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Role of the chemoreceptor trigger zone in histamine-induced emesis

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1. In unanaesthetized dogs, the emetic action of histamine was studied after its injection into the cerebral venricles through chronically implanted cannulae in order to elucidate the role of the chemoreceptor trigger zone (CT-zone), situated in the area postrema, for this emesis.

2. On injection into the lateral cerebral ventricle, about 10 times larger doses of histamine (3 mg) were required regularly to produce emesis, and it occurred after a longer latency than on injection into the fourth ventricle. This is in accord with an action of histamine on the CT-zone.

3. After bilateral ablation of the CT-zone, intraventricular injections of histamine no longer produced emesis even when injected in doses which were three to four times greater than those which regularly elicited vomiting in dogs with intact CT-zone. The emesis produced in dogs by intraventricular injections of histamine is thus fully accounted for by an action on the CT-zone.

4. Injections of chlorpromazine intramuscularly or of the two antihistamines cyclizine and mepyramine, either intramuscularly or into the lateral ventricle, prevented the emesis caused by histamine injected into the lateral ventricle. This protective action of the antihistamines—which did not extend to the emesis produced by oral copper sulphate—suggests the presence of histaminergic receptors in the CT-zone.

With the discovery of the emetic chemoreceptor trigger zone (CT-zone), a new concept for the neural mechanism of vomiting has emerged (Wang & Borison, 1952). Several emetic agents—namely apomorphine (Wang & Borison, 1952), morphine, hydergine (Wang & Glaviano, 1954), emetine (Bhargava, Gupta & Chandra, 1961), reserpine (Bhargava, Dixit & Gupta, 1967), cardiac glycosides (Borison & Wang, 1951) and catecholamines (Borison, 1959)—are now known to act selectively on the CT-zone to evoke emesis. Histamine is particularly rich in the region of the area postrema which is the anatomical site of the emetic CT-zone (Adam, 1961). The purpose of the present investigation was to study the emetic effect of histamine injected into the cerebral ventricles and to determine the role of the CT-zone in this histamine-induced emesis in dogs.

The earliest report of emesis following intravenous or subcutaneous injection of histamine in conscious cats is that of Dale & Laidlaw (1910). In dogs, vomiting has been observed after intravenous histamine by Peng & Pi (1967), and in man, admini-

stration of histamine for shock therapy of schizophrenic patients regularly leads to nausea, retching and vomiting (Nadeau, Rouleau, Delage, Coulombe & Bouchard, 1955).

There are few observations which suggest an action of histamine on the CT-zone. In dogs, Hatcher & Weiss (1923) elicited vomiting within 30 sec of applying histamine to the exposed surface of the fourth ventricle. On injection into a lateral cerebral ventricle, Light & Bysshe (1933) obtained vomiting in one of four monkeys using large doses of histamine, and Feldberg & Sherwood (1954), using much smaller doses, elicited violent retching in cats, but not actual vomiting. Peng & Pi (1967) recently showed that the emesis produced in dogs by intravenous injections of histamine was only in part accounted for by an action on the CT-zone. After its ablation higher doses of histamine were required to produce vomiting than in dogs with an intact CT-zone.

In the present experiments the dose of histamine required to elicit vomiting when injected into a lateral ventricle was first compared with that which elicited vomiting on injection into the fourth ventricle. If histamine were to act on the CT-zone, it should be more effective on injection into the fourth ventricle. To obtain direct evidence for the role of the CT-zone, the effect of its bilateral ablation was examined on the emetic response to intraventricular histamine. Finally, the paper includes experiments which show that chlorpromazine and the two antihistamines, cyclizine and mepyramine, exert a protective action against this response.

Methods

The experiments were carried out on dogs of either sex weighing between 6 and 8 kg. Chronic implantation of a cannula into either a lateral or the fourth cerebral ventricle was performed aseptically under pentobarbitone sodium anaesthesia (25 mg/kg intravenously). To cannulate a lateral ventricle, we used the method of Bhargava *et al.* (1961), and to cannulate the fourth ventricle that of Bartlestone, Reilly & Wang (1958). The correct placement of the cannulae was ascertained by withdrawal of clear cerebrospinal fluid from the implanted cannula, by a positive emetic response to an injection of apomorphine into the cannulated lateral (2 μg) or fourth ventricle (0.5 μg) 3 to 4 days after the implantation and finally on autopsy.

