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Comparison of intracisternally and intraperitoneally injected harmaline on body temperature and tremor in the rat

J. BRUINVELS

Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, *Utrecht, The Netherlands*

Low doses of harmaline (1–10 mg/kg) injected intraperitoneally into rats caused hypothermia, while higher doses (10–30 mg/kg) induced tremor in addition to hypothermia. Harmaline injected intracisternally decreased body temperature without inducing tremor. To induce a maximal fall in body temperature following intraperitoneal injection of harmaline, 1000 times more harmaline was needed than after intracisternal administration. Harmaline by this route induced hypothermia much faster than by intraperitoneal injection. It is concluded that harmaline-induced hypothermia is at least partly localized in the central nervous system and is not associated with the tremor.

Harmaline injected intraperitoneally into rats induces hypothermia (Schmidt & Fähse, 1964). Recently it was shown that harmaline did not provoke hypothermia if the biosynthesis of noradrenaline was inhibited (Bruinvels & Sourkes, 1968). This suggested that the actual lowering of body temperature is mediated by noradrenaline.

That noradrenaline is involved in hypothermia is in agreement with the results of Feldberg & Lotti (1967), who showed that intraventricular administration of noradrenaline can lower body temperature in rats. Also Schmidt & Fähse (1964) demonstrated a fall in body temperature after intracerebral injection of this amine into rats. The observation that noradrenaline injected intravenously into rats results in an increase in body temperature (Jori, Paglialunga & Garattini, 1967) may suggest that the hypothermic effect of harmaline is of central origin.

Harmaline, like harmine, also causes tremor in rats (Marković & Giaja, 1951). Whether harmaline-induced tremor is associated with alterations in amine metabolism or with hypothermia is unknown. The present experiments were designed to further explore the action of harmaline on body temperature and to investigate whether or not tremor is associated with the hypothermic effect of this compound.

EXPERIMENTAL

Material and methods

Male albino rats, 100–110 g, were placed in individual cages 1·5 h before the first injection, in a room maintained at 24·5 $\pm$ 1°.

Harmaline hydrochloride (Fluka) and saline were administered intracisternally (20 μl/rat) according to Jeffers & Griffith (1962). For intraperitoneal injection a volume of 1 ml/rat was used.

Body temperature was measured with a Telethermometer (Yellow Spring Co.). A probe was inserted 3 cm into the rectum of the rats until the recorded temperature

remained constant. The change in body temperature was calculated from the area of the temperature curves of the control and the harmaline-treated animals during a constant period of time after the administation of saline or harmaline respectively.

The frequency of the tremor was measured with an electro-magnetic vibration transducer (Philips, type PR 9262), which was used in combination with a recorder.

RESULTS AND DISCUSSION

The effect of different doses of intraperitoneally injected harmaline on body temperature is shown in Fig. 1A. The deepest fall in body temperature was reached after 1 h for doses of 1–10 mg/kg, whereas higher doses (10–30 mg/kg) showed a maximum after 1·5 h. After the administration of 10–30 mg of harmaline per kg weight, a tremor with a frequency of about 10 Hz was found in addition to the hypothermia. After injection of 8 mg/kg, 50% of the rats had tremor. Lower doses of harmaline did not induce tremor.

