PREFRONTOCORTICAL DOPAMINE DEPLETION INDUCES ANTIDEPRESSANT-LIKE EFFECTS IN RATS AND ALTERS THE PROFILE OF DESIPRAMINE DURING PORSOLT’S TEST

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Abstract—The objective of this study was to investigate whether bilateral dopamine depletion within the medial prefrontal cortex affects depression state, as well as the antidepressant efficacy of desipramine, in the forced swimming test. The rat’s behaviour was evaluated by quantifying duration of immobility, climbing, swimming and diving. Immobility latency was also quantified and proved to be a suitable novel parameter. Monoamine levels within the medial prefrontal cortex were measured by high-performance liquid chromatography during Porsolt’s test, as well as one week after it. While Porsolt’s test was followed by a typical depression-like profile in sham rats, depletion of prefrontocortical dopamine (86% vs sham controls) reduced immobility and enhanced swimming, which is consistent with a diminished depression tonus. The observed enhancement of swimming was correlated with a high prefrontocortical serotonergic neurotransmission. On the other hand, desipramine induced antidepression-like effects in sham rats by increasing prefrontocortical noradrenaline and serotonin neurotransmission, but also by blocking the normal increase in dopamine activity during the swimming test. Interestingly, desipramine behaved in a quite different manner in lesioned rats. Thus, immobility duration was not further reduced and only climbing, but not swimming, was enhanced. These effects were correlated with a preferential enhancement of noradrenaline neurotransmission.

In conclusion, the results indicate that: (i) dopamine neurotransmission within the medial prefrontal cortex is a factor involved in depression, since dopamine reduction led to a low depression tonus; (ii) desipramine induces antidepressive effect not only by enhancing prefrontocortical noradrenaline and serotonin neurotransmission, but also by blocking the normal increase in dopamine neurotransmission during a depressant situation; (iii) a selective enhancement of prefrontocortical serotonergic neurotransmission mediates swimming; and (iv) a selectively augmented prefrontocortical noradrenaline activity mediates climbing during Porsolt’s test.

Key words: depression, medial prefrontal cortex, dopamine, forced swimming test, 6-OHDA, desipramine.

The prefrontal cortex (PFCX) has been repeatedly proposed as an area involved in depression, since positron emission tomography studies revealed that depressed patients show functional changes in the PFCX. Among the biogenic amines located within the PFCX, serotonin (5-HT) seems to play a role in depression, but the role of PFCX dopamine (DA) in depression is far from clear. Acute administration of antidepressants which are active on the noradrenaline (NA) reuptake carrier increases extracellular DA concentrations in the PFCX, which suggests that PFCX DA might play a role in the antidepressant properties of these drugs.

The forced swimming test (FST) is a behavioural model which predicts the efficacy of antidepressant treatments, being quick and reliable across laboratories. Immobility, defined by Porsolt et al. as when “a rat makes only those movements necessary to keep its head above water”, is usually selected to evaluate the state of depression during the FST. Recently, more active behaviours such as swimming and climbing have also been proposed as suitable indicators for measuring antidepressant activity. A full behavioural study including all responses displayed by rats in the FST gives a more complete picture of the structure of the rat’s behaviour, and allows better discernment of drug effects.

The objectives of this study were: (i) to investigate if 6-hydroxydopamine (6-OHDA)-induced lesions of the medial prefrontal cortex (mPFCX) affect the depression state as well as the efficacy of the antidepressant desipramine in the FST, and (ii) to establish the neurochemical changes in monoamine

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Abbreviations: DA, dopamine; EDTA, ethylenediamine-tetra-acetate; FST, forced swimming test; 5-HT, serotonin; mPFCX, medial prefrontal cortex; NA, noradrenaline; 6-OHDA, 6-hydroxydopamine; PFCX, prefrontal cortex.
concentrations within the mPFCX in both 6-OHDA-lesioned and sham rats during the FST and one week after it. The mPFCX was selected because it is a hub area in the DA system network, since it receives inputs from the mesocortical DA system, and sends efferents to the nucleus accumbens, striatum and midbrain DA cell groups. The rat’s behaviour in the FST was analysed from an ethological point of view, including the quantification of latency for the first occurrence of immobility, a parameter which has not been employed previously for evaluating depression in the FST.

