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The role of α-adrenergic mechanisms within the area postrema in dopamine-induced emesis

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Abstract

Intracerebroventricular injection of dopamine (0.5–4.0 mg) produced dose-dependent and short-lasting emesis (1–8 min) in cats, which was abolished after ablation of the area postrema. Relatively selective α_2-adrenoceptor antagonists (yohimbine and idazoxan) and a mixed α_1- and α_2-adrenoceptor antagonist (tolazoline), but not a non-selective α_1-adrenoceptor antagonist (prazosin), injected intracerebroventricularly inhibited the emesis induced by intracerebroventricular dopamine. However, dopamine receptor antagonists (chlorpromazine, droperidol, spiperone, domperidone, trifluprazine, sulpiride and metoclopramide), an antimuscarinic drug (atropine), a ganglionic blocking agent (mecamylamine), an opioid receptor antagonist (naloxone) and a 5-HT receptor antagonist (methysergide), all injected intracerebroventricularly, had no significant effect on emesis evoked by intracerebroventricular dopamine. The emetic response to intracerebroventricular dopamine was attenuated in cats pretreated with intracerebroventricular reserpine, 6-hydroxydopamine, α-methyl-*p*-tyrosine and hemicholinium-3. It is postulated that dopamine-induced emesis is mediated through the release of noradrenaline acting at α_2-adrenoceptors and that it depends on the integrity of monoaminergic and possibly cholinergic structures within the area postrema. It appears, therefore, that the emetic effect of intracerebroventricular dopamine is mediated by adrenergic rather than dopaminergic mechanisms in the area postrema, at least in the cat.

Keywords: Emesis; Dopamine; α_2-Adrenoceptor; Area postrema; (Cat); (Intracerebroventricular injection)

1. Introduction

Within the last few decades central dopaminergic mechanisms have attained considerable importance in interpretations of the emetic effects of dopamine receptor agonists as well as of the antiemetic actions of dopamine receptor antagonists (Wampler, 1983; Barnes, 1984; Andrews and Hawthorn, 1988; Samardžić and Beleslin, 1989; Leslie et al., 1990; Beleslin, 1992). However, little is as yet known about the mechanisms of dopamine-induced emesis. In fact, to date, only Samardžić et al. (1985), Jovanović-Mićić and Beleslin (1988) and Jovanović-Mićić et al. (1989a); Jovanović-Mićić et al. (1989b) have reported that dopamine injected into the cerebral ventricles can induce emesis in cats. In addition, when studying the influence of the α_2-adrenoceptor antagonist yohimbine and the dopamine receptor antagonist chlorpromazine in dopamine-induced emesis, it was observed that intracerebroventricular yohimbine, but not intracerebroventricular chlorpromazine, inhibited the emesis induced by dopamine injected into the cerebral ventricles of the cat (Samardžić et al., 1985; Jovanović-Mićić et al., 1989a). Thus, these reports suggest that the emetic effect of dopamine is mediated by central adrenergic rather than central dopaminergic mechanisms.

In the light of these observations it was of further interest to extend these experiments and to define more fully (1) the central site/s of action, (2) the contribution of central adrenergic mechanisms and (3) the subtypes of receptors underlying the emesis evoked by dopamine injected into the cerebral ventricles of unanaesthetized cats. In addition, the contribution of dopaminergic, cholinergic and 5-hydroxytryptaminergic mechanisms to dopamine-induced emesis was investigated.

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2. Materials and methods

2.1. Subjects

In this study we used male and female cats weighing between 2 and 4 kg. Under standard laboratory conditions, the cats were housed individually in stainless steel cages (80 × 60 × 60 cm).

2.2. Surgical procedures

Each cat was anaesthetized using pentobarbital sodium (35–40 mg/kg i.p.). Under aseptic conditions, a hole was drilled 7–8 mm from the stereotaxic zero line and 4–5 mm from the midline. A Collison cannula was then screwed into the calvarium, so that the tip of the cannula rested in the left lateral cerebral ventricle (Feldberg and Sherwood, 1953). The lower end of the shaft of the cannula was made of polyethylene tubing with a side opening 1 mm from its closed tip and was positioned with the lumen facing the foramen of Monro. Post-mortem dye studies indicated that the injected material passed from the lateral ventricle into the third and fourth ventricles. Postoperatively, penicillin procaine (20 000 i.u./kg once daily) was administered intramuscularly for 3 days. The recovery of the animals postoperatively was uneventful and the animals were healthy. An interval of 5 days elapsed after surgery before an experiment was started.

2.3. Ablation of the area postrema

In one group of cats, the area postrema was destroyed electrolytically. After pentobarbital sodium (35–40 mg/kg i.p.) anaesthesia, an incision was made on the midline through the skin, subcutaneous tissue and muscles, the dura and the cisterna magna were opened and the vermis of cerebellum was elevated. Electrolytic current was delivered by a d.c. generator through a 10 MΩ resistor in series with an electrode. A 4–5 mA d.c. current was delivered to the area postrema by an electrode moved over its surface for approximately 1 min. In another group of cats the area postrema was exposed as described above, but no current was applied to the region. After these surgical procedures, a Collison cannula was implanted into the left lateral cerebral ventricle of both group of cats as described above. At least 14 days elapsed after surgery before the studies were performed. At the conclusion of each series of experiments the ablation of the area postrema was verified by standard histological procedures.

At the end of the experiments the animals were killed with an overdose of pentobarbital sodium (60 mg/kg i.p.).

