ANTIDEPRESSIVE PROPERTIES OF PROPRANOLOL

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The attention of clinicians at the present time is being drawn ever more frequently to the psychotropic properties of β-adrenoblockers. However, various aspects both of the therapeutic manifestations and of the side effects of these properties still remain in dispute [8]. In particular, there are serious disagreements as regards the effect of these substances on affective symptoms. According to some observations, β-adrenoblockers provoke depressive disorders in patients with physical diseases [6], whereas according to others, on the contrary, they exhibit antidepressive activity and can even be used in the treatment of depression [2].

To solve this problem we have studied the action of propranolol on a model of forced swimming in rats. This model is currently in wide use for antidepressant screening. Admittedly, as our observations show, the chronobiological approach is more informative than simple measurement of the duration of periods of immobility of the animals in water for the discovery of an antidepressive effect on such a model [1, 3]. In the investigation described below, a model of forced swimming by rats was used to assess the properties of the β-adrenoblocker propranolol.

EXPERIMENTAL METHOD

Experiments were carried out on 66 noninbred male albino rats weighing 150-170 g. The statistical parameters of swimming and its rhythmic structure were evaluated by the method described previously [3], with calculation of the duration of states of immobilization and of active (vigorous propulsive movements by all the limbs) and passive (weak propulsive movements) swimming. To determine the time course of swimming behavior, the number of periods (cycles), of unequal duration, of immobilization and active swimming were recorded visually: under 6, 6 to 18, 18 to 36, and over 36 sec. The results obtained were immediately led into a computer ("Vesta") and analyzed by an original program developed in our laboratory. A rhythmologic index of depression was determined as the ratio of the number of the shortest (under 6 sec) immobilization cycles to the total number of episodes of active swimming. Some results were recorded oscillographically by means of an ink-writing system. There were two series of experiments. The aim of the 1st series (three groups, 10 rats in each group) was to detect antidepressive activity of different doses of propranolol when administered under acute and chronic conditions. To avoid repeated use of the swimming test and the associated adaptation of the animals to the experimental procedure, the following program was used. Two groups of rats were forced to swim 20-30 min after injection of a certain dose of propranolol (1 or 5 mg/kg, intraperitoneally, as also of the remaining substances), and again for a 2nd time 2 weeks after daily chronic administration of the substance in the same dose. The 3rd group served as the control (physiological saline was injected by

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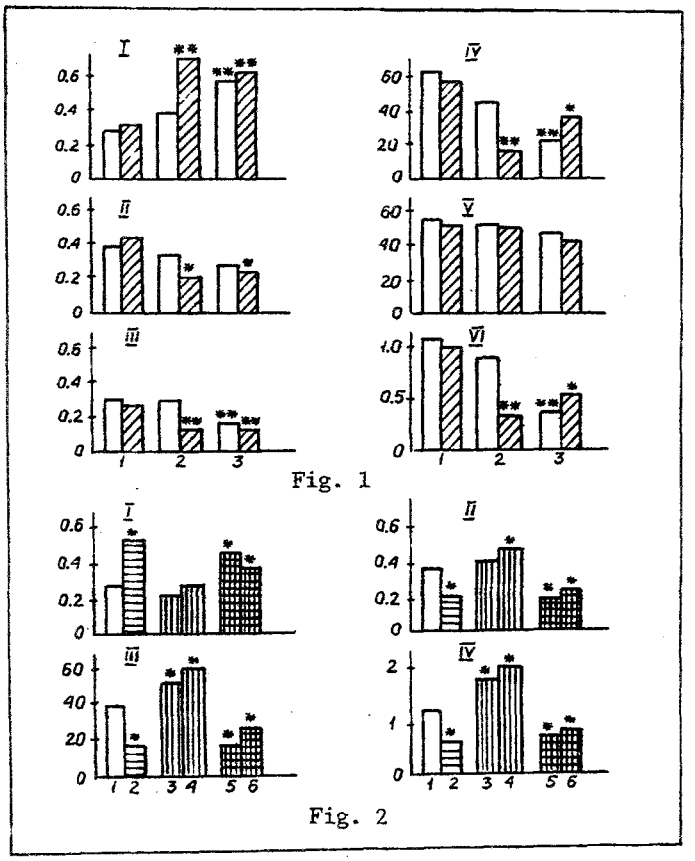

Fig. 1. Effect of propranolol on total (I-III) and rhythmic (IV-VI) parameters of forced swimming in rats. Columns represent mean values of parameters of immobilization (I), and active (II) and passive (III) swimming, and also the number of shortest (under 6 sec) cycles of immobilization (IV) and the total number of cycles of active swimming (V) and the index of depression (VI). Unshaded columns – acute, shaded – chronic administration of physiological saline (1) and different doses of propranolol: 1 mg/kg (2) and 5 mg/kg (3). *$p < 0.05$, **$p < 0.01$ – Statistically significant differences compared with control data.

