) receptors and consequent triggering of a cascade of intracellular events ultimately leading
to autophagic cell death, agents capable of preventing or limiting EAA neurotoxicity in brain have been proposed to be of potential therapeutic value (1).

The known ability of exogenous gangliosides to incorporate into neuronal plasma membranes (9) and to modify cell behavior in response to external stimuli (5) has prompted an examination of a possible ganglioside action in modulating the neurotoxic effects of GM$_1$ in vitro. Such studies have shown that gangliosides, including GM$_1$ (nomenclature according to 29) are able to limit EAA-related neurotoxicity (7, 8, 10, 27). Furthermore, GM$_1$ has been shown to potentiate in vitro the action of neuronotrophic factors, the latter now known to regulate expression of neuroplastic reparative processes following CNS injury (16, 27). Parallel studies have shown that systemically administered GM$_1$ is efficacious in providing for functional recovery following a variety of acute CNS insults, including cerebral hypoxia-ischemia (12-14). The following article briefly summarizes these latter results, in particular those following cerebral ischemia, and provides evidence that the GM$_1$ effects in vitro have, in fact, an in vivo counterpart.

GM$_1$ EFFECTS FOLLOWING CEREBRAL ISCHEMIA

Acute neuroprotective effects of systemically administered GM$_1$ have been evaluated in experimental models of both global and focal cerebral ischemia. In particular, results are available indicating that the GM$_1$ is efficacious in limiting morphological, biochemical, neurophysiological and/or behavioral manifestations of hypoxic-ischemic brain damage occurring in gerbils following unilateral carotid artery occlusion (12) as well as in rats (13) or cats (14) subjected to middle cerebral artery occlusion. Furthermore, experiments conducted with the inner ester derivative of GM$_1$ (termed siagoside, AGF$_2$ or GM$_1$-L) have shown that this ganglioside is also capable of exerting neuroprotective effects (3, 23, 26). This latter compound, like its parent molecule, limits EAA-related neurotoxicity in vitro and displays, following its systemic administration, higher bioavailability and incorporation into brain with respect to GM$_1$ (15).

Another important point to note is that systemic GM$_1$ treatment has also been reported to decrease secondary neurodegenerative events as well as facilitate functional neurological recovery following not only ischemic (14) but also traumatic (11, 22, 24, 30) or toxic insults (17-19, 25) in different CNS areas. This indicates that the ganglioside may exert cerebroprotective and reparative effects independently of the type of insult or neuronal system injured.
ANTI-EXCITOTOXIC AND PRO-NEURONOTROPHIC GM₁ EFFECTS IN VIVO: MECHANISTIC CONSIDERATIONS

Due to the largely recognized involvement of EAAs in the evolution of secondary brain damage, one feasible interpretation is that the GM₁ neuroprotective effects in the acute phase following CNS injury, reflect its capability to reduce EAA-related neurotoxicity in vivo as in vitro. This is further supported by experimentation demonstrating the capability of GM₁ to decrease excitotoxic-induced brain damage. For example, intracerebroventricular injection (i.c.v.) of N-methyl-D-aspartate (NMDA) in seven-day old rats results, five days later, in extensive brain lesions positively correlated with a reduction in hemispheric weight and neurochemical parameters such as choline acetyltransferase activity. GM₁ administration (20 mg/kg, s.c., 1 hour before and immediately after NMDA) significantly limits these effects and reduces dramatically the extent of morphological damage (17). Likewise, there is evidence that systemic GM₁ treatment is efficacious in reducing quinolinic acid-induced striatal damage (18) as well as ibotenic acid-induced (19) injury to forebrain cholinergic pathways in adult rats. Thus GM₁ exerts anti-excitotoxic effects not only in developing but also in adult rats.

Studies of the molecular mechanisms underlying GM₁ capability to limit excitotoxicity have clearly demonstrated that the GM₁ effect occur without affecting the functional properties of EAA receptor-gated cationic channels (10). Rather, the GM₁ effect resides in antagonism solely of intracellular toxic-related events (sustained, elevated protein kinase C translocation and protracted increases in intracellular calcium content) resulting from persistent overstimulation of EAA receptors (20, see also Manev et al., this volume). This and other evidence (10) suggest that the ganglioside limits the neurotoxic but not the physiological EAA-mediated processes, thereby clearly differentiating GM₁ from competitive and non-competitive EAA antagonists. This is of therapeutic importance as the latter compounds, although neuroprotective, elicit an indiscriminate blockade of EAA-mediated neurotransmission throughout the CNS and dampen neuroplastic responses necessary for brain repair (21).

Another, not mutually exclusive possibility, concerns the relationship between GM₁ and neuronotrophic factors. Much evidence is available suggesting that neuronotrophic factors in brain play an important role in maintenance of neuronal function and in regulation of neuronal repair. GM₁ is known to potentiate the action of neuronotrophic factors both in vitro and in vivo (4, 6, 31; for a recent review see Skaper et al. 27). This effect may contribute, in concert with its anti-neuronotoxic effects, to its neuroprotective action in the acute phase following CNS
damage. Furthermore the GM₁ pro-neuronotrophic action most likely underlies its capability to facilitate long-term functional recovery following brain injury.

THERAPEUTIC PERSPECTIVES

Neurological outcome following acute CNS damage, including cerebral ischemia, requires, at least in part, interventions that are directed towards reduction of secondary brain damage in the acute phase and manipulation of neuroplastic reparative processes at later times. Furthermore, knowledge of the underlying processes have led to the identification of gangliosides, in particular GM₁, as pharmacological agents capable of improving nerve cell dysfunction of impairment following CNS injury. In this context, information is today available indicating that systemically administered GM₁ can potentially exert dual effects in a variety of experimental models of acute CNS injury: reduction of secondary brain damage due, at least in part, to antagonism of EAA-related toxicity in the acute phase; facilitation at later times of recovery processes presumably via potentiation of endogenously-occurring neuronotrophic factors. This evidence has, in turn, led to studies on the potential use of GM₁ in the pharmacotherapy of acute CNS injury, especially stroke, in humans. The results today available have shown that GM₁ treatment ameliorates neurological outcome in patients afflicted by acute cerebrovascular insufficiency (2). Together these results support the continuation of both experimental and clinical studies aiming to better define its therapeutic utility in human neuropathological conditions resulting from hypoxia-ischemic as well as traumatic CNS injury.

REFERENCES


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