2.4. Testing procedures

Successive experiments carried out on 6–12 cats were separated by an interval of at least 72 h for dopamine-induced emesis and 6 days when various receptor antagonists were used. In control experiments, repeated intracerebroventricular injections of dopamine 3 days after a single injection of the drug, as well as the injection of dopamine 6 days after the injection of a receptor antagonist (chlorpromazine, yohimbine, propranolol, or atropine), indicated complete recovery of the emetic response to dopamine. When inhibitors of the synthesis of acetylcholine, catecholamines and 5-HT were used, the experiments were separated by intervals of 4–6 weeks. The regimen for the intracerebroventricular injection of dopamine, pharmacological antagonists and inhibitors of amine synthesis was randomized so that each animal was included in each of the experimental conditions. Each cat was used in four to six experiments.

On the test day, before any behavioural or emetic measures were taken, the cats were fed and acclimatized to the test environment in a wire-mesh cage, measuring 110 × 130 × 150 cm, for at least 1 h before intracerebroventricular injection of drugs. Only expulsion of the gastric content was taken as a positive emetic response. The behaviour of the animals was under direct continuous observation throughout the experiments for a period of 2 h and intermittently for 24 h. The emesis data included in the results section are derived only from the first 2 h observation period.

Each of the substances injected intracerebroventricularly was dissolved in sterile, pyrogen-free 0.9% sodium chloride solution. The solution was injected manually, in a volume of 0.1 or 0.2 ml, from a 1.0 ml syringe, over a period of 15–20 s and washed in with 0.1 ml of saline. The α-adrenoceptor antagonists, due to their relative insolubility, were injected in somewhat greater volumes of 0.3 ml. To enhance solubility, these solutions of drugs were gently heated. Throughout the experiments, reasonable aseptic conditions were used. The inhibitors of monoamine synthesis were injected in doses previously used for intracerebroventricular and intracerebral purposes in the cat (Cranston et al., 1972; Lewis et al., 1974; Beleslin and Štrbac, 1987; Beleslin and Nedelkovski, 1988).

2.5. Drugs

The compounds used were: dopamine hydrochloride (Sigma, St. Louis, USA), chlorpromazine hydrochloride (Smith, Kline and French Labs, Philadelphia, USA), spiperone (Janssen Pharmaceutica, Beerse, Belgium), domperidone (Janssen Pharmaceutica, Beerse, Belgium), trifluprazine hydrochloride (Serva, Heidelberg, Germany), droperidol (Krka, Novo Mesto, Slove-

nia), haloperidol (Krka, Novo Mesto, Slovenia), sulpiride (Serva, Heidelberg, Germany), metoclopramide chloride (Alkaloid, Skopje, FYR Macedonia), yohimbine hydrochloride (Sigma, St Louis, USA), idazoxan hydrochloride (Sigma, St. Louis, USA), prazosin hydrochloride (Pfizer Canada, Kirkland, Quebec), tolazoline hydrochloride (Aldrich, Milwaukee, USA), atenolol (ICI, Alderley Park, England), propranolol chloride (ICI, Alderley Park, England), atropine sulphate (Sigma, St. Louis, USA), mecamylamine hydrochloride (Sigma, St. Louis, USA), naloxone hydrochloride (Endo Lab, New York, USA), methysergide bimaleate (Sandoz, Switzerland), α-methyl-*p*-tyrosine methylester (Sigma, St. Louis, USA), reserpine (Ciba-Geigy, Switzerland), 6-hydroxydopamine hydrobromide (Sigma, St. Louis, USA), 5,6-dihydroxytryptamine creatinine sulphate (Serva, Heidelberg, Germany) and hemicholinium-3 (Aldrich, Milwaukee, USA). Droperidol was dissolved in 0.1 M tartaric acid, while 6-hydroxydopamine and 5,6-dihydroxytryptamine were dissolved in 0.9% saline containing 0.1 mg/ml ascorbic acid. All doses of drugs refer to the salts except those of droperidol, atenolol, haloperidol, spiperone, domperidone and reserpine, which refer to the base. An aqueous solution of 0.1 M tartaric acid in volumes of 0.1–0.3 ml had no visible effects on the behaviour of the cat.

As far as the doses of antagonists are concerned, in our previous (Beleslin and Štrbac, 1987; Beleslin and Nedelkovski, 1988), as well as in our present experiments, we started with minimal doses. Thereafter, the doses were gradually increased. Maximal doses of the various receptor antagonists used in our experiments did not induce visible toxic symptoms like sedation, motor impairment or excitation of the cat. Similarly, Boyd et al. (1955) used the antihistamine drugs in doses which were at, or near, the minimal toxic doses that prevented apomorphine-induced emesis in dogs.

2.6. Statistics

Dose-response curves were constructed using linear regression according to the method of least squares. A coefficient of correlation (r) of linear regression was used to determine the existence of a dose-response relationship. An analysis of variance followed by Dunnett's statistics was used to test for differences between treatment and appropriate control groups. Student's t-test was used to determine the significance of the difference between controls and various experimental groups. The results were considered statistically significant when $P < 0.05$.

