CENTRAL MECHANISM OF THE HYPERTHERMIC EFFECT AND ITS POTENTIATION BY ANTIDEPRESSANTS FOLLOWING INJECTION OF LARGE DOSES OF NORADRENALIN INTO THE CEREBRAL VENTRICLES OF MICE

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Injection of large doses (26 μg) of noradrenalin hydrotartrate into the lateral ventricle of the mouse brain at an ambient temperature of 18-22°C caused an increase in body temperature which was not abolished by ganglion-blocking agents and was potentiated by antidepressants but not by cholinolytics. Intraperitoneal injection of imipramine and chloracizine* iodomethylates in a dose of 5 mg/kg, by contrast with their hydrochlorides, did not potentiate the hyperthermic effect of noradrenalin, but when injected directly into the cerebral ventricle, imipramine iodomethylate was more effective than the hydrochloride. Intraventricular injection of small doses (2.5-5 μg) of imipramine and its iodomethylate potentiated the hyperthemic effect of intraventricular, but not of subcutaneous (1-1.5 mg/kg) injection of noradrenalin. When injected simultaneously into the cerebral ventricle imipramine and its iodomethylate, in a dose of 2.5 μg, potentiated the hyperthermic effect of noradrenalin, but if injected intraperitoneally, the threshold dose of imipramine was about 125 μg, while that of imipramine iodomethylate was higher still. The results of this analysis indicate a central mechanism of the hyperthermic effect of noradrenalin and its potentiation by antidepressants.

When injected into the cerebral ventricles of mice in doses not exceeding 20 μg, noradrenalin induces hypothermia [2, 6, 9]. The writer has shown that antidepressants (imipramine, dimethylimipramine, and chloracizine) potentiate this response [5]. Interest in this effect of noradrenalin is due to the importance attached to the activation of central adrenergic structures in the interpretation of the antidepressive action of modern thymoanaleptics [3, 7, 13]. However, intraventricular or intracisternal injection of noradrenalin or adrenalin usually evokes symptoms of inhibition and behavioral depression, and this explains attempts to revise ideas concerning the activating role of central adrenergic structures and the importance of their activation for the antidepressive effect [10, 12].

The localization of the hyperthermic effect of noradrenalin and its potentiation by tricyclic antidepressants is analyzed in this paper.

EXPERIMENTAL METHOD

Experiments were carried out on 900 noninbred albino mice of both sexes weighing 23-25 or 28-32 g. Mice of one sex and differing in weight by not more than 3 g were used in each experiment. The preparations (0.005 or 0.0025 ml) were injected into the lateral ventricles of the brain by means of a special device [15]. When the two substances were used simultaneously, the original solutions were mixed immediately before injection. The iodomethylates of imipramine ("quaternary" imipramine, QI) and of chloracizine

*2-chloro-10-(3-dimethylaminopropionyl)phenothiazine.

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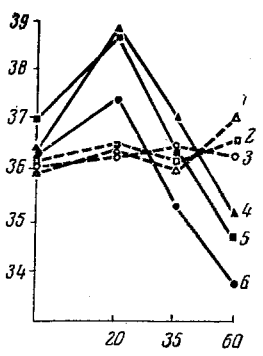

Fig. 1

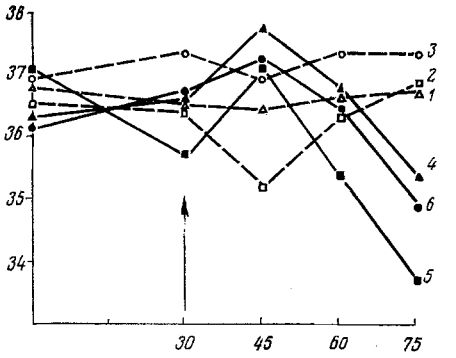

Fig. 2

Fig. 1. Effect of imipramine and its iodomethylate (QI) on the hyperthermic effect of noradrenalin injected intraventricularly. Experiment on December 18, 1968. Ambient temperature 22°C. Each point is the mean of measurements on eight mice. Imipramine or QI (5 mg/kg in each case) injected intraperitoneally 50 min before injection of 10^{-7} mole noradrenalin or bidistilled water (H_2O) in a volume of 0.005 ml into the lateral ventricle. Imipramine significantly ($P < 0.01$) potentiated the hyperthermic effect of noradrenalin while QI was ineffective. Here and in Fig. 2: abscissa, time from injection of noradrenalin (in min); ordinate, body temperature of mice (in °C); 1) imipramine + H_2O; 2) QI + H_2O; 3) H_2O + H_2O; 4) imipramine + noradrenalin; 5) QI + noradrenalin; 6) H_2O + noradrenalin.

Fig. 2. Effect of intraventricular injection of imipramine and QI on hyperthemic effect of intraventricular injection of noradrenalin. Experiment on January 21, 1969. Ambient temperature 21°C. Imipramine, QI (5 μg), or H_2O were injected into right lateral ventricle 30 min before injection of 10^{-7} mole noradrenalin into it. QI potentiated ($P < 0.01$) the hyperthermic effect of noradrenalin while imipramine showed only a tendency toward potentiation.

were synthesized at the Department of Dyestuffs Technology, Lensovet Leningrad Technological Institute, by I. Ya. Kvitko. The rectal temperature was measured by the TÉMP-60 electric thermometer. Both the initial temperature and its changes were taken into account during analysis of the results [4].

