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Effect of novel AMPA antagonist, NS1209, on status epilepticus An experimental study in rat

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Summary The current first line treatment of status epilepticus (SE) is based on the use of compounds that enhance GABAergic transmission or block sodium channels. These treatments discontinue SE in only two-thirds of patients, and therefore new therapeutic approaches are needed. We investigated whether a novel water-soluble AMPA antagonist, NS1209, discontinues SE in adult rats. SE was induced by electrical stimulation of the amygdala or subcutaneous administration of kainic acid. Animals were monitored continuously with video-electroencephalography during SE and drug treatment. We found that NS1209 could be safely administered to rats undergoing electrically induced SE at doses up to 50 mg/kg followed by intravenous infusion of 5 mg/kg for up to 24 h. NS1209 administered as a bolus dose of 10—50 mg/kg (i.p. or i.v.) followed by infusion of 4 or 5 mg/kg h (i.v.) for 2—24 h effectively discontinued electrically induced SE in all animals within 30—60 min, and there was no recurrence of SE after a 24-h infusion. Kainate-induced SE was similarly blocked by 10 or 30 mg/kg NS1209 (i.v.). To compare the efficacy and neuroprotective effects of NS1209 with those of diazepam (DZP), one group of rats received DZP (20 mg/kg, i.p. and another dose of 10 mg/kg 6 h later). By using the administration protocols described, the anticonvulsant effect of NS1209 was faster and more complete than that of DZP. NS1209 treatment (20 mg/kg bolus followed by 5 mg/kg h infusion for 24 h) was neuroprotective against SE-induced hippocampal neurodegeneration, but to a lesser extent than DZP. These findings suggest that AMPA receptor

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blockade by NS1209 provides a novel and mechanistically complimentary addition to the armamentarium of drugs used to treat SE in humans.
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Introduction

Status epilepticus (SE) is a major neurologic emergency that occurs in approximately 0.05—0.1% of the population (Shorvon, 1994; DeLorenzo et al., 1996). An estimated 152,000 cases occur per year in the United States, resulting in 42,000 deaths and an inpatient cost of $3.8—7 billion per year (Sirven and Waterhouse, 2003). The current first line treatment of SE is based on the administration of compounds that decrease perisomatic excitation by binding to the gamma-amino butyric acid A ($GABA_A$) receptor complex (e.g., diazepam, lorazepam, phenobarbital) or by blocking Na^+-channels (e.g., phenytoin, fos-phenytoin) (Sirven and Waterhouse, 2003; Walker, 2003). SE is discontinued in only up to 65% of patients, however, after administration of the first treatment (Treiman et al., 1998), which leads to a testable hypothesis of whether compounds with different mechanisms of action would be more efficacious.

Competitive and noncompetitive alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonists are broad-spectrum anticonvulsants in animal seizure models (Rogawski and Donevan, 1999). Subcellular analysis of AMPA receptor distribution indicates that they are located in the dendrites (Loup et al., 1998). Thus, AMPA antagonists represent a group of compounds with different mechanisms and sites of action than currently used SE treatments. Currently, studies of the efficacy of AMPA antagonists for suppressing SE activity are limited by their poor water solubility and blood—brain-barrier permeability.

NS1209 [8-methyl-5-(4-(*N*,*N*-dimethylsulfamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2-*h*]-iso-quinoline2,3-dione-3-*O*-(4-hydroxybutyric acid-2-yl)oxime] is a novel AMPA receptor-selective antagonist (Nielsen et al., 1999). One of the major advantages of NS1209 compared to other AMPA antagonists like NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline) is its higher aqueous solubility, which makes is suitable for intravenous administration (Nielsen et al., 1999). Furthermore, systemic administration of NS1209 suppresses excitability both *in vitro* and *in vivo* (Nielsen et al., 1999). Electroshock-induced seizures are suppressed at doses of NS1209 at which there are no adverse effects (Nielsen et al., 1999). Finally, post-treatment with NS1209 in the same dose range protects CA1 pyramidal cells from ischemia-induced degeneration in gerbils (Nielsen et al., 1999). Thus, we examined whether systemic administration of NS1209 suppresses and/or discontinues SE activity.

The present study was designed to provide proof-of-principle evidence that a systemically administered AMPA-antagonist, NS1209, suppresses SE activity *in vivo*. Second, we investigated the dose range of NS1209 that discontinues SE. Third, we determined how long the NS1209 has to be administered to obtain burst suppression without SE recurrence. Fourth, we examined whether the effect occurs in different animal models of SE. Finally, we compared the anticonvulsant and neuroprotective effects of NS1209 with those of diazepam (DZP).

Methods

The study design is summarized in Fig. 1A (amygdaloid stimulation model) and B (kainate model). The number of rats used in the different experimental groups is shown in Table 1.

Animals

Adult male Harlan Sprague—Dawley ($n = 40$; 280—384 g; amygdala stimulation model) or Wistar rats (Taconic, Denmark $n = 22$;

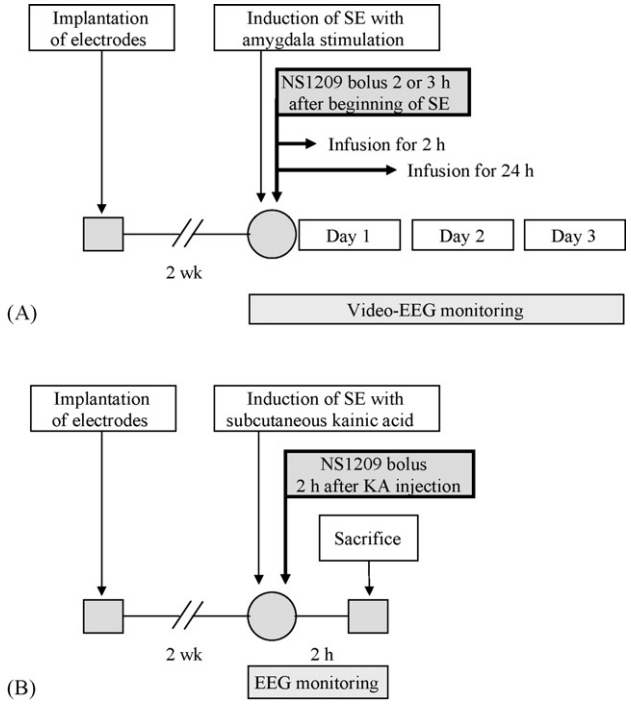

Figure 1 Study protocol to investigate the effects of NS1209 in two rat models of status epilepticus (SE). (A) Electrical amygdala stimulation model. The amygdala was stimulated 2 weeks after electrode implantation. Treatment with NS1209 (10—100 mg/kg) was started either 2 or 3 h after the beginning of self-sustaining SE (*i.e.*, end of amygdala stimulation). Bolus injection was followed by intravenous infusion of NS1209 for 2 or 24 h. Behavioral and electrographic seizure activity of the rats were continuously monitored with video-EEG for up to 3 days after SE. One group of animals was allowed to survive for 16 weeks, after which the animals were perfused for histology to assess the neuroprotective effects of NS1209 treatment. For administration of DZP, see section ''Methods''. (B) Kainic acid model. SE was induced with subcutaneous injection of kainic acid. NS1209 bolus was administered 2 h after kainate injection. EEG activity was recorded starting 15 min before kainate injection, and for 235 min thereafter.

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