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SOME OBSERVATIONS CONCERNING THE MODE OF ACTION OF THE ANTIHISTAMINIC DRUG "LERGIGAN" (N(α-METHYL-β-DIMETHYL AMINOETHYL)PHENOTHIAZINE HYDROCHLORIDE) IN MOTION SICKNESS

BY

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During recent years many reports have been published concerning the beneficial action of certain antihistamine drugs in the treatment and prevention of motion sickness. Thus Gay and Carliner (1949a, b) found dramamine, the 8-chlorotheophylline salt of diphenhydramine, to be effective against nausea and vomiting in motion sickness. Their findings were confirmed by others. Chinn and Oberst (1950) found benadryl as effective as dramamine in the prevention of air sickness; the best effect, however, was obtained when benadryl was combined with hyoscine. Chen and Ensor (1950) were able to prevent apomorphine-induced emesis in dogs by using benadryl. Engquist (1950, 1951) tested the drug lergigan (Halpern and Schmiterlöw, unpublished) against sea sickness with good results. Chinn, Waltrip, and Massengale (1951) and Chinn, Handford, Cone, and Smith (1952) tested different drugs against sea sickness and found lergigan to be one of the most effective drugs in this respect.

The question naturally arises why antihistamine drugs exert this protective action against motion sickness. The effect is obviously not due to the histamine antagonizing action, since not all antihistamine drugs exert this effect (see Chinn *et al.*, 1952). It has been suggested (Chinn *et al.*, 1950) that the degree of central anticholinergic action might determine in large part the effectiveness of the drug. This suggestion is of great interest when compared with the findings of Johns and Himwich (1950). These authors made intracarotid injections of DFP on animals, and observed that benadryl, dramamine, and lergigan could cure the DFP-induced cortical seizures. Other antihistamines such as thephorin, antistine, pyribenzamine, etc., were without effect. They stated that the curative ability of certain antihistamine drugs in DFP-induced seizures depended upon a cerebral action of these drugs and might be related to an atropine-like quality. It has also been argued that the sedative effect of some antihistamine drugs might be the explanation of their action against motion sickness. Bjerver and Goldberg (1951), using the flicker test and the blink reflex test, showed that a number of antihistamines exerted a central depressant action, and they also studied the effect of these drugs in experimentally induced motion sickness.

It is well known that the blood pressure often falls in motion sickness. If the blood pressure is raised, for example by infusion of dextran, the symptoms may disappear (Engquist, 1951). It is but natural to connect this phenomenon with the early observations of Spiegel and Démétriades (1922) that not only caloric and galvanic stimulation of the labyrinth but also rotatory stimulation cause a fall of blood pressure. The mechanism behind this blood pressure fall seems similar to the reflex effect caused by stimulation of the vagal depressor nerves.

The present investigation was performed in order to find out how the antihistaminic drug lergigan (Recip, Co., Stockholm), known to be active against motion sickness, would influence the blood pressure fall obtained when stimulating the eighth cranial nerve in cats.

METHODS

Electrical Stimulation of the Eighth Cranial Nerve.—Cats have been used throughout the experiments. Most animals were lightly anaesthetized with allobarbital, 0.03–0.04 g. per kg. body weight given intravenously. In addition some cats were anaesthetized with 0.06 g. chloralose per kg. A tracheal cannula was inserted.

The skin and muscles above the occipital bone were removed. The occipital bone was excised to expose the cerebellum, which was sucked out in order to

make the eighth cranial nerve fully visible between the internal auditory meatus and the medulla oblongata.

The electrode used for stimulation of the eighth nerve consisted of a fine needle, the diameter of which did not exceed 0.05 mm. The insulated electrode, with the tip exposed, was inserted by means of a micromanipulator into the eighth nerve just outside the internal auditory meatus. The stimulating current was generated by thyratron discharges. The electrical stimuli were of rectangular shape, and the pulse duration of the stimulating current was about 5 msec. at the maximal strength used. The frequency of the shocks used was 1–2 per second at intensities of 8–10 volts. After locating a point within the eighth nerve which in response to stimulation gave a maximal fall in blood pressure, recorded with a mercury manometer from the femoral artery, the electrode was left in that position during the experiment.

