Facilitation of amphetamine-induced hypothermia in mice by GABA agonists and CCK-8

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1 Amphetamine-induced hypothermia in mice is facilitated by dopaminergic stimulation and 5-hydroxytryptaminergic inhibition. The present study was designed to investigate: (a) the involvement of other neuronal systems, such as the γ -aminobutyric acid (GABA), the opioid and the cholecystokinin (CCK-8) systems; (b) the possible contribution of hydroxylated metabolites of amphetamine to the hypothermia; (c) the capacity of dopamine itself to induce hypothermia and its mechanisms, in order to clarify the resistance of amphetamine-induced hypothermia to certain neuroleptics.

2 Pretreatment with the GABA antagonists, bicuculline and picrotoxin, did not inhibit amphetamine-induced hypothermia. The GABA_B agonist, baclofen (2.5 mg kg^{-1} , i.p.) potentiated this hypothermia, whereas the GABA_A agonist, muscimol, did not. γ -Butyrolactone (GBL) (40 mg kg^{-1} , i.p.) and the neuropeptide CCK-8 (0.04 mg kg^{-1} , i.p.) also induced potentiation. The opioid antagonist, naloxone, was without effect.

3 Dopamine itself (3, 9, 16 and $27 \mu\text{g}$, i.c.v.) induced less hypothermia than the same doses of amphetamine. Sulpiride did not block dopamine-induced hypothermia, but pimozide (4 mg kg^{-1} , i.p.), *cis(z)*flupentixol (0.25 mg kg^{-1} , i.p.) and haloperidol ($5 \mu\text{g}$, i.c.v.) did. The direct dopamine receptor agonist, apomorphine, did not alter the hypothermia. Neither the 5-hydroxytryptamine (5-HT) receptor blocker, cyproheptadine, nor the inhibitor of 5-HT synthesis, *p*-chlorophenylalanine (PCPA), modified dopamine-induced hypothermia. Fluoxetine, an inhibitor of 5-HT reuptake, had no effect, whereas quipazine (6 mg kg^{-1} , i.p.), a 5-HT agonist, totally prevented the hypothermia. Hypothermia was unaffected by pretreatment with CCK-8.

4 These data indicate that the hypothermia induced by amphetamine involves not only dopaminergic and 5-hydroxytryptaminergic systems which are functionally antagonistic, but is also facilitated by direct or indirect GABA and CCK-8 receptor stimulation. This facilitation could result, in part, from modulation of dopaminergic neurotransmission. This may explain the apparent resistance of amphetamine-induced hypothermia to some neuroleptics, while dopamine-induced hypothermia is not resistant. The possible action of hydroxylated metabolites of amphetamine may also help to explain these differences.

Keywords: Amphetamine; hypothermia in mice; GABA systems; CCK-8; dopamine; hydroxylated metabolites

Introduction

Our earlier studies on amphetamine-induced hypothermia in mice demonstrated that this effect has a central origin and occurs when (+)-amphetamine is injected either intraventricularly, or directly into the hypothalamus or dopamine-containing areas, such as the nucleus caudatus, the olfactory tubercle or the nucleus accumbens (Boschi & Rips, 1982). The latter area appears to be the most responsive. Interaction studies have shown that dopaminergic and 5-hydroxytryptaminergic mechanisms are at least partially involved in this hypothermia and that these two systems display a functional antagonism (Boschi & Launay, 1985). Thus, stimulation of dopaminergic or inhibition of 5-hydroxytryptaminergic neurotransmission facilitates the hypothermic response to amphetamine.

However, our findings suggested that the mechanism underlying this hypothermia is more complex. As the nucleus accumbens is generally considered to be a major target in amphetamine-induced hypothermia, we have examined, in addition to the contributions of the dopaminergic and 5-hydroxytryptaminergic systems, the possible contributions of other neurotransmitter or neuromodulator systems which are involved in this brain area. We have therefore investigated the effects of pretreatment with γ -aminobutyric acid (GABA)-related substances, the neuropeptide cholecystokinin (CCK-8), and drugs acting on opioid systems, such as naloxone, on the hypothermia elicited by intraventricular amphetamine in mice.