EXPERIMENTAL PROCEDURES

Subjects

Male Wistar rats (250–300 g) from the breeding colony of the Faculty of Medicine of Seville, Spain, were housed in groups of six. Laboratory temperature was kept at 22 ± 1°C, and a 12-h light-dark cycle (lights on at 08.00) was maintained throughout the experiment. Food (lab chow) and water were available ad libitum. Animals were not handled routinely prior to experiments.

Forced swimming test

The procedure was quite similar to that described by Porsolt et al.,1 except for the depth of water. Rats were placed in individual glass cylinders (45 cm high × 18 cm diameter) containing water at 23–25°C of 26 cm depth. At this depth, the rat cannot support itself by touching the bottom with its feet, although it can touch the bottom with its tail. Two swimming sessions were carried out: an initial 15-min pretest followed 24 h later by a 5-min test (experimental FST). Drugs were administered during the period between the two sessions. Tests were performed during the last phase of the light period (18.00–20.00).

Drugs and groups

Desipramine hydrochloride and 6-OHDA hydrobromide were obtained from RBI (Natick, MA, U.S.A.). Desipramine was dissolved in saline solution (0.9% NaCl) and injected i.p. at a volume of 1 ml/kg body weight. Each microlitre of the 6-OHDA solution contained 2 µg of 6-OHDA dissolved in 0.9% saline and 0.2% ascorbic acid. First, animals were randomly assigned to two groups: (i) sham-operated and (ii) 6-OHDA-lesioned rats. Desipramine was injected i.p. at doses of 0, 5, 10 and 15 mg/kg; 23.5, 5 and 1.5 µl of the 6-OHDA solution was injected and slowly withdrawn at the end of each injection, and slowly withdrawn at the end of each injection. Rats were then placed into a Kopf stereotaxic apparatus with the incisor bar set 3.3 mm below the interaural line. After scalp incision, Burr holes were drilled over the injection sites and a blunted 30-gauge cannula, connected to a 10-µl Hamilton syringe, was lowered into the injection site. The following coordinates were used: AP +3.5, L ±0.8, V −3.3, −4.3 mm with respect to bregma.16 At each injection site, 1 µl of the 6-OHDA solution was injected over 6 min. The cannula was left in place for 1 min after the injection, and slowly withdrawn at the end of injections. Sham rats followed the same protocol except for the fact that a 6-OHDA-free solution (0.9% NaCl plus 0.2% ascorbic acid) was injected. The first FST was carried out seven days after surgery.

Behavioural scoring

The rat’s behaviour was scored following the complete sampling method.19 The ethogram of the rat’s behaviour in the FST was composed of: (i) immobility—the animal floats in the water making only those movements necessary to keep its head above water; (ii) climbing—the rat makes active movements with its forepaws directed against the wall; (iii) swimming—the animal displays active swimming motions, more than necessary to maintain its head above water; (iv) diving—the entire body is submerged.2 Swimming, climbing and diving were quantified either separately or as a whole (active behaviour). Behaviour was videotaped under white light illumination, by using a video camera located 75 cm above the cylinder. Videotapes were later played and behaviour analysed by keyboard entry to a computer programmed to perform ethological and statistical analyses. Videotapes were scored “blind” by a highly trained observer (intra-rater reliability ≥0.9). The duration of each pattern and latency for the first occurrence of immobility were evaluated.

Neurochemical analysis

One week after the last swimming session, subjects were killed by decapitation followed by immediate head freezing in liquid nitrogen for 10 s. On the other hand, as explained, the effects of surgery plus saline or desipramine on monoamine levels within the PFCX during the FST were also evaluated. Thus, 16 sham and 6-OHDA-lesioned animals were killed just after being picked up from the water during the last minute of the FST, and their heads frozen in liquid nitrogen for 10 s. The frozen heads were then stored at −10°C to allow it to reach a more manageable temperature before brain removal. Later, brains were sectioned in a cutting box,10 the mPFCX was localized and sectioned,10 and mPFCX sections were stored in liquid nitrogen. Frozen tissue samples were homogenized in 500 µl of 0.4 M HClO4, at 27000 r.p.m. for 60 min at 4°C. Aliquots (10–20 µl) of the supernatants were injected into the high-performance liquid chromatography system after dilution with appropriate volumes of mobile phase. The mobile phase was as follows: 60 mM NaH2PO4, 0.1 mM disodium EDTA, 0.2 mM octane sulphonic acid and 7% methanol, adjusted to pH 3.9 with orthophosphoric acid and filtered through a 0.45-µm Millipore filter. This mobile phase was delivered at a flow rate of 1.1 ml/min (Pump 116, System Gold, Beckman) through a Chromasyl column (C8, 150 mm × 4.6 mm, 5 µm) protected by a Brownlee–Newgard precolumn (RP-8, C18, 5 µm).
15 mm x 3.2 mm, 7 µm). A refrigerated injector (Injector 507, System Gold, Beckman) was used. Detection of DA, NA and 5-HT was carried out with a coulometric detector (Coulochem I, ESA) coupled to a dual electrode analytical cell (model 5011) and a conditioning cell (model 5021). The conditioning cell was set at +100 mV, the first electrode at +350 mV and the second at −270 mV.