Injections were made through the external jugular vein. In order to abolish the motor activity of the muscles in response to vestibular stimulation the animals were curarized. Artificial respiration was given.

The Effect of Lergigan on Some Other Autonomic Reflexes.—The effect of lergigan was studied on:

1. The blood pressure rise caused by carotid occlusion. The experiments were carried out on cats under chloralose anaesthesia.

2. The blood pressure fall caused by stimulation of the sinus nerve. Cats under sodium pentobarbitone were used. The right sinus nerve was dissected free and stimulated electrically, using a frequency of 20 per second at an intensity of about 2 volts. The duration of each stimulus was 1 msec.

3. The blood pressure fall caused by stimulation of the depressor nerve. Rabbits under urethane anaesthesia were used.

4. The blood pressure fall caused by stimulation of the peripheral end of the vagus. Cats under chloralose were used.

5. The effect on respiration caused by electrical stimulation of the central end of the superior laryngeal nerve. Cats under chloralose were used. The cut right superior laryngeal nerve was stimulated at a frequency of 20 per second. Stimulus length 1 msec., intensity about 0.5 volt.

The Influence of Rotation upon the Blood Histamine.—Some experiments were performed in order to find out whether rotation would cause any change in the histamine content of the blood. Rabbits were used for these experiments. They were put in the rotation apparatus described by Gernandt (1949). After rotation the rabbits were immediately killed and the blood collected in acid alcohol. The amount of histamine was then determined according to the method described by Schmiterlöw (1949).

The Action of Lergigan on Gastric Motility.—In order to study the effect of lergigan on gastric motility caused by vagus stimulation the following experiments were performed. Cats under chloralose were used. A rubber balloon was inserted into the stomach and connected with a Marey tambour. The thorax was opened on the right side, artificial respiration being given. After removal of the lower lobes of the right lung an electrode was placed on the peripheral part of one of the cut vagus branches running along the oesophagus. Blood pressure was recorded from one of the carotid arteries.

Results

Stimulation of the Eighth Cranial Nerve.—When the eighth cranial nerve was stimulated in the way described above a fall in blood pressure and a slowing of the heart were regularly observed. This blood pressure fall comes on gradually and persists during the stimulation. Fig. 1 A shows this effect of stimulation. On the same record is seen the effect of varying doses of histamine dihydrochloride, injected intravenously, and also the effect of acetylcholine hydrochloride. When lergigan in a dose of 2 mg./kg. body weight was given intravenously and the same experiment was repeated it was observed that the stimulation of the eighth cranial nerve no longer caused a fall in blood pressure (Fig. 1 B). The effect of histamine was totally abolished, whereas the action of acetylcholine persisted, although markedly impaired. In order to find out whether this blocking of the effect of histamine was of any importance in the mechanism which enabled lergigan to block the blood pressure fall, caused by stimulation of the eighth cranial nerve, the following experiment was performed. After stimulation of the eighth cranial nerve the effects of acetylcholine and histamine were studied (Fig. 2 A), and atropine (0.3 mg./kg.) was then given. After atropine the

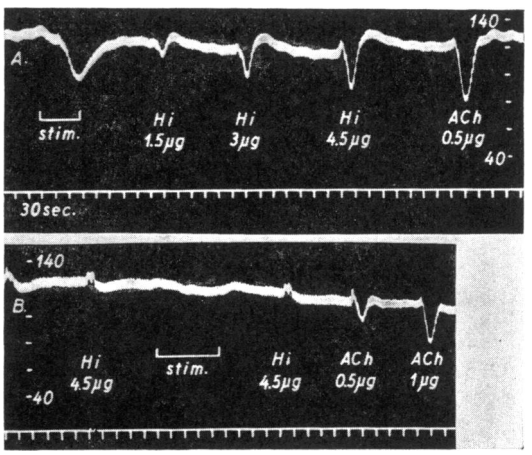

FIG. 1.—Cat (allobarbital). Blood pressure record. Stim.=electrical stimulation of eighth cranial nerve. Hi=histamine dihydrochloride. ACh=acetylcholine hydrochloride. Between A and B 2 mg./kg. lergigan intravenously.

