Altered hypothermic responsiveness to (+)-amphetamine

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Dopaminergic mechanisms are believed to mediate the dose-dependent hypothermic response to (+)-amphetamine in rats maintained at an ambient temperature of 4° (Yehuda & Wurtman, 1972a). The following observations by Yehuda & Wurtman (1972b) lend support to this belief:

(1) A direct dopamine receptor agonist, apomorphine, is also effective in producing hypothermia; (2) pretreatment with haloperidol or pimozide abolishes the response, which is consistent with the dopamine receptor blocking action of these drugs; (3) (+)-amphetamine-induced hypothermia is not prevented by drugs which presumably block α- or β-noradrenergic or 5-hydroxytryptamine receptors.

Amphetamine- and apomorphine-induced stereotyped behaviour are also felt to be directly related to the activation of dopamine receptors (Randrup & Munkvad, 1967). We have investigated whether the responses of the dopamine receptors involved in hypothermia are analogous to those of the striatal receptors involved in stereotyped behaviour. Since both chlorpromazine-induced and (+)-amphetamine-induced hypersensitivity has been demonstrated in guinea-pigs, the influence of two separate drug regimes were studied in this species.

I. Chronic treatment with drugs, such as chlorpromazine, that block (+)-amphetamine-induced stereotyped gnawing behaviour results in a subsequent supersensitivity to the induction of this behaviour when the chronic course is terminated (Klawans & Rubovits, 1972; Tarsy & Baldessarini, 1974). It is hypothesized that prolonged pharmacological blockade of the dopamine receptors involved in stereotyped gnawing induces a supersensitive change in the receptors, analogous to the denervation supersensitivity seen in the peripheral nervous system. We have examined the hypothermic response in animals previously given a chronic course of chlorpromazine.

II. Recently, it has been demonstrated that animals receiving a chronic course of (+)-amphetamine sulphate develop a long-lasting supersensitivity to (+)-amphetamine- and apomorphine-induced gnawing (Klawans, Crosset & Dana, 1975). We have also investigated the hypothermic response in animals previously given a chronic course of (+)-amphetamine.

White male guinea pigs, 225–250 g, were housed in groups of six in pen-type cages with free access to Wayne Guinea Pig Chow and water. A light period of 0700–1800 h was maintained, and all experiments took place during 1100–1400 h. Injections were administered intraperitoneally except where indicated, the controls received an appropriate volume of saline.

Apomorphine hydrochloride (Merck & Co.) and (+)-amphetamine sulphate (Smith Kline & French) were dissolved in saline; chlorpromazine (Thorazine, Smith Kline & French) was diluted in saline; and pimozide (McNeil) was injected as a suspension in Methocel.

Several of the experiments used animals that had previously received a chronic drug pretreatment. One group, designated "chronic chlorpromazine," received a 21 day course of chlorpromazine (10 mg kg^{-1}) by single daily subcutaneous injection. Another group, designated "chronic amphetamine," were similarly treated with (+)-amphetamine sulphate 5 mg kg^{-1}. Both groups were tested 7 days after completion of the pretreatment course (i.e., Day 28). Both the chronic pretreatment schedules

described have been previously shown to render the animals supersensitive to the stereotyped behaviour-inducing action of (+)-amphetamine and apomorphine (Klawans & Rubovits, 1972; Klawans & others, 1975).

For the hypothermia testing, animals were transferred to single cages and, 30 min before injection, were placed in a thermostatically-controlled cold room with a temperature of 4° and a relative humidity of 40%. Colonic temperatures were determined by a YSI telethermometer inserted 6–7 cm. Measurements were taken at 10 min intervals, beginning 30 min before injection and continuing 60 min after treatment. With multiple drug treatment, the animals were placed in the cold room, given Drug I 30 min later, then Drug II after a further 30 min, and were then monitored for 60 min.

Significance was evaluated by Student's *t*-test. In no case did the initial 30 min pre-injection cold room acclimatization period have a significant effect on colonic temperature, and all results are comparisons with time zero just before (first) drug injection.

Both (+)-amphetamine (10 and 15 mg kg^{-1} Δt −3·0 s.d. 0·5°, −3·8 s.d. 0·6°) and apomorphine (5 and 10 mg kg^{-1} Δt − 1·8 s.d. 0·4°, 3·1 s.d. 0·6°) caused a highly significant ($P < 0{\cdot}005$) fall in colonic temperature (saline Δt 0·5 s.d. 0·3° h = 6 for each group). Table 1 summarizes the effect of various pretreatments on the hypothermic response. Pimozide 10 mg kg^{-1} markedly reduced the effect of apomorphine and (+)-amphetamine. Chlorpromazine 10 mg kg^{-1} caused a 3·2° fall in temperature when administered with saline, and larger falls when administered with apomorphine or (+)-amphetamine, although these did not achieve statistical significance. Chronic pretreatment with 10 mg kg^{-1} of chlorpromazine and (+)-amphetamine markedly reduced ($P < 0{\cdot}005$) the hypothermic effect of (+)-amphetamine 15 mg kg^{-1}, saline-amphetamine −3·7 s.d. 0·6°; chlorpromazine-amphetamine −1·6 s.d. 0·4°; amphetamine-amphtamine −1·8 s.d. 0·5° (n = 6 for each group).

