THE REVERSAL BY METOCLOPRAMIDE OF APOMORPHINE-INDUCED INHIBTION OF RESPONSES TO STIMULATION OF THE CARDIOACCELERATOR NERVES IN THE CAT

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Summary : The effect of metoclopramide on presynaptic dopamine receptors was investigated in the cat cardioaccelerator nerve preparation.

Metoclopramide, a substituted benzamide derivative, antagonized inhibitory action of apomorphine on positive chronotropic responses induced by sympathetic nerve stimulation in cat hearts, *in vivo*. Neither phentolamine, an α-adrenergic blocking agent, nor indomethacin a prostaglandin synthesis inhibitor, antagonized the effect of apomorphine. Apomorphine did not alter the positive chronotropic effects of intravenously administered noradrenaline. Metoclopramide potentiated stimulation-induced positive chronotropic responses.

These results suggest that metoclopramide blocks the presynaptic dopamine receptors at the cat heart.

Key words : apomorphine presynaptic dopaminergic receptors metoclopramide cardioaccelerator nerve stimulation cat heart

INTRODUCTION

Scientific reports on several naturally occurring substances acting on specific presynaptic receptors which are localized in noradrenergic nerve terminals have increased substantially in recent years. Stimulation of presynaptic receptors can increase or decrease the stimulation-evoked release of noradrenaline (11). Activation of presynaptic dopamine receptors by dopamine and dopaminergic agonists reduces the stimulation evoked release of the neurotransmitter from noradrenergic nerve endings. Dopamine receptor blocking agents antagonize the inhibitory effects of dopamine and its analogs (6–10, 12).

The purpose of the present investigation was to evaluate the presynaptic dopamine receptor blocking activity of metoclopramide, an antagonist of dopaminergic receptors in the central nervous system.

MATERIAL AND METHOD

Cats of either sex, weighing between 2.0 and 5.0 *kg*, were anesthetized with α-chloralose (80 *mg/kg*, iv). A tracheal cannula was inserted for the patency of airway.

The right femoral vein was cannulated for intravenous administration of drugs. Systemic blood pressure was recorded from the cannulated right femoral artery via a Statham P23AC pressure transducer, connected to a Grass polygraph. The heart rate was monitored by a Grass cardiotachometer (model 7P4D). Artificial respiration was carried out with a Harward ventilator.

The right stellate ganglion was exposed following the midsternal incision of the chest. The right postganglionic cardioaccelerator nerve was placed on bipolar silver electrodes for stimulation. Stimulation parameters were 2Hz, 5 msec duration, and supramaximal voltage (15–20 V). Each stimulation was applied for 30 sec. All animals were pretreated with hexamethonium bromide (10 *mg/kg*) and atropine sulphate (200 *µg/kg*).

Mean values of the measurements are given along with standard errors of the mean (±S.E.M.). Statistical analysis were performed by using Student's "t" tests for paired and unpaired data.

The following drugs were used in this study : Metoclopramide (Sifar), phentolamine (Ciba), indomethacin (Merck, Sharp and Dohme), norepinephrine (Winthrop), atropine (Mallinckrodt), hexamethonium (Sigma), α-chloralose (Sigma).

