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Comparison of the Effects of Pretreatment With Competitive or Noncompetitive NMDA Antagonists on Vestibular Compensation

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SANSOM, A. J., DARLINGTON, C. L. AND SMITH, P. F. *Comparison of the effects of pretreatment with competitive or noncompetitive NMDA antagonists on vestibular compensation.* PHARMACOL BIOCHEM BEHAV **46**(4) 807–811, 1993.—Unilateral labyrinthectomy (UL) results in a syndrome of ocular motor and postural disorders which abates over time in a process of behavioural recovery known as *vestibular compensation*. We have previously reported that a single systemic pre-UL injection of the organic Ca^{2+} channel antagonist verapamil or the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 reduces the behavioural effects of UL in guinea pigs. The present study was conducted to determine if similar effects would be obtained with single injections of the competitive NMDA receptor antagonists 3-[(±)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid (CPP) or *cis*-4-(phosphonomethyl)-piperidine-2-carboxylic acid (CGS 19755). Guinea pigs received an IP injection of 5 mg/kg CPP 2.5 h pre-UL, 5 or 10 mg/kg CPP 1 h pre-UL, 10 or 20 mg/kg CGS 19755 1 h pre-UL, or 1 ml/kg vehicle (saline) 1 h pre-UL, and the effects on the compensation of spontaneous nystagmus were measured over the following 52 h post-UL. Pretreatment with CPP had no significant effect on spontaneous nystagmus frequency or its compensation over 52 h post-UL. However, pretreatment with CGS 19755 resulted in a significant decrease in spontaneous nystagmus frequency without any acceleration of the rate of compensation.

CPP CGS 19755 Vestibular compensation NMDA receptor

IN humans and other animals, surgical removal of the vestibular receptor cells in one labyrinth (unilateral labyrinthectomy, UL) results in a syndrome of ocular motor and postural disorders which disappears over time in a process of behavioural recovery known as *vestibular compensation* (see 18,21 for reviews). Although vestibular compensation is correlated with a partial recovery of resting activity in vestibular nucleus (VN) neurons ipsilateral to the UL, the neurochemical mechanisms responsible for the behavioral recovery are unknown (18, 21,23).

We have suggested that ipsilateral VN neuron resting activity may decrease immediately following UL partly due to an increase in intracellular Ca^{2+} in VN neurons, caused by high frequency injury discharges in the vestibular nerve during its deafferentation and an increased release of excitatory amino acid(s) into the VN (6,7,19). The recovery of resting activity in the ipsilateral VN which occurs during vestibular compensation may depend partially on overcoming this Ca^{2+} overload (6,7,19). At present, the evidence relating Ca^{2+} influx in ipsilateral VN neurons to vestibular nerve activity is limited (7). Recent in vitro studies in rats suggest that tetanic stimulation of the vestibular nerve can cause a potentiation or a depression of field potentials recorded in different areas of the ipsilateral VN and that these effects can be blocked by the *N*-methyl-D-aspartate (NMDA) receptor antagonist D,L-2-amino-5-phosphovalerate (DL-AP5), which reduces Ca^{2+} influx via NMDA receptor channels (2). Using fluorometry, tetanic stimulation of the vestibular nerve has been shown to cause an increase in Ca^{2+} influx in ipsilateral VN neurons, which can also be blocked by the NMDA antagonists 2-amino-5-phosphonovalerate (APV) and [(+)-5-methyl-10, 11-dihydro-5H-dibenzo [a,d] cyclo-hepten-5,10-imine hydrogen maleate] (MK-801) (27). Induction of the immediate early gene *c fos*, which is associated with Ca^{2+} influx via NMDA receptor channels during long term potentiation (13), is also increased in the ipsilateral VN following UL (14). These latter results are consistent with the suggestion that intracellular Ca^{2+} plays a pivotal role in vestibular compensation (6). However, it is not clear from the available studies whether increased or reduced Ca^{2+} influx occurs in ipsilateral VN neurons immediately after UL, since following the injury discharge the deafferented vestibular nerve becomes hypoactive and remains that way throughout compensation (see 18,21 for reviews).