Bilateral ablation of the CT-zone was performed by gentle thermal cauterization of the area postrema under pentobarbitone sodium anaesthesia. Intramuscular injections of strepto-penicillin were given post-operatively for 5 days. Functional elimination of the CT-zone was shown to have occurred when the dogs failed to vomit in response to intravenous apomorphine (200 μg/kg 8 times the *ED*100; Borison & Wang, 1952). On the other hand, the intactness of the vomiting centre was proved by a positive emetic response to copper sulphate administered orally through an intragastric tube on an empty stomach (300 mg in 25 ml. of water).

All drugs injected into the cannulated cerebral ventricles were dissolved in 0.9% NaCl solution and injected in a volume of 0.2 ml. For studying the emetic response to intraventricular histamine, the dogs were fed 10–30 min before the injection and observed until they vomited, or for a period of 2 hr. The emetic response was considered positive only when there was actual expulsion of the stomach contents; retching alone was not sufficient. The tests were made at intervals of at least 3 days.

Drugs. Histamine acid phosphate (Ward, Blenkinsop Co., London); apomorphine hydrochloride (Mallinckrodt Chemical Works, New York); copper sulphate; chlorpromazine hydrochloride (May & Baker Ltd., Bombay); cyclizine lactate (Marzine, kindly supplied by Burroughs Wellcome, Bombay); mepyramine maleate (May & Baker Ltd., Bombay). The doses of histamine refer to the base; those of the other drugs to the salts.

Results

Table 1 shows that histamine causes vomiting when injected into the cerebral ventricles and that it is less effective when injected into the lateral than into the fourth ventricle. To produce vomiting regularly with each injection, 3 mg histamine had to be injected into the lateral and 0.3 mg into the fourth ventricle. Further, on injection of 0.3 mg into the fourth ventricle, emesis occurred earlier, the mean latency being 3.5 min, as compared with 10 min on injection of 3 mg into the lateral ventricle. Other effects observed with these injections were licking, salivation, retching, tachypnoea, restlessness, muscular inco-ordination, and sometimes urination and defaecation.

Bilateral ablation of the CT-zone

After ablation of the trigger zone, the dogs did not respond to emetic action of intraventricular histamine. As shown in Table 1, no vomiting occurred when histamine was injected into the lateral ventricle (12 mg) or into the fourth ventricle (1 mg), in other words, with 4 and more than 3 times the dose that regularly produced vomiting in dogs with intact CT-zone.

Chlorpromazine, cyclizine and mepyramine

Table 2 shows the protective action of these three compounds. The chlorpromazine was injected intramuscularly, the two antihistamines intramuscularly or into the lateral ventricle 15–30 min before the injection of histamine (6 mg) into the lateral ventricle. This dose no longer elicited vomiting although normally 3 mg would have been sufficient to do so. Table 2 further shows that injections into the lateral ventricle of cyclizine or mepyramine did not prevent emesis in response to the oral administration of copper sulphate.

TABLE 1. *Emetic effect of intraventricular histamine in normal and CTZ-ablated dogs*

Condition of dog	Route	Dose of histamine (mg)	No. of dogs tested	No. of dogs who vomited	Latency of vomiting average and range (min)
Normal	Lat. vent.	0·15	5	1	4·00
	Lat. vent.	0·30	7	4	12·0 (8·0–25·0)
	Lat. vent.	2·00	8	6	20·0 (7·0–45·0)
	Lat. vent.	3·00	10	10	10·0 (7·0–15·0)
	Fourth vent.	0·01	4	1	14·0
	Fourth vent.	0·03	4	3	12·5 (10·0–15·0)
	Fourth vent.	0·15	4	3	6·0 (2·0–10·0)
	Fourth vent.	0·30	4	4	3·5 (2·0–5·0)
CTZ-ablated	Lat. vent.	3·0	1	0	—
	Lat. vent.	6·00	3	0	—
	Lat. vent.	12·00	2	0	—
	Fourth vent.	1·00	2	0	—

