# EFFECT OF SUBSTANCES CHANGING THE MONOAMINE LEVEL ON AUDIOGENIC FITS IN RATS

I. B. Prakh'e

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Substances increasing the serotonin concentration in the brain (5-hydroxytryptophan, 200 mg/kg; nialamide, 100 mg/kg) weaken or completely suppress audiogenic fits in rats. Substances lowering the brain serotonin concentration (reserpine, 2 mg/kg; p-chlorophenylalanine, 300 mg/kg) strengthen fits of this type. The effect of reserpine is abolished by 5-hydroxytryptophan. Deseryl, an agent blocking serotoninergic receptors, in a dose of 1 mg/kg abolishes the anticonvulsant effect of 5-hydroxytryptophan. Substances selectively affecting the noradrenalin level – dihydroxyphenylalanine (200 mg/kg) and α-methyl-p-tyrosine – do not change the character of the fits. It is concluded from these results that a serotoninergic component participates in the mechanism of the anticonvulsant action of the drugs.

The ability of certain drugs to weaken or intensify paroxysmal states of varied etiology, including the condition known as audiogenic fits, is linked by some workers with an increase or decrease in the activity of central serotoninergic or adrenergic processes [9, 12, 17].

This paper describes the results of a study of the effect of drugs increasing and decreasing the concentrations of serotonin and noradrenalin in the brain on the course of audiogenic fits in rats.

## EXPERIMENTAL METHOD

Rats of both sexes weighing 230-250 g, responding to the sound of an electric bell by fits (belonging to L. V. Krushinskii's strain), were used. The animals were exposed to acoustic stimulation with a strength of 102 dB in a special chamber for 90 sec. The strength of the fits was assessed by a 4-point scale [1].

The animals were decapitated immediately after acoustic stimulation. The total monoamine concentration was determined in the brain stem and subcortex (thalamus, hypothalamus, pons, corpora quadrigemina, and medulla) fluorimetrically by the ninhydrin method [2]. The catecholamines were oxidized by the method of Anton and Sayre [5]. All drugs were injected intraperitoneally.

## EXPERIMENTAL RESULTS AND DISCUSSION

As Table 1 shows, 5-hydroxytryptophan (5-HT) and nialamide, which increase the brain serotonin concentration, sharply reduced the intensity of the audiogenic fits in rats. Of 32 rats receiving 5-HT in a dose of 200 mg/kg, the fits were totally abolished in 6 animals and weakened to 1-2 points in half of the animals ($P < 0.01$). The protective action of 5-HT still persisted 24 h after its injection, and it was combined with an increase in the serotonin concentration in the brain. It should be emphasized that an increase in the serotonin level was observed in all rats regardless of whether any anticonvulsant effect was observed or not.

The anticonvulsant activity of nialamide 18 h 30 min after its injection was combined with a significant increase in the concentrations of serotonin and noradrenalin in the brain; just as in the experiments with 5-HT, no correlation was found between the intensity of the anticonvulsant effect and the degree of increase in the brain monoamine concentration.

Laboratory of Psychopharmacology, V. M. Bekhterev Leningrad Psychoneurological Research Institute.
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TABLE 1. Effect of Substances Increasing Monoamine Concentration in the Brain on Audiogenic Fits in Rats (M ± m)

| Substance | Time from inject. of substance to acoustic stimulat. | Dose (mg/kg) | Number of rats | Strength of fit (in points) | Conc. of monoamines (in μg/g) | |
|---|---|---|---|---|---|---|
| | | | | | serotonin | noradrenalin |
| Control | | | 32 | 4,0±0 | 0,98±0,02 (10) | Not determined |
| 5-HT | 30 min | 200 | 32 | 1,8±0,25** | 3,06±0,12** (12) | |
| | 24 h | | 11 | 1,8±0,7* | 1,35±0,02** (11) | |
| Control | | | 34 | 4,0±0 | 0,89±0,1 (8) | 0,64±0,1 |
| Nialamide | 30 min | 100 | 34 | 2,8±0,3** | 0,87±0,1 (10) | 0,68±0,05 |
| | 18 h 30 min | | 24 | 2,0±0,2** | 1,61±0,05* (24) | 1,06±0,02 |
| Control | | | 19 | 4,0±0 | 1,1±0,08 (8) | Not determined |
| Serotonin | 30 min | 15 | 19 | 2,4±0,3* | 0,95±0,1 (11) | |
| Control | | | 8 | 4,0±0 | | |
| DOPA | 45 min | 200 | 8 | 4,0±0 | No change | Increase |
| Ro4-4602 | 30 min | 40 | 8 | 3,8±0,5 | | |
| DOPA + | The same | 200 | | | No change | Increase |
| Ro4-4602 | The same | 40 | 8 | 3,9±0,5 | | |

Note. Here and in Table 2, one asterisk signifies $P < 0.01$, two asterisks $P < 0.001$. Number of determinations shown in parentheses.

