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A pimozide-sensitive effect of apomorphine on body temperature of the rabbit

(+)-Amphetamine may cause hyperthermia in rabbits by promoting the release of catecholamines from neurons of the cns (Hill & Horita, 1970). Antagonism of (+)-amphetamine hyperthermia by pimozide (Hill & Horita, 1971), a selective dopamine antagonist (Anden, Butcher & others, 1970), indicated that the hyperthermia was mediated by central dopaminergic neurons. These and other considerations have led us to speculate that, by releasing dopamine from central neurons, (+)-amphetamine enhances dopamine receptor activity and consequently induces hyperthermia. Before this speculation could be considered a working hypothesis, it was necessary to determine whether the hyperthermic effect of (+)-amphetamine could be replicated by direct stimulation of central dopamine receptors. Toward this goal, we examined the effect of apomorphine, a dopamine receptor stimulant (e.g. Ernst, 1969), on body temperature of the rabbit.

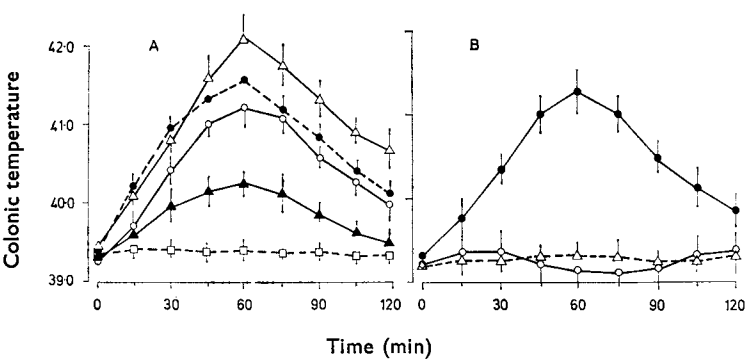

FIG. 1. A. The effect of apomorphine on the colonic temperature of rabbits. All solutions were injected via marginal ear vein at zero time. Each point represents the mean colonic temperature of 5 rabbits after the injection of isotonic saline (□); apomorphine: 1 mg/kg, (▲) 2·5 mg/kg, (○) 5 mg/kg, (△); (+)-amphetamine 5 mg/kg (●). The vertical lines indicate s.e.

B. The effect of pimozide on the time course of apomorphine-induced hyperthermia. Rabbits received an intraperitoneal injection of either dilute tartaric acid (pimozide solvent) or 4 mg/kg pimozide 3 h before injection of apomorphine (5 mg/kg, i.v.) or isotonic saline (i.v.) at zero time. Each point represents the mean colonic temperature of 5 rabbits injected with: pimozide before saline (△), solvent before apomorphine (●), or pimozide before apomorphine (○). The vertical lines indicate s.e.

In one experiment, apomorphine hydrochloride was administered intravenously to groups of six, male New Zealand rabbits (1·8–2·0 kg). Colonic temperatures were electronically monitored. Each of 3 dosages of apomorphine elevated body temperature (Fig. 1A). The peak temperature elevation was directly proportional to the dose of apomorphine. The hyperthermic effect was characterized by a short latency (<5 min), a peak at about 45 min, and a duration of about 4 h. After returning to normal, the body temperature of all rabbits remained normal during the next 4 h.

Within 2 min of apomorphine injection, pupillary diameter increased to about 8 mm from a normal diameter of about 4 mm. Vasodilatation in the ear was evident fom 15 to 90 min after apomorphine injection. However, aside from the temperature elevation, the most striking effect of the drug was an increase in motor activity. Rabbits treated with either of the two largest doses of apomorphine began gnawing and biting nearby objects within 2 min of injection and continued to do so for about 90 min after injection. During this time, limb movements were minimal.

In another experiment, rabbits received either pimozide solvent (dilute tartaric acid or pimozide solution 3 h before administration of apomorphine hydrochloride. Pretreatment with pimozide abolished the hyperthermic effect of apomorphine (Fig. 1B). The colonic temperature of rabbits treated with pimozide and apomorphine did not differ significantly from control (viz. pimozide solvent plus saline treatment) at any of the observation times. The apomorphine-induced gnawing syndrome was prevented by pimozide in 4 of the 5 test animals. In all 5 rabbits, apomorphine produced no activity in fore- or hind-limbs. The effect of apomorphine on the ear vasculature was reduced by pimozide; however, the mydriatic response to apomorphine was unaltered by the antagonist.

The results indicate that apomorphine can produce a hyperthermic response which is temporally similar to (+)-amphetamine hyperthermia. Since both of the hyperthermic responses can be inhibited by pimozide, both drugs may require functional dopamine receptors to elevate the body temperature of the rabbit. Finally, these results suggest that hyperthermia can be induced in the rabbit by direct activation of dopamine receptors. This indication lends strength to the possibility that dopaminergic neurons in the cns mediate the hyperthermic effect of (+)-amphetamine in this species.

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