3. Results

3.1. Emesis and behaviour induced by dopamine

The most impressive feature of intracerebroventricular dopamine (0.5–4.0 mg) was the emesis. The emesis induced by dopamine occurred in bouts of one to eight at irregular time intervals, after a latent period of about 5 min and lasted up to 8 min. The number of vomits evoked by the catecholamine ranged from one

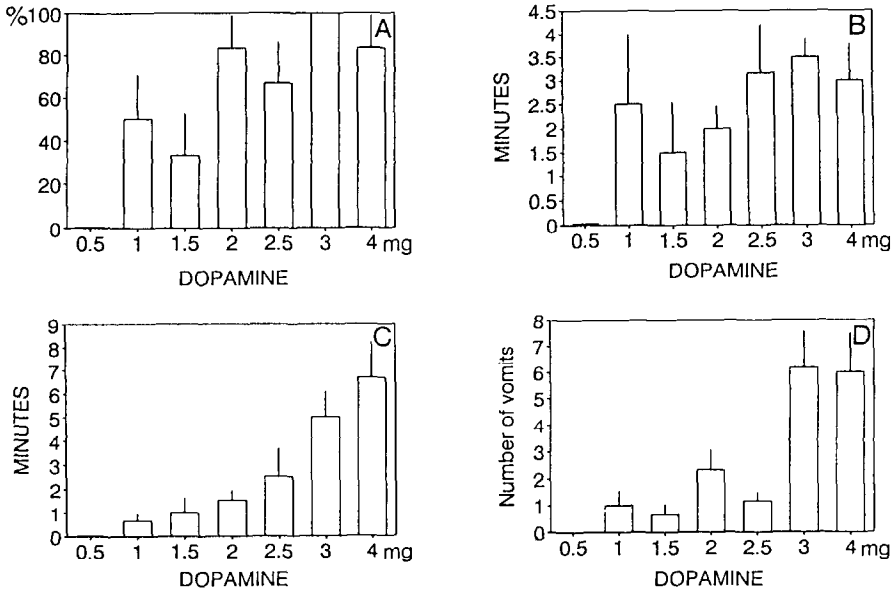

Fig. 1. Emetic responses to single doses of dopamine (abscissa) injected into the cerebral ventricles of the unanaesthetized cat in terms of: (A) percentage of animals showing the emetic response; (B) latency to emesis; (C) duration of emesis; and (D) number of vomits. Each column represents the mean ± S.E.M. for six animals.

Table 1
Behavioural effects of intracerebroventricular dopamine in cats

Symptoms	Incidence of symptoms (No. of cats responded/tested)													
	0.9% NaCl 0.2 ml		Doses of dopamine (mg)											
			0.5		1.0		1.5		2.0		2.5		3.0		4.0	
Restlessness	0/6	0%	0/6	0%	2/6	33%	0/6	0%	1/6	16%	2/6	33%	5/6	83%	5/6	83%
Licking	0/6	0%	0/6	0%	1/6	16%	3/6	50%	4/6	66%	6/6	100%	6/6	100%	6/6	100%
Mydriasis	0/6	0%	1/6	16%	2/6	33%	1/6	16%	3/6	50%	2/6	33%	5/6	83%	0/6	0%
Micturition	0/6	0%	0/6	0%	0/6	0%	1/6	16%	1/6	16%	1/6	16%	1/6	16%	1/6	16%
Defaecation	0/6	0%	1/6	16%	3/6	50%	2/6	33%	2/6	33%	2/6	33%	1/6	16%	2/6	33%
Tachypnoea	0/6	0%	0/6	0%	0/6	0%	0/6	0%	1/6	16%	1/6	16%	2/6	33%	4/6	66%
Ataxia	0/6	0%	0/6	0%	0/6	0%	1/6	16%	1/6	16%	3/6	50%	0/6	0%	2/6	33%

to six, whereas the percentage of cats showing emesis reached 100% only with the dose of 3.0 mg of dopamine. The emetic responses evoked by dopamine were all dose-dependent: the percentage of animals showing emesis at doses from 0.5 to 4.0 mg ($P < 0.05$; $ED_{50} = 1.66 \pm 0.54$ mg) (Fig. 1A), the latency to emesis at doses from 1.5 to 3.0 mg ($P < 0.05$) (Fig. 1B), the duration of emesis at doses from 0.5 to 4.0 mg ($P < 0.01$) (Fig. 1C) and the number of emetic responses at doses from 0.5 to 4.0 mg ($P < 0.01$) (Fig. 1D).

Apart from emesis, dopamine (0.5–4.0 mg), injected into the cerebral ventricles, evoked restlessness, mydriasis, licking, defaecation, micturition, panting, tachypnoea, sedation, ataxia, tremor, akathisia and adynamia. Of these effects, restlessness, licking, mydriasis, micturition, defaecation, tachypnoea and ataxia were quantitatively analysed (Table 1). These actions appeared with a frequency between 16% and 100%, occurring with a latency of a few minutes and lasting up to 60 min. Dose-dependent changes were obtained for licking at doses from 0.5 to 3.0 mg ($r = 0.96$; $P < 0.05$; $ED_{50} = 1.54 \pm 0.49$ mg), restlessness at doses from 0.5 to 3.0 mg ($r = 0.85$; $P < 0.05$; $ED_{50} = 2.78 \pm 0.37$ mg) and tachypnoea at doses from 1.5 to 4.0 mg ($r = 0.99$; $P < 0.01$; $ED_{50} = 3.58 \pm 0.62$ mg). Panting, sedation, tremor, akathisia and adynamia appeared irregularly or rarely and were not dose-dependent. It is interesting to note that with the largest doses of dopamine (2.0–4.0 mg), even though the cat usually lay down on the floor, tachypnoea, akathisia, panting and the emetic response occurred.

