Effect of Chronic Administration of Antidepressants on Duration of Immobility in Rats Forced to Swim

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Abstract—Chronic administration of imipramine and desipramine significantly reduced the duration of immobility in rats forced to swim in comparison with acute administration. However, amitriptyline did not potentiate the reductive effect of chronic administration. Chlorimipramine, a selective serotonin uptake inhibitor, did not affect the duration of immobility in both the acute and chronic administration. On the other hand, the chronic administration of chlorpromazine, haloperidol and diazepam enhanced the duration of immobility, whereas their acute administration had no effect on it. Sulpiride reduced and enhanced the duration of immobility by the acute and chronic administration, respectively. The present results suggest that the chronic administration of drugs to rats in a forced swimming test can clarify the characteristics of the psychotropic drugs.

The forced swimming test in rats and mice is a useful model for the screening of antidepressants. Porsolt et al. described that animals forced to swim in a restricted space ceased to make attempts to escape and became immobile. This immobility was reduced and extended by the acute administration of typical and atypical antidepressants and neuroleptics and anxiolytics, respectively (1–3). A number of investigators supported the usefulness of this test in acute experiments. On the other hand, chronic but not acute administration of antidepressants is necessary in the treatment of human depression. Therefore, it is important to investigate the effects of chronic administration of antidepressants. Kitada et al. (4) reported that the effects of desipramine, amitriptyline and mianserin as monitored using the rat forced swimming test was potentiated by their chronic administration. However, there has been no report studying the difference of the effects on the duration of immobility in rats forced to swim of the chronic administration of antidepressants and other psychotropic drugs.

Sulpiride, a clinically active neuroleptic, is also found to be effective in depressive illnesses. So, we were very interested in investigating the effects of sulpiride in rats forced to swim, particularly, with regard to the difference between its acute and chronic administration. The present study was performed to investigate the effects of the chronic administration of antidepressants, neuroleptics including sulpiride, and anxiolytics on the duration of immobility in rats forced to swim.

Materials and Methods

Animals: Male Wistar rats weighing 160–180 g and male ddY strain mice weighing 18–20 g were used for the forced swimming test and the phsyostigmine lethality test, respectively. Animals were housed in an air-conditioned room at 22±1°C with a 12 hr light-dark schedule (light on at 7:00). Food and water were given ad libitum.

Measurement of immobility: Rats were individually placed in vertical plexiglas cylinders (height: 40 cm, diameter: 18 cm) containing 15 cm of water maintained at 25°C. The rats were placed once in the water for 15 min, and then they were removed and left to dry for 15 min in a 30°C drying room. The next day, they were again tested for 5 min.
after drug administration. The immobility of a rat was judged according to the procedure described in our previous report (5), and the total duration of immobility during 5 min was measured.

**Drug administration and procedure:** In acute experiments, rats were treated intraperitoneally with saline as a control or the following drugs: imipramine, amitriptyline, desipramine, chlorimipramine, sulpiride, chlorpromazine, haloperidol, scopolamine and diazepam. These drugs were administered, and the test was conducted 0.5 or 1 hr later, at the peak time of the drug’s effectiveness (4, 5). In the chronic experiment, rats were administered intraperitoneally once daily (9:00 a.m.) for 15 days with the same drugs that were used in the acute experiment. On the 15th day, 0.5 or 5 hr after the last administration, the duration of immobility was measured.

**Physostigmine lethality test:** Physostigmine exhibited a dose response toxicity, and its LD$_{100}$ value was approximately 0.9 mg/kg, s.c., in our preliminary experiment. Tricyclic antidepressants (imipramine, desipramine, amitriptyline and chlorimipramine) were administered p.o. 1 hr prior to physostigmine administration at a dose of 0.9 mg/kg, s.c. The effect of drugs on physostigmine lethality was assessed the following day.

**Drugs:** The drugs used for this experiment were imipramine (Tofranil, Fujisawa), desipramine (Pertofran, Fujisawa), amitriptyline (Tryptanol, Banyu), chlorimipramine (Anafranil, Fujisawa), sulpiride (Dogmatyl, Fujisawa), chlorpromazine (Contomin, Yoshitomi), haloperidol (Serenace, Dainippon), diazepam (Cercine, Takeda), physostigmine (Tokyokasei) and scopolamine (Tokyokasei).