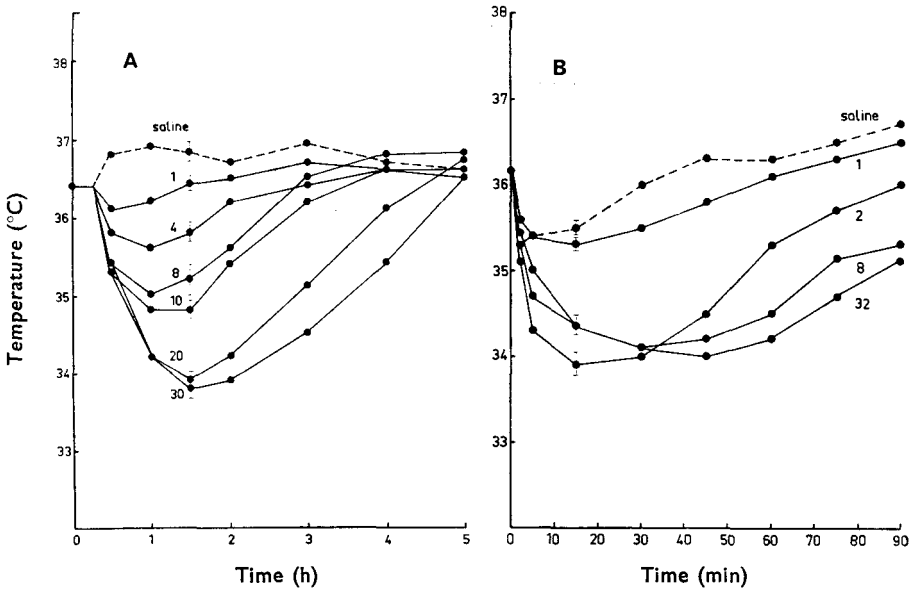

FIG. 1. Effect of (A) intraperitoneal, (B) intracisternal injection of various doses of harmaline on body temperature of the rat. Dots represent the mean of 6 experiments. Bars indicate s.e. and numbers the injected dose in, A, mg/kg, B, reg/rat.

Fig. 1B represents the fall in body temperature after intracisternal injection of different doses of harmaline. A dose of 2 μg of harmaline resulted in a maximal fall in body temperature; higher doses prolonged the duration of the hypothermia. Intracisternal injection of harmaline never caused tremor. Maximum decrease in body temperature occurred 15 min after intracisternal injection (Fig. 1B).

Fig. 2A and B represent dose-response relations after intraperitoneal and intracisternal injection of harmaline respectively. The decrease in body temperature was expressed in arbitrary units, which were proportional to the decrease in body temperature as a function of time (see methods). From Fig. 2A intraperitoneal injection of graded doses of harmaline can be seen to induce a dose-response relation which seems to be the result of two components. One elicited by doses up to 8 mg/kg, which

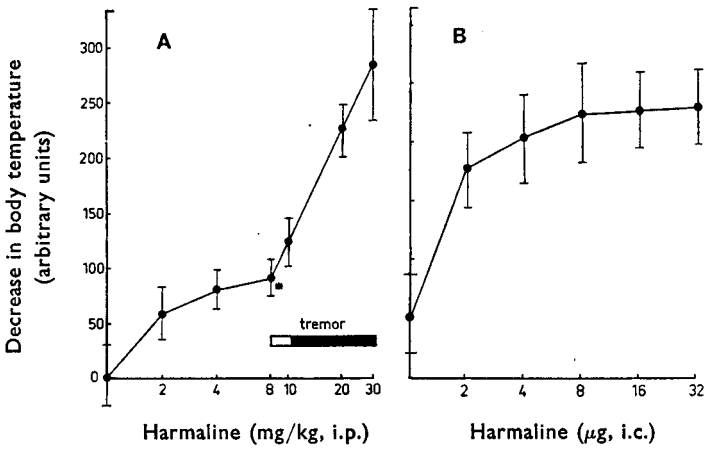

FIG. 2. Dose-response curves of the effect of, A, intraperitoneally, B, intracisternally injected harmaline on body temperature. The decrease in body temperature is expressed in arbitrary units proportional to the area beneath the temperature curves for (A) 285 min (B) 90 min after administration of harmaline or saline. Dots represent the mean of 6 experiments.* Mean of 5 experiments; one measurement was discarded according to the text of Dixon. Open bar 50% of the rats showed tremor. Solid bar 100% of the rats showed tremor.

caused a modest decrease in body temperature without tremor, and one by doses higher than 8 mg/kg which caused a marked fall in body temperature, and tremor. It is possible that the second half of the curve is caused by a facilitating effect of the tremor on the fall in body temperature. However, proof for this has yet to be provided.

Intraperitoneal injection of 32 μg of harmaline did not affect body temperature (Fig. 1A), while the same dose given intracisternally resulted in a maximal decrease of body temperature (Fig. 1B).

Thus intracisternally-injected harmaline in rats causes a fall in body temperature which occurs much more rapidly and with far lower doses than the intraperitoneally injected drug. From these results it may be concluded that the action of harmaline on body temperature is at least partly localized in the central nervous system.

The lower doses of harmaline, which caused hypothermia on intraperitoneal injection did not induce tremor. This suggests that these two phenomena are not necessarily associated. This is supported by the fact that intracisternal injection of harmaline caused hypothermia without provoking tremor. The fact that tremor did not occur in rats after intracisternal injection of harmaline, may indicate that the injected material does not reach those centres in the brain which induce tremor. Lack of association between hypothermia and tremor is also in agreement with previous results, viz. that pretreatment with a dopa-decarboxylase inhibitor or with an inhibitor of dopamine-β-hydroxylase prevents harmaline-induced hypothermia, but not the tremor (Bruinvels & Sourkes, 1968).

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