Finally, we checked that the hypothermia-inducing effects of dopamine were similar to those previously described for

amphetamine under identical experimental conditions. This was necessary for any attempt at explaining why this hypothermia is resistant to the dopamine receptor antagonist effect of some of the neuroleptics used in our previous study (Boschi & Launay, 1985). We therefore evaluated the effects of intraventricular dopamine on the rectal temperature of mice and determined, as in the study of the hypothermic action of amphetamine, the possible implication of the dopaminergic and 5-hydroxytryptaminergic systems, and CCK-8 neurones on dopamine-induced hypothermia.

Methods

Animals

Male OF1 mice (Iffa Credo), 7 weeks old and weighing 30–32 g on the day of the experiment were maintained on a 12 h light-dark cycle in a temperature-regulated room ($22 \pm 1^\circ\text{C}$). Each mouse was used only once.

Injections

Peripheral injections were given intraperitoneally in a volume of $0.1 \text{ ml } 10 \text{ g}^{-1}$ body weight. Central injections were given via a guide cannula implanted into the right lateral ventricle one week prior to the experiment (Boschi *et al.*, 1981). The drugs were injected in a volume of $0.5 \mu\text{l}$ over a period of 50 s. Following the experiments, the location of the cannula was verified histologically after an injection of methylene blue into the cannula.

Control mice were given the same volume of vehicle alone.

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Measurement of rectal temperature

Rectal temperature was measured with a thermocouple probe (Bailey Instruments), inserted to a depth of 1.5 cm. Readings were taken before (60, 30, 0 min) and after (20, 30, 60 min) the central injection of amphetamine. Mice were kept in groups of 3–4 and were free to move in their cages except during the brief time required for temperature measurement. Experiments were carried out between 10 h 00 min and 15 h 00 min in a temperature-regulated room ($22 \pm 1^\circ\text{C}$).

Interaction studies

The hypothermic effects occurred with doses of 3–27 $\mu\text{g}/\text{mouse}$ for amphetamine and dopamine given intraventricularly. Doses of 9 μg amphetamine/mouse and 16 μg dopamine/mouse were selected for investigating antagonist actions and 3 $\mu\text{g}/\text{mouse}$ of both drugs was used to investigate potentiation. Preliminary experiments determined the maximal dose of the different agonists and antagonists used which, alone, induced no change in rectal temperature. Each interaction study was performed at least twice.

Drugs

For central injections, (+)-amphetamine sulphate (De Laire) and dopamine hydrochloride (Fluka) were dissolved in sterile pyrogen-free 0.9% w/v NaCl solution (saline). Controls were given an equal volume of saline. Haloperidol (Janssen) was taken from commercially available ampoules. Controls were given distilled water. All doses refer to the free base.

For systemic injections, the following drugs were dissolved in water: apomorphine hydrochloride (Sigma), *cis*(z)flupentixol dihydrochloride (Lundbeck), cyproheptadine hydrochloride (Merck Sharp and Dohme), DL-*p*-chlorophenylalanine ethyl ester (PCPA) (Sigma), γ -butyrolactone (GBL) (Sigma), muscimol (Sigma), cholecystokinin (CCK-8S) (Sigma), naloxone hydrochloride (Endo). Solutions of pimozide (Janssen) and ($\pm$)-sulpiride (Delagrang) were prepared in water from the commercially available solutions. Fluoxetine (Lilly) and quipazine maleate (Miles) were suspended in an aqueous solution of Tween 80 (2%). ($\pm$)-Baclofen (Ciba-Geigy), picrotoxin (Sigma) and bicuculline (Sigma) were dissolved in 1 M HCl, adjusted to pH 5–6 with 5 M NaOH and diluted in water. Controls were given the appropriate vehicle. Doses of drugs are expressed as the weight of the salt.

Statistical analysis

Each experiment included two groups of animals, a drug-treated group and the appropriate control group. They were compared by the Mann-Whitney U test.

