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Effects of Flunarizine on Ocular Motor and Postural Compensation Following Peripheral Vestibular Deafferentation in the Guinea Pig

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GILCHRIST, D. P. D., C. L. DARLINGTON AND P. F. SMITH. *Effects of flunarizine on ocular motor and postural compensation following peripheral vestibular deafferentation in the guinea pig.* PHARMACOL BIOCHEM BEHAV 44(1) 99–105, 1993.—The aim of the present study was to determine if the calcium channel antagonist flunarizine would affect the time course of vestibular compensation for unilateral labyrinthectomy (UL) in guinea pigs. Animals received either a single IP injection of flunarizine 1 h pre-UL or a series of IP injections every 6 h for 24 h post-UL, starting at 6 h post-UL. Flunarizine was dissolved in 50–100% DMSO or suspended in 10% Tween-80 and administered at a dose of 10 mg/kg in the pre-UL condition and 10 or 20 mg/kg in the post-UL condition. All injections were 1 ml/kg in volume. Spontaneous nystagmus (SN), yaw head tilt (YHT), and roll head tilt (RHT) were measured using video analysis. When dissolved in DMSO and administered 1 h pre-UL, 10 mg/kg flunarizine had a small but significant effect on the rate of RHT compensation; otherwise, flunarizine had no significant effects on SN, YHT, or RHT when dissolved in DMSO. When suspended in Tween-80, 10 mg/kg flunarizine pre-UL resulted in a significant decrease in SN frequency and YHT relative to the control group, although the magnitude of the differences was small. When 20 mg/kg was given post-UL, both SN and YHT showed a small but significant change in the rate of compensation. No significant differences in RHT were observed. These results demonstrate that IP administration of flunarizine at a dose of 10–20 mg/kg IP has little effect on vestibular compensation compared to the effects obtained with low IM doses (0.8 mg/kg) of verapamil given 1 h pre-UL.

Vestibular compensation Flunarizine Unilateral labyrinthectomy Calcium channels

SURGICAL removal of the vestibular receptor cells in one labyrinth [unilateral labyrinthectomy (UL)] causes a syndrome of eye movement and postural disorders that diminishes over time in a process of behavioral recovery known as vestibular compensation [see (10,17,22,34) for reviews]. The various effects of UL have been classified into static and dynamic symptoms: Static symptoms persist in the absence of head movement and include spontaneous ocular nystagmus (SN), yaw head tilt (YHT), and roll head tilt (RHT) [see (6) for a review]; dynamic symptoms occur as a result of head movement and include abnormalities in the amplitude (gain) and timing (phase) of the vestibuloocular and vestibulospinal reflexes. While the static symptoms compensate almost completely within 2–3 days in most species [see (34) for a review], the dynamic symptoms compensate more slowly and incompletely, often persisting for years following UL (16). Electrophysiological studies have demonstrated that immediately following UL there is a large decrease in the resting activity of type I medial vestibular nucleus (MVN) neurons ipsilateral to the UL and that "static" compensation is associated with a partial return of resting activity to these neurons [see (34) for a review]. Because the vestibular receptors do not regenerate following UL (18), nor does the VIIIth nerve exhibit a significant functional recovery (31,33), vestibular compensation is attributed to CNS plasticity.

The mechanism by which resting activity recovers in type I MVN neurons is unknown. Second-order type I neurons in the MVN receive excitatory synaptic input from the ipsilateral vestibular nerve, but also from many other parts of the CNS [see (45) for a review]. While the removal of input from the ipsilateral vestibular nerve would be expected to produce a decrease in the resting activity of type I MVN neurons, it would not necessarily be expected to abolish the resting activity completely (23). As a virtual silencing of type I resting

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activity occurs on the ipsilateral side immediately following UL (20,30,33), other processes associated with UL may be partially responsible for the decrease in resting activity.

It has been hypothesised that deafferentation in the CNS may cause an excessive Ca^{2+} influx into deafferented neurons, resulting in a disruption of normal metabolic processes that, if prolonged, may lead to neuronal death (9,21,27,43). Recently, we suggested that an excessive Ca^{2+} influx into MVN neurons at the time of UL may result in a Ca^{2+} overload, which may contribute to the observed depression of type I resting activity, and that part of the compensation process may be associated with the recovery of MVN neurons from this Ca^{2+} overload (7,8,35). Consistent with this hypothesis are the observations that a single IM injection of the Ca^{2+} channel antagonist verapamil 1 h before UL (7) or intraventricular injections into the IVth ventricle of the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride between 0.5 and 5 h post-UL (25) significantly decrease some UL symptoms. Tolu et al. (40,41) reported that esophageal administration of the Ca^{2+} channel antagonist flunarizine up to 24 h following UL significantly facilitates vestibular compensation.