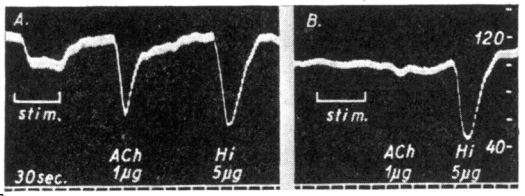

FIG. 2.—Cat (allobarbital). Blood pressure record. Stim.=electrical stimulation of the eighth cranial nerve. Hi=histamine dihydrochloride. ACh=acetylcholine hydrochloride. Between A and B 0.3 mg./kg. atropine sulphate intravenously.

stimulation of the eighth nerve does not lead to any fall in blood pressure, seen in Fig. 2 B, where it can also be observed that the effect of histamine was not influenced by this small dose of atropine. Obviously it is not the histamine antagonizing power of lergigan which is responsible for the effect on the stimulation of the eighth cranial nerve.

If the effects of lergigan and atropine were compared it was noted that the ability of lergigan to block the blood pressure fall induced by stimulation of the eighth cranial nerve was very constant, whereas atropine in the dose used (0.3 mg./kg.) did not always give a complete blocking effect. If, however, both vagi were cut the effect on the blood pressure totally disappeared.

If the stimulation of the eighth cranial nerve was performed in cats under chloralose anaesthesia, and allobarbital (30 mg./kg.) was given, no obvious change in the effect could be observed (Fig. 3). These experiments were done in order to see whether an increase in central depression would have any effect.

The Effect of Lergigan on Other Autonomic Reflexes.—From the experiments cited above it is not clear whether the action of lergigan should be regarded as a central or peripheral action. In order to elucidate this question the experiments on other reflexes, mentioned above (see Methods), were carried out.

1. Clamping both carotids in a cat under chloralose leads to a marked rise in systemic blood pressure.

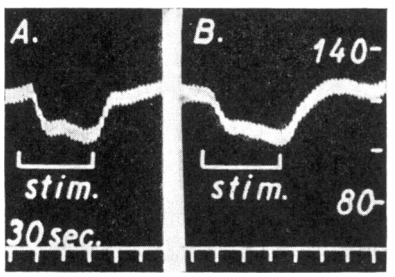

FIG. 3.—Cat (chloralose). Blood pressure record. Stim.=electrical stimulation of the eighth cranial nerve. Between A and B 30 mg./kg. allobarbital intravenously.

This effect is not influenced by lergigan, as can be seen in Fig. 4.

2. If the sinus nerve is stimulated electrically the result on the blood pressure is different for different anaesthetics. Neil, Redwood, and Schweitzer (1949) thus showed that when the sinus nerve is stimulated in cats under pentobarbitone anaesthesia the result is invariably a fall in blood pressure. This observation could easily be confirmed; stimulating the right sinus nerve electrically in cats under pentobarbitone caused a slight but distinct lowering of the blood pressure. This effect was not influenced by lergigan (Fig. 5). In this figure respiration was also registered from the tracheal cannula.

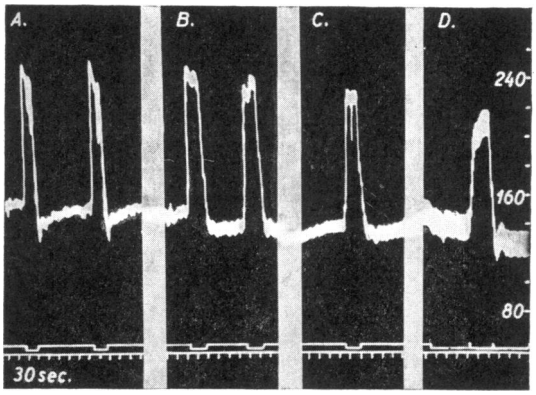

FIG. 4.—Cat (chloralose). Blood pressure record. Blood pressure recorded from femoral artery. Signal indicates clamping of both carotids. A before lergigan, B after 2 mg./kg. lergigan, C and D after 4 mg./kg. lergigan intravenously. In D the cat was allowed to breathe pure oxygen.