3.2. Dopamine receptor antagonists on dopamine-induced emesis

The dopamine receptor antagonists, chlorpromazine (0.3–2.0 mg), droperidol (0.25–1.0 mg), haloperidol (0.3–1.0 mg), spiperone (0.2–1.5 mg), domperidone

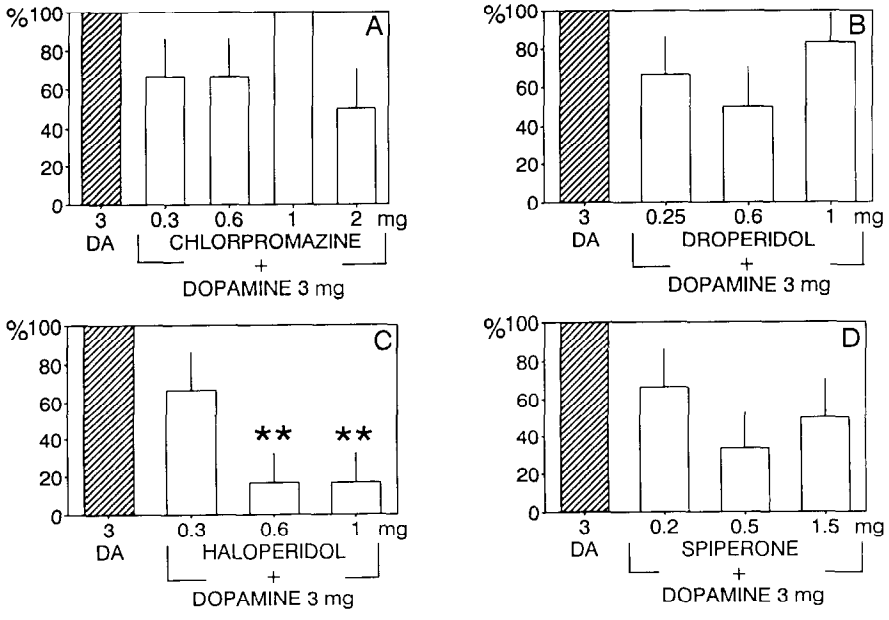

Fig. 2. Effects of chlorpromazine (A), droperidol (B), haloperidol (C) and spiperone (D) on the percentage of animals showing an emetic response to dopamine (DA). Hatched columns in (A), (B), (C) and (D) represent control experiments. Chlorpromazine, droperidol, haloperidol or spiperone was injected into the cerebral ventricles of the unanaesthetized cat, 20–30 min before 3.0 mg of dopamine, given intracerebroventricularly. Each column represents the mean ± S.E.M. for six animals. Differences are significant at ** $P < 0.01$.

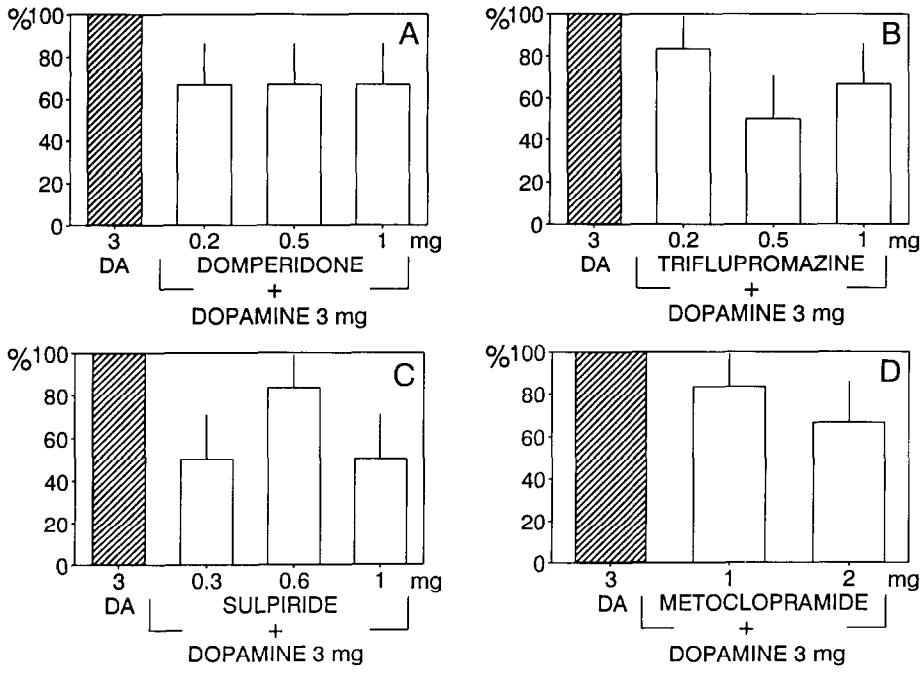

Fig. 3. Effects of domperidone (A), triflupromazine (B), sulpiride (C) and metoclopramide (D) on the percentage of animals showing an emetic response to dopamine (DA). Hatched columns in (A), (B), (C) and (D) represent control experiments. Domperidone, triflupromazine, sulpiride or metoclopramide was injected into the cerebral ventricles of the unanaesthetized cat, 20–30 min before 3.0 mg of dopamine, given intracerebroventricularly. Each column represents the mean ± S.E.M. for six animals.

(0.2–1.0 mg), triflupromazine (0.2–1.0 mg), sulpiride (0.3–1.0 mg) and metoclopramide (1.0–2.0 mg) were used to prevent the emesis produced by 3.0 mg of dopamine. Since dopamine only in doses of 3.0 mg induced emesis in 100% of animals, this dose of the catecholamine was used as a control in this as well as in the experiments presented in Figs. 2, 3, 4, 5 and 6. The antagonists were injected intracerebroventricularly