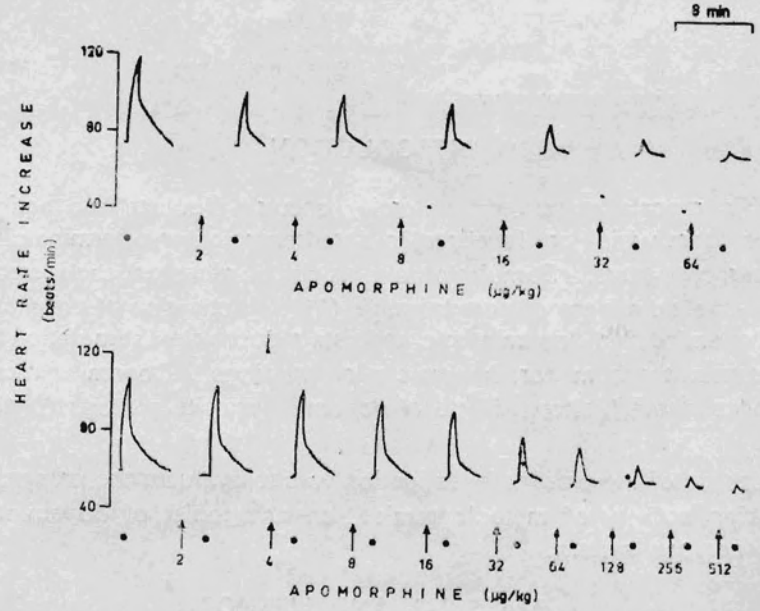

Fig. 1 : Inhibition by apomorphine of the cardioacceleration induced by sympathetic nerve stimulation (2 Hz, 30 sec). Upper and lower panels show the responses before and after metoclopramide (50 *µg/kg*, i.v.) respectively. Numbers under the arrows indicate apomorphine doses (*µg/kg*, i.v.). At ●, the stimulation was made.

RESULTS

Apomorphine, in the given doses (2-64 *μg/kg*, iv), brought about a dose-dependent inhibition of the positive chronotropic effect of cardiac nerve stimulation (Fig. 1). Metoclopramide (50 *μg/kg*, iv) antagonized the inhibitory effects of apomorphine on positive chronotropic responses (Fig. 1) and it shifted the dose-response curve obtained with apomorphine to the right (Fig. 2).

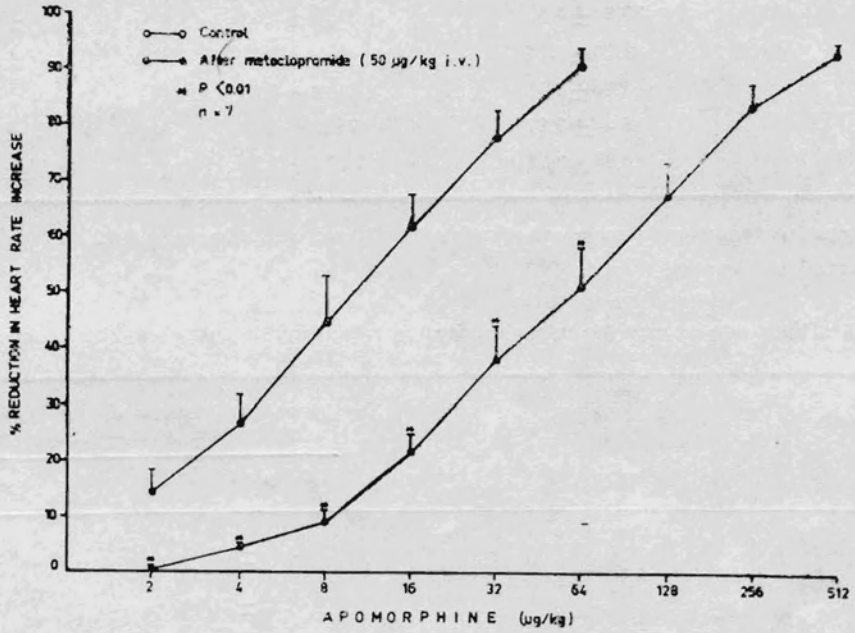

Fig. 2 : Percent reduction of the heart rate increase elicited by sympathetic nerve stimulation (2 Hz, 30 sec) after apomorphine and the antagonistic action of metoclopramide (50 *μg/kg*, i.v.) n=number of animals. Each point and bar represents mean±S.E.M.

The α-receptor blocking agent, phentolamine (5 *mg/kg*, iv) as well as the prostaglandin synthesis inhibitor indomethacin (10 *mg/kg*, iv) did not affect the inhibitory effect of apomorphine (Table I).