We have sought to test the Ca^{2+} hypothesis of vestibular compensation by administering various Ca^{2+} channel antagonists before the UL and determining the effects on the vestibu-

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lar compensation process (6,7,11,19,20). Systemic administration has been used in most of these studies because this route of administration is relevant to human clinical treatment. If the Ca^{2+} hypothesis is correct, then drugs which block Ca^{2+} influx or the effects of Ca^{2+} influx at the level of protein kinases (20) would be expected to reduce the UL symptoms and facilitate the vestibular compensation process when administered before or shortly after the UL. We have previously reported that a single 0.8 mg/kg IM injection of the L-type Ca^{2+} channel antagonist verapamil (10) 1 h before UL significantly reduced the frequency of spontaneous ocular nystagmus caused by the UL (6). By contrast, a single 10 mg/kg IP injection of the T-type Ca^{2+} channel antagonist flunarizine (26) before the UL had little effect on the UL symptoms (11); however, in other studies it has been reported that multiple injections of flunarizine following UL result in an acceleration of the compensation process (16,28). A series of three injections of the calcium-dependent enzyme inhibitor calmidazolium chloride (17) into the ipsilateral VN or IVth ventricle (0.5 mM, by cannula up to 4.5 h post-UL), significantly reduced spontaneous nystagmus frequency following UL (20). Furthermore, a single pre-UL 2.5 mg/kg IP injection of the noncompetitive NMDA receptor/channel antagonist MK-801, which blocks Ca^{2+} influx via NMDA receptor-mediated ion channels (3,30), was also found to reduce spontaneous nystagmus frequency following UL (19).

The relative efficacy of competitive and noncompetitive NMDA antagonists in protecting CNS neurons against ischemic or surgical damage has been a subject of debate (e.g., 1,4,12,29). Relatively few studies have examined competitive NMDA antagonists because of their limited ability to cross the blood-brain barrier (12,29); some authors contend that noncompetitive NMDA antagonists have greater efficacy in neuroprotection (e.g., 4), while others disagree (e.g., 1). The aim of the present study was to compare the effects of pre-UL injections of MK-801 from a previous study (19) and two competitive NMDA antagonists on the compensation of spontaneous nystagmus following UL in guinea pigs. We chose to use the highly potent and selective competitive NMDA receptor antagonists 3-[(±)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid (CPP; 3,8) and *cis*-4-(phosphonomethyl)-piperidine-2-carboxylic acid (CGS 19755; 3,9,15).

METHODS

Subjects

Data were obtained from a total of 30 adult albino and pigmented guinea pigs of both sexes (230–650 g) which were anesthetised with xylazine (12 mg/kg IM) and ketamine hydrochloride (100 mg/kg IM) (6,11,19,20,24); supplementary anesthetic injections were given to two animals in the saline control group to ensure adequate anesthesia during surgery.

Surgery

All animals were prepared for a right surgical UL as described in detail previously (6,11,19,20,24); briefly, wound margins and pressure points were infused with 2% procaine, heart rate was monitored using ECG electrodes inserted in the forelimb muscles, and the right temporal bone was exposed using blunt dissection. With the aid of an operating microscope and a dental drill with a fine burr, the bony labyrinth was exposed and the ampullae of the horizontal and anterior semicircular canals were opened and the contents aspirated; the utricle, saccule, and posterior canal ampulla were also probed and aspirated. Antibiotic cream (Furacin) was topically applied to the opened labyrinth to prevent infection. Following the completion of the UL, the temporal bone was sealed with dental cement, the wound sutured, and the animals allowed to recover in normal light.