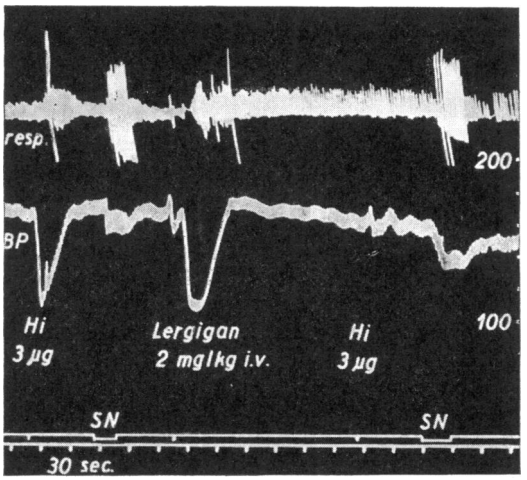

FIG. 5.—Cat (chloralose). Respiration recorded from tracheal cannula (upper curve). Blood pressure record (lower curve). Signal indicates electrical stimulation of the right sinus nerve (SN). Hi=histamine dihydrochloride. The effect of stimulation of the sinus nerve is seen before and after 2 mg./kg. lergigan intravenously.

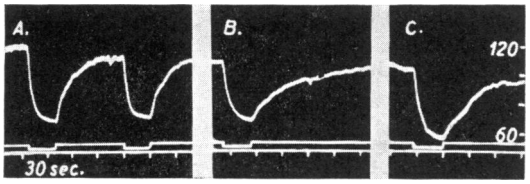

FIG. 6.—Rabbit (urethane). Blood pressure record. Signal indicates electrical stimulation of the right depressor nerve. A before lergigan, B after 2 mg./kg., and C after 4 mg./kg. lergigan intravenously.

3. In the rabbit the depressor nerve can easily be dissected free from the vagus trunk and thus be stimulated separately. The response to such stimulation, a blood pressure fall, was not influenced by lergigan (Fig. 6).

4. So far the experiments have not shown any sign of a central blocking action of lergigan. It would be of interest to see whether lergigan exerts any peripheral action which could explain the ability of the substance to abolish the blood pressure fall caused by the stimulation of the eighth cranial nerve. For that reason the peripheral end of the cut right vagus was stimulated electrically, using such stimulus as would cause a marked blood pressure fall and bradycardia. When lergigan was then given this effect was almost totally abolished (see Figs. 7 A and B). In the same figure it can be noted that the effect of acetylcholine is only partly blocked by the dose of lergigan used, whereas the electrical vagus stimulation is almost completely blocked.

5. Figs. 7 A and B also show that the effect on the respiration produced through stimulation of the right superior laryngeal nerve is not influenced by lergigan.

The Blood Histamine Level in Rabbits After Rotation.—The rabbits were rotated (angular stimulation) for different lengths of time, 10, 15, 25, and 30 minutes. The animals were killed immediately after the rotation had stopped and the blood was collected. When the amount of histamine in the blood was estimated no significant difference from the normal histamine level in rabbits was found. Neither was there any difference between blood from rabbits that had been rotated for different lengths of time.

The Action of Lergigan on Gastric Motility.—When stimulating vagus branches below the heart strong contractions of the stomach were observed. After lergigan these contractions were markedly reduced, as can be seen from Fig. 8.