Discussion

The results of the present experiments show that the emesis produced by injections of histamine into the cerebral ventricles of the dog is fully accounted for by an action on the chemoreceptor trigger zone (CT-zone) located in the area postrema at the caudal end of the fourth ventricle, for the emesis was no longer obtained after ablation of this zone. The finding that in dogs with the CT-zone intact about ten times larger doses of histamine had to be injected into the lateral ventricle to produce emesis, and that it occurred after a longer latency than on injection into the fourth ventricle, is readily explained by this site of action. Similar differences in dosage and latency were observed by Share, Chai & Wang (1965) with apomorphine which also acts on the CT-zone. On injection into the lateral, third or fourth ventricle, the effective dose was smallest and the latency shortest when the apomorphine was injected into the fourth ventricle.

The observations by Feldberg & Sherwood (1954) that injections of histamine into the lateral ventricle of cats produced violent retching without actual vomiting may be because their cats had empty stomachs or that the doses they used (0.15–0.2 mg) were insufficient to elicit the full effect. In our experiments too, vomiting occurred after 0.15 mg in only one out of five, and after 0.3 mg in four out of seven, experiments.

Although the present experiments show that the emesis produced by intraventricular histamine results solely from an action on the CT-zone, the same conclusion does not apply to the emesis resulting from intravenous injections of histamine. According to Peng & Pi (1967), three different receptors are responsible for this emesis: "namely, the CT-zone, the abdominal visceral receptors (with afferents in the vagus and sympathetic) and receptors other than these." A similar situation seems to pertain for the emetic action of adrenaline. Ablation of the CT-zone prevents the emetic response to injections of adrenaline into the cerebral ventricles (Borison, 1959) but the emesis produced by intravenous injections of large doses of adrenaline persists (Peng, 1963). According to Wang (1965), the CT-zone is the primary site for the adrenaline emesis also on parenteral injection. Because intravenous histamine releases the catecholamines from the adrenal medulla as first shown by Burn & Dale (1926) an action of released catecholamines may contribute to the emesis of parenteral histamine particularly so far as an action on receptors other than those in the CT-zone is concerned. This possibility has not been excluded by Peng & Pi.

TABLE 2. *Protection against histamine emesis by drugs*

Anti-emetic agent	Intraventricular histamine (6·0 mg) test		Oral copper sulphate test	
	Number of dogs		Number of dogs	
	Tested	Vomited	Tested	Vomited
Chlorpromazine				
(3 mg/kg i.m.)	3	0	–	–
Cyclizine				
(5 mg/kg i.m.)	2	0	–	–
(5 mg/lat. vent.)	2	0	2	2
Mepyramine				
(5 mg/kg i.m.)	3	3	–	–
(10 mg/kg i.m.)	2	0	–	–
(5 mg/lat. vent.)	3	0	3	3

The blocking action of the two antihistamines, cyclizine and mepyramine, against the emetic response to intraventricular histamine suggests the existence of histaminergic receptors in the CT-zone. A depression of the emetic cenre itself is ruled out because the antihistamines did not prevent the emetic response to oral copper sulphate. It is not certain, however, how far the protective action of the antihistamines is specific for histamine. Ballinger & Borison (1957) found that cyclizine also blocked the emetic response to threshold doses of apomorphine but not of veriloid or copper sulphate. This raises the question whether apomorphine acts through release of histamine in the CT-zone. On the other hand, the action of the antihistamines may resemble that of chlorpromazine which has weak antihistamine properties but nevertheless blocked the emetic response to intraventricular histamine. Brand, Harris, Borison & Goodman (1959) suggested that chlorpromazine acts on more than one type of chemoreceptors in the CT-zone.

Histamine has been implicated in a variety of conditions in which emesis occurs, such as anaphylaxis, allergy, morning-sickness and radiation sickness. It is possible that in these conditions, too, the emesis results partly, or entirely, from an action of histamine in the CT-zone.

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