Statistics and ethics

Behavioural data were analysed using two-way ANOVA with two between factors (surgery and drug dose), followed by post hoc analyses if significant effects were found. For each surgery group (sham or 6-OHDA-induced lesion), post hoc one-way ANOVA followed by Dunnett tests allowed us to discern statistical significances vs the corresponding saline controls due to different desipramine doses. Student’s t-tests (independent samples) were used for comparing two groups at the same drug dose point. As for neurochemical data, Student’s t-tests (independent samples) were carried out for the comparison of each group with respect to the sham rats killed one week after FST (control group). Since size populations were small, the data were logarithmically transformed (log [x]) if variance was not homogeneous. Experiments were performed in accordance with the animal care guidelines of the European Communities Council (86/609/EEC).

RESULTS

Behavioural study

As observed in Fig. 1, desipramine reduced depression level in sham rats, because immobility duration was significantly lower at 10 and 15 mg/kg desipramine vs the saline group (P<0.01), and immobility latency was found to be longer at 15 mg/kg desipramine (P<0.05). In addition, the duration of active behaviour was found to be higher at 15 mg/kg desipramine vs the saline group (F=3.5, P<0.05), as illustrated in Fig. 2. Regarding the 6-OHDA-treated group, desipramine selectively enhanced climbing duration at 10 (P<0.01) and 15 mg/kg desipramine (P<0.05), and it also reduced swimming duration at 10 and 15 mg/kg vs the corresponding saline group (P<0.05), as shown in Fig. 3.

After comparing sham-operated and 6-OHDA-treated rats at the same dose point (Student’s t-test), it was revealed that mPFCX DA depletion led to a very low depression tonus. Thus, immobility duration was reduced in lesioned rats treated with saline (0 mg/kg, t=5.2, P<0.01). This effect was also present but not further reduced after desipramine (5 mg/kg, t=7.8, P<0.0001; 10 mg/kg, t=5.9, P<0.01; 15 mg/kg, t=4.7, P<0.005).

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Immobility latency was enhanced at 10 (t = 7.3, P < 0.01) and 15 mg/kg desipramine (t = 5.5, P < 0.01), as shown in Fig. 1. Active behaviour was also found to be significantly higher in 6-OHDA-treated rats at every dose (0 mg/kg, t = 5.3, P < 0.01; 5 mg/kg, t = 7.8, P < 0.001; 10 mg/kg, t = 5.9, P < 0.01; 15 mg/kg, t = 2.9, P < 0.05), as shown in Fig. 2. Climbing duration was found to be higher in 6-OHDA-treated animals at 10 mg/kg (t = 6.8, P < 0.001). The duration of swimming was significantly higher in 6-OHDA-treated rats after saline (0 mg/kg, t = 3.5, P < 0.03), as illustrated in Fig. 3.

Neurochemical study

Monoamine levels one week after the experimental forced swimming test. Neurochemical contents of DA, NA and 5-HT in the mPFCX of sham-operated and 6-OHDA-lesioned rats one week after the experimental FST are shown in Table 1. Prefrontocortical contents of DA, NA and 5-HT were significantly reduced in the 6-OHDA-lesioned group vs sham control rats (DA, t = 11.7, P < 0.01; NA, t = 2.6, P < 0.05; 5-HT, t = 2.7, P < 0.05). DA, NA and 5-HT were reduced by 86%, 15.3% and 15.5%, respectively.

Monoamine levels during the experimental forced swimming test. As illustrated in Table 1, the swimming test alone induced a significant enhancement of DA (126.2%, P < 0.01), NA (29.1%, P < 0.05) and 5-HT (28.5%, P < 0.05) in the sham group vs basal levels of controls ( sham rats killed one week after the FST). With respect to the 6-OHDA-lesioned group, the swimming test alone induced a selectively high increase in 5-HT (76.2%, P < 0.01), but NA values were not modified. DA levels remained diminished (~26.6%, P < 0.05) vs controls, although dopamine levels were not significantly modified. 

