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BRIEF COMMUNICATION

Effects of Imipramine on Separation-Induced Vocalizations in Young Rhesus Monkeys

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PORSOLT, R D., S. ROUX AND M. JALFRE *Effects of imipramine on separation-induced vocalizations in young rhesus monkeys* PHARMACOL BIOCHEM BEHAV 20(6) 979–981, 1984.—Three Rhesus monkeys were removed from their mothers at birth and reared together in a group cage. When they were one year old they were subjected to repeated separations during which they were placed alone for 1 hour in another cage in an acoustically isolated adjacent room. The number of vocalizations and gross body movements were recorded automatically. Single injections of imipramine (3.75, 7.5 and 15 mg/kg IM) instead of decreasing tended to increase the number of vocalizations without affecting motor activity A similar pattern was observed when imipramine (3.75 and 7.5 mg/kg IM) was administered repeatedly (2 injections/day/4 days) The failure of imipramine to decrease separation-induced vocalizations in our conditions suggests that the procedure would not be useful for testing potential antidepressants

Separation-induced vocalizations Rhesus monkey Animal model of depression Imipramine

YOUNG animals when separated from their mothers, peers or litter-mates generally respond with signs of distress including agitation and frequent vocalizations. In primates, when the period of separation is prolonged, this "protest" reaction frequently but not invariably gives way to signs of "despair" characterized by decreased locomotion, play and social activities with increases in huddling and self-directed behavior [3]. Although "despair" behavior has traditionally been regarded as representing a fairly direct analogue of human depression [3], some authors [5] have suggested that even "protest" behavior might serve as a model of at least some aspects of depression. The present experiments were therefore undertaken to see whether the vocalizations induced by short separations in young group-reared rhesus monkeys could be reduced by either acute or sub-chronic treatment with imipramine. If so the procedure might be useful for identifying antidepressant activity in novel compounds.

METHOD

Subjects

The subjects were 3 one-year-old rhesus monkeys (2 female, 1 male) bred in our laboratory of different mothers but the same father and born within 20 days of each other. They were removed from their mothers within 4 days after birth and were brought up together in a stainless steel cage (70×70×60 cm). See [4] for details of rearing procedure

Procedure

The animals were taken from the colony room to a separate test laboratory each morning at 8–15 and were left together in the common transport cage until it was an individual animal's turn to be tested. The first animal was tested at 9:00. Testing consisted of removing one animal at a time from the common transport cage and placing it alone into another cage (70×70×60 cm) in an acoustically isolated adjacent room. The animal was left alone for 60 minutes but could be observed through a one-way screen.

During the 60 minute test period the animal's vocalizations were recorded automatically by means of a microphone suspended 30 cm above the centre of the cage. At the same time the animal's gross movements were recorded using a Motilimat® photosensitive activity meter (Getra, Munich, W. Germany) also suspended 30 cm above the centre of the cage. After the test the animal was replaced in the group transport cage with the other monkeys and the procedure was repeated until all three animals had been tested. The animals were always tested in the same order from day to day and were given 4 consecutive test sessions per week (Monday through to Thursday).

To test the acute effects of imipramine the animals were given 3 consecutive test sessions preceded by an injection of distilled water and then a test session preceded by an injection of one of three doses of imipramine HCl (3.75, 7.5 or 15 mg/kg as base) or distilled water. Injections were given IM 30 minutes before testing. Tests were repeated each week with

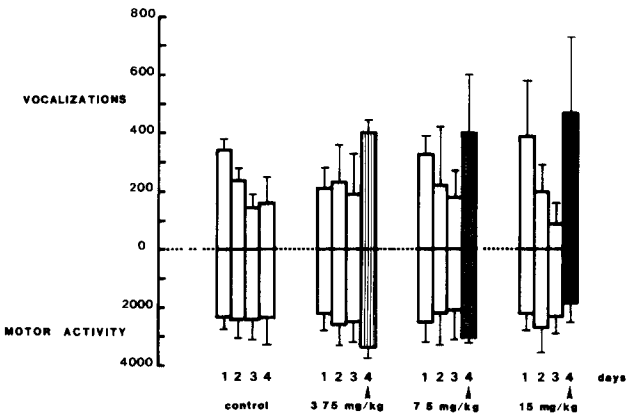

FIG 1 The acute effects of three doses of imipramine (3 75, 7 5 and 15 mg/kg IM) or vehicle on the number of vocalizations and gross body movements (means and standard errors) in young monkeys during one hour separations (N=3). Each drug test day was preceded by 3 control days

