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CGS 19755 (Selfotel): A Novel Neuroprotective Agent Against CNS Injury

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Abstract

The hypothesis that excitotoxicity is a mechanism of damage following different types of cerebral injury including global and focal ischemia (34), and head and spinal cord trauma (6,7,9,25) has been supported by numerous findings. During ischemia for example, glutamate neurotoxicity is mediated in part through N-methyl-D-aspartate (NMDA) receptors, since selective antagonists to this receptor protect against hypoxic-ischemic injury (10,35,41). In the last few years, different NMDA antagonists have been developed and tested; they can be divided into competitive and noncompetitive antagonists. Noncompetitive NMDA antagonists are extremely lipophilic and reach high levels in the brain after systemic administration. Various studies have demonstrated that these agents provide neuroprotection against hypoxic-ischemic injury (for review see ref. 29).

Many competitive NMDA antagonists are hydrophilic and require direct cerebral administration to obtain high brain levels. Newer competitive NMDA blockers, such as cis-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755, selfotel), provide neuroprotection against global ischemia, focal ischemia, and trauma when given systemically (2,3,32,33). Selfotel is currently being studied in multicenter safety and efficacy trials for stroke (17) and head trauma (6).

Keywords

Cerebral ischemia; Excitotoxicity; Glutamate; NMDA; Trauma; Anoxia; Neurotoxicity; Neuroprotection; CGS 19755; Selfotel

CHEMISTRY

Selfotel is a racemic mixture with the chemical name (+/-)-cis-4-(phosphonomethyl)2-piperidine carboxylic acid; it is a rigid analog of 2-amino-5-phosphonopentanoic acid (AP5). Physical and chemical properties include its relatively stable solubility under normal (ambient) conditions, but the compound should be protected from excessive heat, light, and moisture. The chemical structure is depicted in Fig. 1.

ANTAGONIST ACTIVITY ON NMDA RECEPTORS

Selfotel is similar to AP5, 2-amino-7-phosphonoheptanoic acid (AP5), 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), and D-(E)-4-(3-phosphonoprop-2-enyl)-piperazine-2-carboxylic acid (D-CPPene) in that it binds competitively and directly to the

postsynaptic NMDA glutamate receptor. In contrast, noncompetitive NMDA antagonists, such as ketamine, dizolpine (MK-801), dextrophan, dextromethorphan, and phencyclidine (PCP) bind to the NMDA receptor-linked channel. Unlike PCP and MK-801, selfotel does not affect dopamine metabolism in the brain and thus lacks the side effects associated with dopaminergic transmission; that properly may offer some advantages for clinical use.

BRAIN UPTAKE

Preclinical pharmacology has shown that the neuroprotective dose of selfotel in animal models ranges from 10–40 mg/kg for stroke and from 3–30 mg/kg for traumatic brain injury. These dose ranges are generally higher than doses used in clinical trials.

Until recently, however, the extent to which selfotel crosses the blood brain barrier (BBB) was unclear. In a recent study in rabbits, Pérez-Pinzón et al. (33) demonstrated that selfotel readily crosses the BBB, achieving neuroprotective levels in the cerebrospinal fluid (CSF) and brain. For example, CSF and brain levels reached 12 and 5 μM at 1 h, 6 and 5 μM at 2 h, and 13 and 7 μM at 4 h after drug administration, respectively (Fig. 2). These levels were achieved after a single dose of selfotel (40 mg/kg) was administered 10 min following occlusion of the left internal, anterior cerebral, and middle cerebral arteries in rabbits.

The same study in rabbits showed that plasma levels rose quickly, and also decreased rapidly. Contrary to this rapid clearance of selfotel in plasma, levels in CSF and brain remained high for at least several hours, which suggests that continued maintenance dosing of selfotel is not required to sustain high brain levels for up to 4 h (33).

In contrast, other studies have shown very slow uptake of selfotel in the rat brain (21). In a kinetic study the average selfotel brain uptake in regions supplied by the middle cerebral artery was 0.15% (index of selfotel relative to iodoantipyrine) (21). The regional plasma clearance across the BBB during normoxia averaged only 0.015/100 g/min; during ischemia this value was 0.019 in the ischemic hemisphere and 0.009 in the non-ischemic hemisphere. Despite this slow uptake, Daniell (8) showed that selfotel provoked a rapid anesthetic effect in mice. This indicates that selfotel brain uptake is species dependent: it is slow in rats but relatively fast in mice and rabbits (8,21,33).