Table 1. Tissue levels (pg/mg wet weight) of dopamine, noradrenaline and serotonin in the medial prefrontal cortex, in sham and 6-hydroxydopamine-lesioned rats, one week after and during the forced swimming test

<table>
<thead>
<tr>
<th>Group</th>
<th>DA</th>
<th>NA</th>
<th>5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>One week after the FST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>128.5 ± 5.5</td>
<td>84.8 ± 8</td>
<td>97.9 ± 5.5</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>17.8 ± 4.5**</td>
<td>71.8 ± 4*</td>
<td>82.7 ± 7.1*</td>
</tr>
<tr>
<td>During the FST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+Saline</td>
<td>290.7 ± 10.1**</td>
<td>109.5 ± 8.5*</td>
<td>125.8 ± 5.5*</td>
</tr>
<tr>
<td>+Desipramine</td>
<td>134.4 ± 8.2</td>
<td>174.5 ± 3.3**</td>
<td>146.2 ± 2.7**</td>
</tr>
<tr>
<td>6-OHDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+Saline</td>
<td>94.3 ± 4.5*</td>
<td>85.7 ± 8</td>
<td>172.5 ± 8.5**</td>
</tr>
<tr>
<td>+Desipramine</td>
<td>30.1 ± 3.5**</td>
<td>242.7 ± 12**</td>
<td>106.2 ± 8.8</td>
</tr>
</tbody>
</table>

Mean ± S.E.M. *P < 0.05, **P < 0.01 vs controls (sham rats killed one week after the FST; Student’s t-test). Bilateral lesion with 6-OHDA hydrobromide (2 µg/µl two/side).
was enhanced (429.7%) if compared with basal levels of 6-OHDA-lesioned rats killed one week after the FST. As regards desipramine-induced effects on sham rats, desipramine induced a high increase in NA (105.7%, \( P < 0.01 \)) and 5-HT (49.3%, \( P < 0.01 \)), but a very light increase in DA (4.6%) during the FST. In lesioned rats, desipramine significantly enhanced NA (186.2%, \( P < 0.01 \)). However, 5-HT neurotransmission was not significantly enhanced (8.5%), and mPFCX DA levels were found to be very low (\( \sim 76.4\% \) vs sham controls, \( P < 0.01 \)).

**DISCUSSION**

**Behavioural study**

The behavioural study confirmed that the FST was followed by a typical depression-like profile in sham rats, characterized by strong immobility. Interestingly, 6-OHDA lesion induced a reliable shift in the rat’s behaviour, reducing immobility and enhancing swimming, which is consistent with an antidepressant-like effect. This is a remarkable result, since DA is considered to have a general role in behavioural activation, increasing the probability and vigour of responses, and mPFCX DA is activated for coping with several adaptive anxiogenic situations.\(^\text{13}\) The results of the present study suggest that the reduction of mPFCX DA activity is also an adaptive response for dealing with a depressant challenge. These findings might be accounted for by a hyperlocomotion effect as well, since it is well known that hyperlocomotion emerges after reducing prefrontocortical DA content.\(^\text{5,7,9}\) However, increases in active responses such as swimming or climbing and reduction in immobility are considered as behavioural profiles consistent with antidepression, because they indicate that the vulnerability of a rat to passivity after inescapable stress has been changed.

Desipramine clearly acted as an antidepressant in sham rats, reducing immobility and enhancing active behaviour in a dose-dependent manner. Moreover, immobility latency was reliably increased, proving to be a novel suitable indicator for measuring antidepressant efficacy. However, desipramine behaved in a quite different manner in mPFCX DA-depleted rats. Thus, drug doses within their effective dose range selectively enhanced climbing.\(^\text{8,17}\) but immobility duration was not reduced further, probably because a low plateau level had been reached after 6-OHDA lesion. Interestingly, desipramine induced a behavioural shift in these lesioned rats, since swimming, highly enhanced after DA depletion in sham rats, was reduced in parallel to the enhancement of climbing. These results could be accounted for by a psychomotor stimulant effect rather than an antidepressant effect, because a specific enhancement of climbing is typically found after psychomotor stimulation.\(^\text{8}\) Hence, it is worth noting that desipramine, which acted as an antidepressant in sham rats, behaved more as a psychomotor stimulant in 6-OHDA-lesioned rats. In this context, studies of symptom profiles in patients with minor and major depression show that several populations can be identified on the basis of their therapeutic response: predominant sedation, prevailing psychomotor activation, etc.\(^\text{14}\)