Results

Effects of pretreatment with GABA-related drugs on amphetamine-induced hypothermia

The results are shown in Figure 1. The hypothermia elicited by intraventricular (i.c.v.) amphetamine (9 $\mu\text{g}/\text{mouse}$) was not abolished by intraperitoneal (i.p.) injections of the GABA antagonists, bicuculline (2 mg kg^{-1}) or picrotoxin (0.5 mg kg^{-1}), 15 min prior to amphetamine injection.

Pretreatment for 15 min with the GABA_A agonist, muscimol (0.5 mg kg^{-1} , i.p.), did not significantly potentiate the amphetamine-induced hypothermia, whereas the GABA_B agonist, baclofen (2.5 mg kg^{-1} , i.p.), potentiated ($P < 0.05$) the effect of amphetamine (3 μg i.c.v.) at 30 min, which is the time of the maximal amphetamine activity. The concomitant administration of the GABA analogue, γ -butyrolactone (GBL) (40 mg kg^{-1} , i.p.) and amphetamine (3 μg , i.c.v.) also poten-

Figure 1 Time course of the change in rectal temperature ($\Delta^\circ\text{C}$, ordinate scales) in mice produced by a combination of: amphetamine (9 μg , i.c.v.) and vehicle (open columns); amphetamine (3 μg , i.c.v.) and vehicle (stippled columns); amphetamine (9 or 3 μg , i.c.v.) and γ -aminobutyric acid (GABA) drugs (hatched columns). Amphetamine (9 μg) was used to investigate any antagonism and 3 μg to investigate any potentiation. GABA-related drugs or vehicle were given before amphetamine. Bicuc: bicuculline (2 mg kg^{-1} , i.p., 15 min), time zero values: $36.11 \pm 0.14^\circ\text{C}$ (vehicle), $36.11 \pm 0.19^\circ\text{C}$ (Bicuc); Picro: picrotoxin (0.5 mg kg^{-1} , i.p., 15 min), time zero values: $36.31 \pm 0.14^\circ\text{C}$ (vehicle), $36.40 \pm 0.24^\circ\text{C}$ (Picro); Musci: muscimol (0.5 mg kg^{-1} , i.p., 15 min), time zero values: $36.25 \pm 0.19^\circ\text{C}$ (vehicle), $36.40 \pm 0.17^\circ\text{C}$ (Musci); GBL: γ -butyrolactone (40 mg kg^{-1} , i.p., simultaneously), time zero values: $36.37 \pm 0.34^\circ\text{C}$ (vehicle), $36.67 \pm 0.28^\circ\text{C}$ (GBL); Baclo: baclofen (2.5 mg kg^{-1} , i.p., 15 min), time zero values: $36.44 \pm 0.23^\circ\text{C}$ (controls), $36.68 \pm 0.18^\circ\text{C}$ (Baclo). Each column represents the mean of 7 to 12 mice. Vertical bars indicate s.e.mean. * $P < 0.05$, comparison with the appropriate controls (amphetamine + vehicle), Mann-Whitney U test. Abscissa scales: time in min.

tiated ($P < 0.05$) the hypothermia at 30 min. None of the GABA drugs caused a significant change in body temperature when given alone.

Effects of pretreatment with other drugs on amphetamine-induced hypothermia

The effects of a neuropeptide, CCK-8, and naloxone, an opioid antagonist, on amphetamine-induced hypothermia are shown in Figure 2. Simultaneous injections of CCK-8 (0.04 mg kg^{-1} , i.p.) and amphetamine (3 μg , i.c.v.) caused potentiation ($P < 0.05$) 20 and 30 min after amphetamine injection. Naloxone (2 mg kg^{-1} , i.p.) did not prevent amphetamine-induced hypothermia (9 μg , i.c.v.).

