Drug Effects on the Lateral Vestibular Nucleus

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Only a few studies[1,2] on the effectiveness of antihistamines to the neuronal activity in the vestibular nucleus have been published. Those investigators have failed to state neither exact locus of their recording sites nor neuronal type, even though the pattern of afferent and efferent neural connections differ among the four principal vestibular nuclei and there exists functional differences among different types of neurons[3,4,5,6,7,8].

In our previous papers[9,10] the drug effects on the neuronal activity of a tonic type I or type II vestibular neuron in the medial vestibular nucleus (MVN) at rest and during stimulation induced by constant angular acceleration and deceleration were reported. Those results showed that dimenhydrinate (Dramamine®) of 2 mg/kg and 8 mg/kg given intravenously (i. v.) did not produce any significant change in the resting neuronal activity or in the perrotatory neuronal response in the MVN, while diazepam (Valium®) of 0.4 mg/kg given i. v. produced significant depression of the neuronal activity.

The purpose of the present paper is to show what effect, if any, dimenhydrinate and diazepam have upon the spontaneous neuronal activity and the perrotatory response of the lateral vestibular nucleus (LVN) and to explain some comments comparing the results between the LVN and the MVN.

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MATERIALS AND METHODS

The materials and methods used in this study have been described elsewhere[9,10,11,12], and only a brief outline need be given here. Thirty eight adult cats, each weighing 1.9 to 3.5 kg (average 2.5 kg) were used in this study. Under the pentobarbital anesthesia the microelectrode was placed stereotaxically in the LVN as usual, and tonic type I or type II vestibular neuron was selected. The spontaneous activity and the perrotatory response of this unit were recorded through the use of the instrument system[9,10,12] and the frequency histogram was obtained as shown in Fig. 1. The animal was stimulated with constant horizontal angular acceleration of 4°/sq. sec. for 25 seconds, followed by an equal and opposite deceleration. As shown in Fig. 2, total frequency of spikes in one minute at specific time periods in the run was extracted for comparison of change in spontaneous neuronal activity[9]. For comparison of perrotatory response, 10 seconds data samples at specific time periods were extracted[10]. The significance of the difference in the mean neuronal resting activity or in the mean response during angular stimulation was statistically evaluated[13,14].

The elapsed time between the onset of anesthesia and the time of drug injection was 4 hours and 50 minutes in average.

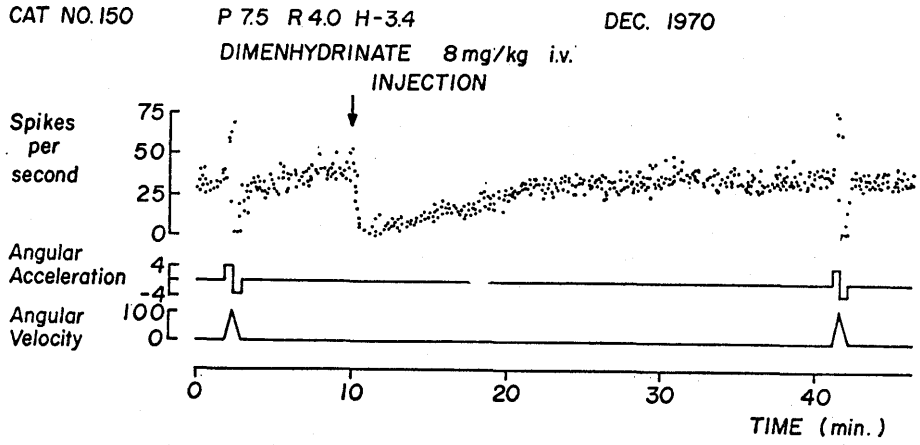

Fig. 1. Frequency Histogram of the Neuronal Activity of the Lateral Vestibular Nucleus and the Test Conditions.

Dotted curve is a frequency histogram of the neuronal activity which was generated by an on-line instrument computer and was displayed on an X-Y oscilloscope. Stimulus was a constant horizontal angular acceleration and deceleration of 4°/sq. sec. for 50 seconds. Initial angular velocity was 0°/sec. with a peak velocity of 100/sec.