NEUROPROTECTIVE PROPERTIES DURING CNS METABOLIC STRESS

In Vitro Studies

A number of studies have demonstrated neuroprotection by NMDA antagonists against NMDA excitotoxicity, hypoxia (12,13), glucose deprivation (30), and oxygen glucose deprivation (OGD) (14). Many of these studies have used noncompetitive NMDA antagonists (11,14,20), and fewer studies have examined protection against excitotoxicity using competitive NMDA antagonists. The competitive effectiveness of NMDA blockers depends on the level of glutamate release: the greater the concentration of excitatory amino acids released, the greater the concentration of competitive antagonist that may be required as seen in studies with D-APV (13,14). Selfotel was previously shown to be neuroprotective against OGD at 100 μM (14), but a dose response curve was not determined. We have recently found that selfotel has an ED_{50} of 25.4 μM against NMDA excitotoxicity and 15.9 μM against 45 min of OGD (33) in dissociated mixed neocortical cultures prepared from fetal Swiss Webster mice at 14–16 days of gestation. These values were in the same range for in vivo neuroprotection (see. later), although variability between different models is expected.

In vitro data suggest, therefore, that selfotel concentration should be in the range of 16–25 μM to achieve protection against excitotoxicity or OGD.

In Vivo Studies

Global Cerebral Ischemia—Selfotel has been shown to be neuroprotective in different animal models of ischemia (Table 1). In a global cerebral ischemia model in gerbils, Boast et al (4) found that repeated doses of selfotel reduced ischemia-induced hippocampal brain damage. In this study, selfotel was injected 4 times at 2 h intervals, beginning 15 min before bilateral common carotid artery occlusion for 20 min. A dose response curve was obtained using selfotel doses of 1, 3, 10, and 30 mg/kg administered intraperitoneally (i.p.). Significant protection by selfotel was afforded only at the two highest doses (10 and 30 mg/kg). This study also determined the time course effect of selfotel. Selfotel was neuroprotective when gerbils were injected 4 times at 2 h intervals (30 mg/kg i.p.) beginning at 1, 2, or 4 h after the onset of occlusion. No neuroprotection was observed when selfotel (100 mg/kg i.p.) was administered at 24 h after occlusion. Thus, this study indicates that selfotel has a maximum therapeutic window of 4 h after onset of occlusion in global ischemia models.

Studies in rat models of global ischemia have also demonstrated the efficacy of selfotel as a neuroprotective agent. Grotta et al. (19), using a model of global ischemia in Wistar rats, studied the neuroprotective properties of selfotel on mortality, histopathology, memory deficits, and calcium accumulation. Administration of selfotel (30 mg/kg i.p.) starting immediately after ischemia, followed by three additional doses separated by 2 h, reduced histological damage after 3 d of reperfusion, but also increased mortality due to respiratory depression. A lower dose of selfotel (10 mg/kg i.p.) administered in the same fashion prior to ischemia followed by four additional doses separated by 2 h significantly reduced calcium influx as measured by calcium/calmodulin binding.

Further information about the temporal therapeutic window for selfotel efficacy against global ischemia came from a study by Swan and Meldrum (48). They showed protection against hippocampal CA1 cell loss when 3.3 or 10 mg/kg of selfotel was injected i.p. 15 min and 5 h after a 10 min incomplete ischemia period followed by 7 d of reperfusion in Wistar rats. Selfotel (10 or 30 mg/kg i.p.) did not provide any protection against pyramidal cell loss when administered 5 and 10 h post-ischemia.

In contrast to these studies, Warner et al. (51) showed that selfotel was unable to protect hippocampus and cortex against 5 min of bilateral carotid occlusion in gerbils. Administration of selfotel (30 mg/kg i.p.) either before or 5 min after occlusion, followed by four additional doses of 25 mg/kg (i.p.) administered between 0.5 and 6.5 h post-ischemia, protected the striatum, but not the hippocampal CA1 area or layer 3 of the neocortex, against ischemic damage.

