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THE MECHANISM OF THE EMETIC ACTION OF SODIUM SALICYLATE

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In the dog, the emetic ED50 for sodium salicylate was 256±113 mg/kg for the intravenous route with a mean latency of 10.4±3.96 min, and for the oral route 228±68 mg/kg with a mean latency of 18.2±2.63 min. Values are means with standard errors. Ablation of the emetic chemoreceptor trigger-zone gave complete protection against the emetic action of 300 mg of sodium salicylate intravenously but only partial protection against the emetic action of the same dose of sodium salicylate orally. Either the intravenous salicylate acted on the trigger-zone or ablation of the trigger-zone interfered with afferent nerves from peripheral receptors responding to intravenous salicylate and which were different from the receptors responding to oral salicylate. After supradiaphragmatic vagotomy, there was equal protection against intravenous and oral salicylate. Two explanations can be advanced. First, the receptors responding to intravenous and those responding to oral salicylate have a common path in the vagus nerves; or second, afferent fibres in the vagus nerve normally maintain the vomiting centre in a reactive state. When these fibres are cut any other afferent fibres become less effective in evoking vomiting. Spinal transection gave partial and spinal transection with vagotomy gave complete protection. It is concluded that further work is necessary to decide which of the two explanations obtained.

Clinically, large doses of sodium salicylate often induce nausea and vomiting. Local gastric irritation need not necessarily play a dominant role in emesis due to salicylate, for vomiting can occur just as frequently after intravenous as after oral administration of the drug and without the appearance of salicylate in the gastric juice (Caravati & Cosgrove, 1946). But emesis can also occur after oral administration of salicylate in the presence of a low plasma concentration of salicylate (Graham & Parker, 1948). The absence of salicylate in the *vomitus* after the intravenous or rectal administration of salicylate seems to suggest a central locus of action. Indeed, Hatcher & Weiss (1923) have evoked emesis in dogs by direct application of sodium salicylate to the floor of the fourth ventricle.

The present investigation was undertaken in an attempt to elicit more information about the roles of the medullary emetic chemoreceptor trigger-zone and of the peripheral receptor sites in the emesis induced by intravenous, oral and intracerebroventricular administration of sodium salicylate into dogs.

METHODS

Dogs weighing from 3.0 to 12.2 kg were used. The effective emetic dose of sodium salicylate was determined by administration of the drug by oral, intravenous and intracerebroventricular routes. Expulsion of gastric contents through the mouth was taken as the criterion of emesis.

The dogs were observed until they vomited or for a period of 2 hr. The oral emetic dose was estimated in dogs which had fasted for 18 hr previously. The dose of sodium salicylate was dissolved in 25 ml. of tap water and was given through a stomach tube. For estimation of the intravenous emetic dose, the dogs were fed 15 min before an intravenous injection of the drug, which was dissolved in 10 ml. of distilled water. Intracerebroventricular injection was made through a chronically implanted cannula (Bhargava, Gupta & Chandra, 1961).

The following procedures were adopted to exclude the receptor sites concerned in the emetic response. The animals were anaesthetized with pentobarbitone sodium (30 mg/kg intraperitoneally). The operations were conducted aseptically and penicillin was given for 3 days after each operation.

(*a*) Ablation of the chemoreceptor trigger-zone was effected by careful thermal cauterization of the area postrema. The ablation was considered successful if the dog did not show an emetic response to apomorphine (50 μg/kg intravenously, twice the emetic ED100). A positive emetic test with oral copper sulphate (300 mg in 25 ml. of water) indicated that the vomiting centre was still intact (Wang & Borison, 1952).

(*b*) Superficial medullary lesions were made by cautery lateral to the chemoreceptor trigger-zone. A positive emetic response to apomorphine (50 μg/kg intravenously) demonstrated that the chemoreceptor trigger-zone was undamaged.

(*c*) The vagus nerve just above the diaphragm was sectioned by the transthoracic route.

(*d*) The spinal cord was exposed by laminectomy at T1, double-ligated within the meninges and sectioned between the ligatures. Salicylate-emetic tests were performed 24 to 48 hr after spinal transection. With animals in which both vagotomy and spinal transection were performed, the former procedure was done first and the animals were allowed to recover before carrying out spinal transection. In all spinal animals, an abdominal binder facilitated mechanically the process of vomiting. In dogs with lesion (*c*), (*d*) or (*c*) and (*d*), vomiting after apomorphine (50 μg/kg intravenously) showed that the medullary emetic mechanism was intact.