Fig. 2. Weakening of depression-inducing effect of clofelin and reserpine by propranolol on model of swimming behavior of rats. As in Fig. 1, mean values of parameters of immobilization (I), passive swimming (II), number of short immobilization cycles (III), and index of depression (IV) after injection of physiological saline (1), propranolol (5 mg/kg) (2), clofelin (150 μg/kg) (3), and reserpine (1 mg/kg) (4), and also of a combination of clofelin and reserpine with propranolol (5 and 6 respectively) are shown. *$p < 0.05$ – statistically significant differences.

a similar schedule). In the 2nd series of experiments (six groups, each consisting of six rats) the effect of propranolol was determined on the depression-inducing properties of clofelin (150 μg/kg) and reserpine (1 mg/kg). For this purpose, besides the two control groups (receiving physiological saline and a single dose of 5 mg/kg propranolol)

effects of the depressants were assessed separately (clofelin 30 min, reserpine 24 h before testing), as well as in combination with propranolol. The animals were kept under animal house conditions with natural alternation of daylight and darkness and with maximal standardization of temperature and diet. The results were subjected to statistical analysis by Student's and the Wilcoxon–Mann–Whitney tests.

EXPERIMENTAL RESULTS

After a single injection of propranolol in the smaller of the doses used (1 mg/kg) no appreciable changes were found either in the values of the statistical parameters of swimming or in its rhythmic structure. Only slight prolongation of episodes of both immobilization and active swimming could be observed, but because of concordance of the shift this had no significant effect on the integral rhythmic parameter of the rhythmologic index of depression (Fig. 1).

Meanwhile, in response to repeated injections of the substance a significant increase (compared with the control experiments) in the time of immobilization of the animals in water was found, and was accompanied by restriction of the duration of active and passive swimming. Against the background of propranolol, the rats more often assumed the horizontal position on the surface of the water, by contrast with regular immersions followed by surfacing, characteristic of the depressive state [3]. For that reason the number of shortest (under 6 sec) immobilization cycles fell sharply (3 times more than after injection of physiological saline) and the relative number of prolonged (18 to 36 and over 36 sec) episodes of immobilization increased, resulting in a distinct fall of the index of depression (Fig. 1).

In the larger dose (5 mg/kg) propranolol caused distinct shifts, even after acute injection, in the static and dynamic parameters of swimming behavior, recalling the effect of chronic administration of the drug in a dose of 1 mg/kg. A significant increase in the number of active attempts by the animals to jump out of the vessel and a simultaneous decrease in the number of immobilization cycles relative to all harmonics were highly characteristic. Although under these circumstances short episodes in the structure of active swimming appeared less frequently, the index of depression was found to be lower than in the control tests. After chronic administration of 5 mg/kg propranolol there was a similar change in the pattern of dynamics of the rats' behavior in water, although admittedly it had a tendency toward returning to normal, judging by the very small increase in the index of depression.

The results of a more adequate chronobiological evaluation of the swimming test are thus evidence of the existence of antidepressive activity of the β-adrenoblocker, manifested in response either to chronic (in a low dose) or acute (the higher dose) administration. This conclusion is confirmed also by the results of a study of relations between propranolol and depressants.

In agreement with previous observations [3] reserpine and clofelin provoked changes in swimming that can be interpreted as depressive manifestations. In particular, due to the significant increase in the number of shortest immobilization cycles, the index of depression rose (compared with data for the control group) (Fig. 2). After a single combination of propranolol (5 mg/kg) and the depressants, the former continued to demonstrate its action on the duration of immobilization and of passive swimming, and also reduced the relative number of short immobilization cycles. For this reason, a significant decrease in the rhythmologic index of depression occurred.

Thus propranolol not only exerts its own antidepressive activity, but can also successfully counteract the effects of depressants on animal behavior.

An unambiguous interpretation of the origin of this activity is evidently impossible. To begin with, it may be the result of another central action of the β-adrenoblockers, which is psychodepressant in character. It is manifested in experimental animals as anxiolytic and antiaggressive effects, and ability to depress even aggressive reactions evoked by hypothalamic stimulation, but in healthy individuals, according to EEG findings and self-assessment data, β-adrenoreceptor blockade causes changes like those arising from administration of benzodiazepines [5, 7]. This

property of propranolol can partly explain the lengthening of the immobilization time observed in our experiments in the structure of the rats' swimming behavior and optimization of the actual strategy of such behavior.

Second, the antidepressive activity may be primary in origin. Like the anxiolytic action, it can be realized through specific β-adrenoreceptors, demonstrated in different brain formations, and which in turn are involved in the formation of the emotional state and the emotions [4]. At least stress-induced depression can be simulated by intraventricular injections of the β-adrenomimetic isoproterenol [10]. On the other hand, the discovery of new antidepressants and also the use of modern receptor and electrophysiological techniques of investigation have thrown into prominence the hypothesis of hypersensitivity of individual receptors during depression. Inter alia, this hypothesis is based on the ability of antidepressants to lower the sensitivity of the brain β-adrenoreceptors [9].

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