The effect of unilateral amygdala lesion on the imipramine action in behavioural despair in rats

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Recently Porsolt et al (1977, 1978) have described a behavioural despair test in rats, which is sensitive to typical and atypical antidepressants. Our previous study (Górka & Wojtasik 1979) confirmed those results. In this paper we wished to examine the effect of a unilateral lesion of the amygdala on the action of imipramine in the behavioural despair test in rats.

The imipramine phenomenon seemed interesting, since there have been many reports about the action of antidepressant drugs on amygdala function. Tricyclic antidepressants (TAD) markedly depressed after-discharges from the amygdala (Kamai et al 1975) and specifically blocked seizures kindled from the rat amygdala (Babington & Wedeking 1973). Imipramine inhibited potentials evoked locally in the amygdaloid complex (Guerrero-Figueroa & Gallant 1967).

Male Wistar rats, 180–240 g, were housed under standard laboratory conditions with free access to food and water. Naive rats were individually placed in cylinders containing 15 cm of water at 25 °C for 15 min, in which they behaved according to Porsolt et al (1977). The duration of immobility was measured during 5 min. Rats were divided into three groups: lesioned, sham-operated and intact animals. Unilateral lesions of baso-lateral part of the amygdala in rats anaesthetized with pentobarbitone (30 mg kg^{-1} i.p.) were made electrolytically (100 KHz, 2 mA, 8 s) with a monopolar platinum electrode (diameter 0·4 mm) implanted stereotaxically in the amygdala according to Ålbe-Fessard et al (1966) (stereotaxic coordinates: A = 5·6, L = 4·2, H = 3·3), using a David Kopf instrument. A unilateral sham-operation was performed with the same electrode implanted in the upper margin of the amygdala complex (coordinates: A = 5·6, L = 4·2, H = 3·3).

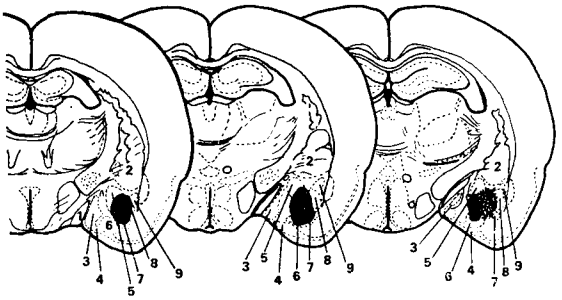

FIG. 1. The diagram shows the site and range of lesion of the amygdala. Section I represents the anterior part of lesion. Abbreviations: 1-optic tract, 2-caudato-putamen, 3-amygdala medialis, 4-amygdala corticalis, 5-amygdala centralis, 6-amygdala basalis medialis 7-amygdala basalis lateralis, 8-amygdala lateralis posterior, 9-amygdala lateralis anterior.

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After one week recovery the spontaneous motility of all the rats was measured in photo-cell cages. On the following day all the rats were immersed for 15 min and 24 h later were injected with imipramine (hydrochloride, Polfa), 15 mg kg^{-1} i.p., at 48, 24 and 1 h before immersion. After histological verification the number of animals was: 10 rats in the lesioned, 8 in the sham-operated and 16 in the control group. Statistical significance was assessed by Student's *t*- and *t*-paired tests.

The lesion took up the major part of baso-lateral nuclei and a small part of central nuclei of the amygdala (Fig. 1). Spontaneous motility of the lesioned and sham-operated rats was identical with that of the control animals. Imipramine administered three times significantly reduced immobility in all the three groups, but this effect was visibly less pronounced in the lesioned rats than both in the control and sham-operated animals. The difference between the immobility of the control and lesioned rats was significant on the level $P < 0{\cdot}001$, and between the sham-operated and lesioned animals—on the level $P < 0{\cdot}01$. There was no difference in the action of imipramine between the control and sham-operated groups (Table 1).

The results presented demonstrate that a unilateral lesion of baso-lateral nuclei of the amygdala complex significantly decreases the potency of imipramine in the behavioural despair test in rats. This may imply that the amygdala is the site of the drug's action, which is also supported by the fact that both tricyclic antidepressants and atypical antidepressants (mianserin, danitracen and trazodone) inhibit seizures kindled from the amygdala (Babington & Wedeking 1973; Stach et al 1978). Also

Table 1. The effects of IMI on the duration (s) of immobility in control, sham-operated and lesioned rats.

