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Release of Brain Dopamine as the Probable Mechanism for the Hypothermic Effect of D-Amphetamine

THE effects of D-amphetamine on the colonic temperature of rats depend on the ambient temperature[1]. Rats kept in cold environments (4°–15° C, relative humidity 45%) exhibit profound hypothermia for at least 90 min after receiving D-amphetamine (7.5–15 mg/kg, given intraperitoneally). The same doses cause marked hyperthermia among rats kept at room temperature (20° C) or in a warm environment (37° C). The evidence we report here suggests that the D-amphetamine-induced hypothermia is mediated by the release of dopamine from brain neurones.

Male Sprague–Dawley rats (Charles River Laboratories), weighing 100–150 g, were housed six per cage at an ambient temperature of 22° C and relative humidity of 45%. They had access to food (Big Red Laboratory Animal Chow, Agway Inc., Syracuse, New York) and water *ad libitum*. Light ('Vita-Lite', Duro-Test Corp., North Bergen, New Jersey) was provided between 0090 h and 2100 h daily. Just before each experiment, rats were placed in individual cages; they were then injected with one of several drugs in 1.0 ml. of medium, and placed in an environmental chamber set at 4°, 20° or 37° C, and a relative humidity of 45%. Thirty minutes later, half of the rats in each experimental group received an intraperitoneal injection of D-amphetamine (15 mg/kg); the other animals received saline. Colonic temperature was measured by telethermometer (Yellow Springs Instrument Co., Yellow Springs, Ohio) just before the first injection and at 10-min intervals thereafter. Each experimental group included at least twelve rats, and each study was repeated at least twice. All experiments were done between 1000 h and 1400 h.

As in previous experiments[1], the administration of D-amphetamine (15 mg/kg) to rats kept in an environment of 4° C caused significant hypothermia (Table 1). Animals receiving tyramine (50 mg/kg) or the amphetamine analogue β,β-difluoroamphetamine (15 mg/kg), two drugs that share the peripheral sympathomimetic effects of D-amphetamine but are much less able to enter the brain, failed to display significant hypothermia. This suggested that the hypothermia results from a direct action of D-amphetamine on the brain.

Hypothermia was also observed among rats pretreated with

Table 1 Effects of Various Drugs on Colonic Temperature in Rats kept at 4° C

Drugs	Change in temperature (° C)
Saline	−0.6±0.3
D-Amphetamine	−2.6±0.6*
Tyramine	−0.8±0.4
β, β-Difluoroamphetamine	−0.6±0.6
Apomorphine	−3.3±0.5*
Clonidine	−6.8±0.9*
L-Dopa	−2.9±0.7*

Rats received the drug intraperitoneally and were immediately placed in an environmental chamber. The changes in temperature were determined by comparing data obtained at zero time and 30 min after treatment. Data in Tables 1 and 2 are given as mean ±s.d.

* $P < 0.001$ differs from animals receiving saline.

drugs thought to increase central dopaminergic tone: apomorphine (10 mg/kg), clonidine (Catapres, 2 mg/kg), or L-dopa (100 mg/kg) (Table 1)[2,3]. Moreover, the hypothermia following D-amphetamine was blocked in rats pretreated with pimozide (25 mg/kg), haloperidol (2 mg/kg), or ditran (JB-329, 4 mg/kg) (Table 2), drugs believed to block brain dopamine receptors[3,4].