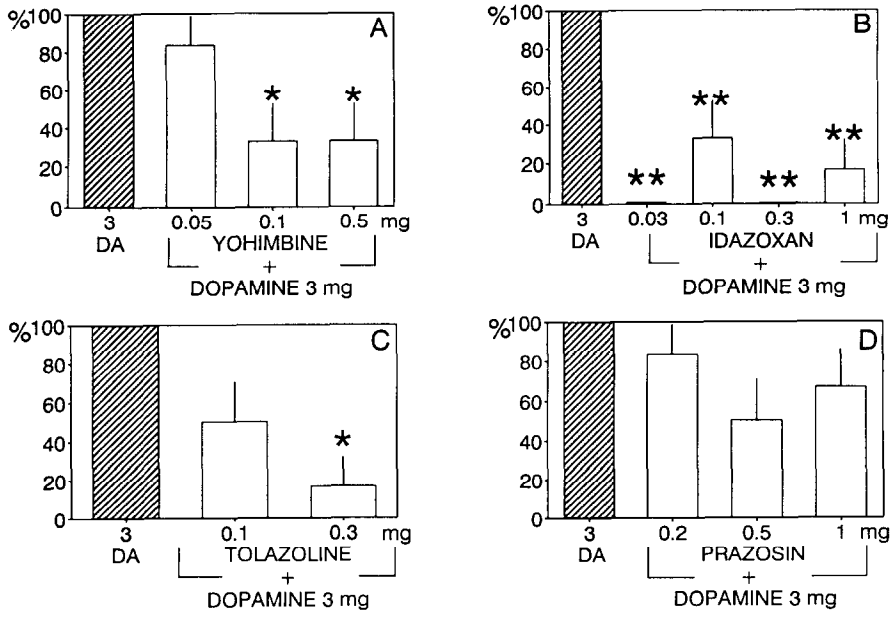

Fig. 4. Effects of yohimbine (A), idazoxan (B), tolazoline (C) and prazosin (D) on the percentage of animals showing an emetic response to dopamine (DA). Hatched columns in (A), (B), (C) and (D) represent control experiments. Yohimbine, idazoxan, tolazoline or prazosin was injected into the cerebral ventricles of the unanaesthetized cat, 20–30 min before 3.0 mg of dopamine, given intracerebroventricularly. Each column represents the mean ± S.E.M. for six animals. Differences are significant at $^{*}P < 0.05$ and $^{**}P < 0.01$.

15–20 min before dopamine was similarly administered. Chlorpromazine, droperidol, spiperone, domperidone, trifluprazine, sulpiride and metoclopramide had no significant effect ($P > 0.05$) on the percentage (Fig. 2A, B, D and Fig. 3A, B, C, D), duration, latency and number of dopamine-induced responses. However, of the dopamine receptor antagonists tested, only haloperidol in doses of 0.6 and 1.0 mg depressed ($P < 0.01$) the percentage (Fig. 2C) as well as the duration, number and latency of dopamine-induced emetic responses (data not shown).

3.3. α-Adrenoceptor antagonists on dopamine-induced emesis

The α-adrenoceptor antagonists, yohimbine (0.05–0.5 mg), idazoxan (0.03–1.0 mg), tolazoline (0.1–0.3 mg) and prazosin (0.2–1.0 mg), were used to prevent the emesis produced by 3.0 mg of dopamine. The antagonists were injected intracerebroventricularly 15–20 min before dopamine was similarly administered. Idazoxan, in all given doses, depressed ($P < 0.05$) or abolished ($P < 0.01$) the percentage (Fig. 4B) and the duration, latency and number of emetic episodes evoked by dopamine. Yohimbine and tolazoline in larger doses depressed ($P < 0.05$) the percentage (Fig. 4A and C), duration and latency, but not the number of emetic episodes evoked by dopamine. Prazosin had no effect ($P > 0.05$) on the percentage (Fig. 4D), duration, latency and number of emetic episodes evoked by dopamine. The inhibitory effects of yohimbine, idazoxan and tolazoline were not dose-dependent ($P > 0.05$).

3.4. β-Adrenoceptor antagonists, an antimuscarinic drug, a ganglionic blocking agent, an opioid receptor antagonist and a 5-HT receptor antagonist on dopamine-induced emesis

The β-adrenoceptor antagonists, atenolol (1.0–2.0 mg) and propranolol (0.5–1.0 mg), the antimuscarinic drug, atropine (0.3–1.0 mg), the ganglionic blocking

