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ROLE OF CATECHOLAMINES AND THE CHEMORECEPTOR TRIGGER ZONE IN RESERPINE INDUCED EMESIS

BY

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The area postrema of the medulla oblongata, which is the anatomical site of the chemoreceptor trigger zone (CT-zone) for emesis, is very rich in catecholamines (Vogt, 1954). The catecholamines produce emesis in dogs and cats when administered by the intracerebroventricular (i.c.v.) route (Feldberg & Sherwood, 1954; Borison, 1959) or by the intravenous route (Peng, 1963). The possibility that drugs may produce emesis indirectly by releasing catecholamines has been explored by Cahen (1964). He concluded that 5-hydroxytryptophane (5-HTP) induced emesis in cats, and that this is mediated through the release of catecholamines because it was prevented by prior catecholamine depletion with intraperitoneal injection of reserpine or L-methyl meta tyrosine (L-MMT) and because the emesis was facilitated by monoamine oxidase inhibitors iproniazid, niamid and isocarboxazid.

Reserpine is a well-known releaser of catecholamines peripherally as well as centrally (Carlsson, Rosengren, Bertler & Nilsson, 1957). It readily induces emesis in pigeons (Earl, 1955; Gupta & Dhawan, 1960) and this response has been employed for the assay of reserpine in partially purified extracts of *rauwolfia* (Earl, Winters & Schneider, 1955). However, there are no reports regarding its emetic action in other species. In a preliminary report* we have shown that intracerebroventricular injection of reserpine (0.5 mg) consistently elicited emesis in dogs. The present study has been undertaken to determine the function of catecholamines and the CT-zone in the reserpine induced emesis.

METHODS

Dogs of either sex weighing from 3–6 kg were prepared with cannulae permanently implanted in the right lateral cerebral ventricle according to the method used by Bhargava, Gupta & Chandra (1961). The effective emetic dose of reserpine was determined by administering it through the cannula within half an hour of feeding the animal. Actual expulsion of gastric contents through

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the mouth was taken as the criterion of emesis. The dogs were observed until they vomited or for a period of 2 hr after the drug was administered. An interval of at least five days was allowed between two successive emetic tests. The drug solution injected into the ventricle did not exceed a volume of 0.5 ml. and was always followed by 0.2 ml. normal saline to wash the drug from the cannula.

Ablation of the medullary emetic chemoreceptor trigger-zone (CT-zone) was done under pentobarbitone anaesthesia (25 mg/kg intravenously). Thermal cauterization of the area postrema was accomplished by gently lifting up the cerebellum covering the calamus scriptorius. The wound was closed aseptically and penicillin was given postoperatively for five days. The ablation of the CT-zone was considered successful when the dog showed an emetic response to oral copper sulphate but not to intravenous apomorphine (100 μg/kg). For testing the emetic response to copper sulphate, the dogs were not given food for 24 hr and 350 mg (total) copper sulphate dissolved in 25 ml. water was given by a stomach tube. The intactness of the vomiting centre was indicated if the dog vomited either while the stomach tube was being passed, or when the copper sulphate reached the stomach. To explore the possibility of mediation of catecholamines in the reserpine induced vomiting, L-methyl-M-tyrosine (MMT) or reserpine was administered intraperitoneally to deplete the catecholamines. MMT (50 or 75 mg/kg) was given either 1½ hr or 24 hr before the emetic test. Reserpine (0.5 mg/kg) was administered daily for two days and the emetic test was performed on the third day.

RESULTS

The results are summarized in Table 1. A dose of 0.5 mg reserpine when administered intracerebroventricularly consistently produced emesis in all the six dogs tested. The average latent period was 8 min.

Pretreatment with reserpine (0.5 mg/kg) intraperitoneally for two days did not prevent the emesis induced by reserpine. Similarly intraperitoneal administration of MMT, 50

TABLE 1

EMETIC EFFECT OF RESERPINE INJECTED INTO THE CEREBRAL VENTRICLES OF NORMAL CT-ZONE ABLATED AND DRUG TREATED DOGS

Condition of dog	Intra-cerebro-ventri-cular Reserpine (mg)	Dogs tested (No.)	Dogs vomited (No.)	Average latent period (min)
Normal	0·1	1	0	—
	0·25	6	2	11
	0·5	6	6	8
Pretreated with Reserpine 0·5 mg/kg i.p. for two days	1·0	3	3	11
MMT 50 mg/kg i.p. 90 min before test	1·0	1	1	10
MMT 75 mg/kg i.p. 24 hr before test	1·0	3	3	9
CT-zone ablated	0·5	1	0	—
	1·0	5	0	—

mg/kg 90 min before or 75 mg/kg 24 hr before, was also ineffective in preventing the reserpine induced emesis.

