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A note on the effect of amantadine on body temperature in mice

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Amantadine hydrochloride caused a dose-dependent fall in rectal temperature in mice. This response was antagonized by haloperidol, which itself produced some hypothermia, and by pretreatment with α-methyl-*p*-tyrosine. The mode of action of amantadine and the possible involvement of dopamine in the control of body temperature is discussed.

Kruk (1972) showed that dopamine, amphetamine and apomorphine, injected intracerebroventricularly into rats, caused a fall in core temperature which was abolished by pretreatment with pimozide. Both Fuxe & Sjöqvist (1972) and Barnet, Goldstein & Taber (1972) demonstrated hypothermia following intraperitoneal injection of apomorphine in mice, and reported that this effect was apparently due to an action on central dopamine receptors. All these results suggest a role for brain dopamine in the control of body temperature.

It has been suggested that the antiparkinsonian action of amantadine is due to the release of dopamine from central dopaminergic neurons (Farnebo, Fuxe & others, 1971), and the same action has been said to account for the reversal of haloperidol-induced inhibition of the conditioned avoidance response in rats (Davies, Jackson & Redfern, 1973). It was therefore of interest to examine the effect of amantadine on body temperature.

METHODS

Groups of 10 female Swiss albino mice, 25–35 g, were used at each dose. Temperature was measured using a rectal probe, inserted to a depth of 2·5 cm, connected to an electric thermometer (Light Laboratories, Brighton) and was recorded 15, 30, 60, 120 and 180 min after amantadine injection.

Drugs were injected in distilled water intraperitoneally, and in those experiments where both amantadine and haloperidol were given, haloperidol was injected 30 min before amantadine. All experiments were performed between 10·00 h and 12·00 h. Statistical significance was calculated using Student's *t*-test and the level of significance is shown in the appropriate figures.

RESULTS

Fig. 1 shows the effect of amantadine on rectal temperature in mice. A dose of 40 mg kg^{-1} (i.p.) caused a fall in temperature of 1·4° at 15 min, while the effects of 57 and 80 mg kg^{-1} were greatest at 60 min (3·0° and 6·6° respectively). After all three doses the maximum decrease was not prolonged, but rectal temperature had not returned to normal after 180 min.

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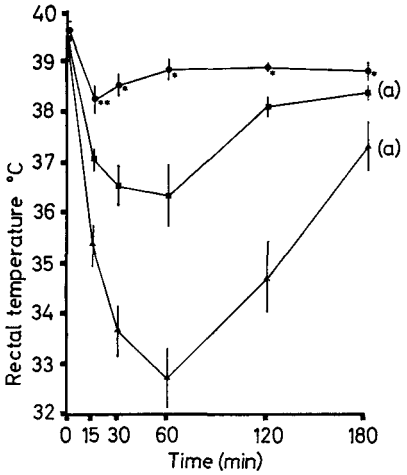

FIG. 1. The effect of amantadine hydrochloride (mg kg^{-1}) on rectal temperature: ●—● 40; ■—■ 57; ▲—▲ 80. Significance of difference from corresponding control value at zero time: * $P < 0.05$; ** $P < 0.01$; (a) $P < 0.001$ for each point.

Although haloperidol also produced a prolonged fall in temperature (Fig. 2), in animals receiving both haloperidol and amantadine the fall in temperature was significantly smaller than that produced by amantadine alone (Fig. 3A).

Pretreatment with α-methyl-*p*-tyrosine (3 daily doses of 200 mg kg^{-1}, i.p.) effectively reduced but did not abolish the response to amantadine (Fig. 3B).

DISCUSSION

Amantadine has here been shown to produce a significant dose dependent fall in rectal temperature. Zetler (1970) has previously reported a hypothermic response to amantadine, although the falls in temperature recorded were considerably smaller than those in our experiments, and only reached significance after a dose of 80 mg kg^{-1}.