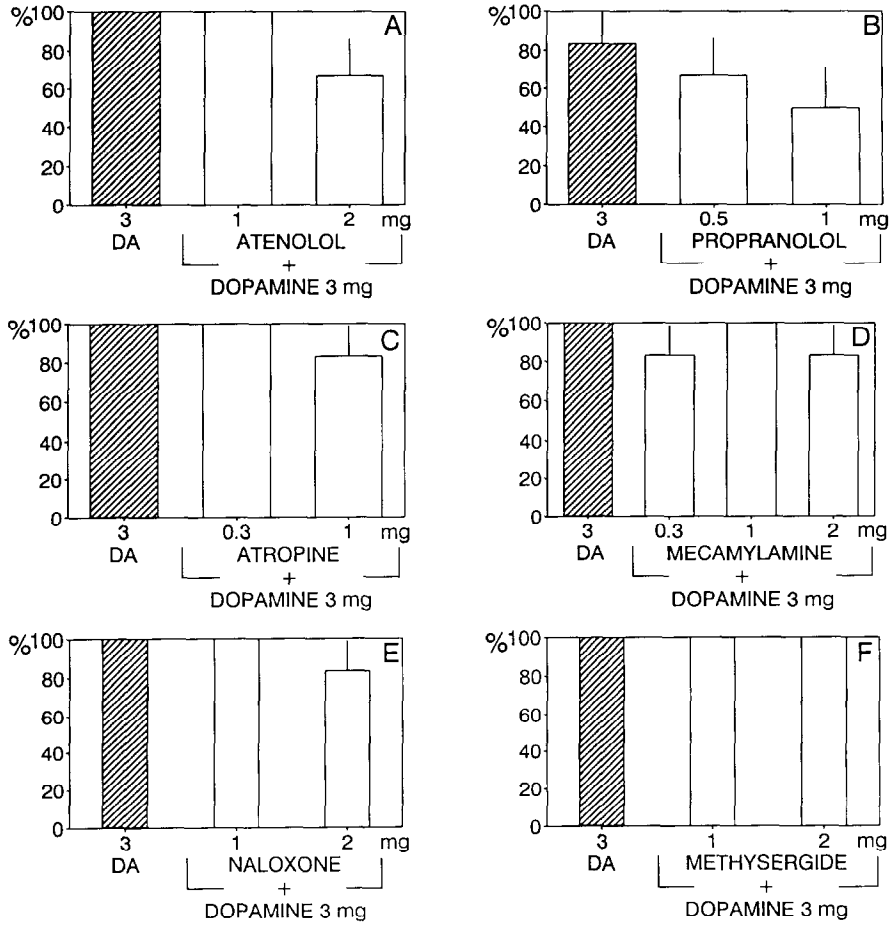

Fig. 5. Effects of atenolol (A), propranolol (B), atropine (C), mecamylamine (D), naloxone (E) and methysergide (F) on the percentage of animals showing an emetic response to dopamine (DA). Hatched columns in (A), (B), (C), (D), (E) and (F) represent control experiments. Atenolol, propranolol, atropine, mecamylamine, naloxone or methysergide was injected into the cerebral ventricles of the unanaesthetized cat, 20–30 min before 3.0 mg of dopamine, given intracerebroventricularly. Each column represents the mean ± S.E.M. for six animals.

agent, mecamylamine (0.3–2.0 mg), the opioid receptor antagonist, naloxone (1.0–2.0 mg), and the 5-HT receptor antagonist, methysergide (1.0–2.0 mg), were used to prevent the vomiting produced by 3.0 mg of dopamine. The antagonists were injected intracerebroventricularly, 15–20 min before dopamine was similarly administered. In cats pretreated with the β-adrenoceptor antagonists, the antimuscarinic drug, the ganglionic blocking agent, the opioid receptor antagonist and the 5-HT receptor antagonist did not significantly alter ($P > 0.05$) the emetic responses to dopamine (Fig. 5A, B, C, D, E, F).

3.5. Reserpine, 6-hydroxydopamine, α-methyl-p-tyrosine, hemicholinium-3 and 5,6-dihydroxytryptamine on dopamine-induced emesis

The effect of intracerebroventricular administration of reserpine on the vomiting response to intracerebroventricular injection of dopamine was tested after a pretreatment time of 24 h following a single injection of reserpine at a dose of 1.0 mg. In cats pretreated with reserpine, given intracerebroventricularly, emesis caused by intracerebroventricular injection of dopamine in doses of 3.0 mg was depressed ($P < 0.01$) (Fig. 6A).

The effect of intracerebroventricular administration of 6-hydroxydopamine on the vomiting response to intracerebroventricular injection of dopamine was tested after 10–14 days, after 2 consecutive days of treatment with daily doses of 1.0 mg of 6-hydroxydopamine. As shown in Fig. 6B, in cats pretreated with intracerebroventricular administration of 6-hydroxydopamine, the emesis caused by intracerebroventricular injection of dopamine at a dose of 3.0 mg was reduced ($P < 0.05$).

α-Methyl-p-tyrosine, in five doses, was given intracerebroventricularly at hourly intervals in total doses of 100 mg. Ninety minutes after the last dose of α-methyl-p-tyrosine, 3.0 mg of dopamine was injected into the cerebral ventricles. As shown in Fig. 6C, in cats pretreated with intracerebroventricular administration of α-methyl-p-tyrosine, the emesis caused by intracerebroventricular injection of dopamine at a dose of 3.0 mg was attenuated ($P < 0.05$).

Hemicholinium-3, at doses of 0.05 mg, was injected into the cerebral ventricles every morning for 5 days. After 5 days the emetic response to intracerebroventricular injection of dopamine at a dose of 3.0 mg was abolished ($P < 0.01$) (Fig. 6D).

The effect of intracerebroventricular administration of 5,6-dihydroxytryptamine on the emesis caused by intracerebroventricular injection of dopamine was tested 10–14 days after 2 consecutive days of treatment with daily doses of 0.4 mg of 5,6-dihydroxytryptamine. In cats ($n = 6$) pretreated with 5,6-dihydroxytryptamine intracerebroventricularly, emesis produced by intracerebroventricular injection of dopamine at a dose of 3.0 mg was not significantly altered ($P > 0.05$).