The lowest doses of amphetamine, apomorphine, or clonidine that produced significant decreases in body temperature (that is, 1.4°–1.7° C) were 5.0 mg/kg, 1.5 mg/kg, and 0.5 mg/kg, respectively. The administration of 4.0 mg/kg of pimozide partially suppressed the hypothermia caused by amphetamine (7.5 mg/kg); 50 mg/kg of pimozide totally blocked the hypothermia that followed apomorphine (1.5 mg/kg) or clonidine (0.5 mg/kg). Hypothermia was not observed following D-amphetamine in animals pretreated 14 and 13 days earlier with intracisternal 6-hydroxydopamine (two doses, each 200 μg) (Table 2), an agent that selectively damages central catecholamine neurones[5,6]. These observations suggested that the hypothermic response to D-amphetamine is mediated by the release of dopamine from brain neurones. In confirmation of this hypothesis, D-amphetamine still caused significant hypothermia among animals pretreated with drugs that block noradrenergic receptors (phenoxybenzamine, 20 mg/kg, or propranolol, 12 mg/kg) or serotoninergic receptors (methysergide, 1 g/kg), as well as by drugs that decrease brain serotonin content (*p*-chloramphetamine, 5 mg/kg)[7], damage brain serotoninergic neurones (5,6-dihydroxytryptamine, 75 μg into the cerebrospinal fluid)[8], or destroy peripheral sympathetic neurones (6-hydroxydopamine, given intraperitoneally, in two doses of 150 mg/kg) (Table 2). Most of those drugs produced

Table 2 Effects of Various Drugs on D-Amphetamine-induced Hypothermia

Drugs	Change in temperature (° C)	
	Drug alone	Drug followed by D-amphetamine
Saline	0.5±0.4	−3.2±0.6*
Pimozide	−1.0±0.5	−1.5±0.4
Haloperidol	−2.0±0.4	1.5±0.6
Ditran	0.2±0.2	−0.3±0.5
6-Hydroxydopamine (intracisternal)+saline (i.p.)	−1.0±0.6	−0.7±0.7
Methysergide	−2.0±0.6	−4.2±0.7*
p-Chloramphetamine	−4.0±0.3	−7.1±0.8*
5,6-Dihydroxytryptamine (intracisternal)+saline (i.p.)	−1.3±0.4	−3.9±0.7*
6-Hydroxydopamine (i.p.)+saline	0.6±0.3	−7.1±0.9*
Phenoxybenzamine	−5.0±0.9	−9.0±0.8*
Propranolol	−4.8±0.9	−7.3±0.9*

Animals received the drug and were immediately placed in an environmental chamber at 4° C. Thirty minutes later half of each group received D-amphetamine. The changes in colonic temperature were determined by comparing data obtained at zero time and 60 min after the first injection (that is, 30 min after D-amphetamine).
* $P<0.001$ differs from rats receiving only the first injection.

hypothermia when given alone and tended to enhance the hypothermia that followed D-amphetamine (Table 2).

The L-isomer of amphetamine also caused hypothermia among animals kept in the cold; its potency was about one-third that of the D-isomer. Colonic temperature fell by 1.9° C among rats receiving 7.5 mg/kg of D-amphetamine or 20 mg/kg of L-amphetamine, and by 2.6° C among animals receiving 15 mg/kg of D-amphetamine or 50 mg/kg of L-amphetamine. The relative potencies of D and L-amphetamine in producing other behavioural or physiological effects thought to be mediated by dopamine are about 1 : 2; however, L-amphetamine is only one-tenth as potent as D-amphetamine in causing responses thought to be mediated by brain noradrenaline[9].

Preliminary observations suggest that lesions destroying the limbic dopaminergic neurones projecting from the ventral tegmental nuclei to the region of the olfactory tubercules also block D-amphetamine hypothermia. These lesions do not alter the hyperthermia that follows D-amphetamine administration to rats kept at 20° C or 37° C.

Central dopaminergic neurones mediate both the stereotypic behaviour caused by D-amphetamine[10,11] and the turning behaviour of rats receiving D-amphetamine after unilateral lesions of the nigro-neostriatal tract[12]. Our results suggest that central dopaminergic neurones are also involved in

thermoregulation and mediate the hypothermia of D-amphetamine-treated rats kept in the cold; this latter phenomenon may provide a relatively simple tool for screening drugs that interact selectively with dopaminergic brain neurones and their receptors.

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SHLOMO YEHUDA
RICHARD J. WURTMAN

Laboratory of Neuroendocrine Regulation,
Department of Nutrition and Food Science,
and Department of Psychology,
Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

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