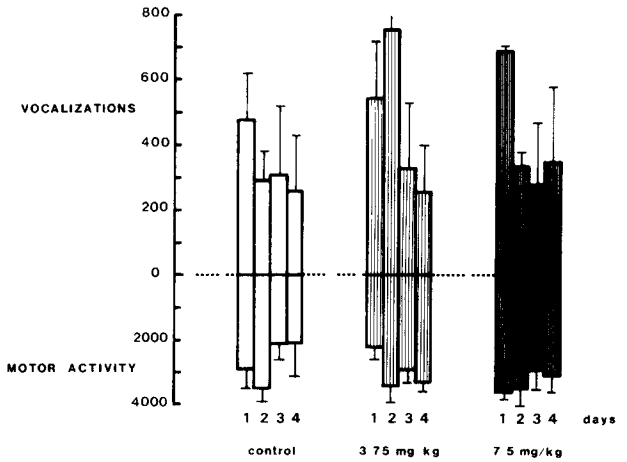

FIG 2 The effects of repeated injections of imipramine (3 75 and 7 5 mg/kg IM) or vehicle on the number of vocalizations and gross body movements (means and standard errors) in young monkeys during one hour separations (N=2) Injections were given twice daily, 30 min before the test in the morning and in the afternoon (3 30 p.m)

each animal being tested at each dose but in a different order per animal. All drug injections and observations were performed under blind conditions using coded solutions.

To test the sub-chronic effects of imipramine the test procedure was the same as that described above except that the animals received two injections per day of the same treatment (3.75 or 7.5 mg/kg imipramine or distilled water) for 4 consecutive days. The first injection was given 30 minutes before testing in the morning and the second in the afternoon (3:30 p.m.). Because tests were conducted in the morning the animals received only a single injection on the fourth day and thus received a total of 7 injections. Tests were repeated each week with each animal being tested with each treatment but in a different order.

RESULTS

Effects of Acute Injections of Imipramine

The results obtained after acute injections of imipramine are shown in Fig. 1. All animals showed consistently high levels of vocalization at the beginning of each four day separation series with a decline occurring with repeated testing on consecutive days. Analysis of variance [8] of the vocalization scores for the first three days, when the animals had received injections of distilled water, showed this decline to be statistically significant, F(2,22) Days: 5.99, $p<0.01$. The decline was, however, reversed when the animals were injected with increasing doses of imipramine on the fourth day. A non-parametric multiple comparison test [1] comparing the vocalization scores on the last pre-drug day (Day 3) with those obtained after injection of imipramine (Day 4) showed that the increase in vocalizations observed with the highest dose of imipramine (15 mg/kg) was statistically significant (Friedman's S=9.0, $p<0.01$). In general, despite the decrease in vocalization observed in control treated animals when they were tested repeatedly on consecutive days there was always a recovery to the initial levels when testing recommenced at the beginning of the following week, confirming observations made during pilot experiments (data not shown)

In contrast to the vocalizations measure, no changes were observed in the measure of locomotor activity either with repeated testing or as a consequence of drug injection. Pilot experiments had shown, however, that doses of imipramine higher than 15 mg/kg caused marked sedation and convulsions were observed in one animal after injection of 30 mg/kg

Effects of Sub-Chronic Injections With Imipramine

Unfortunately, one animal (the male) died at the beginning of the sub-chronic study of an acute dilatation of the stomach unrelated to the experimental treatments. The results presented are those for the two remaining animals

The effects of sub-chronic injections of imipramine on vocalizations and locomotor activity are shown in Fig. 2. As was seen in the acute study (above) repeated testing on consecutive days cause a marked decrease in the number of vocalizations with all treatments, F(3,11) Days: 6.32, $p<0$ 01. When treated with imipramine the animals tended to emit more vocalizations at the beginning of treatment than after control injections but this effect entirely disappeared after repeated treatment and, probably because only two animals were studied, could not be demonstrated statistically, F(6,11) Drug × Days: 2.02, $p>0.05$. In no case did animals repeatedly treated with imipramine emit fewer vocalizations than after treatment with the vehicle.

Similarly to the acute study no changes were observed in motor activity either with repeated testing or as a consequence of drug injection.

DISCUSSION

The findings of the present experiments confirm previous reports [3] and our own observations [4] that social separation induces a high frequency of vocalizations in young mon-

keys. On the other hand our experiments show that imipramine, administered either acutely or sub-chronically, clearly did not decrease the number of vocalizations in our subjects. Indeed, although the number of animals used was small, our experiments suggested that imipramine might even increase the number of vocalizations; a statistically significant increase was observed after acute administration of the highest dose (15 mg/kg).

The results appear to differ from those described in infant rhesus monkeys [6] and beagle puppies [5] where imipramine, in a dose range (1–10 mg/kg) similar to that used in our study, decreased separation-induced vocalizations. One important difference between the experiments in monkeys described by Suomi *et al.* [6] and our own study was that in their study imipramine was administered daily for 60 days, beginning in the middle of a 19 day separation and continuing over a 9 day reunion, a further 19 day separation and then during a final reunion. The difference in length of treatment cannot be a whole explanation, however, because Suomi *et al.* [6] state that the decrease in vocalizations was observed as an immediate of treatment. Similarly the reduction in vocalizations in beagle puppies [5] was observed after acute injections of imipramine.

The clear failure of imipramine to reduce vocalizations in our conditions suggests that "protest" behavior in monkeys is markedly different from "despair" behavior which can be alleviated by treatment with tricyclic antidepressants [2,7]. Our results suggest moreover that "protest" vocalizations would not be useful as a test model for identifying antidepressant activity.

ACKNOWLEDGEMENTS

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