Figure 2 Time course of the change in rectal temperature ($\Delta^{\circ}\text{C}$, ordinate scales) in mice produced by a combination of: amphetamine ($3 \mu\text{g}$, i.c.v.) and vehicle (stippled columns); amphetamine ($9 \mu\text{g}$, i.c.v.) and vehicle (open columns); amphetamine (3 or $9 \mu\text{g}$, i.c.v.) and drugs (hatched columns). Amphetamine ($3 \mu\text{g}$) was used to investigate any potentiation and $9 \mu\text{g}$ to investigate any antagonism. Drugs or vehicle were given before amphetamine. CCK-8: cholecystokinin (0.04 mg kg^{-1} , i.p., simultaneously), time zero values: $36.27 \pm 0.22^{\circ}\text{C}$ (vehicle), $36.04 \pm 0.25^{\circ}\text{C}$ (CCK-8); Nal: naloxone (2 mg kg^{-1} , i.p., simultaneously), time zero values: 37.20 ± 0.23 (vehicle), $36.72 \pm 0.22^{\circ}\text{C}$ (Nal). Each column represents the mean of 6 to 11 mice. Vertical bars indicate s.e.mean. * $P < 0.05$, comparison with the appropriate controls (amphetamine + vehicle), Mann-Whitney U test. Abscissa scales: time in min.

Effects of central injections of dopamine on the rectal temperature of mice

Dopamine (3 , 9 , 16 and $27 \mu\text{g}/\text{mouse}$) produced a significant hypothermia when injected into the lateral ventricle of mice (Figure 3). The maximal effects occurred 20 min after injection. The decrease in rectal temperature was dose-dependent over the range 3 – $16 \mu\text{g}/\text{mouse}$. At $3 \mu\text{g}/\text{mouse}$, the greatest fall in

Figure 3 Time course of the change in rectal temperature ($\Delta^{\circ}\text{C}$, ordinate scale) in mice produced by increasing doses of dopamine given i.c.v. The effect is expressed as the difference between pre- and post-injection temperature corrected for the effect of 0.9% NaCl. Dopamine ($\bullet$) 3 , ($\blacksquare$) 9 , ($\blacktriangle$) 16 and ($\circ$) $27 \mu\text{g}$. Each dose was studied with its own control (saline) on separate days. Time zero values: $36.50 \pm 0.15^{\circ}\text{C}$ (dopamine 3), $36.45 \pm 0.12^{\circ}\text{C}$ (saline); $36.36 \pm 0.18^{\circ}\text{C}$ (dopamine 9), $36.90 \pm 0.29^{\circ}\text{C}$ (saline); $36.13 \pm 0.21^{\circ}\text{C}$ (dopamine 16), $36.24 \pm 0.25^{\circ}\text{C}$ (saline); $36.01 \pm 0.15^{\circ}\text{C}$ (dopamine 27), $36.29 \pm 0.19^{\circ}\text{C}$ (saline). Each point represents the mean of 7 to 11 mice. In order to simplify the figure, the vertical lines indicating the s.e.mean are shown only for the significant values. * $P < 0.05$; ** $P < 0.01$, comparison with the corresponding saline controls (not shown), Mann-Whitney U test. Abscissa scale: time in min.

rectal temperature was $-1.08 \pm 0.14^{\circ}\text{C}$ ($P < 0.05$). Doses of 9 and $16 \mu\text{g}/\text{mouse}$ caused mean maximal changes in body temperature of $-2.52 \pm 0.18^{\circ}\text{C}$ ($P < 0.01$) and $-3.12 \pm 0.26^{\circ}\text{C}$ ($P < 0.01$) respectively. A dose of $27 \mu\text{g}/\text{mouse}$ produced the same degree of hypothermia ($-2.90 \pm 0.24^{\circ}\text{C}$, $P < 0.01$) as did $16 \mu\text{g}/\text{mouse}$.