Flunarizine is an interesting Ca^{2+} antagonist to examine in the context of vestibular compensation because it is used clinically to reduce vertigo and dizziness, although its effectiveness remains questionable (13). Although flunarizine has been shown to act on low-threshold (T-type) Ca^{2+} channels (39), it has also been reported to act on high-threshold N-type Ca^{2+} channels (42). By comparison, verapamil has been reported to act on high-threshold (L-type) (12) and low-threshold (T-type) (3) Ca^{2+} channels and Na^{+} channels (1) and affect GABA and dopamine release under some circumstances (32).

The aim of the present study was to examine further the effects of pre- and post-UL treatment with flunarizine on vestibular compensation in the guinea pig and compare its effects with those of verapamil in previous studies (7).

METHOD

Subjects

Fifty-three guinea pigs (180–500 g) were used in this study. They were maintained in individual boxes and water was available ad lib. Five animals died during the labyrinthine surgery, apparently due to the combined cardiovascular effects of the general anesthetic and the flunarizine. One animal was excluded from the study due to ill health associated with the use of DMSO as a solvent for flunarizine (see below).

Surgery

Animals were anesthetized with xylazine (12 mg/kg, IM) and ketamine HCl (100 mg/kg, IM). Wound margins and pressure points were infused with 2% procaine and heart rate was monitored using electrocardiograph (ECG) electrodes inserted in the forelimb muscles. A right surgical labyrinthectomy (UL) was performed under aseptic conditions with the aid of an operating microscope. A portion of the right temporal bone was removed using a dental drill with a fine burr and the ampullae of the horizontal and anterior semicircular canals were opened and the contents aspirated; the utricle, saccule, and posterior canal ampulla were probed and aspirated (7,15,33,36). At the end of surgery, antibiotic cream (Furacin) was topically applied to the opened labyrinth to prevent infection and the temporal bone was sealed with dental cement. The wound was sutured and the animal allowed to recover in light.

Drug Administration

Initially, Flunarizine (Research Biochemicals, Inc., Natick, MA) was dissolved in 100% dimethylsulphoxide. However, repeated administration of 100% DMSO in the post-UL control condition (see post-UL1 below) was observed to have detrimental effects on animals' health; therefore, in the subsequent experimental condition (post-UL2) flunarizine was dissolved in 50% DMSO/50% saline. However, it became apparent that repeated administration of DMSO, even at this lower concentration, had adverse effects on animals' health; therefore, in the remaining conditions flunarizine was suspended in 10% Tween-80/90% distilled water, and an additional pre-UL experiment was conducted using Tween-80 (see pre-UL3 and pre-UL4 below). The volume for all injections was 1 ml/kg IP. Pre-UL injections were single injections given 1 h before UL and post-UL injections were given every 6 h for 24 h, starting at 6 h post-UL [the latter injection schedule was chosen following Tolu et al. (40,41)]. Each animal was randomly assigned to one of eight groups: (pre-UL1) 100% DMSO (n = 6 animals); (pre-UL2) flunarizine (10 mg/kg)/100% DMSO (n = 5); (pre-UL3) 10% Tween-80/90% distilled water (n = 6); (pre-UL4) flunarizine (10 mg/kg)/10% Tween-80/90% distilled water (n = 6); (post-UL1) 100% DMSO (n = 6); (post-UL2) flunarizine (10 mg/kg)/50% DMSO/50% saline (n = 5) or 100% DMSO (n = 1); (post-UL3) 10% Tween-80/90% distilled water (n = 6); (post-UL4) flunarizine (20 mg/kg)/10% Tween-80/90% distilled water (n = 6). Flunarizine suspended in 10% Tween-80 was used at a dose of 20 mg/kg in post-UL4 because only small differences were observed with 10 mg/kg in pre-UL 4; 20 mg/kg flunarizine was not used in the pre-UL condition because it was observed to produce a lethal cardiac depression when delivered before the general anesthetic.