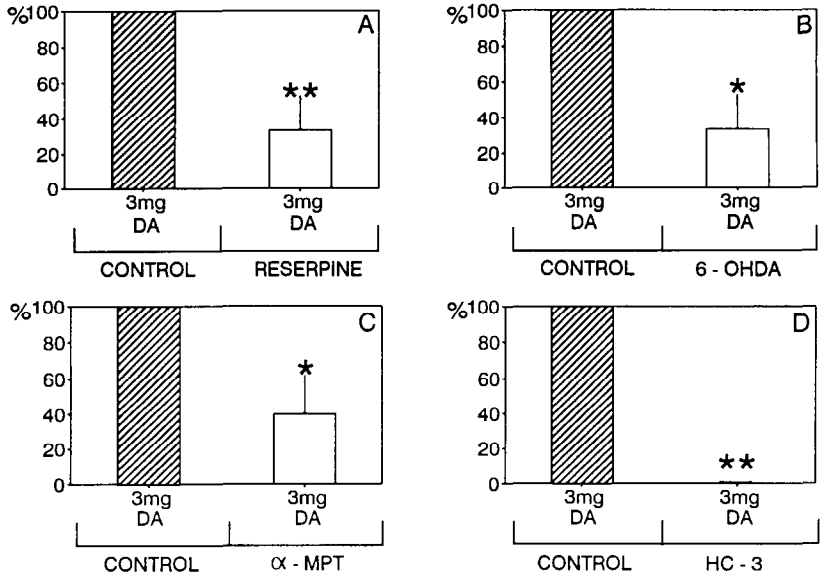

Fig. 6. Effects of reserpine, 6-hydroxydopamine (6-OHDA), α-methyl-p-tyrosine (α-MPT) and hemicholinium (HC-3) on the percentage of emetic responses evoked by dopamine (DA). Emetic response to intracerebroventricular injection of dopamine was tested 24 h after a single injection of reserpine, given intracerebroventricularly, at a dose of 1.0 mg (A), 10–14 days following 2 consecutive days of treatment with daily doses of 1.0 mg of 6-hydroxydopamine (B), 90 min after intracerebroventricular administration of α-methyl-p-tyrosine, given five times at hourly intervals at total doses of 100 mg (C) and following 5 consecutive days of treatment with daily doses of 0.05 mg of intracerebroventricularly injected hemicholinium (D). Hatched columns in (A), (B), (C) and (D) are control experiments. Each column represents mean ± S.E.M. for six animals. Differences are significant at * $P < 0.05$ and ** $P < 0.01$.

3.6. Ablation of the area postrema and emesis induced by dopamine

In cats ($n = 4$) with a lesion of the area postrema, 3.0 mg of dopamine injected into the cerebral ventricles failed to evoke emesis. In three sham-operated cats intracerebroventricular injection of dopamine at a dose of 3.0 mg evoked the same sort of emesis as in normal cats. Histological sections confirmed nearly complete removal of the area postrema, with little damage to adjacent structures.

3.7. Control experiments

In four control experiments, when 0.3 ml of 0.9% solution of sodium chloride was injected into the cerebral ventricles in unanaesthetized cats, the only response was occasional miaowing. Moreover, two repeated intracerebroventricular injections of 0.9% saline ($n = 4$), in volumes of 0.2 or 0.3 ml, at intervals of 15–20 min did not evoke any visible behavioural, autonomic or motor phenomena.

4. Discussion

The results of the present studies confirm the findings of Samardžić et al. (1985), Jovanović-Mićić and Beleslin (1988) and Jovanović-Mićić et al. (1989a); Jovanović-Mićić et al. (1989b) on the emetic action of intracerebroventricular dopamine. The present investigation further revealed that dopamine injected into the cerebral ventricles in large doses evoked short-lasting and dose-dependent emesis. The ED_{50} value for intracerebroventricular dopamine-induced emesis is large and, in comparison with the ED_{50} values for intracerebroventricular noradrenaline- and adrenaline-induced emesis, dopamine is about three and thirty-fold less potent than noradrenaline and adrenaline, respectively (Jovanović-Mićić et al., 1989b). Moreover, the finding that, apart from emesis, behavioural symptoms of intracerebroventricular dopamine, restlessness, licking and tachypnoea, but not mydriasis, micturition and ataxia, were dose-dependent, is consistent with the findings of Jovanović-Mićić and Beleslin (1988). In addition to intracerebroventricular dopamine, noradrenaline, adrenaline and L-dihydroxyphenylalanine (L-DOPA) injected centrally, parenterally or orally also induce emesis in dogs and cats (Feldberg and Sherwood, 1954; Borison, 1959; Peng, 1963; Myers, 1964; Jenkins and Lahay, 1971; Stewart et al., 1977; Bieger et al., 1978; Beleslin and Štrbac, 1987; Beleslin et al., 1987; Jovanović-Mićić et al., 1989b). So far there are no data on intravenous dopamine-induced emesis in cats, and the emetic effect of high doses of dopamine injected into the cerebral ventricles cannot be compared with its effect after parenteral administration. It appears, therefore, that the emetic response is not specific to dopamine, but it is shared by other catecholamines. Apart from quantitative differences, there are qualitative differences in the sensitivity of various species to the emetic action of catecholamines. For instance, dogs are more sensitive to L-DOPA than cats, whereas both are equally sensitive to adrenaline (Peng, 1963). Furthermore, in cats, the most potent catecholamine is adrenaline, while the least effective is dopamine (Jovanović-Mićić et al., 1989b).