**Results**

Fig. 1. Effects of the acute and chronic administration of antidepressants on the duration of immobility in rats forced to swim. Antidepressants were administered i.p. 1 hr before the test in the acute experiment. In the chronic experiment, antidepressants were administered i.p. once daily for 15 days, and the rats were tested 5 hr after the last administration. Results are expressed as a percent of the control. In acute and chronic experiments, the mean duration (±S.E.) of immobility of the saline-administered rats was 215.8±4.2 sec (N=8) and 206.4±6.9 sec (N=16), respectively. Each value is the mean for 8 animals. The significance of the differences from the control was assessed statistically using the two-tailed Student’s t-test (*P<0.05, ***P<0.001, ****P<0.001).
tration of antidepressants on the duration of immobility in rats forced to swim: The effects of the chronic administration of some tricyclic antidepressants on the duration of immobility were compared with those of their acute administration (Fig. 1). In the acute experiment, imipramine and desipramine at a dose of 10 mg/kg did not affect the duration of immobility. Acute administration of 5 mg/kg amitriptyline did not have any effect on the duration of immobility. While 10 mg/kg amitriptyline significantly reduced the duration of immobility. In the chronic experiment, imipramine and desipramine at a dose of 10 mg/kg once daily for 15 days, reduced the duration of immobility significantly. On the other hand, the effect of 5 and 10 mg/kg amitriptyline was not potentiated by its chronic administration. Chlorimipramine at a dose of 10 mg/kg did not affect the duration of immobility in both acute and chronic administration.

Effects of the acute and chronic administration of neuroleptics and anxiolytics on the duration of immobility: As shown in Fig. 2, chlorpromazine, haloperidol and diazepam at a dose of 2 mg/kg, 0.1 mg/kg and 2 mg/kg, respectively, did not have any effect on the duration of immobility in their acute administration, while sulpiride at a dose of 50 mg/kg significantly reduced the duration of immobility. In the chronic experiment, although the doses of chlorpromazine, haloperidol, diazepam and sulpiride were the same as those of the acute experiment, they successfully enhanced the duration of immobility.

Effects of the acute and chronic administration of scopolamine on the duration of immobility: In the acute experiment, scopol-

![Fig. 2](image-url)
Amine at a dose of 5 mg/kg significantly reduced the duration of immobility (Fig. 3). However, the effect in the acute administration of scopolamine was attenuated by its chronic administration.

Effects of antidepressants on physostigmine lethality in mice: Amitriptyline at a dose of 50 mg/kg completely antagonized physostigmine lethality (Fig. 4). Although imipramine, desipramine and chlorimipramine antagonized the physostigmine lethality, their effects were remarkably weaker than that of amitriptyline.

Discussion

Reductive effect of the duration of immobility in rats forced to swim was potentiated by the chronic administration of imipramine and desipramine. Kitada et al. (4) also suggested that the effect of desipramine, amitriptyline and mianserin on the duration of immobility in rats forced to swim was potentiated by chronic treatment. In the present study, the acute administration of amitriptyline showed the most significant reductive effect on the duration of immobility. However, the reductive effect was not potentiated by the chronic administration of amitriptyline. On the other hand, amitriptyline strongly antagonized physostigmine lethality as compared with imipramine, desipramine and chlorimipramine. It is well-known that anticholinergic agents reduce the duration of immobility by increasing the general motor activity (6, 7). It is conceivable that the significant effect of amitriptyline in the acute administration on the duration of immobility is due to both the antidepressive and anticholinergic effect. By the way, in the present study, we found that the immobility-reducing effect of an anticholinergic drug, scopolamine, in acute administration was attenuated by its chronic administration. Majocha and Baldessarini (8) and Herman and Slominska-Zurek (9) reported that the chronic exposure to scopolamine and atropine led to tolerance to its behavioral activating effects. Therefore, it is conceivable that the reason why the chronic administration of amitriptyline did not potentiate the duration
of immobility may be due to its tolerance to the behavioral activating action of the anticholinergic effect.