Apparatus and Measurements

Three static symptoms of UL were quantified in this study: SN, YHT, and RHT. Measurements were made at 10, 25, 30, 45, and 50 h post-UL. These symptoms were videotaped at each measurement time using a videocamera (Panasonic NV-M7) with a zoom lens and a videorecorder (Mitsubishi E7 Black Diamond). SN frequency was initially measured by gently retracting the skin behind the animal's left eye to expose the sclera and counting the number of SN quick phases in a 15-s interval (beats/15 s), as defined by an electronic timer that emitted an audio signal at the end of the specified period. This procedure was performed five times at each measurement time and the means obtained. SN was then videotaped and the frequency verified retrospectively using the videorecorder and a color monitor (Sony Trinitron). The SN quick phase is easily seen as a rapid, large-amplitude, mainly horizontal eye movement, contralateral to the UL (6,7,15,19,36). Measurements were made only when the animal's head was stationary to avoid contamination of SN by vestibuloocular nystagmus induced by head movement. Animals were allowed to choose a natural posture and were not restrained in any way because stress induced by restraint has been observed to increase SN frequency (19,36). We estimate that the measurement error involved in using this method of SN frequency analysis is of the order of 1 beat/15 s (15). YHT was defined as the angle of deviation (in degrees) between a line through the midscapular point and sacrum and a line through the midscapular point

and the center of the animal's head in the horizontal plane; RHT was defined as the angle of deviation (in degrees) between gravitational vertical and the center of the animal's head in the vertical plane [see (6) for a review]. Postural symptoms were measured by first positioning the videocamera directly above the animal to videotape YHT and then directly in front of the animal to videotape RHT. The videotapes were replayed using the freeze-frame facility on the videorecorder and a protractor was fitted over the screen of the monitor to make measurements of YHT and RHT (11). All measurements began at 10 h post-UL, when all animals had recovered sufficiently from the anesthetic to display typical UL symptoms.

Data Analysis

Mean SN, YHT, and RHT were calculated for each measurement time within each group of animals. Drug and vehicle groups for each symptom were compared using two-factor analyses of variance (ANOVAs) with repeated measures on time (Stateview package). Factor A represented the drug effect on SN frequency, YHT, or RHT; factor B, the repeated measure, represented time; and the interaction (AB) represented the change in the rate of compensation as a result of treatment (38). As factor B, the repeated measure, was always significant, it will not be discussed further. The significance level was set at 0.05 for all comparisons.

RESULTS

Flunarizine Dissolved in DMSO

When flunarizine dissolved in DMSO was administered pre-UL (pre-UL2), the only significant difference from the control group was a small difference in the rate of change of RHT, indicated by a significant interaction, $F(5, 45) = 4.92$, $p < 0.001$ (see Fig. 1C). There were no significant differences in SN, YHT, or RHT between drug and control groups when flunarizine was dissolved in DMSO and administered post-UL (see Figs. 1 and 2).

Flunarizine Suspended in 10% Tween-80

When flunarizine was suspended in 10% Tween-80, pretreatment with 10 mg/kg flunarizine (pre-UL4) resulted in a small but significant decrease in mean SN frequency, $F(1, 10) = 20.64$, $p < 0.001$; however, there was no significant interaction between time and drug, indicating no effect on the rate of compensation (see Fig. 3A). YHT was also significantly reduced, $F(1, 10) = 5.92$, $p < 0.05$; however, there was no significant interaction (see Fig. 3B). No significant differences in RHT were observed (see Fig. 3C).

When 20 mg/kg flunarizine suspended in 10% Tween-80 was delivered between 6 and 24 h post-UL (post-UL4), there was no significant difference in SN frequency between drug and control groups; however, there was a significant interaction, $F(6, 60) = 6.05$, $p < 0.0001$ (see Fig. 4A). There was also no significant difference in YHT independently of time; however, there was a significant interaction, $F(6, 54) = 3.83$, $p < 0.005$ (see Fig. 4B). No significant differences in RHT were observed (see Fig. 4C).

DISCUSSION

The present results demonstrate that at doses of 10–20 mg/kg IP flunarizine has little effect on the static symptoms of vestibular compensation in the guinea pig: Even the few statistically significant differences were only small in magnitude (e.g., see mean SN differences in Fig. 3A). The lack of effect of a single 10-mg/kg IP injection of flunarizine at 1 h pre-UL contrasts with the large decrease in SN frequency observed following a single 0.8-mg/kg IM injection of verapamil 1 h pre-UL [see Fig. 5; (7)].