These studies clearly indicate that there is a narrow dose threshold and temporal therapeutic window for selfotel to be neuroprotective. In addition, high concentrations of selfotel may be very harmful and even cause mortality.

Focal Cerebral Ischemia—The neuroprotective efficacy of selfotel has also been demonstrated in focal ischemia models. In models of permanent middle cerebral artery occlusion, selfotel administered intravenously (i.v.) at 40 mg/kg immediately after occlusion reduced cortical edema by 23% in Fisher rats (37). Infusion of selfotel (10 mg/kg bolus i.v., followed by an infusion of 5 mg/kg/h i.v. for 4 h) significantly reduced the volume of cortical infarct but not basal ganglia infarct in Sprague Dawley rats (49). Interestingly, the same study showed that selfotel at this dosage increased blood flow and corrected pH in the ischemic and non-ischemic brain areas.

Selfotel administered at 10 mg/kg i.p. 5 min, 6 h, and 18 h after 96 h of permanent unilateral coagulation of the middle cerebral artery in mice prevented by 50% the increase in ω_3 sites (peripheral-type benzodiazepine binding, which is an accurate index for the detection of ischemic brain lesions) (15).

A correlation between neuroprotection afforded by selfotel and its ability to diminish glucose hypermetabolism during focal ischemia was established by Simon and Shiraishi (40). Selfotel (10 mg/kg i.v.) administered 5 min prior to or 5 min after permanent middle cerebral artery occlusion reduced the infarct size and the post-ischemic glucose hypermetabolism.

Delayed therapy with selfotel was evaluated in a reversible spinal cord ischemia model in rabbits: selfotel (30 mg/kg i.v.) showed significant efficacy if given at 5 min, but not 30 min after the ischemic episode (27).

In a recent study we also showed excellent neuroprotection by selfotel against cortical ischemic neuronal damage (76% decrease) and ischemic edema (48% decrease in cortical edema, 54% decrease in hemispheric edema) using a rabbit model of focal ischemia (33) (Fig. 3). While this was not a dose-response study, the robust neuroprotective effect compared with other neuroprotective agents we have previously examined (CGP 40 1 16, dextrorphan, dextromethorphan, MK-80 1, dexmedetomidine) (28,43,44,46,47) suggests that at 40 mg/kg selfotel may provide maximal protection. It is likely that lower doses of selfotel (achieving lower brain and CSF levels) would also provide some neuroprotection.

Selfotel failed to attenuate significantly ischemic neuronal damage in the striatum. This finding is consistent with our previous work using this model of focal ischemia showing no benefit in this region with other neuroprotective drugs (CGP 401 16, dextrorphan, dextromethorphan, MK-80 1, dexmedetomidine) (28,44,46,47) and may relate to a lack of collateral blood supply or to a less important role of NMDA excitotoxic injury in the striatum.

The good correlation between *in vitro* and *in vivo* neuroprotective levels found by Pérez-Pinzón et al. (33) supports the contention that experiments in cell culture may aid in determining an approximate concentration for neuroprotection *in vivo*. In the cell culture injury paradigm of that study, selfotel was administered at the onset of either NMDA toxicity or oxygen-glucose deprivation and reached the cells immediately. As observed by Goldberg and Choi (14), the glutamate concentration required to kill energy-depleted neurons may be lower than that required to kill neurons in normal mixed cultures; this may have relevance to the ischemic areas used in that study. When working with cell cultures, cells are isolated from important systemic components, such as the circulatory system, which may influence the extent of neuronal damage (e.g., hyperemia or hypoperfusion during the reperfusion phase). Despite these considerations, the *in vitro* results (an ED₅₀ of 25.4 μ M against NMDA excitotoxicity and 15.9 μ M against 45 min of OGD) correlated well with the *in vivo* findings (brain levels ranged from 5–7 μ M at 1–4 h post dose) in that study (33).

These studies indicate that selfotel protects against permanent and transient focal cerebral ischemia. This protection appears to be mediated by improvements in cerebral metabolism (i.e., reducing glucose hypermetabolism, increasing cerebral blood flow, and correcting tissue pH) and by direct blockade of NMDA receptors.