Effects of pretreatment with drugs acting on dopamine receptors on dopamine-induced hypothermia

Neuroleptics were tested for their ability to block dopamine-induced hypothermia (Figure 4). The hypothermia induced by dopamine ($16 \mu\text{g}$, i.c.v.) was not abolished by injection of sulpiride (40 mg kg^{-1} , i.p.) 2 h prior to dopamine. In contrast, pretreatment with pimozide (4 mg kg^{-1} , i.p., 2 h) and haloperidol ($5 \mu\text{g}$, i.c.v., 45 min) inhibited ($P < 0.05$ and $P < 0.01$,

Figure 4 Time course of the change in rectal temperature ($\Delta^{\circ}\text{C}$, ordinate scales) in mice produced by the combination of: dopamine ($16 \mu\text{g}$, i.c.v.) and vehicle (open columns); dopamine ($3 \mu\text{g}$, i.c.v.) and vehicle (stippled columns); dopamine (16 or $3 \mu\text{g}$, i.c.v.) and dopamine-related drugs (hatched columns). Dopamine ($16 \mu\text{g}$) was used to investigate any antagonism and $3 \mu\text{g}$ to investigate any potentiation. Dopamine drugs or vehicle were given before dopamine. Sul: sulpiride (40 mg kg^{-1} , i.p., 2 h), time zero values: $36.99 \pm 0.19^{\circ}\text{C}$ (vehicle), $36.41 \pm 0.26^{\circ}\text{C}$ (Sul); FPT: *cis(z)*flupentixol (0.25 mg kg^{-1} , i.p., 2 h), time zero values: $37.37 \pm 0.18^{\circ}\text{C}$ (vehicle), $36.77 \pm 0.14^{\circ}\text{C}$ (FPT); Pim: pimozide (4 mg kg^{-1} , i.p., 2 h), time zero values: $36.86 \pm 0.12^{\circ}\text{C}$ (vehicle), $35.69 \pm 0.48^{\circ}\text{C}$ (Pim); Halo: haloperidol ($5 \mu\text{g}$, i.c.v., 45 min), time zero values: $36.54 \pm 0.22^{\circ}\text{C}$ (vehicle), $36.66 \pm 0.22^{\circ}\text{C}$ (Halo). Apo: apomorphine (0.025 (a), 0.1 (b), 0.4 (c) mg kg^{-1} , i.p., 10 min). Each column represents the mean of 7 to 12 mice. Vertical bars indicate s.e.mean. * $P < 0.05$; ** $P < 0.01$, comparison with the appropriate controls (dopamine + vehicle), Mann-Whitney U test. Abscissa scales: time in min.

Figure 5 Time course of the change in rectal temperature ($\Delta^{\circ}\text{C}$, ordinate scales) in mice produced by the combination of: dopamine ($3 \mu\text{g}$, i.c.v.) and vehicle (stippled columns); dopamine ($16 \mu\text{g}$, i.c.v.) and vehicle (open columns); dopamine (3 or $16 \mu\text{g}$, i.c.v.) and 5-hydroxytryptamine-related drugs or cholecystokinin (CCK-8) (hatched columns). Dopamine ($3 \mu\text{g}$) was used to investigate any potentiation and $16 \mu\text{g}$ to investigate any antagonism. Drugs or vehicle were given before dopamine. Cypro: cyproheptadine (0.5 mg kg^{-1} , i.p., 30 min), time zero values: $36.97 \pm 0.26^{\circ}\text{C}$ (vehicle), $36.36 \pm 0.13^{\circ}\text{C}$ (Cypro); Fluo: fluoxetine (10 mg kg^{-1} , i.p., 30 min), time zero values: $36.94 \pm 0.18^{\circ}\text{C}$ (vehicle), $36.77 \pm 0.23^{\circ}\text{C}$ (Fluo); PCPA: *p*-chlorophenylalanine (300 mg kg^{-1} , i.p., 48 and 24 h), time zero values: $36.48 \pm 0.24^{\circ}\text{C}$ (vehicle), $36.40 \pm 0.23^{\circ}\text{C}$ (PCPA); Qui: quipazine (6 mg kg^{-1} , i.p., 10 min), time zero values: $37.15 \pm 0.12^{\circ}\text{C}$ (vehicle), $36.18 \pm 0.24^{\circ}\text{C}$ (Qui). CCK-8: cholecystokinin (0.04 mg kg^{-1} , i.p., simultaneously), time zero values: $36.68 \pm 0.18^{\circ}\text{C}$ (vehicle), $36.20 \pm 0.09^{\circ}\text{C}$ (CCK-8). Each column represents the mean of 7 to 14 mice. Vertical bars indicate s.e.mean. ** $P < 0.01$, comparison with the appropriate controls (dopamine + vehicle), Mann-Whitney U test. Abscissa scales: time in min.