The present experiment fails to replicate the results of previous experiments by Tolu et al. (40,41) using guinea pigs. These authors report both a large decrease in SN frequency and the magnitude of static postural symptoms and an acceleration of compensation following esophageal administration of 5 mg/kg flunarizine suspended in gum arabic every 6 h for 24 h post-UL. In our experiment, the four post-UL conditions were an attempt to replicate the experiments of Tolu et al., albeit with IP administration of flunarizine. Our experiments using flunarizine dissolved in DMSO are difficult to interpret because using 50 or 100% DMSO as a solvent appears to reduce the effects of flunarizine on vestibular compensation. Nonetheless, even when flunarizine was suspended in 10% Tween-80 its effects on vestibular compensation were minimal: Neither 10 mg/kg IP 1 h pre-UL nor 20 mg/kg IP between 6 and 24 h post-UL resulted in large effects on compensation, although some small differences were statistically significant. The most obvious explanation for the apparent discrepancy between our results and those of Tolu et al. is the difference in route of administration (IP vs. esophageal) and drug preparation (suspension in 10% Tween-80 vs. suspension in gum arabic). It may be that flunarizine is more effectively absorbed from the gut when suspended in gum arabic than it is absorbed from the peritoneal cavity when suspended in 10% Tween-80. If this were the case, the 20-mg/kg IP injection of flunarizine we administered every 6 h between 6 and 24 h post-UL may have resulted in lower blood plasma levels of flunarizine than the 5-mg/kg esophageal administration of flunarizine used by Tolu et al. It is possible, therefore, that higher IP doses of flunarizine would have resulted in an acceleration of vestibular compensation, although we observed that animals could not tolerate doses higher than 10 mg/kg IP 1 h before administration of the general anesthetic; further experiments will be needed to determine whether doses higher than 20 mg/kg IP, administered post-UL, will accelerate compensation. An alternative explanation for the discrepancy between our observations of SN and those of Tolu et al. is that flunarizine reduces the amplitude of SN. In our experiments, we consistently observed that flunarizine/10% Tween-80 resulted in a reduction of the amplitude of SN, as judged from the videorecordings of eye movement. Given the noise inherent in electrooculographic recordings of eye movement, it is possible that in Tolu et al.'s studies small-amplitude SN was obscured by noise and that this led to an underestimation of SN frequency in the flunarizine conditions. More accurate recordings of SN, using the scleral search coil technique, are needed to resolve this question. It is also worth noting that in all of Tolu et al.'s flunarizine studies (40,41) chemical rather than surgical labyrinthectomies were used to produce deafferentation of one vestibular nerve. The static symptoms of chemical UL reliably disappear more rapidly than those produced by a surgical UL [e.g., compare (36) and (40)] and studies by Jensen (19) demonstrate that chemical ULs may not produce a complete peripheral lesion.

Previous studies have shown that pre-UL IM administration of the Ca^{2+} channel antagonist verapamil (7) or intraventricular administration (IVth ventricle) of the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride, up to 5 h post-UL (25), causes a reduction in the severity of some of the static symptoms of UL. Recent studies have demonstrated that pre-

