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The effects of diethyldithiocarbamate and L-dopa on body temperature in mice

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Diethyldithiocarbamate (DDTC) raises body temperature in reserpinized mice, an effect that is unlikely to be an intrinsic action of the compound since DDTC lowers temperature in normal mice. DDTC has no effect on body temperature of reserpinized rats. The effects of DDTC on body temperature in normal and reserpinized mice are mimicked qualitatively by L-dopa indicating that the effects may reflect increased dopamine levels. Pargyline pretreatment does not influence the hypothermia produced by DDTC.

DIETHYLDITHIOCARBAMATE (DDTC), an inhibitor of the enzyme dopamine-β-hydroxylase, blocks the temperature-elevating action of L-dopa in reserpinized rats (Jori, Carrara & Garattini, 1966), presumably by interfering with the conversion of exogenous dopa to noradrenaline. While attempting to replicate these findings in another species, we found that DDTC raised body temperature in reserpinized mice. In contrast, other experiments in our laboratory confirmed the lack of effect of DDTC on body temperature of reserpinized rats. After these preliminary, findings, the effects of DDTC on body temperature were examined in normal reserpinized or monoamine oxidase inhibitor (pargyline)-treated mice. In all these situations, DDTC was compared with L-dopa to determine whether the effects of DDTC are direct, related to a decrease in brain noradrenaline or to an increase in brain dopamine. Dopa increases both brain dopamine and noradrenaline whereas DDTC increases brain dopamine but lowers noradrenaline levels (Everett & Wiegand, 1962; Carlsson, Lindqvist, Fuxe & Hökfelt, 1966).

Experimental

METHODS

Groups of five male CF # 1 mice (20–24 g) were housed in plastic cages in a temperature-controlled room (20° ± 1·0°) 19 hr before administration of DDTC or L-dopa. These were given 18 hr after reserpine (5·0 mg/kg) and 3½ hr after pargyline (25 mg/kg). All drugs were injected intraperitoneally. Body temperatures were taken orally with an Ellab temperature probe (Brittain & Spencer, 1964).

Results

The effects of graded doses of DDTC and L-dopa on body temperature of mice made hypothermic by reserpine is shown in Fig. 1. Temperatures decreased an average of 15–16° after reserpine. DDTC raised body temperature in a dose-related manner, and was more effective than

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L-dopa at each dose level tested. The dose-response curve for L-dopa was non-linear with a peak effect at 150 mg/kg.

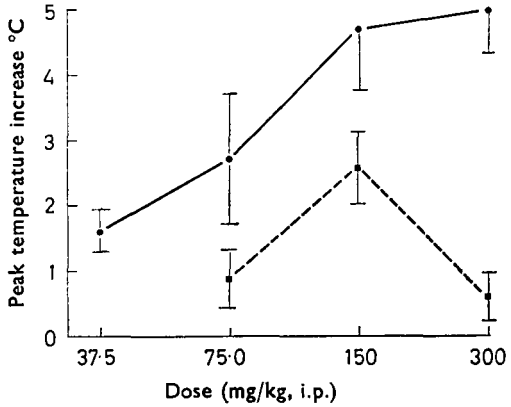

FIG. 1. Hyperthermic effects of DDTC and L-dopa in mice pretreated 18 hr previously with reserpine (5 mg/kg, i.p.) and housed at 20°C (room temperature). Each point represents the mean ± s.e. of 10 mice and is the net maximum change in temperature after the average change of the saline control group has been subtracted. ● —● DDTC. ■ —— ■ L-Dopa.

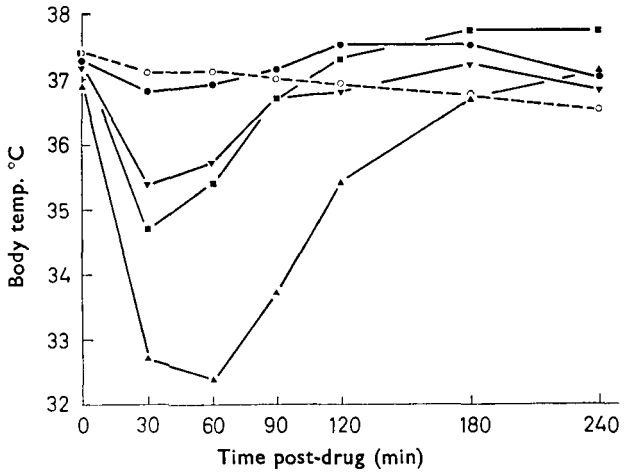

FIG. 2. Hypothermic effect of DDTC in normal mice housed at 20°C. Each point represents the average of 10 mice. DDTC was given at zero time. ○ – – ○ Saline. DDTC: ● —— ● 37·5, ▼ —— ▼ 75, ■ —— ■ 150, ▲ —— ▲ 300 mg/kg.