Drug Injections

Animals were randomly assigned to one of six groups: 1) saline controls, (n = 5 animals), 1 ml/kg 0.9% saline 1 h pre-UL; 2) 5 mg/kg CPP (RBI, USA), 2.5 h pre-UL (n = 4); 3) 5 mg/kg CPP, 1 h pre-UL (n = 5); 4) 10 mg/kg CPP, 1 h pre-UL (n = 5); 5) 10 mg/kg CGS 19755 (RBI), 1 h pre-UL (n = 5); and 6) 20 mg/kg CGS 19755, 1 h pre-UL (n = 5). To investigate the behavioral effects of higher doses of CGS 19755 in guinea pigs, one additional labyrinthine-intact animal received 40 mg/kg IP CGS 19755 before the pre-UL anesthetic combination, followed by a sham operation. For all animals receiving a UL, single injections of the drug or saline were given IP before the UL. For the majority of animals, both CPP and CGS 19755 were dissolved in 1 ml/kg 0.9% saline; however, for the animal receiving 40 mg/kg CGS 19755 and one animal receiving 20 mg/kg CGS 19755, slightly larger vehicle volumes were used (3 ml/kg and 2 ml/kg, respectively), due to difficulty in dissolving the drug. The effects of CGS 19755 on the animal receiving 20 mg/kg in the larger vehicle volume were similar to those for the other three animals for whom data were collected; therefore, the data from the entire 20-mg/kg CGS 19755 group were pooled. The doses and injection times for CPP were based on our previous experiments in guinea pigs (5,22). The CGS 19755 doses and injection times were based on a previous study using gerbils in which doses from 10–30 mg/kg IP were found to be effective in reducing ischemic brain damage (1). Studies using rats suggest that the IP administration of 10–30 mg/kg CGS 19755 prior to the onset of ischemia results in a high mortality rate due to respiratory depression (60% and 70% of animals used in the 30- and 10-mg/kg IP conditions, respectively; 12). In the present study, the one animal which received a 40-mg/kg IP injection of CGS 19755 remained heavily sedated with shallow and irregular respiration for approximately 24 h and then died. One animal in the 20-mg/kg IP group showed similar abnormal respiration and generally poor health during postoperative recovery and consequently was overdosed at 25 h post-UL. Since the primary purpose of the present study was to compare, under identical conditions, the effects of pretreatment with CGS 19755 or CPP with those of MK-801 (19), and since guinea pigs are especially prone to respiratory depression during anesthesia (6,11,19,20,24), we decided not to use doses of CGS 19755 above 20 mg/kg IP before UL. Only single pre-UL injections of CPP or CGS 19755 were used so that the data were directly comparable to those obtained with MK-801 (19) and because many previous studies have shown that injections of NMDA antagonists following UL disrupt vestibular compensation (see 23 for a review).

Measurements

Measurements of spontaneous nystagmus frequency, one of the major static symptoms of UL (i.e., symptoms which persist in the absence of head movement; 21), were made in normal light at approximately 8, 10, 20, 25, 30, 35, 45, 50, and 52 h post-UL, following previous studies which have shown that measurements at these times provide an accurate characterization of the vestibular compensation process in guinea pigs (5,6,11,19,20,24). Spontaneous nystagmus fre-

quency was measured visually by counting the number of nystagmic quick phases (beats) occurring in a 15-s interval, as defined by an electronic audiotimer. This procedure was usually performed five times for each animal at each measurement time. The quick phase of spontaneous nystagmus is directed to the left side following a right labyrinthectomy (i.e., contralateral to the labyrinthectomy) and is usually a large amplitude, predominantly horizontal eye movement which is easy to detect in the left eye (5,6,11,19,20,24). Measurements were made only when the animal's head was stationary to avoid contamination of spontaneous nystagmus with vestibulo-ocular reflex nystagmus induced by head movement; the animal was not restrained, but the skin behind the left eye was gently retracted to observe the sclera more clearly. To confirm these measurements, spontaneous nystagmus was also videotaped at each measurement time, using a Panasonic NV-M7 video camera with a zoom lens; eye movements were then replayed using a Mitsubishi E7 Black Diamond video recorder and a Sony Trinitron colour monitor (6,11,19). By comparing measurements of different observers and video recordings of spontaneous nystagmus, we have estimated that the measurement error incurred in using this method of frequency analysis is of the order of 1 beat/15 s (6). Since we are interested in spontaneous nystagmus frequency differences larger than this measurement error, and the measurement error estimate applies equally to data obtained in the control and experimental groups, we regard this degree of error as tolerable. Furthermore, even though it relies on visual measurement of spontaneous nystagmus frequency, the video analysis technique has the advantage that the animals are measured noninvasively and therefore the data obtained are not influenced by stress or changes in head position induced by restraint (5,6,11,19,20,24).