The positive chronotropic effects of intravenously administered noradrenaline was not altered by apomorphine (Table II).

Metoclopramide potentiated stimulation-induced positive chronotropic responses (%, 36.10±9.79; n=7).

TABLE I : The effects of phentolamine and indomethacin on the inhibitory action of apomorphine on the cardioacceleration induced by sympathetic nerve stimulation.*

Drug	Percent reduction of heart rate increase (Mean±S.E.M.) (n=5)**		
Apomorphine (μg/kg)	*Control*	*After phentolamine (5 mg/kg)*	*After indomethacin (10 mg/kg)*
2	15.7 ±4.36	17.36±1.75	18.41±3.25
4	28.34±4.05	31.76±3.84	32.58±3.88
8	48.26±4.28	48.64±5.17	51.04±3.96
16	61.58±4.78	61.86±5.38	63.1 ±5.7
32	75.46±3.97	75.51±4.57	73.54±5.0
64	86.54±3.09	86.58±3.29	84.58±3.71

*The right cardioaccelerator nerve was stimulated for 30 sec with a frequency of 2 Hz.

**n = number of animals.

TABLE II : Heart rate increase (beats/min) elicited by norepinephrine before and after apomorphine.

	Heart rate increase due to norepinephrine (beats/min; Mean±S.E.M.) (n=4)	
	0.5 *μg/kg*	1 *μg/kg*
Control	42.37±12.60	54.37±16.34
Apomorphine (*μg/kg*, iv)		
4	47.25±14.14	53.87±15.70
8	47.75±12.78	57.87±14.05
16	50.75±10.22	59.5 ±12.39

*n = number of animals.

DISCUSSION

In a number of biochemical and behavioral tests which measures antidopaminergic effects, metoclopramide has been shown to be roughly equipotent to chlorpromazine (17). In the rat, metoclopramide elevates serum prolactin (13), antagonizes apomorphine-induced-stereotypy (3), and amphetamine-induced checking (15), causes catalepsy (2), and enhances dopamine turnover in mesolimbic as well as in striatal structures (17). In contrast to classic neuroleptics, metoclopramide is completely inactive as an antagonist of the dopamine stimulated adenylate cyclase (16).

Since this substance is a dopaminergic antagonist in the central nervous system, it should theoretically affect the dopaminergic system of the postganglionic noradrenergic nerve terminals which, as known, is responsible for the inhibition of neurotransmitter release.

Previous studies have shown that dopamine and dopamine agonists inhibit the stimulation evoked increase of heart rate in cats by stimulating the presynaptic dopamine receptors of the postganglionic cardioaccelerator nerve. The inhibitory actions of dopamine and other dopaminergic agonists are antagonized by haloperidol, pimozide, chlorpromazine and bulbocapnine which are dopamine receptor blocking agents (6–10, 12). Similarly, in this study, metoclopramide antagonized the inhibitory effect of apomorphine on the stimulation induced heart rate increase. On the other hand, the positive chronotropic effects of intravenously administered noradrenaline was not altered by apomorphine. It implies that apomorphine acts at a presynaptic site.

Presynaptic α-adrenoceptors and prostaglandin receptors can not be held responsible for the effects of apomorphine, since phentolamine and indometacin did not alter the effect of apomorphine. Also, metoclopramide has no significant α-adrenoceptor antagonist activity (4,5).

Metoclopramide potentiated the response of cardioaccelerator nerve stimulation. It is reported that pimozide and haloperidol, the other dopaminergic antagonists, also potentiate stimulation-induced positive chronotropic response (10). Our results provide an additional evidence that the presynaptic dopaminergic inhibitory system might play a physiological role in adrenergic transmission in sinoatrial node region of heart.

There are some reports on hypertensive effect of metoclopramide (1, 14). Our results can partly explain the hypertensive effect of metoclopramide, on the basis that it increases the release of noradrenaline by blocking presynaptic-dopaminergic receptors in the sympathetic system.

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