Absence of Relation between the Vocalization Response and the Intestinal Motility Induced by Intra-arterial Administration of Aza-azepinophenothiazine (RPP-201) into the Mesenteric Artery of the Dog

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NAKAYAMA, K., TAIRA, N. and HASHIMOTO, K. *Absence of Relation between the Vocalization Response and the Intestinal Motility Induced by Intraarterial Administration of Aza-azepinophenothiazine (RPP-201) into the Mesenteric Artery of the Dog.* Tohoku J. exp. Med., 1972, 106 (3), 271-274 — In conscious dogs intra-arterial injection of aza-azepinophenothiazine (RPP-201) and acetylcholine into a branch of the superior mesenteric artery induced the vocalization response. No substantial difference was found between doses of acetylcholine for vocalization in the conscious state and those for strong intestinal contractions in the anesthetized state. In contrast, RPP-201 produced no intestinal spasm in doses which caused vocalization in the conscious state. — aza-azepinophenothiazine; vocalization; intestinal motility

Previously Hashimoto and Kumakura (1964) and Hashimoto *et al.* (1964, 1965) observed that dimethylaminopropyl-tetrahydro-aza-azepinophenothiazine maleate (RPP-201) elicited pseudoaffective reflexes such as fluctuation of blood pressure and respiratory excitation when given into the cross-circulated femoral and superior mesenteric artery of anesthetized dogs. Hirata *et al.* (1966) also observed that in conscious dogs injection of RPP-201 into the femoral artery produced vocalization without tachyphylaxis.

On the other hand, Taira *et al.* (1968) demonstrated that in conscious dogs a variety of algescic substances, *i.e.*, bradykinin, elidoisin, histamine and acetylcholine, given into a branch of the superior mesenteric artery evoked the vocalization response which was prevented by prior injection of a smooth muscle relaxant, papaverine. On the basis of this finding they suggested that vigorous contractions of the intestine may probably be the primary factor for induction of the vocalization response to these substances. However, the possibility that some algescic agents may cause the vocalization response by stimulating directly endings of visceral nociceptive afferents cannot be excluded.

The present experiments were attempted to investigate whether the vocalization response of conscious dogs to intra-arterial injection of RPP-201 and acetylcholine into a branch of the superior mesenteric artery is related to the intestinal motility.

METHODS

Experiments were carried out on six dogs weighing 2–5 kg. All of the animals were initially used for vocalization experiments. Three to four days prior to the experiment, an indwelling catheter made of polyvinyl tubing was chronically implanted into a branch of the superior mesenteric artery as described previously (Taira *et al.*, 1968). The vocalization response was picked up with a microphone and registered on a chart after integration by means of a passive circuit with a time constant of 2 sec.

After the schedule of the chronic experiments had been finished, the animals were subjected to acute experiments under pentobarbital anesthesia (30 mg/kg, i.v.). The animals were laparotomized and polyvinyl tubing was inserted into a branch of the superior mesenteric artery in the same way as was employed in the chronic experiments. In order to measure intraluminal pressure, a water-filled rubber balloon was placed in that portion of the intestine which drugs injected through the tubing would reach.

Compounds used were as follows: Dimethylaminopropyl-tetrahydro-aza-azepinophenothiazine maleate (RPP-201, molecular weight of 455) and acetylcholine chloride. Acetylcholine chloride was dissolved in 0.9% saline and RPP-201 in 0.1 N HCl in a concentration of 100 μ moles/ml. These stock solutions were diluted with 0.9% saline. Drug solutions were injected into the catheter in a constant volume of 0.1 ml and flushed into the artery with 0.5 ml of 0.9% saline at a rate of 0.05 ml/sec. Injection of hydrochloride in concentrations used as vehicle of RPP-201 caused no vocalization.

RESULTS AND DISCUSSION

In conscious dogs RPP-201 produced the vocalization response and its threshold dose was 0.09 ± 0.02 μ moles (mean $\pm$ S.E., Table 1). The vocalization response was dose-dependent (Fig. 1) and occurred after a definitely short latency (Fig. 2). There was no tachyphylaxis in the response. RPP-201 was more potent and gave the less variable threshold dose than acetylcholine (Table 1).

In the anesthetized state acetylcholine caused intestinal contractions in a dose-dependent manner when injected into a branch of the superior mesenteric

Fig. 1. Vocalization responses of a dog to increasing doses of RPP-201 and 2 μ moles of acetylcholine (Ach).

TABLE 1. Threshold doses for vocalization of RPP-201 and acetylcholine injected into a branch of the superior mesenteric artery of dogs

	Number of experiments	Threshold dose (μ mole)	
		Range	Mean $\pm$ S.E.
RPP-201	5	0.08–0.16	0.09 ± 0.02
Acetylcholine	5	0.08–1.36	0.45 ± 0.26

Fig. 2. Dose-response relations for latency and duration of vocalization obtained by injection of RPP-201. Abscissa: one-, two-, four- and eight-fold threshold doses. Ordinate: time in sec. Vertical bars indicate s.e. of the mean. Numerals in parentheses refer to the number of experiments.

artery. Acetylcholine caused a strong contraction of the intestine in a dose range which had induced consistently vocalization in the conscious state. In contrast, RPP-201 produced no noticeable effect on the intestinal motility even by increasing doses up to those which had induced consistently the vocalization response in the conscious state. Fig. 3 shows summarized results obtained in six animals. In this figure areas circumscribed by contractile responses and a base line on the

Fig. 3. Effects of RPP-201 and acetylcholine (Ach) on the intestinal motility of anesthetized and laparotomized dogs. Abscissa: dose of RPP-201 and acetylcholine. Ordinate: areas of contractile responses of the intestine as expressed in per cent of those caused by 2 μ moles of acetylcholine. Vertical bars related to open and solid circles refer to s.e. of the mean of the intestinal response to RPP-201 and acetylcholine. Long vertical continuous and dashed lines in shaded areas refer to the mean threshold doses of RPP-201 (left) and acetylcholine (right). Width of the shaded areas refers to $\pm$ s.e. of the mean threshold dose.

chart were expressed in per cent of those induced by 2 μ moles of acetylcholine. Threshold doses of RPP-201 and acetylcholine for vocalization are also presented in the figure.

These results clearly indicate that RPP-201 injected into a branch of the superior mesenteric artery elicits the vocalization response having its origin in the intestinal area. The results also indicate that in the intestinal area, unlike acetylcholine, RPP-201 induces the nociceptive response presumably by direct excitation of nociceptive nerves.

Acknowledgment

This study was aided by a grant from Sankyo Central Laboratories, Tokyo. We are grateful to the Laboratories for supplying RPP-201.

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