In five CT-zone ablated dogs, twice the 100% emetic dose of reserpine failed to evoke emesis.

DISCUSSION

The role of catecholamines in emesis is far from clear. That the catecholamines may be concerned in emesis is suggested by (1) the very high concentration of these amines in the chemoreceptor trigger-zone (CT-zone) for emesis situated in the area postrema of the medulla oblongata (Vogt, 1954); (2) epinephrine and its precursors have been shown to potentiate the apomorphine induced emesis (Boyd & Cassell, 1957); Forster & Günther, 1962); (3) epinephrine induces emesis by intracerebroventricular or intravenous routes in cats and dogs (Borison, 1959; Peng, 1963); and (4) the catecholamine depletors afford protection against emesis induced by 5-HTP (Cahen, 1964), apomorphine (Malhotra & Sidhu, 1956; Boyd & Cassell, 1957; Forster & Kunze, 1962) and staphylococcal enterotoxin (Sugiyama, Bergdoll & Wilkerson, 1960). Although these studies may suggest a role of catecholamines in the emetic response, it cannot be stated whether the catecholamines present in the area postrema have a role in exciting the underlying vomiting centre.

It seems that the depletion of catecholamines from the area postrema renders the CT-zone unresponsive to some drugs or toxins which act through this mechanism. Most investigators have employed reserpine to deplete the stores of catecholamines and it cannot be assessed how far the sedative action of the drug was responsible for the protection against various emetic agents. Moreover, Ballinger & Borison (1957) failed to observe protection against apomorphine induced emesis in dogs pretreated with reserpine for several days. Similarly, reserpine pretreatment was ineffective in preventing the emesis induced by veratrum (Gourzis, 1955). There was no alteration in the level of catecholamines in the area postrema of dogs treated with apomorphine or morphine (Vogt, 1954). It appears that an intact CT-zone is essential for the emesis induced by intracerebroventricular epinephrine and intravenous dopa. An alternative mechanism is, however, possible for the emesis induced by intravenous epinephrine (Peng, 1963). If an emetic response is thought to be mediated *via* the catecholamine release centrally, it must be assumed to act through the CT-zone. The possibility that a humoral rather than a neural mechanism may be involved in the activation of the emetic centre following stimulation of the chemoreceptor trigger zone has been suggested by some workers (Brizzee & Neal, 1954; Brizzee, 1956). The cytoarchitecture of the area postrema may suggest that catecholamines could excite the neuro-elements in the CT-zone or the neurohumour be carried to the vomiting centre through the rich network of blood vessels in the region (Clemente & Van Breemen, 1955).

In view of the potent catecholamine releasing property of reserpine, the role of catecholamines in reserpine emesis is highly presumptive. In order to test the possibility that the emetic action of reserpine may be mediated through the catecholamines, the drug was administered intracerebroventricularly to dogs depleted of catecholamines by pretreatment either with reserpine or with L-MMT. The dosage of reserpine employed

in our study for depleting catecholamines was five times the dose employed by Cahen (1964). The dose of MMT employed was that which protected the animals against the 5-HTP induced emesis (Cahen, 1964). The results showed that the catecholamine depletion does not prevent reserpine emesis and hence it seems probable that the emetic action of reserpine is not through the release of catecholamines.

Intracerebroventricular injection of reserpine in a dose of 0.5 mg regularly produced vomiting. Ablation of the CT-zone in dogs rendered them refractory to twice the 100% emetic dose of reserpine. These results suggest that the drug acts directly on the CT-zone.

SUMMARY

1. Reserpine (0.5 mg) administered intracerebroventricularly regularly produced emesis in dogs. The average latent period was 8 min.

2. To explore the possibility that the reserpine emesis might be due to the liberation of catecholamines the drug was administered intracerebroventricularly to dogs pre-treated intraperitoneally either with reserpine (0.5 mg/kg for two days) or L-methyl meta tryosine, MMT (75 mg/kg one day before). The emetic response was still elicited.

3. Chemoreceptor trigger-zone (CT-zone) ablation in five dogs made them refractory to 1 mg (twice the 100% emetic dose) of intracerebroventricularly administered reserpine.

4. It is concluded that the site of emetic action of reserpine may be the CT-zone and that the emetic action of reserpine is due to the drug *per se* and not to the release of catecholamines.

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