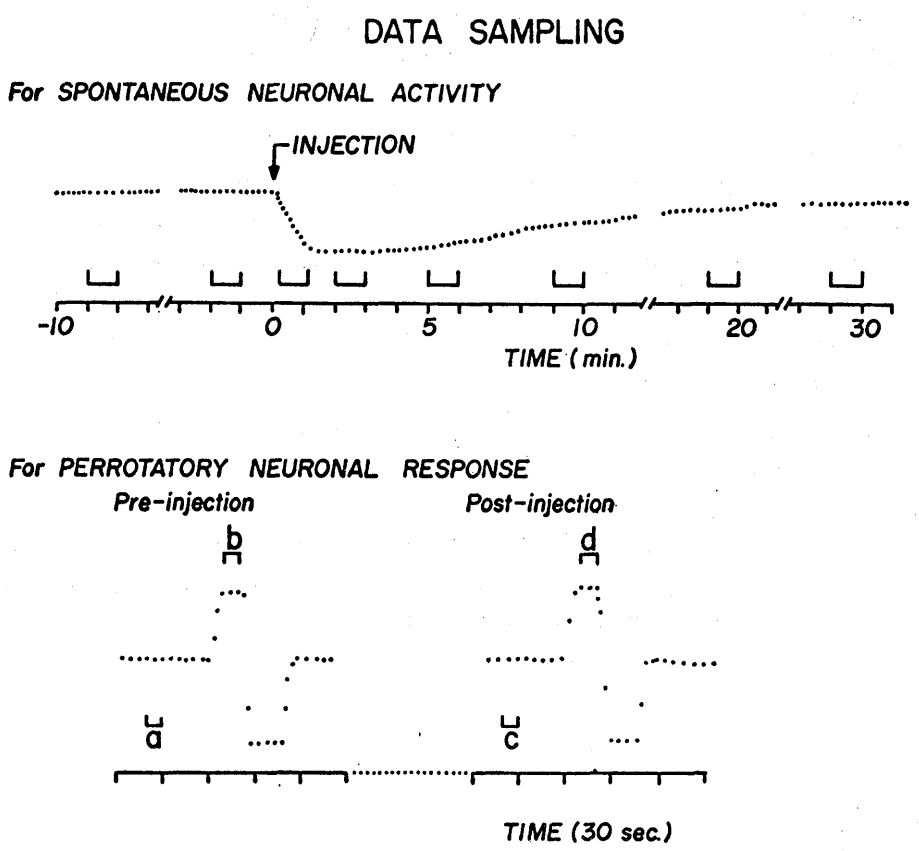

Fig. 2. Data Sampling.

Upper figure shows sample collection for study of the spontaneous neuronal activity with one minute sample at each specific time periods.
Lower figure shows data collection for study of the perrotatory response with 10 seconds sample at each phase time.

RESULTS

Spontaneous Neuronal Activity of the Lateral Vestibular Nucleus:

Comparison of the significance of change in the data between Ringer's solution and drug-dose groups was done statistically. As the results, no significant depression of the spontaneous neuronal activity after i. v. administration of dimenhydrinate of 2 mg/kg was observed (Fig. 3, Table 1, 2, and 3). Dimenhydrinate of 8 mg/kg given i. v. yield significant depression showing the lowermost depression at 10 minutes after injection, and then, suggesting a tendency of recovery to the resting level.

Diazepam of 0.4 mg/kg produced significant depression of the spontaneous activity of the LVN through this recording periods of 30 minutes.

Perrotatory Neuronal Response of the Lateral Vestibular Nucleus:

Mean percentage change in the perrotatory responses at 30 minutes after drug administration was calculated and statistically evaluated. As the results there is no significant change in cases of dimenhydrinate of 2 mg/kg and 8 mg/kg given i. v. Diazepam of 0.4 mg/kg showed significant depression (Fig. 4, Table 4 and 5).

Anatomical localization:

The location of units studied in this experiment are diagrammed in Fig. 5, according to their type. Histological mapping, mapped with reference of Berman's Atlas[15] of the cat brain, showed that all units studied were located in the LVN and units were rather widely scattered throughout the nucleus and neither clear topological arrangement nor specific difference among drug-dose groups was shown.