respectively) the hypothermia. *Cis(z)*flupentixol (0.25 mg kg^{-1} , i.p.), 2 h prior to dopamine, slightly reduced ($P < 0.05$) this hypothermia. Pretreatment for 10 min with the direct dopamine receptor agonist, apomorphine (0.025 , 0.1 , 0.4 mg kg^{-1} , i.p.), did not alter dopamine-induced hypothermia (3 and $16 \mu\text{g}$, i.c.v.). At these doses, these drugs alone had no effect on body temperature in mice.

Effects of pretreatment with drugs acting on 5-HT receptors and CCK-8 on dopamine-induced hypothermia

Neither the 5-HT receptor blocker, cyproheptadine (0.5 mg kg^{-1} , i.p.) given 30 min before dopamine, nor the inhibitor of 5-HT synthesis, PCPA (300 mg kg^{-1} , i.p.), administered 48 and 24 h before dopamine ($3 \mu\text{g}$, i.c.v.), modified

dopamine-induced hypothermia (Figure 5). A 30 min pretreatment with fluoxetine (10 mg kg^{-1} , i.p.), which inhibits the reuptake of 5-hydroxytryptamine, had no effect on dopamine-induced hypothermia ($16 \mu\text{g}$, i.c.v.). In contrast, the 5-HT receptor agonist, quipazine (6 mg kg^{-1} , i.p.) given 10 min prior to dopamine, totally prevented ($P < 0.01$) the hypothermia. Simultaneous injections of CCK-8 (0.04 mg kg^{-1} , i.p.) and dopamine ($3 \mu\text{g}$, i.c.v.) did not potentiate dopamine-induced hypothermia (Figure 5).

Discussion

We have previously shown that the nucleus accumbens may be one of the sites involved in amphetamine-induced hypothermia in mice (Boschi & Rips, 1982) and that this hypothermia is mediated by dopaminergic and 5-hydroxytryptaminergic mechanisms (Boschi & Launay, 1985). These findings confirm and extend the results of other authors (Yehuda & Wurtman, 1975; Wirtshafter *et al.*, 1978) showing that the dopamine release from the mesolimbic system, especially from the nucleus accumbens, may underlie the effects of amphetamine on thermoregulation. However, the nucleus accumbens receives not only dopaminergic (Ungerstedt, 1971) and 5-hydroxytryptaminergic (Conrad *et al.*, 1974) projections, but also contains a high concentration of GABA (Balcom *et al.*, 1975) corresponding to very dense GABA projections (Walaas & Fonnum, 1979). The present study was undertaken to obtain further information on the mechanisms of the hypothermic action of amphetamine by use of drugs which alter the function of the GABA systems in the brain. Pretreatment with the GABA_A agonist muscimol (Penney *et al.*, 1981) did not potentiate the hypothermia, whereas the GABA_B agonist baclofen (Bowerly *et al.*, 1983; 1985) did. This facilitation of the action of amphetamine may result from GABA release induced by baclofen (Kerwin & Pycock, 1978; Roberts *et al.*, 1978). Biochemical and behavioural studies have shown that GABA exerts an inhibitory control on dopaminergic systems (Davidson, 1976; Scheel-Krüger, 1986). An attenuation of the activity of dopaminergic neurones by GABA would result in decreased dopamine release and intraneuronal catabolism, which in turn would increase the neuronal concentration of dopamine. More endogenous dopamine could then be available at the presynaptic nerve endings to be released by amphetamine. However, baclofen has also been reported to reduce the evoked release of dopamine (Reimann, 1983), to increase the dopamine in the mesolimbic dopaminergic terminals (Kelly & Moore, 1978) and to inhibit the firing rate of dopaminergic nerves (Fuxe *et al.*, 1975). All these mechanisms may be implicated in the potentiation of hypothermia by baclofen, using the explanation given above. In the same way, the combined treatment with amphetamine and γ -butyrolactone (GBL), a GABA congener which blocks nerve impulses at dopaminergic neurones (Roth *et al.*, 1973), also facilitated hypothermia. This facilitation may result from a marked increase in dopamine synthesis caused by the blockade of the impulse flow (Roth *et al.*, 1973). Nevertheless, our results disagree with a previous report indicating that GABA drugs, such as baclofen and GBL, antagonize the locomotor activity produced by such diverse stimulants as morphine, apomorphine and amphetamine (Cott & Engel, 1977). The reasons for this discrepancy remain to be elucidated, but they may result from differences in the doses of drugs used. The doses used in the present work were generally smaller than theirs (at least for GBL), so as not to modify the rectal temperature by pretreatment.