Farnebo & others (1971) have suggested that the anti-Parkinsonian activity of amantadine depends on the ability of amantadine to release dopamine from central neurons. On the other hand Heimans, Rand & Fennessy (1972) have reported that amantadine effectively blocks the uptake of dopamine by synaptosomes prepared from rat basal ganglia. From our results it would seem that either action could account for the hypothermic response since pretreatment with α-methyl-*p*-tyrosine,

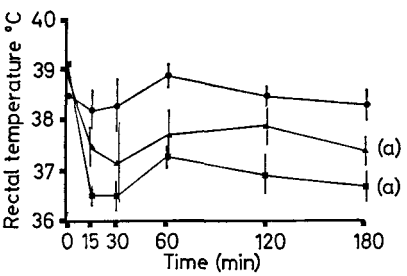

FIG. 2. The effect of haloperidol (mg kg^{-1}) on rectal temperature: ●—● 0·5; ▲—▲ 1; ■—■ 2. Significance of difference from corresponding control value at zero time: (a) $P < 0.001$ for each point.

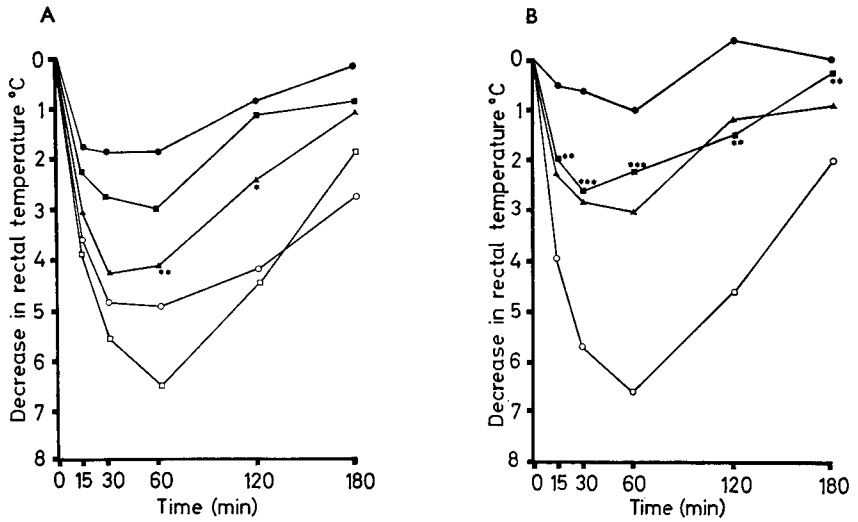

FIG. 3A. The effect of haloperidol on amantadine (mg kg^{-1}) induced hypothermia: ■—■ amantadine 57; □—□ amantadine 80; ●—● haloperidol 1 + amantadine 57; ○—○ haloperidol 1 + amantadine 80; ▲—▲ haloperidol 2 + amantadine 80. Significance of difference from corresponding value for amantadine alone: * $P < 0.05$; ** $P < 0.01$.

B. The effect of α-methyl-*p*-tyrosine (200 mg kg^{-1} for 3 days) on amantadine (mg kg^{-1}) induced hypothermia. ▲—▲ amantadine 57; ○—○ amantadine 80. ●—● α-methyl-*p*-tyrosine + amantadine 57; ■—■ α-methyl-*p*-tyrosine + amantadine 80. Significance of difference from corresponding value for amantadine alone: ** $P < 0.01$; *** $P < 0.001$.

which by inhibiting synthesis will cause depletion of both dopamine and noradrenaline in central neurons, produced a significant decrease in the hypothermic response to amantadine. We know of no evidence that haloperidol has a specific blocking action at any central receptors other than dopamine receptors (Janssen, 1965) and it therefore seems likely that the fall in temperature produced by haloperidol is caused by a non-specific depression of hypothalmic centres common to many major tranquillizers. However the fact that the hypothermia produced by amantadine was prevented by haloperidol would indicate that an effect on dopaminergic neurons rather than on noradrenergic neurons is the important factor in the amantadine response.

These results are therefore in agreement with those of Kruk (1972), Fuxe & Sjöqvist (1972) and Barnet & others (1972) in suggesting a role for brain dopamine in the regulation of body temperature.

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