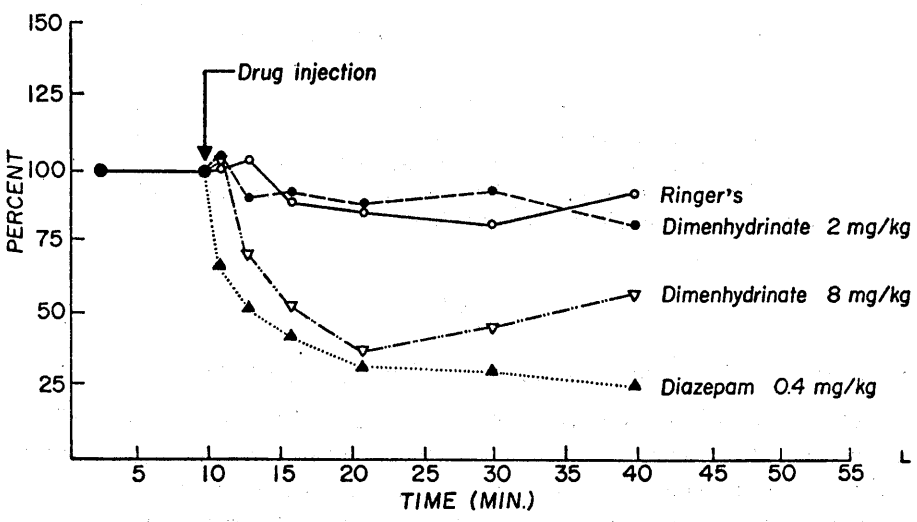

Fig. 3. Percentage Change in Frequency of Spontaneous Neuronal Activity After Drug Administration.
Comparison is made on the basis of a preinjection frequency of 100%.

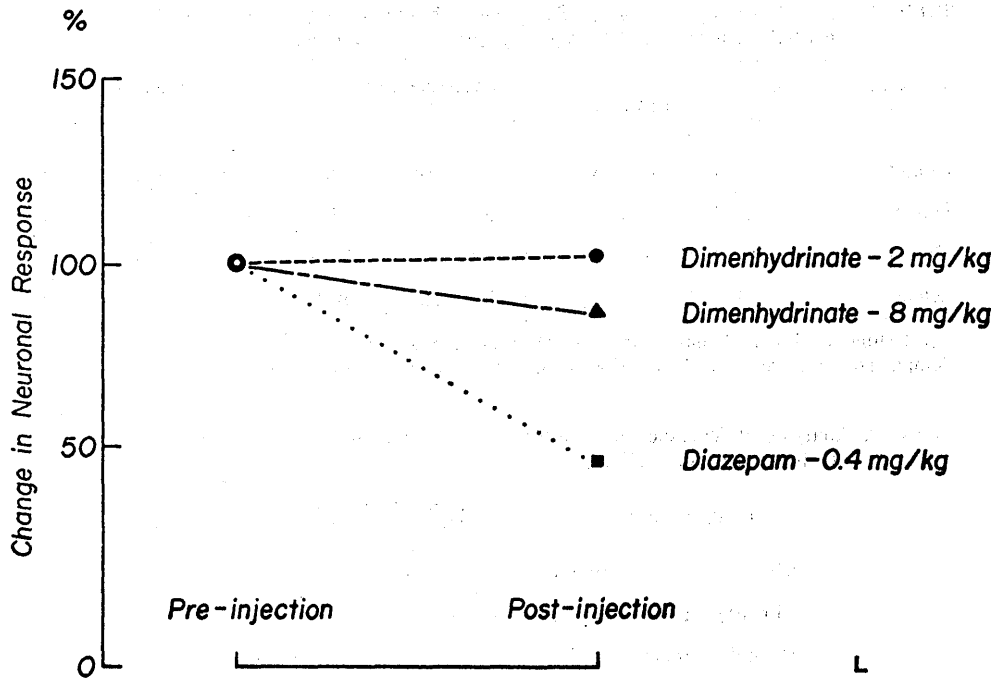

Fig. 4. Percentage Change in Response Frequency After Drug Administration (30 minute interval).
Comparison is made on the basis of a preinjection response frequency of 100%.