EXPERIMENTAL RESULTS AND DISCUSSION

Pharmacological tests [2] show that QI penetrates much less readily into the brain than imipramine and, when injected intraperitoneally (5 mg/kg), unlike imipramine, it did not potentiate the hyperthermia produced by intraventricular injection of noradrenalin (Fig. 1). Chloracizine iodomethylate, unlike its hydrochloride, likewise did not potentiate the hyperthermic effect of noradrenalin.

The iodomethylates of imipramine and chloracizine (unlike their hydrochlorides), however, did not potentiate the hyperthermia arising after subcutaneous injection of noradrenalin (1.5-2.0 mg/kg). In 5 of 7 experiments imipramine (5 mg/kg) significantly potentiated and (or) prolonged the noradrenalin hyperthermia whereas QI in the same dose was ineffective. This agrees with data in the literature showing that QI is much less effective than imipramine in certain "peripheral" tests [8]. Consequently, the fact that QI does not potentiate the hyperthermia produced by intraventricular injection of noradrenalin cannot be taken as evidence in support of the central localization of the hyperthermic effect of noradrenalin; on the contrary, these results are in harmony with the view that the mechanism of noradrenalin hyperthermia is peripheral in character, on account of the departure of noradrenalin from the brain.

Accordingly, a series of experiments was carried out in which imipramine and QI were injected intraventricularly before or simultaneously with the intraventricular injection of noradrenalin. If imipramine and QI were injected in doses of 2.5 or 5 μg 30 min before or at the same times as noradrenalin (26 μg), QI was more effective in potentiating the noradrenalin hyperthermia (Fig. 2). If imipramine of QI (5 μg in each case) was injected 90 min or 60 min before noradrenalin, no potentiation of the hyperthermic effect of noradrenalin was observed.

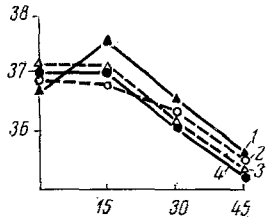

Fig. 3. Comparison of effect of intraventricular and intraperitoneal injection of imipramine on hyperthermic effect of intraventricular injection of noradrenalin. Experiment on January 10, 1969. Ambient temperature 20°C. Noradrenalin (10^{-7} mole) or H_2O injected into lateral ventricle simultaneously with injection of 2.5 μg imipramine into ventricle or 5 μg imipramine intraperitoneally. Noradrenalin by itself does not change the temperature of the animals, whereas intraventricular injection of imipramine leads to the manifestation of the hyperthermic effect of noradrenalin ($P < 0.05$), while injection of twice the dose of imipramine intraperitoneally is ineffective. 1) 2.5 μg imipramine intraventricularly + noradrenalin intraventricularly; 2) H_2O intraperitoneally (i.p.) + H_2O intraventricularly (i.v.); 3) H_2O i.v. + noradrenalin i.v.; 4) 5 μg imipramine i.p. + noradrenalin i.v. Remainder of legend as in Fig. 1.

After simultaneous injection of imipramine or QI (2.5 μg in each case) and noradrenalin (26 μg) into the ventricle, the effect of noradrenalin was potentiated, whereas the intraventricular injection of imipramine or QI simultaneously with the subcutaneous injection of noradrenalin did not potentiate the hyperthermic effect of the latter. By intraperitoneal injection (30 min before injection of noradrenalin into the lateral ventricle) the threshold dose of imipraminewas about 5 mg/kg (125 μg for a mouse weighing 25 g), i.e., much greater than for intraventricular injection of the compound (Fig. 3). In this case the threshold dose of QI was higher still.

These results indicate a central localization of the hyperthermic effect of noradrenalin when injected into the cerebral ventricles and also a central localization of the interaction between the imipramine-like antidepressants and noradrenalin which leads to potentiation of the hyperthermic effect of noradrenalin. The fact that QI is more effective than imipramine when injected intraventricularly can be explained by the slower release of QI from the brain because of its difficulty in passing through biological membranes. Probably both imipramine and QI have been removed from the brain 60 min after intraventricular injection, for at that time both these substances were ineffective.

Hexamethonium does not block the hyperthermic effect of noradrenalin injection intraventricularly, ruling out a peripheral mechanism through the sympathetic nervous system. This fact is in agreement with results obtained by the analysis of the hyperthermic effect of amphetamine in rabbits [1]. Recent findings conflict with the view that the central hyperthermic effect of noradrenalin is potentiated by antidepressants because of their effect on peripheral adrenergic mechanisms.

The data described above suggests that the response of the body temperature to injection of noradrenalin into the cerebral ventricles is the resultant of hyperthermic and hypothermic components (probably formed chiefly in different structures of the brain), and the imipramine-like antidepressants, which block the absorption of noradrenalin by the tissues and increase its concentration in the brain, change the balance in support of the hyperthermic response, which is observed only in the presence of high concentrations of noradrenalin. This may explain both the initial decrease or "distortion" of the hypothermic effect by antidepressants after intraventricular injection of small doses (under 20 μg) of noradrenalin and also the potentiation of the hyperthermic phase following its injection in large doses. Evidence of the central character of the hyperthermic effect of noradrenalin is given by the hyperthermic effect observed after its injection into the lateral ventricles in a dose of 3 μg at a high ambient temperature [14].

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