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MECHANISM OF SPECIES DIFFERENCES IN SENSITIVITY OF MONKEYS AND DOGS TO THE EMETIC ACTION OF VARIOUS DRUGS

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Monkeys and dogs differ significantly in their sensitivity to emetics acting on the chemoreceptive trigger zone (CTZ) of the vomiting center [3]. Agonists of dopamine receptors do not cause vomiting in monkeys [15], whereas injection of apomorphine and other dopaminomimetics into dogs is accompanied by a marked vomiting reaction [14, 17]. Meanwhile certain drugs, such as cardiac glycosides, induce vomiting in both monkeys and dogs [15, 17].

The object of the present investigation was to study the mechanisms determining species differences in the responses of monkeys and dogs to the emetic action of various drugs.

EXPERIMENTAL METHOD

Experiments were carried out on male monkeys *Macaca mulatta* weighing 3.5-4.5 kg and on mongrel dogs of both sexes weighing 8-16 kg. The sensitivity of the experimental animals was determined to the emetic action of apomorphine, L-dihydroxyphenylalanine (L-dopa), adrenaline, clonidine, 5-hydroxytryptophan (5-HTP), and sodium salicylate. The ability of reserpine, mexamine (5-methoxytryptamine), trimeperidine, metoclopramide, and phentolamine to prevent the emetic effect of sodium salicylate also was studied. Reserpine was given 24 h, and the other drugs 30 min, before injection of the emetic. The doses of the drugs tested are given in Tables 1 and 2. Apomorphine and trimeperidine were injected subcutaneously, mexamine, metoclopramide, and phentolamine intramuscularly, and the remaining drugs intravenously. The numerical results were subjected to statistical analysis by Fisher's accurate method [2].

EXPERIMENTAL RESULTS

The experiments in which drugs selectively exciting different monoaminergic structures of CTZ were administered to monkeys and dogs (Table 1) showed that a vomiting response was observed in monkeys only to injection of 5-HTP, a specific agonist of serotonin receptors [1, 4]. Meanwhile dogs, unlike monkeys, were highly sensitive to the emetic action of apomorphine and L-dopa, substances exciting dopaminergic receptors of CTZ [11, 12], and of the α-adrenomimetic clonidine. Doses of 5-HTP whose action is accompanied by marked behavioral disturbances did not induce vomiting in the animals of this species.

The results suggest that CTZ in monkeys does not possess dopaminergic and adrenergic receptors, and in dogs it does not contain serotonin receptors. Meanwhile sodium salicylate, whose emetic action in the modern view [1] is mediated through the serotoninergic structures of CTZ, induces vomiting both in monkeys and in dogs (Table 2).

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TABLE 1. Frequency of Development of Vomiting in Monkeys and Dogs after Injection of Agonists of Dopaminergic (apomorphine, L-dopa), α-Adrenergic (adrenaline, clonidine), and Serotoninergic Receptors (5-HTP)

Drug	Dose, mg/kg	Species of animals	Number of animals in which vomiting was induced
Apomorphine	0,1—0,5*	Monkeys	0
	0,1	Dogs	100
L-dopa	5,0—100,0†	Monkeys	0
	3,0	Dogs	100
Adrenaline	0,05—1,0†	Monkeys	0
Clonidine	0,03	Dogs	100
5-HTP	15,0	Monkeys	100
	15,0—25,0‡	Dogs	0

*After injection of apomorphine in a dose of 0.5 mg/kg — signs of marked stereotyped behavior.
†After injection of L-dopa in doses of 50-100 mg/kg and adrenaline in a dose of 1 mg/kg — inhibition, dyspnea, cyanosis.
‡After injection of 5-HTP in a dose of 25 mg/kg — dyspnea, inhibition, tremor, ataxia.

TABLE 2. Effect of Various Drugs on Emetic Action of Sodium Salicylate in Monkeys and Dogs

Drug	Dose, mg/kg	Species of animals	Number of animals	Number of animals in which vomiting was induced, absolute	Number of animals in which vomiting was induced, %
Sodium salicylate (control)	300,0	Monkeys	8	8	100
		Dogs	5	5	100
Reserpine	0,5	Monkeys	5	0	0
		Dogs	10	0	0
Trimeperidine	1,0	Monkeys	5	0	0
		Dogs	8	0	0
Mexamine	15,0	Monkeys	5	1*	20
		Dogs	5	5	100
Metoclopramide	3,0	»	6	6	100
Phentolamine	2,5	»	6	1*	17

*Differences significant ($P < 0.05$) compared with control.

Preliminary injection of reserpine, which exhausts reserves of endogenous amines [6], into monkeys and dogs completely prevented the emetic effect of salicylate. Mexamine and trimeperidine, which selectively block serotonin receptors of D- and M-types respectively [1, 4], also had a distinct inhibitory action on salicylate-induced vomiting in monkeys.

In dogs the emetic action of sodium salicylate was prevented only by trimeperidine and the α-adrenoblocker phentolamine. Mexamine and the dopamine blocker metoclopramide [13] were ineffective after administration of salicylate.

These results suggest that the emetic effect of salicylate in monkeys is mediated through serotonin receptors of M- and D-types, which are excited by a neurotransmitter liberated under

the influence of the drug; i.e., it is produced by the same mechanisms as in cats [1].

In dogs a leading role in the genesis of salicylate vomiting is evidently played by other neurotransmitter systems of CTZ and, in particular, adrenergic systems. This hypothesis also is confirmed by the results of histochemical investigations, which revealed catecholaminergic neurons in CTZ in dogs [5, 9].

The inhibitory action of trimeperidine on salicylate vomiting in dogs may be connected not so much with the antiserotoninergic properties of the drug as with its effect on opiate receptors, which many workers have shown to be present in CTZ [7, 10]. Activation of opiate receptors is known to inhibit liberation of catecholamines from nerve endings [16] and so to prevent the action of these transmitters on the postsynaptic membrane.

In conclusion it must be pointed out that the monoaminergic neurons of CTZ play an important role in the mechanism not only of salicylate vomiting. We know, for example, that vomiting following administration of cardiac glycosides and, in particular, of ouabain also is prevented by reserpine [8]. The emetic action of different drugs, of endogenous and exogenous toxins, and of other central-humoral emetics is evidently mediated through excitation of monoamine-containing neurons of CTZ, irrespective of whether these are catecholaminergic or serotoninergic.

These factors evidently account for the fact that sodium salicylate and cardiac glycosides induce vomiting both in monkeys and in dogs, despite the significant differences in the neurochemical structure of CTZ in animals of these species, due to predominance of catecholaminergic or serotoninergic neurons.

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