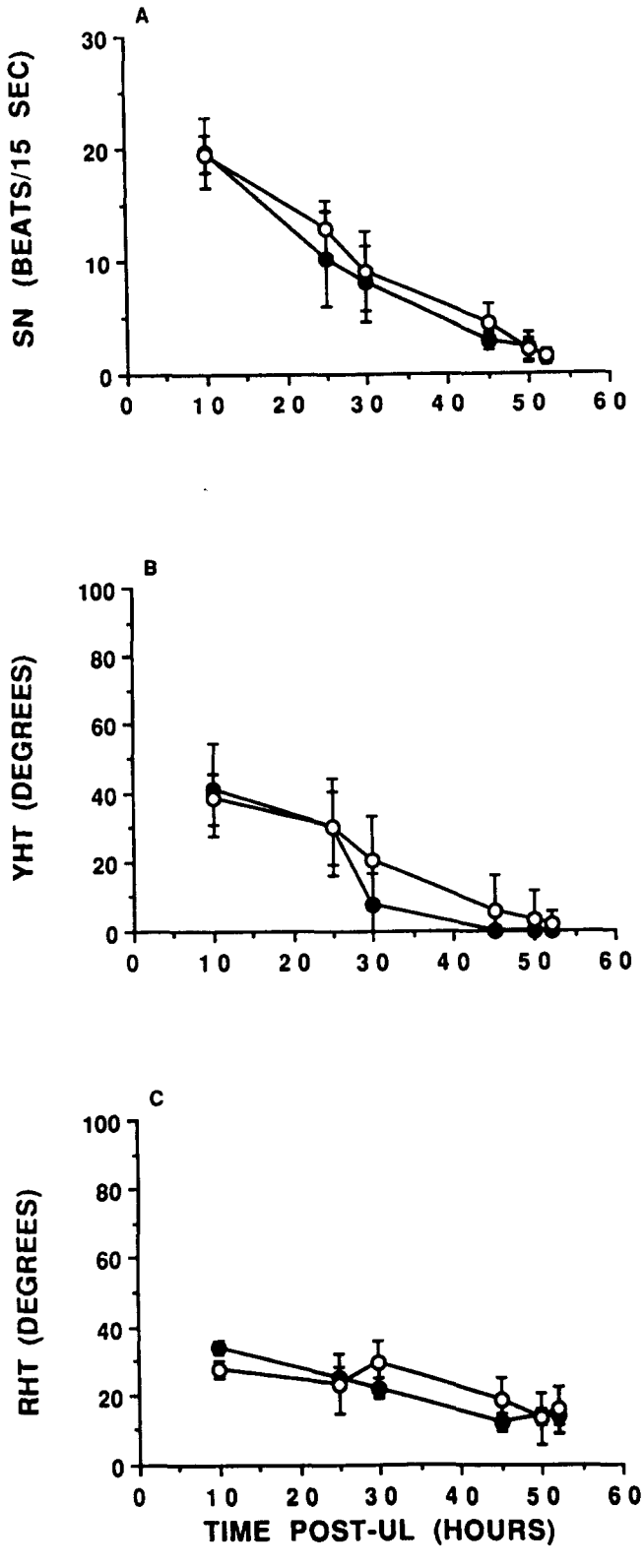

FIG. 1. Comparison of vestibular compensation of (A) spontaneous nystagmus (SN, in beats/15 s), (B) yaw head tilt (YHT, in degrees), and (C) roll head tilt (RHT, in degrees) for guinea pigs (n = 5) receiving a single IP injection of 10 mg/kg flunarizine dissolved in 1 ml/kg 100% DMSO 1 h pre-UL (●) and guinea pigs (n = 6) receiving a similar injection of vehicle alone (○). POST-UL, postunilateral labyrinthectomy. All data points represent means ± 1 SD.

