CONTENT OF CATECHOLAMINES IN THE BRAIN STEM OF ALBINO RATS DURING DEVELOPMENT OF TOLERANCE TO TRIFLUOPERAZINE

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During daily subcutaneous injection of trifluoperazine for 3 months into rats, the noradrenalin concentration in the brain stem first falls and then rises rapidly toward the end of the second week, although no signs of tolerance (as shown by behavioral tests) are found at this period. Complete recovery of the catecholamine level takes place after three months and coincides with the development of tolerance as shown by a conditioned-reflex test.

The development of tolerance to tranquilizers of the phenothiazine series when administered for long periods has been demonstrated [3, 5, 11, 12]. The work of Vysotskaya and Shugina [1] showed a fall in the noradrenalin concentration in the brain stem following administration of a single dose of trifluoperazine.

To discover the possible mechanisms of tolerance to trifluoperazine, it was decided to study changes in the catecholamine concentration in the brain stem during prolonged administration of the compound.

EXPERIMENTAL METHOD

The writers have previously shown [3] that habituation to trifluoperazine, as shown by a conditioned-defensive test, develops after 2-3 months of daily administration of the compound in a dose of 2 mg/kg body weight. In the present investigation observations were carried out for 3 months, using the same dose of trifluoperazine. Albino rats weighing 180-220 g were used. On the 1st, 14th, 30th, 60th, 75th, and 90th days after the beginning of administration of trifluoperazine, the animals were decapitated 2 h after injection (the time of the maximal sedative action of trifluoperazine when given by this route).

The concentrations of noradrenalin and adrenalin were determined in the brain stem, as the region richest in catecholamines [13]. The brain was rapidly removed, the brain stem isolated, washed with physiological saline to remove blood, and frozen in liquid oxygen. Catecholamines were adsorbed from a trichloroacetic filtrate on a column with aluminum hydroxide by the method of Euler and Lishaiko [8] as modified by É. Sh. Matlina. Differentiation between adrenalin and noradrenalin was carried out by oxidation at different pH values (6.5 for noradrenalin, 4.2 for adrenalin). Fluorescence was recorded by an improved "Analiz-1" photofluorometer. The concentrations of noradrenalin and adrenalin were expressed in μg/g fresh tissue. The results were analyzed by statistical methods.

EXPERIMENTAL RESULTS AND DISCUSSION

The catecholamine concentrations in the brain stem of the control animals were determined throughout the experiment. At each of the 6 periods of the investigation, three control rats were sacrificed along with the experimental animals. The mean concentration of noradrenalin in the brain stem of the control

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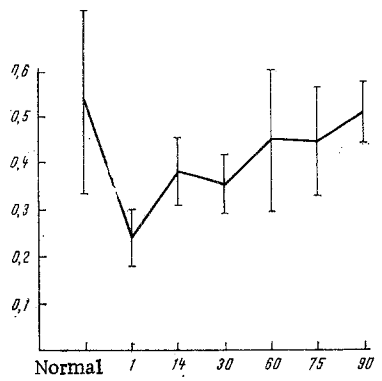

Fig. 1. Concentration of noradrenalin in brain stem of albino rats following chronic administration of trifluoperazine. Ordinate, concentration of noradrenalin (in μg/g fresh tissue); abscissa, day of injection of compound. Limits of standard deviation shown on curve.

animals was 0.53 $\pm$0.061 μg/g. No statistically significant difference was found between males and females.

On the first day of the experiment, 2 h after a single subcutaneous injection of 2 mg/kg trifluoperazine, the level of the catecholamines was considerably raised to 0.23 $\pm$0.025 μg/g. This result is in agreement with the findings of Vysotskaya and Shugina [1], who found a lowering of the noradrenalin level following intravenous injection of trifluoperazine in a dose of 0.5 mg/kg.

On the 14th day from the beginning of daily administration of trifluoperazine the noradrenalin concentration in the brain stem was appreciably increased, to 0.38 $\pm$ 0.033μg/g body weight. No signs of tolerance to trifluoperazine were found by behavioral tests. Hence, after two weeks of the chronic experiment, no correlation could be found between the effect of trifluoperazine on the animal's behavior and changes in the general level of noradrenalin in the brain stem.

At later periods the concentration of noradrenalin in the brain stem was virtually indistinguishable from that in the control (Fig. 1).

The initial concentration of adrenalin in the brain stem of the rats was very low (hundredths of a microgram), and the direction of its changes following administration of trifluoperazine corresponded to changes in the noradrenalin level, in agreement with data in the literature [1].

Vysotskaya and Shugina [1] found, after injection of a single dose of trifluoperazine, that the decrease in the noradrenalin concentration in the brain was more prolonged than the sedative effect. This also indicates lack of correlation between changes in the catecholamine level and the sedative effect of trifluoperazine.

Granular reserves of monoamines detected in the brain stem are known to consist of at least two fractions: stable and labile [4, 6, 7, 9, 10]. Stable granules form a large part of the noradrenalin contained in central adrenergic structures. Labile fractions constitute only 10-15% of the total noradrenalin content of the brain stem, and in all probability it is with changes in this fraction that the sedative effect is associated. This was demonstrated clearly by Haggendal and Lindqvist [10] during a study of the action of reserpine.

The rapid increase in the noradrenalin concentration during the first two weeks, shown in Fig. 1 (in the absence of any signs of tolerance to trifluoperazine in behavioral responses), subsequently changes into a slow increase in its level. The total concentration of noradrenalin returns closer to its normal level only later, reaching it in only a few animals. At this same time, as the writers' previous investigation [2, 3] showed, tolerance develops to trifluoperazine, as shown by behavioral tests.

It can be postulated that the rapid rise in the noradrenalin level during the first two weeks of the chronic experiments was associated with recovery of its stable fraction. The sedative effect of trifluoperazine, on the other hand, could be associated with its effect on the labile fractions of noradrenalin, recovery of which coincides with the development of tolerance to trifluoperazine, as shown by a conditioned-reflex test.

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