On the other hand, chlorimipramine, a selective serotonin uptake inhibitor, did not affect the duration of immobility in both its acute and chronic administration. This finding was supported by the fact that the rat forced swimming test is not suitable for the screening of antidepressants which act mainly through serotonergic mechanisms (10, 11). In contrast to antidepressants, chlorpromazine, haloperidol and diazepam enhanced the duration of immobility by their chronic administration. Porsolt et al. (2, 12) reported that chlorpromazine and Ro-1284, a reserpine-like compound increased the duration of immobility in their acute administration and speculated that decreasing the levels of catecholamine will lead to an increase in the duration of immobility. Nagatani et al. (13) and Nomura et al. (14) suggested diazepam had the ability to enhance the immobility in the acute administration in mice and indicated that GABAergic functions played some role in the mechanism of this immobility. The atypical neuroleptic sulpiride is also prescribed for depression because of its activating effect. However, the effect of sulpiride in the animal models of depression has been studied less thoroughly. Sulpiride reduced and enhanced the duration of immobility by the acute and chronic administration, respectively. Recently, Vacher et al. (15) found that (-)-sulpiride worked in a similar way to haloperidol. (+)-Sulpiride significantly and dose dependently ameliorated the response to the behavioral despair test. Racemic sulpiride is the clinically used form and is used in this experiment. The findings in the acute and chronic administration of sulpiride in the present experiment may be explained by the opposite effect of the isomers of sulpiride. However, additional research will be necessary to gain an understanding as to how the isomers of sulpiride are involved in the duration of immobility in rats forced to swim.

From the present results, it was concluded that the chronic administration of drugs can clarify the characteristics of the psychotropic drugs on the forced swimming test.

References
1 Porsolt, R.D., Bertin, A. and Jalfre, M.: Behavioral despair in mice: A primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther. 229, 327–336 (1977)
2 Porsolt, R.D., Pichon, M.L. and Jalfre, M.: Depression: A new animal model sensitive to antidepressant treatment. Nature 222, 730–732 (1977)
3 Porsolt, R.D., Anton, G., Blavet, N. and Jafre, M.: Behavioral despair in rats: A new model sensitive to antidepressant. Eur. J. Pharmacol. 47, 379–391 (1978)
4 Kitada, Y., Miyachi, T., Satoh, A. and Satoh, S.: Effect of antidepressants in rat forced swimming test. Eur. J. Pharmacol. 72, 145–152 (1981)
5 Araki, H., Kawashima, K. and Aihara, H.: The difference in the site of action of tricyclic antidepressants and methamphetamine on the duration of the immobility in the behavioral despair test. Japan. J. Pharmacol. 35, 67–72 (1984)
6 Herman, Z.S., Plech, A., Bien, E., Wieloch-Depta, L. and Jez, W.: Effects of cholinomimetics, cholinolytics and atypical antidepressants in the “behavioral despair” test in the rat. Pol. J. Pharmacol. Pharm. 33, 485–489 (1981)
7 Browne, R.G.: Effects of antidepressants and cholinergics in a mouse “behavioral despair” test. Eur. J. Pharmacol. 58, 331–334 (1979)
8 Majocha, R. and Baldessarini, R.J.: Tolerance to an anticholinergic agent is paralleled by increased binding to muscarinic receptors in rat brain and increased behavior response to a centrally active cholinomimetic. Life Sci. 35, 2247–2255 (1984)
9 Herman, Z.S. and Slominska-Zurek, J.: Central cholinergic receptor supersensitivity after long-term atropine administration. Psychopharmacology (Berlin) 64, 337–340 (1979)
10 Araki, H., Kawashima, K. and Aihara, H.: The role of amygdala on the effect of antidepressants in the rat behavioral despair test. Japan. J. Pharmacol. 33, Supp. 53P (1983)
11 Satoh, H., Mori, J., Shimomura, K., Ono, T. and Kikuchi, H.: Effect of zimelidine, a new antidepressant, on the forced swimming test in rats. Japan. J. Pharmacol. 35, 471–473 (1984)
12 Porsolt, R.D., Bertin, A., Blavet, N., Deniel, M. and Jafre, M.: Immobility induced by forced swimming in rats: Effect of agents which modify central catecholamine and serotonin activity. Eur. J. Pharmacol. 57, 201–210 (1979)
13 Nagatani, T., Sugihara, T. and Kodaira, R.: The effect of diazepam and of agents which change GABAergic function in immobility in mice. Eur. J. Pharmacol. 97, 271–275 (1984)
14 Nomura, S., Kinjo, M., Nakamura, T. and Kametani, H.: Forced swimming in mice for screening test of antidepressants. Japan. J. Neuropharmacol. 2, 67–71 (1981)
15 Vaccheri, A., Dall’Olio, R., Gaggi, R., Gandolfi, O. and Montanara, N.: Antidepressant versus neuroleptic activities of sulpiride isomers on four animal models of depression. Psychopharmacology (Berlin) 83, 28–33 (1984)