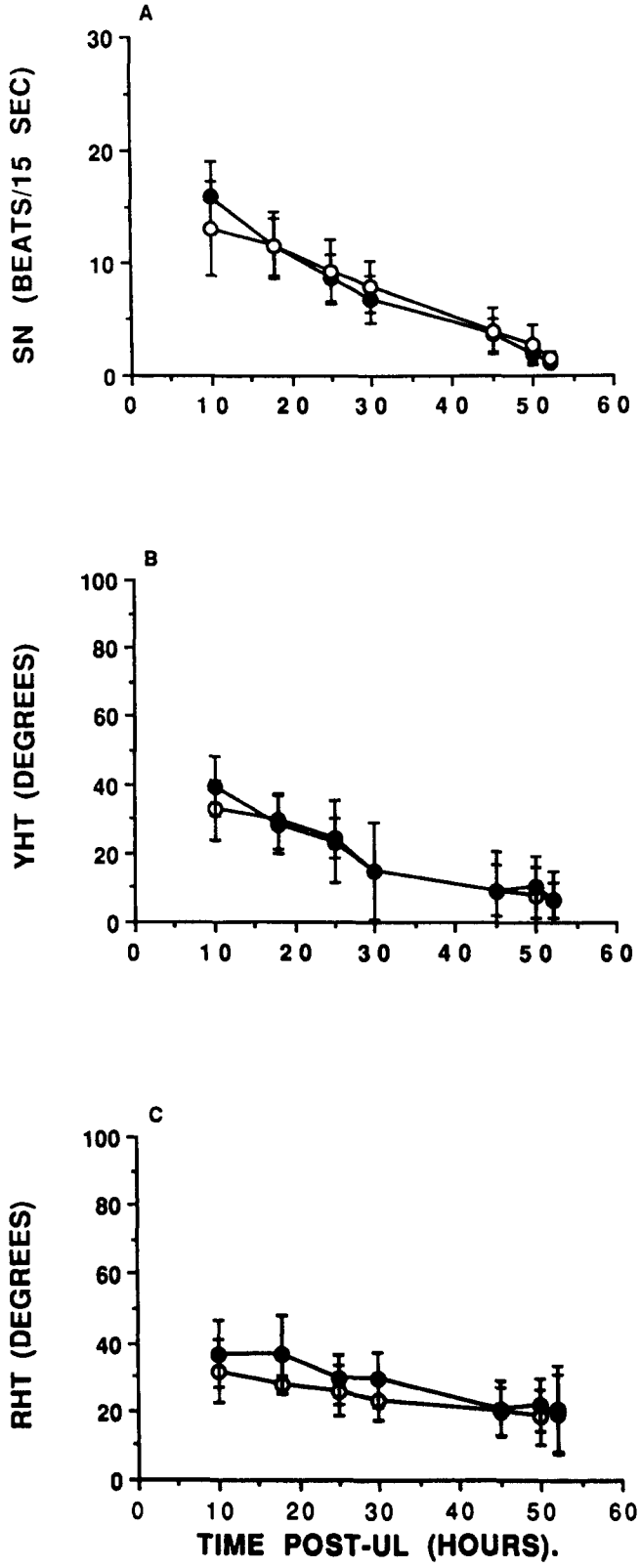

FIG. 2. Comparison of vestibular compensation of (A) spontaneous nystagmus (SN, in beats/15 s), (B) yaw head tilt (YHT, in degrees), and (C) roll head tilt (RHT, in degrees) for guinea pigs (n = 5) receiving IP injections of 10 mg/kg flunarizine dissolved in 1 ml/kg 50% DMSO/50% saline or 100% DMSO (n = 1) every 6 h for 24 h postunilateral labyrinthectomy (UL), starting at 6 h post-UL (●), and guinea pigs (n = 6) receiving similar injections of vehicle (i.e., 100% DMSO) alone (○). POST-UL, postunilateral labyrinthectomy. All data points represent means ± 1 SD.