Statistical Analysis

Mean spontaneous nystagmus frequency was calculated for each group at each measurement time. Separate comparisons of the three CPP groups and the two CGS 19755 groups against the saline controls were made using two 2-factor analyses of variance (ANOVA) with repeated measures ($\alpha = 0.05$) (25). Factor A represented the drug effect independently of time. Factor B, the repeated measure, represented time; since the severity of the UL symptoms changes over time as a result of compensation, Factor B was always significant and will not be discussed further. The interaction, AB, represented the drug effect over time and was used as an index of the drug effect on the rate of vestibular compensation (6,11,19,20).

RESULTS

The CPP groups did not show a significantly different spontaneous nystagmus frequency (factor A) or rate of compensation (AB) following UL, compared to the saline controls. Pretreatment with CGS 19755 resulted in a significant reduction in spontaneous nystagmus frequency ($p < 0.05$), probably due to the low average nystagmus frequencies in the 20-mg/kg group between 20 and 52 h post-UL (see Fig. 1). However, there was no change in the rate of compensation. It should be noted that the 20-mg/kg CGS 19755 data are based on four animals only, since one animal in this group died during postoperative recovery (see Methods).

CONCLUSION

The present data provide evidence that single pre-UL IP injections of even high doses of the competitive NMDA receptor antagonist CPP (e.g., 10 mg/kg) do not have a facilitative effect on spontaneous nystagmus compensation comparable to that obtained with the noncompetitive NMDA antagonist MK-801 (19). However, pretreatment with the competitive NMDA antagonist CGS 19755 does result in a significant reduction in spontaneous nystagmus frequency, although high doses are needed to achieve this (e.g., 20 mg/kg IP). These results compare with the large decrease in spontaneous nystagmus frequency obtained with a single pre-UL 2.5-mg/kg IP injection of MK-801 (19). Differences in experimental methodology cannot explain the difference in the results obtained with the different NMDA antagonists, since exactly the same