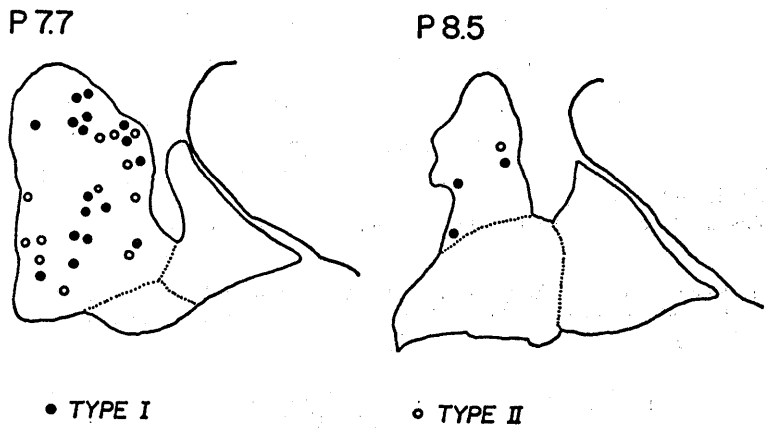

Fig. 5. Anatomical Localization of the Recording Sites.
Numbers on the left side represent planes of respective transverse sections of the brain stem in millimeters posterior to the interaural line.
Closed circles indicates a type I unit; and open circles, type II.

Table. 1. Mean Percentage Change of Spontaneous Neuronal Activity in Lateral Vestibular Nucleus (LVN) in each group in time process.

Drug and Doses	No. of Units	Prejnjec.	Post-injection			Minutes		
			1	3	6	10	20	30
Ringer's	5	100.0%	101.3	104.1	89.0	86.1	80.9	92.9
Dimen.	−(2)12	100.0	105.0	91.1	92.9	89.0	93.2	80.3
Dimen.	−(8)13	100.0	104.1	71.2	53.6	38.1	46.2	57.1
Diaze.	−(0.4) 8	100.0	67.7	52.1	42.5	32.2	30.2	25.3

Note: Dimen.=dimenhdrinate (mg/kg) Diaze.=diazepam (mg/kg)
Comparison is made on the basis of a pre-injection mean value of 100%.

Table. 2. Analysis of Variance of Spontaneous Neuronal Activites of Lateral Vestibular Nucleus (LVN).

Drug and Dose		Number of Neurons	χ^2
Ringer's	One ml.	5	2.72
Dimenhydrinate	2 mg/kg	12	4.78
Dimenhydrinate	8 mg/kg	13	35.29*
Diazepam	0.4 mg/kg	8	14.33*

*Statistically significant

Table. 3. Comparison of Differences in Mean Spontaneous Activities in LVN between Control (Ringer's) and Drug-Dose group

	df	1	3	6	10	20	30min.
Dimen. −(2)	15	0.236	1.680	0.308	0.167	0.509	0.419
Dimen. −(8)	16	0.177	4.404*	1.569	2.164*	1.539	1.245
Diaze. −(0.4)	11	3.319*	3.845*	2.792*	2.840*	2.215*	2.626*

*Statistically significant
Note: Dimen.=dimenhydrinate (mg/kg) Diaze.=diazepam (mg/kg)

Table. 4. Mean Percentage Change of the Perrotatory Neuronal Response of the Lateral Vestibular Nucleus before and 30 minutes after drug administration

Drug and Dose		Number of Animal	
Dimenhydrinate	2 mg/kg	12	100.8%
Dimenhydrinate	8 mg/kg	13	87.5%
Diazepam	0.4 mg/kg	8	47.8%

Table. 5. Comparison of Difference in Perrotatory Neuronal Response of the LVN between the pre- and the 30 minute postinjection

Drug and Dose	Number of Animal	t
Dimenhydrinate 2 mg/kg	12	0.024
Dimenhydrinate 8 mg/kg	13	1.771
Diazepam 0.4 mg/kg	8	2.037*

*Statistically significant

COMMENT

The present study showed that the spontaneous neuronal activity of type I and II vestibular neurons of the LVN was not affected by dimenhydrinate of 2 mg/kg given i. v. (as a physiological dosage)[16], but significantly depressed by that of 8 mg/kg (above physiologic dosage). The results in cases with 8 mg/kg of dose reveal considerably different with that of results obtained in the medial vestibular nucleus (MVN)[8] which was not affected at all.