The hypothermia induced by amphetamine may also be modified by the cholecystokinin (CCK-8) and opioid systems. CCK-8 is present in high concentration in a subpopulation of dopamine-containing neurones (Hökfelt *et al.*, 1980). There is considerable controversy as to whether CCK-8 potentiates or decreases dopaminergic transmission. In our study, CCK-8 clearly potentiated the hypothermia induced by amphetamine

at a dose which, given alone, did not produce a hypothermia (Zetler, 1982). This potentiation may depend, at least partially, on dopaminergic mechanisms, since it has been suggested that CCK-8 potentiates the effect of dopamine on dopamine receptors (Studler *et al.*, 1985). Consequently, the activity of amphetamine would be enhanced.

Taken together, these results seem to indicate that endogenous dopamine modulates the hypothermia produced by amphetamine via GABA and CCK-8 interactions.

There is some evidence to suggest that endogenous opiates can alter body temperature (Rosow *et al.*, 1980) and may mediate part of the hypothermic response to dopamine receptor agonists (Weiss *et al.*, 1984). The failure to demonstrate any action of naloxone on amphetamine-induced hypothermia indicates that the naloxone-sensitive opioid systems are probably not implicated in this response.

Finally, we compared the effects of dopamine itself with the effects previously described of amphetamine so as to obtain more information on the resistance of the hypothermia induced by amphetamine to some neuroleptics. The hypothermia induced by dopamine was less intense and shorter than that produced by amphetamine. It was reduced by three neuroleptics, pimozide, *cis*-flupentixol and haloperidol, whereas the hypothermia induced by amphetamine was only blocked by haloperidol (Boschi & Launay, 1985). These differ-

ences may be attributed to the fact that the effects of amphetamine were not as pure as those of dopamine but included contributions from other functional systems such as the 5-HT and CCK-8 systems. Such contributions do not seem to be required for the hypothermia induced by dopamine, as we found that CCK-8 had no action on this hypothermia and that only one 5-HT drug affected the hypothermia. It has also recently been reported that the hydroxylated metabolites of amphetamine are capable of influencing dopaminergic and 5-hydroxytryptaminergic transmission (Matsuda *et al.*, 1989), like amphetamine (Boschi & Launay, 1985). If indeed these metabolites are involved in the hypothermic response to amphetamine, their effects may help to explain the differences in the mechanisms by which amphetamine and dopamine act.

In conclusion, the way in which amphetamine causes hypothermia in mice implicates not only the dopaminergic and 5-hydroxytryptaminergic systems, but is also subject to a further direct or indirect modulation by systems having GABA and CCK-8 components. These additional mechanisms may be the reason why the hypothermia produced by amphetamine is apparently resistant to some neuroleptics, while the hypothermia induced by dopamine is not. The hydroxylated metabolites of amphetamine formed *in vivo* might also help to explain these differences. We are now investigating the role of these metabolites.

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