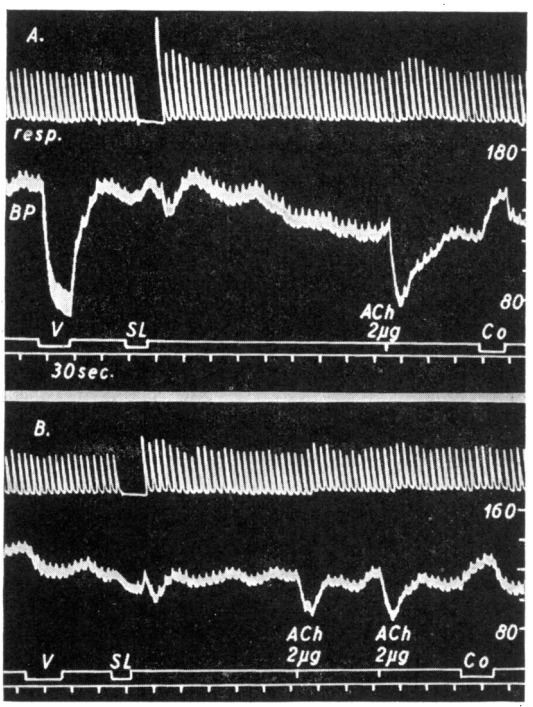

FIG. 7.—Cat (chloralose). Respiration recorded from tracheal cannula (upper curve). Blood pressure record (lower curve). Signal indicates electrical stimulation of the cut peripheral vagus (V) and of central end of the cut superior laryngeal nerve (SL) and clamping of right carotid (Co). ACh=acetylcholine hydrochloride. A before, B after, 2 mg./kg. lergigan intravenously.

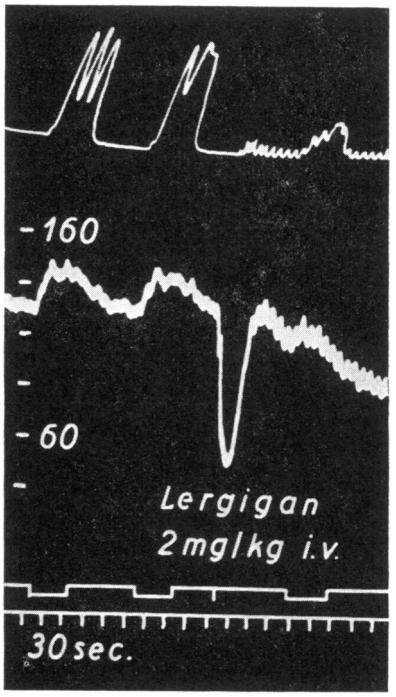

FIG. 8.—Cat (chloralose). Motility of the stomach (upper curve). Blood pressure record (lower curve). Signal indicates electrical stimulation of the cut peripheral vagus below the heart. Artificial respiration. The effect of stimulation is seen twice before and after 2 mg./kg. lergigan intravenously.

Discussion

The experiments described here have shown that the antihistamine drug lergigan is able to prevent in anaesthetized cats the lowering of the blood pressure induced by electrical stimulation of the eighth cranial nerve.

It appears reasonable to assume that the ability of such a drug as lergigan to prevent or cure motion sickness at least to some extent is due to this prevention of the blood pressure fall which is a common symptom in motion sickness. If such drugs as would raise the blood pressure are given to persons suffering from motion sickness, the nausea and vomiting disappear (Engquist, 1951). It is but natural to think that a beneficial effect will be obtained with a drug which will prevent the lowering of the blood pressure.

Lergigan also blocks the effect of vagus stimulation on the stomach. This fact will also offer an explanation to the ability of lergigan to prevent or cure motion sickness.

However, one must take into account the fact that lergigan also exerts a sedative effect (see Bjerver and Goldberg, 1951), which might certainly be of importance in the prophylaxis and treatment of motion sickness in man.

There still remains to answer the question in which way lergigan (and other antihistamine drugs, reported in the literature to be of value against motion sickness) exerts this effect to prevent a blood pressure fall.