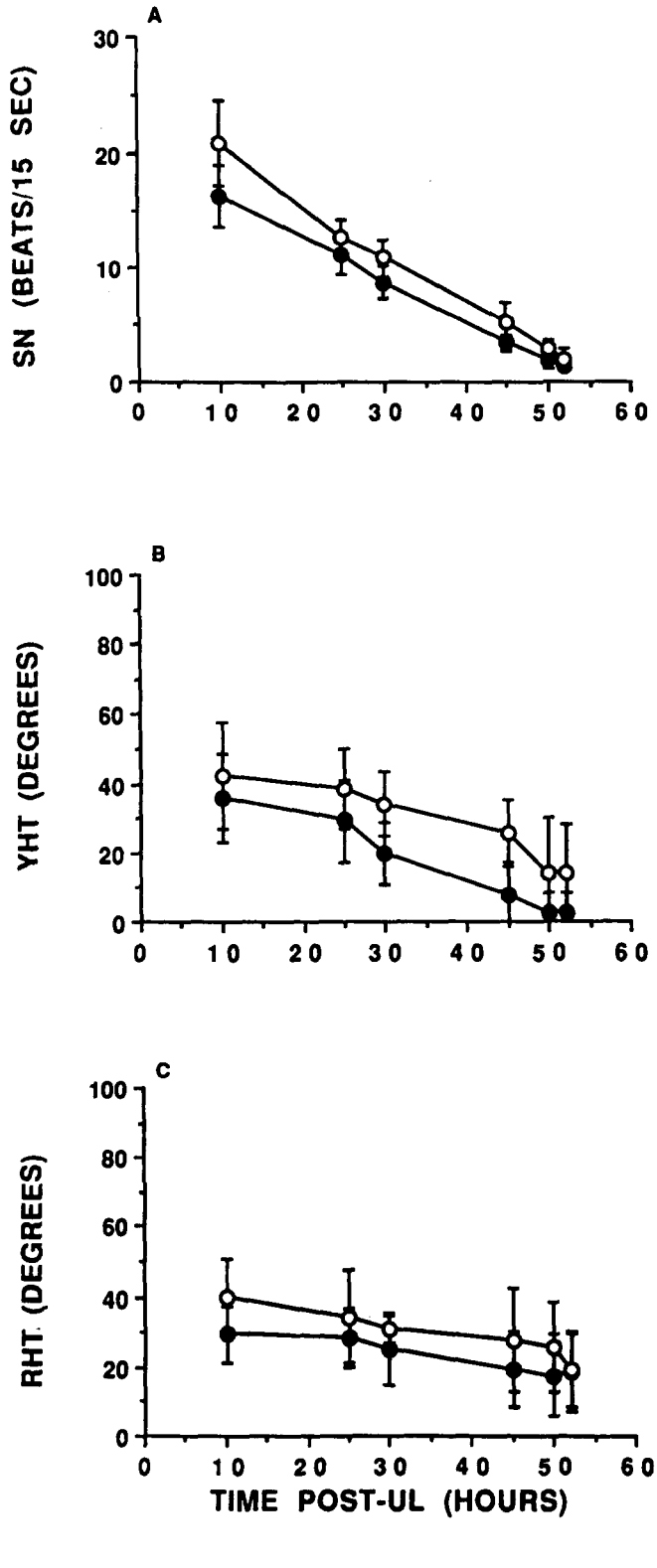

FIG. 3. Comparison of vestibular compensation of (A) spontaneous nystagmus (SN, in beats/15 s), (B) yaw head tilt (YHT, in degrees), and (C) roll head tilt (RHT, in degrees) for guinea pigs (n = 6) receiving a single IP injection of 10 mg/kg flunarizine suspended in 1 ml/kg 10% Tween-80/90% distilled water 1 h preunilateral labyrinthectomy (●) and guinea pigs (n = 6) receiving a similar injection of vehicle alone (○). POST-UL, postunilateral labyrinthectomy. All data points represent means ± 1 SD.