RESULTS

Incidence of vomiting after oral or intravenous sodium salicylate. Fig. 1 relates the number of dogs vomiting in response to oral or intravenous sodium salicylate (150 to 600 mg/kg). The oral ED50 ($\pm$standard error) was 228.0$\pm$68 mg/kg (n=24) and the intravenous ED50 was 255.7$\pm$113 mg/kg (n=25); the difference between these two values was not statistically significant. The emetic ED100 was 600 mg/kg (n=4), but this dose was not selected for the study because it was poorly tolerated and it caused depression, hyperpnoea and death within 2 hr in two dogs. Two other dogs, which survived, became anorexic and weak; they died from inanition within a few days. Sodium salicylate (300 mg/kg) was well tolerated and dogs which initially vomited after this dose were used for subsequent experiments. Vomiting in response to intravenous salicylate (300 mg/kg) occurred within a latent period of 10.4$\pm$3.96 (standard error) min while with oral salicylate the latency was 18.2$\pm$2.63 min. In two dogs, intravenous salicylate (300 mg/kg) evoked the emetic response when given on four occasions separated by intervals of 4 or 5 days.

In six dogs sodium salicylate, 1 to 10 mg/kg in 0.5 ml. introduced through a chronically implanted cannula in a lateral cerebral ventricle, invariably caused excitement, salivation, licking, hyperpnoea, barking and defaecation, but never emesis.

Chemoreceptor trigger-zone ablation. In thirteen dogs in which ablation was successful, intravenous sodium salicylate (300 mg/kg, three dogs; 400 mg/kg, six dogs; 600 mg/kg, two dogs; and 1,200 mg/kg, two dogs) never caused vomiting. With 600 mg/kg or more of salicylate, the dogs exhibited signs of salicylate intoxication

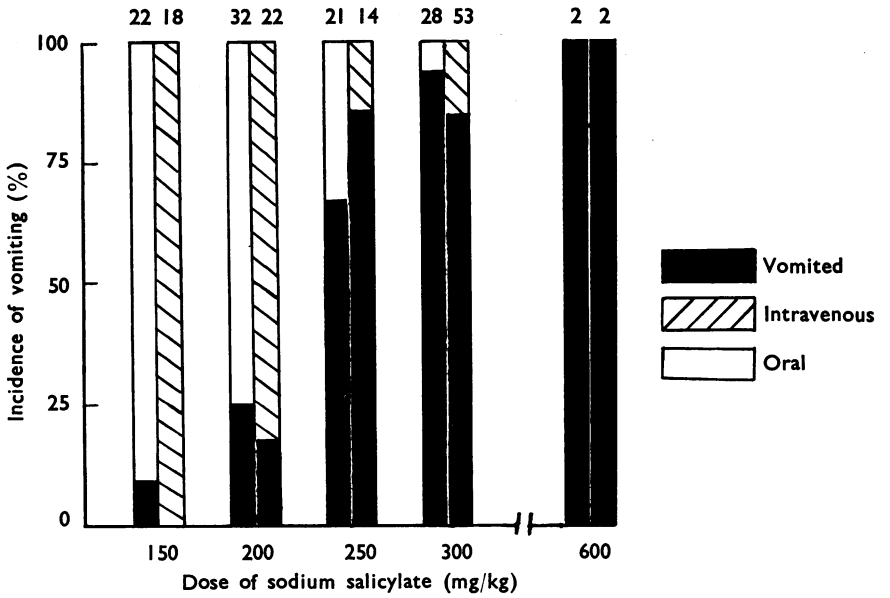

Fig. 1. The incidence of vomiting expressed as a percentage in dogs given sodium salicylate orally (left-hand) or intravenously (right-hand columns). The figure at the top of each column represents the number of dogs tested.

and sometimes even died, but never vomited. However, ablation of the chemoreceptor trigger-zone afforded protection from vomiting to only two of seven dogs given sodium salicylate (300 mg/kg) by mouth. Thus the chemoreceptor trigger-zone appears essential for emesis after intravenous injections of salicylate; whereas other sites appear to be involved in emesis following oral salicylate.

Superficial medullary lesions lateral to the area postrema but not including the chemoreceptor trigger-zone. Six dogs which initially vomited after sodium salicylate (300 mg/kg intravenously) were prepared by making discrete superficial medullary lesions, parallel with and lateral to the area postrema, but leaving the chemoreceptor trigger-zone intact since all dogs vomited after apomorphine (50 μg/kg intravenously). None of these six dogs vomited after intravenous injection of sodium salicylate in doses of 400 mg/kg (four dogs) and 600 mg/kg (two dogs), but in two dogs oral salicylate (300 mg/kg) still caused vomiting.

Supradiaphragmatic vagotomy. The effects of chronic vagotomy on the emetic response, 4 days after operation, to oral and intravenous salicylate are shown in Table 1. After the oral emetic dose of sodium salicylate three of twelve dogs vomited, while after the intravenous emetic dose twelve of twenty-nine vomited.

Spinal cord transection at T1. When salicylate was given 24 hr after spinal cord transection, one of three dogs vomited, while intravenous salicylate produced emesis in two of seven animals.