The present study reports a hypothermic response to (+)-amphetamine sulphate or apomorphine hydrochloride in guinea-pigs maintained at 4°, in agreement with previous observations in the rat (Yehuda & Wurtman, 1972a,b). A dopaminergic mechanism is implicated by the ability of apomorphine, a compound which is thought to act directly on dopamine receptors (Ernst, 1969) to elicit hypothermia; and by the ability of pimozide, a blocker of dopamine receptors (Andén, Butcher & others, 1970) to eliminate the hypothermic response. However, the data presented here concerning acute chlorpromazine pretreatment is difficult to interpret with regard to antidopamine properties alone; possibly the drug interacts with a number of thermoregulatory

Table 1. *Effects of acute pretreatments on (+)-amphetamine- and apomorphine-induced hypothermia at 4°.*

Pretreatment drug (10 mg kg^{-1})	Drug II (mg kg^{-1})	Change in temperature (°)
Pimozide	Saline	−0·8 (0·5)
Pimozide	Apomorphine 10	−1·3 (0·5)*
Pimozide	(+)-Amphetamine 15	−1·2 (0·5)*
Chlorpromazine	Saline	−3·2 (0·7)
Chlorpromazine	Apomorphine 10	−4·0 (0·9)*
Chlorpromazine	(+)-Amphetamine 15	−3·8 (0·8)*

Data given as mean with standard deviation ( ). Each group consisted of at least six animals. Temperature was taken immediately before pretreated injection (time zero); Drug II was given 30 min later, and final temperature reading taken 60 min after Drug II (time 90). Change in temperature = $T_{(time\ zero)}$—$T_{(time\ 90)}$. Saline was given as the acute pretreatment injection for all chronically prepared animals. * Not significant. $P > 0{\cdot}05$ when compared with respective saline control.

systems. The hypothermia (−3·2°) we obtained with acute chlorpromazine is less than the −9° change seen in the rat after the same 10 mg kg^{-1} dose (Yehuda & Wurtman, 1972a).

Curiously, two chronic pretreatments which are known to produce lasting supersensitivity to the stereotyped gnawing induced by (+)-amphetamine or apomorphine (Klawans & Rubovits, 1972; Klawans & others, 1975) resulted in partial *tolerance* to the hypothermic effect of (+)-amphetamine. The chronic course of (+)-amphetamine we used resulted in a reduction of the hypothermia to 49% of non-chronic controls. Recently, Chiel, Yehuda & Wurtman (1974) noted that the effectiveness in producing hypothermia of (+)-amphetamine and apomorphine is reduced respectively to 72 and 19% after a 7 week course of 15 mg kg^{-1} (+)-amphetamine in the rat. They also observed a marked decrease in the hypothermia produced by the dopamine receptor activator pyrimidylpipenonyl piperazine (ET-495) strongly implicating alterations in the receptor itself in this development of tolerance.

The chronic course of chlorpromazine described resulted in a reduction of the hypothermia to 43% of non-chronic controls strongly in the direction of tolerance. This finding is possibly in conflict with that of Reid (1975) who found a 168% increase in the hypothermic response to ET-495 after 6-hydroxydopamine-induced neuronal destruction. It is perhaps simplistic to view these results as antagonistic, in view of the uncertainty in the mode of action of chlorpromazine in thermoregulatory systems, and in view of the widespread destruction of catecholaminergic neurons induced by 6-hydroxydopamine.

The present study supports the role of dopamine in thermoregulation, and indicates that such mechanisms are susceptible to pharmacological alteration. With stereotyped gnawing, chronic receptor blockade by chlorpromazine or chronic receptor activation by (+)-amphetamine result in *supersensitivity*. However, with the (+)-amphetamine-induced hypothermia, these treatments each result in *tolerance*. It is difficult to explain the similarity of the results of chronic (+)-amphetamine and chronic chlorpromazine treatments in view of their opposing acute actions. Yet, in two separate dopaminergic systems this interesting parallel has been maintained. More significantly, these results show that chronic pretreatment schedules which induced hypersensitivity to one dopaminergic response can produce tolerance to another response. The observation that the same drug regime can at the same time produce hypersensitivity and tolerance in different dopaminergic systems must be kept in mind in an attempt to draw pharmacologic generalizations.

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