It is obvious that this effect has nothing to do with the histamine antagonizing action of the drugs in question. This is clear from several facts. It has been shown by other authors that only some of the antihistamines exert this beneficial action against motion sickness, and amongst those are not the most specific histamine antagonizing drugs. Our experiments also show that rotation does not increase the blood histamine level. And, finally, even if the effect of histamine is not counteracted it is possible by using atropine to block this blood pressure fall.

If the action was on the central nervous system, as suggested by, e.g., Chinn *et al.* (1950), it seems natural that also other autonomic reflexes would be abolished by lergigan. This is, however, not the case, as is shown in our experiments. The stimulation of the central part of the sinus nerve, for example in cats under chloralose, leads to a blood pressure fall which is not abolished by lergigan. The carotid occlusion test is not affected by lergigan. The blood pressure fall following stimulation of the depressor nerve is not counteracted by lergigan. The effect of stimulation of the central end of the superior laryngeal nerve is not influenced by lergigan.

Lergigan is able to prevent the blood pressure fall caused by stimulation of the peripheral end of the vagus. It seems natural to assume that this effect is similar to its ability to block the blood pressure fall when the eighth cranial nerve is stimulated. The blood pressure fall caused by this stimulation is very likely brought about by an activation of the vagus centre, an assumption which is supported by the fact that if both vagi are cut the stimulation of the eighth cranial nerve no longer leads to a fall in blood pressure. Both atropine and lergigan are able to prevent the blood pressure fall following upon electrical stimulation of the eighth cranial nerve. It is thus obvious that the effect of lergigan in this respect is due to a blocking of the peripheral vagus transmission. This view is supported by the fact that lergigan has a very strong anti-acetylcholine action.

It was assumed by Spiegel (1926) that the blood pressure fall induced by stimulation of the eighth cranial nerve was due to a mechanism similar to that observed when the depressor nerve is stimulated. This does not, however, seem very likely from the present experiments. The depressor reflex is not influenced by lergigan. The blood pressure fall caused by stimulation of the depressor nerve is, as shown by Folkow, Ström, and Uvnäs (1950) and Celander and Folkow (1951), due to an inhibition of the vasoconstrictor centre leading to a diminished vasoconstrictor outflow. Therefore this reflex will not be influenced by lergigan, since it does not involve the activation of the vagus. When the eighth cranial nerve is stimulated the ensuing blood pressure fall is due to an increased outflow in the vagus, the effect of which can be blocked by lergigan. The activation of the vagus seems to be rather natural when it is taken into account that vestibular fibres are distributed to the reticular formation of the medulla oblongata where they, *inter alia*, appear to reach the vagus and glossopharyngeal nuclei. This would be in accordance with the occurrence of vomiting and cardiovascular changes observed in vestibular stimulation.

From our experiments we think it is justified to draw the conclusion that the beneficial action exerted by lergigan and certain other antihistamines on motion sickness is partly due to their ability to block the activity of the vagus, thus preventing a blood pressure fall and also inhibiting gastric motility, etc. This effect is due to an atropine-like, peripheral action. In this connexion it should be pointed out that the antihistamines which have been used against motion sickness have in common

that they are fairly non-specific antihistamines, e.g,, they do not only antagonize histamine, but they also counteract the effect of acetylcholine. It must, however, also be remembered that antihistamines usually have a sedative action which certainly plays a role in the prevention of motion sickness. This fact could be illustrated by the well-known superiority of hyoscine over atropine as regards prevention of motion sickness.

Summary

1. The eighth cranial nerve has been stimulated electrically in cats. The result is a fall of blood pressure.

2. This blood pressure fall is abolished by moderate doses of the antihistamine lergigan and by atropine.

3. Lergigan does not interfere with the central part of other autonomic reflexes.

4. Lergigan blocks the effect of peripheral vagus stimulation.

5. The blood pressure fall caused by stimulation of the eighth cranial nerve is obviously due to an activation of the vagus centre.

6. The effect of lergigan against motion sickness is partly due to its atropine-like action, which abolishes vagus effects.

7. Angular stimulation does not change the amount of histamine in the blood.

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