The results of the present experiments confirm that dopamine does not produce its emetic effect by an action on central dopamine receptors (Samardžić et al., 1985; Jovanović-Mićić et al., 1989a) and at the same time allow one to assess the pharmacological characteristics and types or subtypes of receptors involved. Dopamine antagonists are known to be potent antiemetics in dogs and humans. In the present investigation of the eight dopamine antagonists acting on pre- and postsynaptic dopamine D_1 and dopamine D_2 receptors (Iversen et al., 1976; Kebabian and Calne, 1979; Kendler et al., 1982), only haloperidol in large doses depressed the dopamine-induced emesis. It follows then that the dopamine-induced emesis cannot be attributed to an action on the central dopamine receptors. In this context, haloperidol is also an α-adrenoceptor antagonist (Peroutka et al., 1977). In fact, the α-adrenoceptor antagonists, yohimbine and idazoxan, attenuated or abolished the dopamine-induced emesis. However, yohimbine, apart from its effect on α_2-adrenoceptors, acts on dopamine receptors as well (Scatton et al., 1980; Van Oene et al., 1984). Idazoxan, besides its action on α_2-adrenoceptors, acts also on imidazoline binding sites (Michel and Insel, 1989). Since the dopamine receptor antagonists had no effect on the dopamine-induced emesis and imidazoline sites have not yet been implicated in emesis, it is apparent that dopamine acted via α_2-adrenoceptors to produce emesis in the cat. The findings that the predominantly α_1-adrenoceptor antagonist, prazosin, had no effect, and that the nearly equipotent α_1- and α_2-adrenoceptor antagonist, tolazoline, depressed the dopamine-induced emesis support the interpretation that dopamine acted through α_2-adrenoceptors. The failure of the β-adrenoceptor antagonists, atenolol and propranolol, the ganglionic blocking agent, mecamylamine, the antimuscarinic drug, atropine, the opioid receptor antagonist, naloxone, and the 5-HT receptor antagonist, methysergide, to inhibit the dopamine-induced emesis further strengthens this view. The α_2-adrenoceptors appear to be located in the area postrema, because the destruction of this brain area abolished the dopamine-induced emesis. This would be consistent with the results of Beleslin and Štrbac (1987) and Hikasa et al. (1992a) in cats, as well as with the findings of Hikasa et

al. (1992b) and Lang and Sarna (1992) in dogs, that α_2-adrenoceptors in the area postrema mediate emesis. When catecholaminergic nervous elements were damaged by 6-hydroxydopamine, the storage elements were impaired by reserpine and the synthesis of catecholamines was attenuated by the competitive inhibitor, α-methyl-*p*-tyrosine, the dopamine-induced emesis was inhibited. One of the simplest explanations, therefore, is that dopamine injected into the cerebral ventricles releases noradrenaline and acts at postsynaptic α_2-adrenoceptors within the area postrema. Additional evidence for this view is the finding that intracerebroventricular dopamine evoked emesis only at large doses, as well as the observation that intracerebroventricular noradrenaline is several times more potent than dopamine in inducing emesis in the cat (Jovanović-Mićić et al., 1989b). However, since haloperidol significantly reduced and the other dopamine receptor antagonists decreased the incidence of dopamine-induced emesis by up to 50%, although not significantly, the dopamine mechanisms in the area postrema cannot be entirely excluded. In this connection, it has been postulated that the mechanism of the peripheral cardiovascular action of dopamine depends on the dose used. Namely, dopamine in small doses primarily acts on vascular dopamine D_1 receptors leading to vasodilatation, whereas in large doses it affects vascular α_1-adrenoceptors producing vasoconstriction. In addition, dopamine in large doses exerts a positive inotropic effect by acting via β_1-adrenoceptors and by releasing noradrenaline from nerve endings (Goldberg and Rajfer, 1985). The mechanism of the emetic action of dopamine, therefore, is similar to that of its action on the peripheral cardiovascular system.

As expected in hemicholinium-treated cats, the dopamine-induced emesis, like noradrenaline-induced emesis (Beleslin and Štrbac, 1987; Beleslin et al., 1989), was inhibited. It is postulated that a functional link exists between cholinergic terminals and noradrenaline neurones within the area postrema and that both are needed for the emetic response. When one component of the link is damaged, the emesis is impaired (Beleslin and Nedelkovski, 1988; Beleslin et al., 1989). There is no evidence, so far, of an effect of hemicholinium on the synthesis, storage and release of noradrenaline (see Kosterlitz and Lees, 1972). It follows then that dopamine cannot evoke emesis in hemicholinium-treated cats, since the cholinergic terminals within the area postrema subserving emesis are damaged. Contrary to the situation in hemicholinium-treated cats, the dopamine-induced emesis was virtually not altered in cats treated with 5,6-dihydroxytryptamine, which is known to damage 5-HT neurones. These results are consistent with the view that 5-HT mechanisms are not involved in the control of emesis within the area postrema, at least in the cat (Samardžić and Beleslin, 1989; Beleslin, 1992).

Finally, it should be emphasized that the cat is relatively insensitive to the emetic effects of apomorphine (mixed dopamine agonist), requiring doses up to 25 mg/kg when administered subcutaneously (Borison, 1959; Laffan and Borison, 1957) whereas the dog only requires 0.01–0.15 mg/kg. There are also differences in sensitivity between the cat and the dog to apomorphine administered intracerebroventricularly (i.e. the cat is some 25–250 times less sensitive; Costello and Borison, 1977; Harding et al., 1987). The insensitivity is not exclusive to the cat, as the *Macaca* cynomolgus and *Macaca mulatta* monkeys are also unresponsive (Brizee et al., 1955). However, man is very sensitive to the emetic effects of apomorphine (Isaacs and Macarthur, 1954; Klein et al., 1968; Isaacs, 1971; Shields et al., 1971; Rausten and Ochs, 1973; Proctor et al., 1978). Thus, species differences may exist, i.e. dopamine receptors may actually directly mediate dopamine-induced emesis in other species. In this context it should be mentioned that dopamine D_2 receptors have been detected in the area postrema of humans (Schwartz et al., 1986) and dogs (Stefanini and Clement-Cormier, 1981). However, to date there is no conclusive evidence about the existence of dopamine receptors in the area postrema of the cat. It is apparent, therefore, that the presence or absence of dopamine receptors in the area postrema is associated with species differences.

The principal conclusions of this investigation are that intracerebroventricular injection of dopamine in large doses induces emesis. This emesis is dose-dependent and short-lasting, depends on the integrity of the area postrema, and is due to the release of noradrenaline and to an action at α_2-adrenoceptors within the area postrema of cats. Species differences in the mechanism of dopamine-induced emesis may exist.

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