**Neurochemical study**

Neurochemical data during the FSTs gave a good picture of the neurochemical correlation of behavioural changes. Thus, Porsolt’s test plus saline induced an increase in every monoamine in sham rats, in accordance with earlier studies.\(^\text{11}\) On the other hand, in lesioned rats, 6-OHDA treatment plus saline induced an antidepressant-like profile which was correlated with reduced DA levels and augmented 5-HT neurotransmission. The behavioural profile of low immobility and enhanced swimming was hence correlated with a selectively high mPFCX serotonergic activity. Furthermore, it seems that the depressant situation induced an enhancement of mPFCX DA activity with respect to 6-OHDA-lesioned rats killed one week after the FST, although DA levels remained lower if compared with sham rats killed one week after the FST. As for desipramine-induced effects, this drug induced antidepression in sham rats, as expected. This compound enhanced mPFCX NA and 5-HT levels, but also blocked the normal increase in DA seen during the FST. Taken together, these findings indicate that: (i) the enhancement of mPFCX NA and 5-HT neurotransmission, together with the blocking of DA increase, appear to mediate the normal antidepressive activity of desipramine, and (ii) when mPFCX DA levels had been either reduced or their normal increase blocked, an antidepression-like profile was observed. Early studies have revealed that DA release is enhanced within the mPFCX after desipramine treatment in naive rats,\(^\text{5}\) but the present study suggests that this drug blocks mPFCX DA hyperactivity during a depressant situation. On the other hand, desipramine further enhanced mPFCX NA but not 5-HT neurotransmission in lesioned rats, which was correlated with a selective increase in the climbing response. An up-regulation of 5-HT and NA receptors could also contribute to the behavioural effects mediated by these biogenic monoamines in lesioned rats. These findings are in accordance with earlier studies suggesting that enhancement of 5-HT neurotransmission mediates swimming, and augmented NA neurotransmission mediates climbing in the FST.\(^\text{8}\) A summary of monoamine changes in relation to the observed behavioural profile is shown in Table 2.

Neurochemical data one week after the FST in selected rats indicated that DA content in the mPFCX was reduced by 86% after 6-OHDA lesion, beyond the range where compensatory mechan-
This table shows that: (i) the depression-like profile was characterized by enhanced mPFCX DA, NA and 5-HT neurotransmission; (ii) antidepression was always correlated with a low mPFCX DA tonus; (iii) enhanced swimming was correlated with a preferential enhancement of mPFCX 5-HT neurotransmission; (iv) enhanced climbing was correlated with a preferential enhancement of mPFCX NA neurotransmission. Symbols: +, enhanced; =, normal; −, reduced levels vs controls.

**Table 2. Changes in monoamine levels within the medial prefrontal cortex and behavioural profile during the forced swimming test**

<table>
<thead>
<tr>
<th></th>
<th>DA</th>
<th>NA</th>
<th>5-HT</th>
<th>Behavioural profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Depression (high immobility)</td>
</tr>
<tr>
<td>+Saline</td>
<td>=</td>
<td>++</td>
<td>++</td>
<td>Antidepression (enhanced active behaviour, reduced immobility)</td>
</tr>
<tr>
<td>+Desipramine</td>
<td>=</td>
<td>=</td>
<td>+++</td>
<td>Antidepression (enhanced swimming, reduced immobility)</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>−</td>
<td>=</td>
<td>+++</td>
<td>Psychomotor stimulation (enhanced climbing)</td>
</tr>
</tbody>
</table>

The findings of the present study indicate that: (i) DA neurotransmission within the mPFCX is a factor involved in depression, since mPFCX DA reduction led to a lower depression tonus; (ii) desipramine induces antidepression not only by enhancing mPFCX NA and 5-HT neurotransmission, but also by blocking the normal increase in DA neurotransmission during the FST; (iii) a selective enhancement of mPFCX 5-HT neurotransmission mediates swimming; (iv) a selectively augmented mPFCX NA activity mediates climbing in the FST.

**REFERENCES**


*Accepted 29 April 1998*