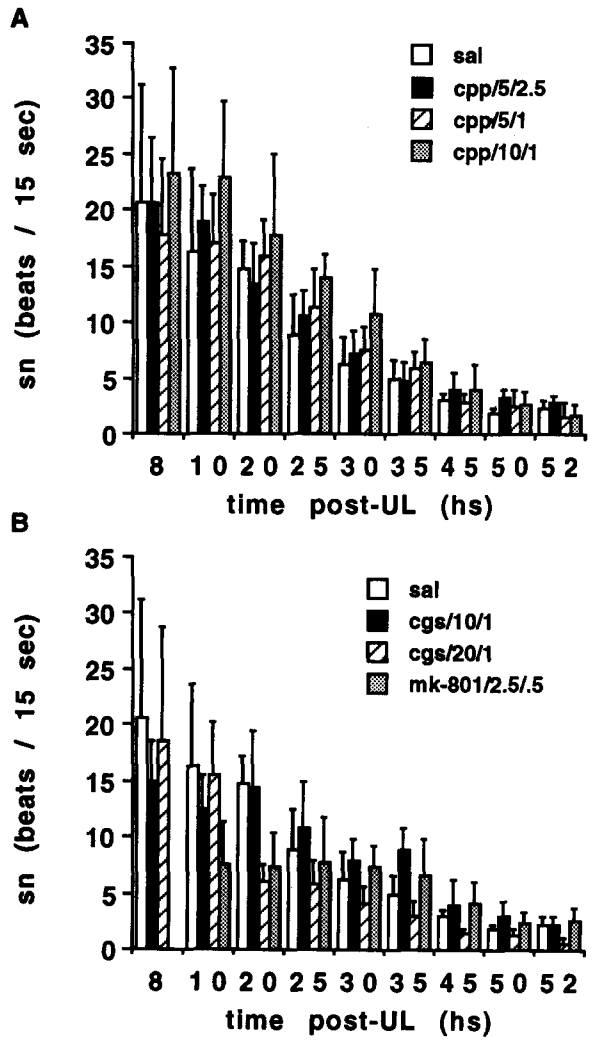

FIG. 1. Compensation of spontaneous nystagmus (sn, in beats/15 s) in guinea pigs receiving a single injection of saline, CPP, or CGS 19755 before unilateral labyrinthectomy (UL). (A) Sal = 1 ml/kg saline, 1 h pre-UL ($n = 5$); cpp/5/2.5 = 5 mg/kg CPP, 2.5 h pre-UL ($n = 4$); cpp/5/1 = 5 mg/kg CPP, 1 h pre-UL ($n = 5$); cpp/10/1 = 10 mg/kg CPP, 1 h pre-UL ($n = 5$). (B) Sal, same data as in A; cgs/10/1 = 10 mg/kg CGS 19755, 1 h pre-UL ($n = 5$); cgs/20/1 = 20 mg/kg CGS 19755, 1 h pre-UL ($n = 4$); mk-801/2.5/.5 = 2.5 mg/kg MK-801, 0.5 h pre-UL ($n = 6$, data from Sansom et al. [19]). Note that the MK-801 data begin at 10 h post-UL. All injections were given IP. Histograms show mean + 1 SD.

procedures were used in the two studies by the same investigators.

Although the effects on spontaneous nystagmus frequency of CGS 19755 were statistically significant, it should be noted that one animal in the 20-mg/kg group had to be overdosed due to abnormal respiration and general poor health. The one animal which received 40 mg/kg CGS 19755 also suffered from respiratory depression and subsequently died. These results are consistent with previous reports that, in the dose range (10–30 mg/kg IP) where CGS 19755 is effective in neuronal protection, some animals die due to respiratory depression (12).

Previously, we have reported that a single 0.8-mg/kg IM injection of the L-type Ca^{2+} channel antagonist verapamil (10) 1 h before UL significantly reduced spontaneous nystagmus frequency up to 30 h post-UL (6). Injection into the ipsilateral VN of the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride (R 24571) (17) from 0.5 to 4.5 h post-UL also reduced spontaneous nystagmus frequency and yaw head tilt up to 20 h post-UL (20). Consistent with these results, a single 2.5-mg/kg IP injection of MK-801 before UL was found to reduce spontaneous nystagmus frequency and the magnitude of yaw head tilt (19) (see Fig. 1B). However, results from the present experiment demonstrate that the competitive NMDA antagonists CPP and CGS 19755 are not as potent as MK-801 in reducing the behavioural effects of UL. Pretreatment with CPP had no significant effect on spontaneous nystagmus frequency or rate of compensation, and pretreatment with CGS 19755 reduced nystagmus frequency only at high doses (i.e., 20 mg/kg IP). At present, the explanation for the different effects of the competitive and noncompetitive NMDA antagonists is unclear. Since the competitive NMDA antagonists CPP and CGS 19755 must "compete" with endogenous NMDA agonists for the NMDA binding site, it is possible that higher and/or multiple doses of competitive NMDA antagonists must be used to obtain effects on vestibular compensation similar to those obtained with MK-801, which blocks the ion channel associated with the NMDA receptor and therefore does not compete with endogenous agonists (3). However, using higher doses of CPP or CGS 19755 would increase the adverse side effects on respiration and locomotion and therefore undermine their potential clinical benefit (9,12). In studies of ischemic brain damage it has also been reported that competitive antagonists such as CGS 19755 require higher doses [e.g., 10–30 mg/kg IP (1,12)] than MK-801 [e.g., 2 mg/kg IV (29), 3 mg/kg IP (4)] to achieve neuronal protection; even with high doses, the protection afforded by CGS 19755 is sometimes modest (12). It is therefore possible that noncompetitive NMDA antagonists such as MK-801 are more useful for neuronal protection following ischemia or surgical deafferentation than competitive NMDA antagonists because lower doses of noncompetitive antagonists are effective. This may be due either to their greater ability to penetrate the blood–brain barrier or to their different actions on CNS neurons (4,29).

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