Vagotomy together with spinal cord transection. Of seven dogs, none of four vomited after intravenous and none of three after oral emetic doses of sodium salicylate. All seven dogs vomited after intravenous apomorphine (50 μg/kg).

TABLE 1

EFFECT OF SUPRADIAPHRAGMATIC VAGOTOMY AND/OR SPINAL CORD TRANSECTION AT T1 ON EMESIS INDUCED BY SODIUM SALICYLATE (300 MG/KG)

Preparation	Route of administration	Proportion of dogs vomiting	Latency (min)	
			Mean	Range
Normal	Intravenous	45/53	10·4	(1–100)
	Oral	26/28	18·4	(1–56)
Supradiaphragmatic vagotomy	Intravenous	12/29	30	(1–65)
	Oral	3/12	22	(1–40)
Spinal transection	Intravenous	1/3	20	—
	Oral	2/7	24	(20–28)
Vagotomy+ spinal transection	Intravenous	0/4	—	—
	Oral	0/3	—	—

DISCUSSION

The procedure suggested by Wang & Borison (1952) to ascertain the site of action of an emetic agent was followed in the present study. The chemoreceptor trigger-zone has not been as clearly defined morphologically in the dog as in the cat (Borison & Brizzee, 1951). In the cat, the emetic chemoreceptor trigger-zone is only an extremely small part of the area postrema, but all lesions made by Borison (1957) in the dog for ablation of the chemoreceptor trigger-zone encroached on the contiguous vagal and vestibular nuclei. As histological examination of the medullary lesion provided no morphological basis for the patterns of protection against the emetic, he considered that functional emetic tests provide satisfactory evidence for the ablation of the emetic receptor site. Dogs in which the chemoreceptor trigger-zone was ablated were refractory to twice the emetic ED100 of intravenous apomorphine but vomited after oral copper sulphate.

Ablation of the chemoreceptor trigger-zone completely protected against the action of intravenous salicylate but not of oral salicylate. There would thus seem to be sites of action of oral salicylate other than the chemoreceptor trigger-zone in the brain. Interruption of vagal afferent pathways from the abdominal region protected nine of twelve animals from the emetic effect of oral salicylate. Similar protection against oral salicylate was obtained by spinal transection. Complete protection against oral salicylate was seen only when both vagal and spinal afferent pathways were interrupted, which suggests peripheral sites of action. The localization of the peripheral abdominal receptors of the sites concerned in the emesis remains to be established. It appeared that emesis following administration of salicylate, like that after copper sulphate, depends on the stimulation of peripheral receptors and then of central receptors in the chemoreceptor trigger-zone (Wang & Borison, 1952).

That intraventricularly administered sodium salicylate failed to induce emesis may indicate the absence of an action of the drug at central receptor sites or of its access to such sites. It is difficult to reconcile our observation with that of Hatcher & Weiss (1923), who found an emetic response to the local application of sodium salicylate to the floor of the fourth ventricle.

The mechanism operating at the chemoreceptor trigger-zone and its relation to the deeper-lying vomiting centre require re-evaluation in view of the histological findings of Kuru (1956), who demonstrated the terminations of visceral afferent nerves close to the chemoreceptor trigger-zone. Borison (1957) also contends that a discrete lesion in the chemoreceptor trigger-zone of the dog would be expected to interrupt more emetic afferent nerves of different origin than a similar lesion in the cat since the centripetal emetic pathways are probably more tightly funnelled through this region in the former species.

In the dogs with superficial lesions in the medulla which did not damage the emetic zone responsive to apomorphine, vomiting after oral salicylate was not prevented. Whereas this finding does not minimize the role of the chemoreceptor trigger-zone in emesis due to apomorphine, it seems to rule out the chemoreceptor trigger-zone as the site of emetic action of intravenous salicylate. In earlier experiments Bhargava & Verma (1959) reported the site of emetic action of intravenous sodium salicylate to be the chemoreceptor trigger-zone, but they may have damaged the afferent terminations from peripheral receptors which are concerned with emesis due to salicylate. In this connexion chemoreceptor trigger-zone ablation was first reported to prevent the emetic response to radiation in monkeys (Brizzee, Neal & Williams, 1955) but later supradiaphragmatic vagotomy alone proved sufficient to prevent the emesis (Brizzee, 1956).

It may be emphasized that, if the emetic action of an agent is completely blocked by chemoreceptor trigger-zone ablation, this does not necessarily mean that the agent was acting solely at that site. In order to localize a drug action to the chemoreceptor trigger-zone it is necessary to show that the emetic response is not altered by cutting afferent nerves from the periphery.

We conclude that the site of emetic action of salicylates is peripheral. Perhaps the receptors for the oral salicylates lie in the mucosa of the upper alimentary canal, while those for circulating salicylate probably lie elsewhere in the abdomen. The afferent nerves mainly concerned in the emetic response to oral salicylates seem to lie deeper in the medulla than those concerned with the vomiting after intravenous salicylate.

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