	Duration of immobility (in s) Groups of animals		
Treatment	Control	Sham-operated	Lesioned
Solvent	249·2 ± 13·1	235·7 ± 13·2	228·7 ± 12·6
	a	a	a, b, c
Imipramine	114·8 ± 16·4	113·1 ± 29·2	208·3 ± 16·4

a difference between the solvent and IMI-treated rats in control, sham-operated and lesioned groups, significant on the level $P < 0{\cdot}001$, $P < 0{\cdot}001$, $P < 0{\cdot}05$ respectively.

b difference between the IMI-treated control group and the IMI-treated lesioned group, significant on the level $P < 0{\cdot}001$.

c difference between the IMI-treated sham-operated group and the IMI-treated lesioned group, significant on the level $P < 0{\cdot}01$.

Furgiuele et al (1964) have found that lesion of the amygdala decreases depression of the locomotor activity in rats, induced by single dose of imipramine or desipramine.

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A new method for measuring variations of rat paw volume

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A useful parameter for assessing the anti-inflammatory activity of new compounds is their effect on the increase of rat paw volume induced by phlogogenic stimuli. In this communication a new method is described for measuring the volume of the rat paw by determining the time required for a constant delivery pump to replace the volume occupied by the paw. The volume is read after the paw has been removed from the chamber, and is thus less sensitive to the operator bias. An advantage of the method is that it does not involve the use of mercury.

A schematic diagram of the apparatus is shown in Fig. 1 (left panel). A constant volume peristaltic pump delivers saline to the side entry tube of the translucid polycarbonate chamber from the reservoir beneath the chamber. The saline contains lauryl sulphate, 2 mg ml^{-1}, and ethanol, 50 ml $litre^{-1}$, to reduce surface tension. The saline overflow leaves the chamber from a V-shaped notch in the top edge, flows down the side and forms into drops on the thin piece of polyethylene attached to its bottom. The volume of the drops can be control by adjusting the size of this piece. The flow (2·4 $\mu l\ min^{-1}$) was adjusted to provide 20 drops per 10 s (20 μl/drop).

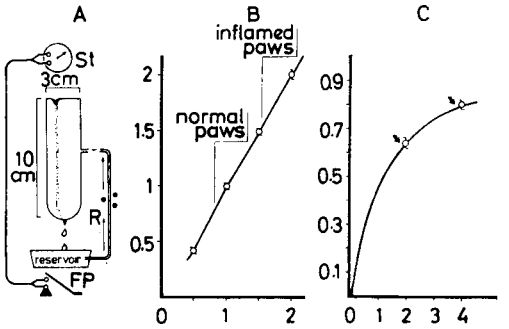

FIG. 1. The replacement volume technique. (A) gives a graphic representation of the method. A roller pump (R) maintains a constant flow dripping from the bottom of the cuvette. The paw is removed after 20 s of immersion and the fluid displaced is measured by the time necessary to refill the cuvette, indicated by the fall of the second drop. The stopwatch is activated by a foot switch (FS) simultaneously with the removal of the paw. (B) is a calibration curve. The piston of a syringe was immersed into the cuvette to displace a pre-defined volume (abscissa: ml). The volume calculated by the method is given on the ordinate (ml). The values are the mean ±s.e.m. of 5 measurements. (C) shows the mean value ±s.e.m. of five measurements of a single paw which received 100 μg of carrageenan. The increase in volume (ordinates: ml) was calculated by subtracting the value of the contralateral paw, injected with saline (0·1 ml). The arrows indicate that a sixth measurement fell within the s.e.m. Ordinate: time (h).

For measurements the rat paw is immersed in the chamber up to the tibiotarsic articulation for 15–20 s until the overflow drop frequency is constant and equal to that before paw introduction. The paw is removed and simultaneously a foot-switch activates a stopwatch (Digital Gauges, England). The time required to refill the chamber (indicated by the second drop to fall from the bottom of the chamber) is recorded. The volume displaced by the paw is directly related to refil time because pump delivery is constant. A calibration curve obtained by immersing a syringe piston in the chamber is shown in Fig. 1. There was linearity when the volume of the piston was varied from the values equivalent to a normal paw to these observed with inflamed paws. The right panel (C) shows the volume change of a rat paw after treatment with 100 μg of carrageenan (Marine Coloids, USA). The increment of the rat paw volume can be calculated either by subtracting the value measured at any time from the value obtained at zero time or by subtracting the volume of contralateral paw (control) injected with saline. Routinely two readings of the same paw were made. If there was a difference greater than 1 s between readings, a third reading was made. A trained experimenter takes about 2 min to measure both paws. The replacement volume technique was successfully used for measuring the variations of mouse paw volume. In this instance the size of the chamber was reduced (1·5 cm diameter/7·5 cm high).

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