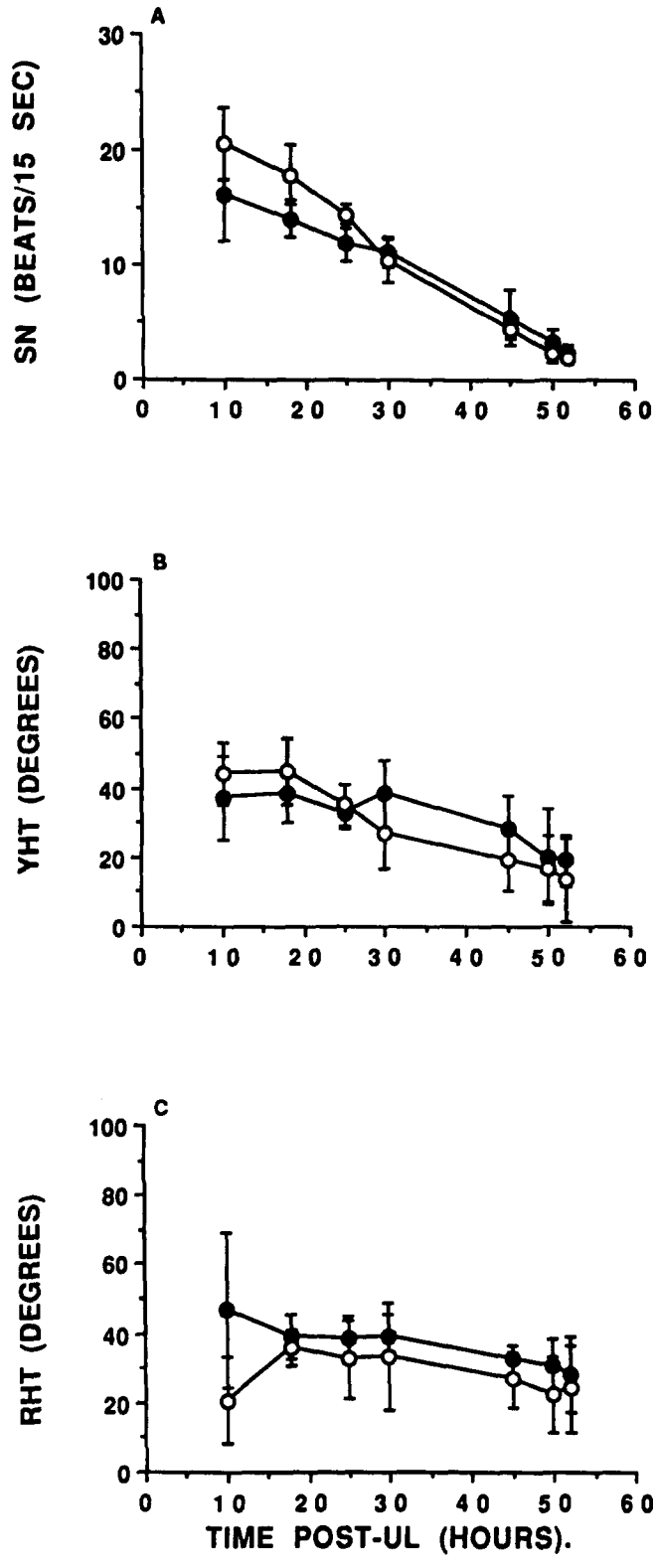

FIG. 4. Comparison of vestibular compensation of (A) spontaneous nystagmus (SN, in beats/15 s), (B) yaw head tilt (YHT, in degrees), and (C) roll head tilt (RHT, in degrees) for guinea pigs (n = 6) receiving IP injections of 20 mg/kg flunarizine suspended in 1 ml/kg 10% Tween-80/90% distilled water every 6 h for 24 h postunilateral labyrinthectomy (UL), starting at 6 h post-UL (●), and guinea pigs (n = 6) receiving similar injections of vehicle alone (○). POST-UL, postunilateral labyrinthectomy. All data points represent means ± 1 SD.

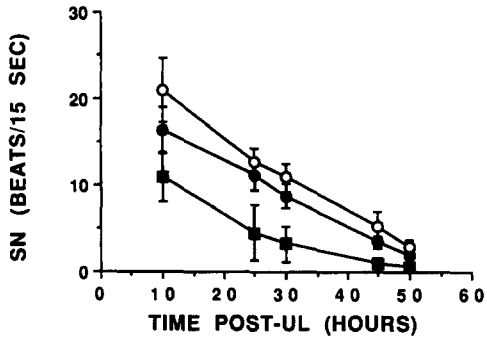

FIG. 5. Comparison of the effect of a single IP injection of 10 mg/kg flunarizine suspended in 1 ml/kg 10% Tween-80/90% distilled water 1 h preunilateral labyrinthectomy (UL), (●; same data as in Fig. 3) and a single IM injection of 0.8 mg/kg verapamil dissolved in 0.1 ml/kg saline 1 h pre-UL [■; data are from Darlington and Smith (7)] on the compensation of spontaneous nystagmus (SN) in guinea pigs. The control data (○) are those shown in Fig. 3, for which animals received a single IP injection of 1 ml/kg 10% Tween-80/90% distilled water 1 h pre-UL. POST-UL, postunilateral labyrinthectomy. All data points represent means ± 1 SD.

UL IP administration of (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate (MK 801), which blocks Ca^{2+} influx through NMDA-mediated Ca^{2+} channels [see (5) for a review], also reduces SN frequency following UL (24). Although most of these results were obtained using systemic administration, it is conceivable that the drugs exerted their effects on vestibular compensation via MVN neurons because in vitro studies have shown that, in addition to NMDA receptors [(4,14; see (37) for a review], MVN neurons have both high-threshold L-type and low-threshold T-type Ca^{2+} channels (28,29). The small effect of flunarizine on vestibular compensation compared to verapamil may be due to substantially different actions of the two drugs on voltage-sensitive Ca^{2+} channels: Flunarizine may act predominantly on T-type Ca^{2+} channels (2,39) whereas verapamil may act mainly on L-type Ca^{2+} channels (12). At present, the selectivity of the various Ca^{2+} channel antagonists for specific Ca^{2+} channel subtypes is controversial and unclear [see (26,44) for reviews]. Studies using more selective Ca^{2+} channel antagonists (e.g., nifedipine) and direct injection into the ipsilateral MVN will be necessary to further test the hypothesis that Ca^{2+} influx into ipsilateral MVN neurons is important at the time of UL.

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