Fig. 2 illustrates the decrease in body temperature induced by DDTC in normal mice. A dose of 75 mg/kg produced a significant decrease in body temperature, and 300 mg/kg produced a precipitous and long-lasting hypothermia. L-Dopa also produced hypothermia in normal mice housed under similar conditions (Fig. 3). The dose-response curve for L-dopa was not uniform; 75 mg/kg produced a greater and longer-lasting hypothermia than did 150 mg/kg, whereas 300 mg/kg produced

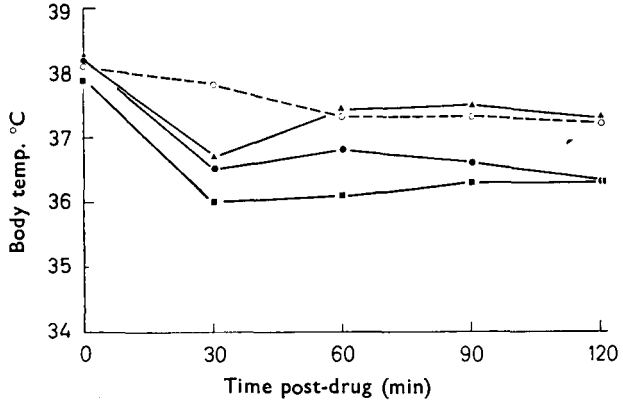

FIG. 3. Hypothermic effect of L-dopa in normal mice at 20°C (room temperature). Each point represents the average of 10 mice. L-dopa was given at zero time. ○ – – ○ Saline. L-Dopa: ● —— ● 75, ▲ —— ▲ 150, ■ —— ■ 300 mg/kg.

the largest temperature decrease. Although the potency of L-dopa varied from experiment to experiment, the shape of the curve remained the same.

Pargyline pretreatment did not significantly affect the dose-response curve for DDTC (Fig. 4); with L-dopa the qualitative effect was similar, there was a small but significant decrease in temperature which was not greater than that produced in normal mice. The dose-response relation for DDTC in normal, resperpinized or pargyline-treated mice at 20° is shown in Fig. 4; the smaller doses of DDTC are more active in producing hyperthermia in reserpinized mice than hypothermia in normal or pargyline-treated mice.

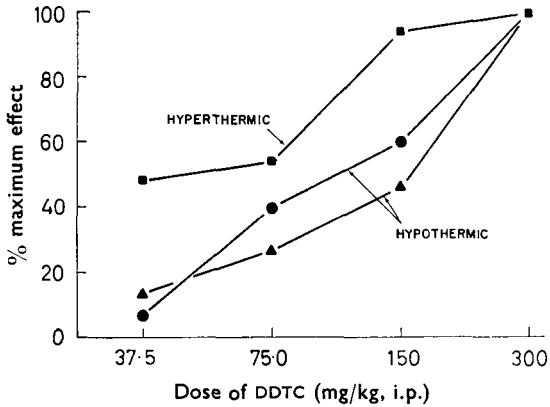

FIG. 4. Comparative dose-response curves for DDTC in normal, reserpinized (5 mg/kg, i.p.) and pargyline-treated (25 mg/kg, i.p.) mice plotted as percent of maximum increase in temperature for the reserpinized mice, and percent of maximum decrease in temperature for the other two groups. Each point represents the average of 10 mice and is corrected for changes in temperature of the saline control group. ● —— ● Normal mice. ▲ —— ▲ Pargyline-treated mice. ■ —— ■ Reserpine-treated mice.

Discussion

DDTC raises body temperature in reserpinized mice but has no effect on body temperature of rats under the same conditions. The temperature-elevating effect of DDTC in reserpinized mice is probably not due to it having an intrinsic action since it lowers temperature in normal mice. Its effects on body temperature in normal and reserpinized mice are mimicked qualitatively by L-dopa, thus indicating that these effects are probably due to increased brain dopamine levels rather than to changes in noradrenaline levels. This conclusion is substantiated by the finding that, 60 min after an intraperitoneal administration of [^{14}C] dopa to mice, 13·8% of the recovered total body-radioactivity was in the form of [^{14}C] dopamine, while only 1·2% was [^{14}C]noradrenaline (Weiss, 1966).

Pargyline inhibits monoamine oxidase for which dopamine is considered to be a good substrate; thus, pargyline pretreatment should theoretically enhance the hypothermia produced by DDTC. But pargyline pretreatment did not affect the dose-response curve for DDTC. In contrast, other investigators have reported dopa-induced hyperthermia in monoamine oxidase-inhibited mice (Jori & Garattini, 1965). In that study, however, the ambient temperature was relatively high (30°) and the *hyper*thermia observed in the mice was transient, becoming a *hypo*thermia after 90–120 min. Temperature studies with dopa in monoamine oxidase-inhibited mice are also complicated by increases in spontaneous motor activity (Everett & Wiegand, 1962) which would tend to raise body temperature. We found dopa to lower body temperature at doses which had no effect on overt motor activity.

The failure of pargyline to potentiate the hypothermic effects of DDTC in mice may be explained by the biochemical findings of others. Goldstein, Anagnoste & others (1964) found that, after administering [^{14}C] dopamine to rats treated with pheniprazine and disulfiram (an inhibitor of dopamine-β-hydroxylase whose activity is thought to be due to its conversion to DDTC *in vivo*) the amount of [^{14}C] dopamine in heart tissue was not elevated more than with disulfiram alone. These findings were essentially confirmed in rat brain stem by Carlsson, Fuxe & Hökfelt (1967) using DDTC and nialamide. Levels of brain dopamine may be limited by other factors such as binding rather than by monoamine oxidase in DDTC-treated animals.

It is postulated that in reserpinized mice DDTC raises temperature by elevating depleted dopamine stores and that in normal mice, DDTC lowers temperature by causing an increase in dopamine levels above a critical point. Some support for this concept is that dopa has been shown to reduce spontaneous motor activity in mice with low doses but to increase it with higher doses (Boissier & Simon, 1966). This biphasic effect occurs within 60 min of administration. Based on the findings of Weiss (1966), it seemed likely that the effect was due to an increase in brain dopamine rather than noradrenaline. The present data indicate that dopamine probably has a role in the central regulation of temperature in mice. Changes in brain dopamine levels with time measured after dopamine-β-hydroxylase inhibition would help to elucidate this.

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