Head and Spinal Trauma—Selfotel has been tested in models of mild to moderate fluid percussion injury (32,36) and acute subdural hematoma (24). Post-traumatic increases in

glutamate were attenuated by selfotel (3–30 mg/kg i.v. or i.p.) administered 15 min before moderately severe fluid percussion brain injury in rats (32). Heat shock protein expression was decreased by selfotel (10 mg/kg), when given at 10 min (i.v.) and 12 and 24 h (i.p.) after impact in combination with a free radical scavenger (36).

Intravenous selfotel (10 mg/kg) administered 25 min after the induction of acute subdural hematoma significantly reduced brain damage and lowered intracranial pressure (ICP) by 29% compared with controls (24).

These studies indicate that selfotel protects against head trauma models by attenuating post-traumatic increases in glutamate concentration and decreasing intracranial pressure.

PUTATIVE MECHANISMS FOR NEUROPROTECTION

Selfotel may protect against ischemic cerebral injury by blocking excitotoxicity, thus preventing a subsequent cascade of detrimental events (39). Among the effects of selfotel in the CNS are: inhibition of spreading depression (31), accompanied by decreases in mRNA for nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (28); inhibition of NMDA-induced convulsions (2,3); and inhibition of NMDA-evoked depolarizations in cortical slices (38). Several possible mechanisms may underlie these effects: a) selfotel competitively displaces glutamate from NMDA receptors in the rat brain (16); b) it partially inhibits glycine binding to the NMDA receptor (16); and c) selfotel attenuates extracellular glutamate release post-traumatically (32). These mechanisms may also explain the depression of somatosensory evoked potentials in brains treated with selfotel (33).

Other possible mechanisms of selfotel neuroprotection may relate to intracellular Ca^{2+} levels or effects on brain metabolism. Selfotel (10 mg/kg i.p.) can reduce Ca^{2+} influx for up to 24 h of reperfusion after global ischemia, preventing Ca^{2+} entry into neurons (18). This decrease in Ca^{2+} entry may reflect decreased synaptic activity and, therefore, depression of electrical activity. Selfotel also attenuated post-ischemic cerebral glucose hypermetabolism in rats with middle cerebral artery occlusion and markedly reduced infarct size (40). This decrease in glucose hypermetabolism could explain the improvement in cerebral pH during focal ischemia in rats when selfotel was administered (49). Alternatively, Takizawa et al. (49) suggested that the benefit in maintaining normal cerebral pH during ischemia may also be due to increased perfusion induced by selfotel. In fact, other studies have suggested that improved collateral perfusion during ischemia and post-ischemia with NMDA antagonist treatment may be an important protective mechanism (5,26,44,50). Selfotel increased collateral blood flow in permanent ligation of the middle cerebral artery in rats (49) but not during reperfusion after temporary MCA occlusion in rabbits (33).

CLINICAL SAFETY TRIALS

In a multicenter, ascending dose Phase IIa clinical trial, Grotta et al. (17) evaluated the safety and tolerability of selfotel in patients treated 12 h after hemispheric ischemic stroke. This study demonstrated that selfotel caused CNS adverse experiences in a dose-dependent fashion. The adverse experiences with selfotel administration included agitation, hallucinations, confusion, paranoia, and delirium. At a dose of 1.5 mg/kg or less, these adverse effects were milder and were controlled with sedation and low doses of lorazepam or haloperidol. Doses of selfotel above 1.5 mg/kg produced more severe side effects and required more intense management. These adverse experiences were more pronounced in stroke patients than in normal volunteers, possibly because of increased tissue bioavailability of drug due to BBB disruption or because of tissue sensitivity due to altered NMDA receptor activity and kinetics in stroke patients.

In a study of neurosurgical patients undergoing craniotomy for vascular malformation resection, aneurysm clipping, and tumor resection, selfotel was found to be well tolerated without prohibitive adverse effects (45). At the 1–2 mg/kg doses tested, the majority of patients exhibited NMDA antagonist symptoms that paralleled the long duration that selfotel remained in the CSF. The temporary side effects observed in patients receiving selfotel were similar to those reported by Grotta et al. (17). Our preliminary results indicated that CSF drug concentrations detected in neurosurgical patients ranged from 0.2–4.76 μM at 1.5–6 h after administration. These values were lower than CSF levels required for neuroprotection in our rabbit ischemia model, which ranged from 12–6 μM at 1–4 h after administration. A multicenter Phase III clinical efficacy studies using selfotel is currently underway.

