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Repeated treatment with imipramine and amitriptyline reduced the immobility of rats in the swimming test by enhancing dopamine mechanisms in the nucleus accumbens

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Abstract—Bilateral injections of 1 μg sulpiride in the rat nucleus accumbens antagonized the effect of a seven-day treatment with 20 mg kg^{-1} day^{-1} imipramine or amitriptyline in the swimming test. The data suggest that dopamine mechanisms in the limbic regions of the rat brain are involved in the effect of repeated treatment with imipramine and amitriptyline in that test.

A selective increase in mesolimbic dopamine (DA) function was found in rats repeatedly treated with desipramine (Spyraki & Fibiger 1981). Since DA receptor blockers counteracted the effect of desipramine in the swimming test (Borsini et al 1984; Pulvirenti & Samanin 1986) it was suggested that the drug reduces the immobility by enhancing DA transmission in particular brain areas (Borsini et al 1984). A selective role of DA in the nucleus accumbens was recently suggested by Cervo & Samanin (1987) who found that injection of sulpiride, 1 μg, into that area but not into the caudate putamen, completely antagonized the anti-immobility effect induced by a seven-day treatment with desipramine.

Having used the same procedure, we now report that injection of sulpiride into the nucleus accumbens counteracts the anti-immobility effect of two other commonly used tricyclic antidepressant drugs, imipramine and amitriptyline.

Materials and methods

Animals. Male CD-COBS rats (Charles River, Italy), 220–250 g, at the beginning of the experiment, were individually housed, at constant room temperature (21 ± 1 °C) and relative humidity (60%), with free access to water and food.

Cannulae implantation. Rats were anaesthetized with equitensine and placed in a Kopf stereotaxic frame for bilateral implantation of guide cannulae, made of 23 gauge stainless steel tubing, 2 mm above the sites to be injected. To prevent clogging, stainless steel stylets, 30 gauge, were placed in the guide cannulae until the animals were given intracerebral injections 14 days later.

The rats were accustomed to handling and on the day of the test the stylets were withdrawn and replaced by bilateral injection units terminating 2 mm below the tip of the guides.

The coordinates used for the nucleus accumbens were A = 9·8; L = 1·0; H = −0·7 (König & Klippel 1963). The locations of the cannulae were determined histologically after the experiments. Only data from rats in which the cannulae were exactly located bilaterally in the nucleus accumbens were included in the results.

Measurement of immobility. Rats were placed individually in Plexiglas cylinders (height 40 cm, diameter 18 cm) containing 17 cm of water at 25 °C, and 15 min later they were removed to a 30 °C drying room for 30 min. To evaluate the drug's effect, animals were replaced in the cylinders 7 days later and the total period of immobility was recorded for 5 min by an observer who did not know which treatment the rats had received. A rat was judged to be immobile when it remained floating in the water, in an upright position, making only small movements to keep its head above water.

Drug treatment. One week after surgery, rats were given intraperitoneal injections of 10 mg kg^{-1} imipramine hydrochloride (Ciba Geigy, Milan, Italy) or 10 mg kg^{-1} amitriptyline hydrochloride (Lepetit, Milan, Italy), dissolved in saline, or vehicle (2 mL kg^{-1}), twice daily, for seven consecutive days. The first dose was injected immediately after the 30 min drying period and the last dose was given 1 h before the 5 min test.

Sulpiride (Dobren, Ravizza, Milan, Italy) or 0·9% NaCl (saline) was administered bilaterally through the cannulae at a concentration of 1 μg/0·5 μL 5 min before the test, at a rate of 0·5 μL min^{-1}. The dose of sulpiride was selected on the basis of previous evidence (Cervo & Samanin 1987) that 1–5 μg but not 0·5 μg in the nucleus accumbens antagonized the anti-immobility effect of desipramine.

Statistics. The data were analysed by ANOVA (2 × 2) factorial analysis followed by Tukey's test for unconfounded means (Rochetti & Recchia 1982).

Results

As shown in Table 1, immobility was found to be significantly reduced by seven days' treatment with imipramine and amitryptyline. Sulpiride 1 μg injected bilaterally into the nucleus accumbens did not modify the immobility time but it antagonized the anti-immobility effect of both drugs (ANOVA values for imipramine and amitriptyline were, respectively, $F = 46·8$, df = 1/28 $P < 0·01$ and $F = 15·6$, df = 1/28 $P < 0·01$).

Table 1. Effect of sulpiride injected in the nucleus accumbens on the reduction of immobility caused by imipramine and amitriptyline.

Treatment	Dose (mg kg^{-1} day^{-1})	Immobility time (s)	
		Saline	Sulpiride
Vehicle	—	261·8 ± 6·3	257·1 ± 7·1
Imipramine	20	108·2 ± 10·2*	216·7 ± 8·9[a]
Vehicle	—	250·4 ± 13·0	252·2 ± 10·2
Amitriptyline	20	127·4 ± 10·7*	216·5 ± 10·2[a]

Values are means ± s.e. of 8 animals. Sulpiride (1 μg/0·5 μL) was injected bilaterally 5 min before the test. The test was made 60 min after the last dose of the antidepressants.

* $P < 0·01$ vs vehicle group (Tukey's test).

[a] $P < 0·01$ (ANOVA).

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Rats injected with sulpiride, 1 μg, in the nucleus accumbens displayed no sedation or catalepsy which could have interfered with the measurement of immobility. Preliminary experiments had shown that sulpiride, 1 μg, in the nucleus accumbens had sedative and cataleptic effects at relatively long intervals after injection (1–4 h) but had no effect at the time selected for the present experiments (5 min) or even at 30 min from injection.

Discussion

Bilateral injections of sulpiride, 1 μg, in the nucleus accumbens reduced the anti-immobility effect of seven days treatment with imipramine and amitriptyline. The fact that at the dose used sulpiride in the nucleus accumbens completely blocked a DA-mediated effect (Costall et al 1978; Woodruff & Andrews 1979) and the high selectivity of sulpiride as a DA receptor antagonist (Jenner & Marsden 1981), suggest that activation of DA mechanisms in the brain area is involved in the action of both imipramine and amitriptyline. It is unlikely that the effect was due to diffusion of sulpiride to the adjacent caudate-putamen since moving the injection site 0·5 mm towards this area caused loss of the effect; it was recently reported that sulpiride, 5 μg, in the dopamine-rich regions of the caudate-putamen did not modify the effect of desipramine (Cervo & Samanin 1987).

Repeated treatment with desipramine is associated with an increase in DA function in the nucleus accumbens (Spyraki & Fibiger 1981; Cervo & Samanin 1987). Altered sensitivity of DA receptors could be involved since repeated doses of desipramine have recently been shown to result in a significant increase of behavioural effects of dopamine agonists in the nucleus accumbens (Plaznik & Kostowski 1987). A similar mechanism could be involved in the anti-immobility effects of imipramine and amitriptyline. Considering the selective action of sulpiride on D_2 receptors (Jenner & Marsden 1981), these receptors could be considered to mediate the effect of the antidepresants. However, that D_1 receptors are also involved cannot be excluded.

The exact mechanism by which chronic antidepressants increase limbic function is not clear. Since a single dose has little or no effect on DA uptake, release or receptors in-vitro or in intact animals (Randrup & Braestrup 1977; Hall & Ogren 1981), changes in other neurochemical mechanisms may be involved in the ability of tricyclic antidepressant drugs to increase DA mesolimbic function.

In conclusion, together with previous findings (Cervo & Samanin 1987), the present data suggest that an increase in mesolimbic DA function is one mechanism by which various antidepressant drugs reduce the immobility of rats in the swimming test.

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