TABLE 2. Effect of Substances Lowering Brain Monoamine Concentration on Audiogenic Fits in Rats (M ± m)

| Substance | Time from inject. of subst. to acoustic stimulation | Dose (mg/kg) | No. of rats | Strength of fit (in points) | Conc. of monoamines (in μg/g) | |
|---|---|---|---|---|---|---|
| | | | | | serotonin | noradrenalin |
| Control | | | 29 | 1,0±0 | Not determined | Not determined |
| Reserpine | 3 h | 2 | 29 | 2,3±0,3** | | |
| Reserpine | 24 h | 2 | 29 | 2,5±0,6* | | |
| Control | | | 20 | 2,0±0 | 1,11±0,03 | 0,77±0,04 |
| Reserpine | 3 h | 2 | 20 | 3,6±0,16** | 0,78±0,33* (10) | 0,17±0,07* |
| Reserpine | 24 h | 2 | 10 | 3,3±0,2** | 0,7±0,015* (10) | 0,26±0,1** |
| Control | | 3 | 14 | 1,0±0 | Decrease | No change |
| p-CPA | 24 h | 100 | 14 | 2,6±0,2* | | |
| Control α-MT | 4 h | 100 | 12 | 1,5±0,1 | No change | Decrease |
| | | | 12 | 1,5±0,1 | | |
| Control | | | 20 | 2,0±0 | 1,11±0,03 | Not determined |
| Reserpine + 5-HT | 3 h 30 min | 2 200 | 20 | 1,9±0,3 | 2,6±0,4** (10) | |
| Reserpine + 5-HT | 24 h | 2 200 | 10 | 1,3±0,5 | 0,97±0,2 (10) | |

TABLE 3. Action of Deseryl on Effects of 5-HT

| Substance | Dose (mg/kg) | No. of rats | Strength of fits (in points; M ± m) | Percent of rats with clonic-tonic fits |
|---|---|---|---|---|
| Control | | 11 | 4,0±0 | 100 |
| Deseryl (1 h before acoustic stimulation) | 1 | 11 | 4,0±0 | 100 |
| 5-HT | 200 | 11 | 1,5±0,6 | 12,5 |
| Deseryl + 5-HT | 1 200 | 11 | 3,3±0,48 | 81,8 |

Serotonin creatinine-sulfate, 30 min after injection, significantly weakened the audiogenic fits: in eight of the 19 rats motor excitation or clonic spasms were observed, while in four animals the fit was completely suppressed. However, intraperitoneal injection of serotonin did not change its concentration in the brain.

The noradrenalin precursor dihydroxyphenylalanine (DOPA) had no anticonvulsant action on the rats 45 min after its injection. According to data in the literature [16], DOPA doubles the noradrenalin concentration during this time interval. Even a combination of DOPA with the peripheral decarboxylase inhibitor $R_0$4-4602, which raises the noradrenalin concentration by 10 times, did not change the character of the audiogenic fits.

Data showing the effect of substances lowering the monoamine concentration in the brain on audiogenic fits in rats are given in Table 2. Reserpine intensified the fits three and 24 h after injection. Since reserpine affected the concentrations of both amines it was interesting to discover the effect of selective inhibitors of serotonin and noradrenalin synthesis.

The tryptophan-hydroxylase inhibitor p-chlorophenylalanine (p-CPA) 24 h after its last injection strengthened the audiogenic fits in the rats. This was accompanied by a decrease of 83% in the serotonin concentration but there was virtually no change in the noradrenalin level [7].

The tyrosine-hydroxylase inhibitor $\alpha$-methyl-p-tyrosine ($\alpha$-MT), which lowered the noradrenalin concentration by 64% without affecting the serotonin concentration in the brain [8], did not change the character of the audiogenic fits in the rats.

The ability of serotonin to weaken audiogenic fits was confirmed by experiments in which the effects of reserpine were suppressed by 5-HT (Table 2) and in which the anticonvulsant activity of 5-HT was abolished by deseryl, which blocks serotoninergic receptors (Table 3).

The anticonvulsant activity of 5-HT and nialamide is shown only against audiogenic fits [4, 10]. These substances have no effect on fits produced by leptazol and an electric current [7, 17]. Conversely, reserpine and p-CPA intensify not only audiogenic fits, but also fits of other types [3, 11, 13, 15, 18].

The anticonvulsant effect of 5-HT coincided in time with an increase in the brain serotonin concentration, suggesting that the two effects are connected. The anticonvulsant action of nialamide was observed 30 min after its injection, when the monoamine concentration in the brain had not yet increased. However, after 18 h 30 min, against the background of an increase in the monoamine concentration, the anticonvulsant effect of nialamide was increased.

The intensification of the audiogenic fits after administration of reserpine also correlated with a decrease in the brain monoamine concentration. The altered character of the response to acoustic stimulation persisted for 4 days, in agreement with data for the duration of the exhausting action of reserpine [6, 14]. It is interesting to note that the exhausting effect of reserpine was the same in intact rats and in the rats sensitive to sound. However, no fits were observed in the intact rats in response to acoustic stimulation. Under normal conditions no differences are found between the serotonin and noradrenalin concentrations in these two groups [13].

The use of substances selectively affecting the level of serotonin (5-HT, p-CPA) and noradrenalin (DOPA, $\alpha$-MT) showed that a change in the concentration only of serotonin and not of noradrenalin leads to a change in the character of the audiogenic fits. Experiments to study the combined effect of reserpine and 5-HT and of deseryl and 5-HT confirmed this conclusion.

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