Other NMDA antagonists used in clinical trials have exhibited side effects similar to those found with selfotel. For example, the commonly used cough suppressant, dextromethorphan, has been used in clinical trials for patients with stroke, amyotrophic lateral sclerosis and Huntington's disease (1,22,42). These studies found tolerable side effects, such as dizziness, dysarthria and ataxia at lower doses, and hallucinations and fatigue at higher doses. Recently, a safety and tolerability clinical trial was carried out in neurosurgical patients undergoing intracranial surgery and endovascular procedures (42). Side effects occurred at neuroprotective levels, including nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. All symptoms were reversible and no patient suffered adverse reactions. Unlike dextromethorphan, however, selfotel could be given at an individual dose, which did not increase symptom severity over time.

CONCLUSIONS

In summary, selfotel has been found to be neuroprotective in different models of CNS injury. CSF levels indicate that selfotel readily crosses the BBB in humans, however, values are lower than those required for neuroprotection in most preclinical animal models of CNS injury. These low values produce adverse side effects in humans, but can be controlled with sedation and low doses of lorazepam or haloperidol. The multicenter Phase III clinical efficacy trial that is currently underway will determine if these doses are sufficient to protect against strokes in humans.

Among the issues that need clarification and that can be tested in experimental animal models of CNS injury are: a) the therapeutic window at lower doses; b) the behavioral effects of selfotel during chronic infusion; c) the interaction of selfotel with other neurotransmitter systems; and d) selfotel putative synergistic interaction with other neuroprotective therapies (e.g. hypothermia)

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FIG. 1.
Chemical structure of CGS 19755 or selfotel.

FIG. 2. Selfotel levels found in blood, brain and cerebrospinal fluid at 1, 2, and 4 h after a single dose of 40 mg/kg i.v. was given 10 min following three-vessel arterial occlusion (with permission, from ref. 33).

FIG. 3.

Percentage area of ischemic neuronal damage and edema (measured by MRI) in the left cerebral hemisphere in rabbits following temporary focal cerebral ischemia. Selfotel (40 mg/kg) or saline was administered 10 min after onset of ischemia as a single bolus (based on data presented in ref. 33).

TABLE 1

Studies with selfotel in different animal models of traumatic brain injury

Model	Endpoint	Dose (mg/kg)	Protection	Reference
Global ischemia in gerbils	CA1 cell damage	10	Histologic score 1	3
Global ischemia in rats	CA1 cell damage	30	Histologic score 1	18
	Calcium influx	10	Reduced	
Global ischemia in rats	CA1 cell damage	10	61%	45
Global ischemia in gerbils	CA1 cell damage	30	–	48
	Striatum cell damage		76%	
Permanent MCAO rats	Infarct volume MRI	40/5 min post	37%	35
Permanent MCA and bilateral CCA occlusion in rats	Infarct volume	10/immediate post	+	46
	Brain pH			
	LCBF			
Permanent MCAO mouse	Cortical ω_3 density site	1	–	14
		3	31%	
		10	46%	
Permanent MCAO rats	Infarct size and cerebral metabolism	10/5 min pre	64%	38
		10/5 min post	50%	
		10/1 hr post	–	
Temporary MCAO rabbits	Cerebral edema (MRI)	40 mg/kg i.v.	76%	31
		bolus immediate post	54%	
	Infarct volume			
Transient (1 h)	paraplegia	10/5 min post	–	25
	spinal cord	30/5 min post	+	
	ischemia rabbits	30/30 min post	–	
		30/60 min post	–	
Severe lateral fluid percussion in rats	Microdialysis levels of glutamate	30/15min pre	42%	30
			inhibition of presynaptic release	
Lateral fluid percussion in rats	Heat shock protein expression	10/10 min post	Reduced	34
		10/12 h post		
		10/24 h post		
Subdural hematoma in rats	Intracranial pressure	10/25 min post	29%	22