To comment the difference of mode of action between the LVN and the MVN, we should have referred the anatomical and physiological differences between them. As well stated by Shimazu and Precht[5], based on their classification of Gernandt[6] and of Duensing and Schaefer[7], type I vestibular neuron is unit that increased their discharge frequency with ipsilateral acceleration and decreased their frequency with contralateral acceleration. In other words, type I neuron showed increased response when the cupula of the semicircular canal deflected ampullopetally, and showed decreased response during ampullofugal deflection of the cupula. Type II neuron shows their response opposite to type I. So, these two neurons might exactly have neuronal connection supplying the cupula origin fibers, primarily or secondarily.

Stein and Carpenter[17] (in the monkeys) and Gacek[18] (in the cats) studied on the central projection of the first order neurons supplying vestibular end-organs and revealed that scanty or none of the primary vestibular fibers of the lateral semicircular canal terminated in the lateral vestibular nucleus.

Based on those anatomical findings, most of the neurons in the LVN should not be so-called type I or type II vestibular neurons. However, we, in this experiment and the previous work[8], have obtained significant number of type I and type II vestibular neurons, which are responding to

the lateral semicircular stimulation, in the LVN. Although Shimazu and Precht[5] explained that type I and type II neurons are the second order neurons in the vestibular nuclei which are primarily connected with receptors in the semicircular canals and activated by deflection of the cupulae, those specifically responding neurons in the LVN are not likely directly connected to the primary fibers but seemingly connected indirectly through other vestibular nuclei via internuclear fibers or other nucleus in the brain stem reticular formation or through the cerebellum[3].

As based on these findings, type I and II neurons we studied in the LVN are likely to be third order neurons. And it is highly possible to consider that these structural difference between the MVN and the LVN might cause the difference in the neuronal response to the drugs between them.

Diazepam of 0.4 mg/kg showed the depressive effect on the spontaneous activity and perrotatory response of the neurons in the LVN. This depressive effect was stronger in the LVN than that of the MVN[9,10]. A study[19] of the effect of diazepam on the postlabyrinthectomy nystagmus showed that the quick phase velocity, whose origin is likely in the reticular formation[20], was affected stronger than any other parameters of the nystagmus studied. Since the RF is seemingly the major locus of the CNS depressant action of diazepam[21,22], and since the LVN has seemingly received more fibers from the RF[23,24,25] it is reasonably understood that the LVN was more affected by diazepam and by a higher dose of dimenhydrinate than the MVN.

Considering the following results, i. e., 1) no effect of dimenhydrinate of 2 mg/kg on the spontaneous activity of the LVN, as the same as of the MVN; 2) 8 mg/kg of dimenhydrinate depressed the spontaneous activity of the LVN, but 3) no significant change in the perrotatory response in that dosage; 4) diazepam depressed both spontaneous activity and perrotatory response of the LVN strongly more than that of the MVN; and 5) the lower dose of diazepam (0.1 mg/kg) will suppress the spontaneous activity first and then suppress the perrotatory response later[26], we might be able to say that these drugs will act on elsewhere the brain stem reticular formation or other part of the CNS but not appear to be the end-organ or the second order neurons those which have neuronal connection originating from the semicircular canal receptor.

SYNOPSIS-ABSTRACT

The effects of dimenhydrinate (Dramamine®) and diazepam (Valium®) on the spontaneous neuronal activity and on the perrotatory response of

the lateral vestibular nucleus in the cats was investigated. Tonic type I and type II vestibular neurons were selected stereotaxically. Discharge frequency was recorded through the run at rest and during constant angular acceleration and deceleration, using an instrument computer and evaluated by statistical methods.

Dimenhydrinate of 2 mg/kg given i. v. did not show any effect on the spontaneous activity and the perrotatory response. Dimenhydrinate of 8 mg/kg produced significant depression of the spontaneous activity but not on the perrotatory response. Diazepam of 0.4 mg/kg yield significant depression on both of the activities.

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