Effects of Minaprine and Sulpiride Injected into the Amygdaloid Nucleus on the Duration of Immobility in Rats Forced to Swim

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Abstract—We examined the effects of minaprine and sulpiride injected into the medial amygdaloid nucleus on the duration of immobility in rats forced to swim. Minaprine (50 μg/ml) significantly reduced the duration of immobility, while sulpiride (50 μg/ml) remarkably enhanced it. These results suggest that the medial amygdaloid nucleus might be involved in the suppressive effect of minaprine on the duration of immobility, as was seen with the tricyclic antidepressants. The pattern of behavior seen with sulpiride administrations differs considerably from that seen with the tricyclic antidepressants.

The forced swimming test in rats is a useful model for evaluating the effects of antidepressants (1, 2). We reported that the medial amygdaloid nucleus might play an important role in the suppressive effects of tricyclic antidepressants and those of electroconvulsive shock (ECS) on the duration of immobility in rats forced to swim, and that catecholaminergic but not serotonergic mechanisms in the medial amygdaloid nucleus were linked to the action of tricyclic antidepressants and ECS (3-5). These results suggest that the medial amygdaloid nucleus may be the site of action of antidepressants in rats forced to swim. However, there seems to be no documentation of the site of action of atypical antidepressants on the duration of immobility in rats forced to swim. Minaprine (3-(2'-morpholinoethylamino)-4-methyl-6-phenylpyridazine) is an atypical psychotropic drug which has proven to be effective for states of depression seen in laboratory animals and humans (6, 7). Sulpiride is a clinical neuroleptic with an antidepressive effect (8). In the present study, we investigated whether or not the effects of minaprine and sulpiride on the duration of immobility of rats forced to swim were also involved in the medial amygdaloid nucleus.

Male Wistar rats weighing 160-180 g were purchased from SLC (Shizuoka, Japan). The rats were placed individually in vertical plexiglas cylinders (height 40 cm, diameter 18 cm) containing 15 cm of water maintained at 25°C. After swimming for 15 min, the rats were left to dry out in a room at 30°C. The following day, they were again put into the cylinders for 5 min, and the duration of immobility during 5 min was measured. A rat was judged to be immobile whenever it remained floating in the water, in an upright position, showing only the small amount of movement necessary to keep its head above the water (3). A chronic cannulation was made by the following method: The rats were anesthetized with pentobarbital-Na and the guide cannula, which was constructed of a stainless steel cannula having a 0.7-mm outer diameter and 15-mm total length, was bilaterally implanted, according to the stereotaxic coordinates of König and Klippel (9) into the medial amygdaloid nucleus (anterior: 5.1, lateral: 3.5, horizontal: −3.2) (3). The drug experiments were started from 7 days after implantation of the cannula. Minaprine (Sanofi) was dissolved in a 0.9% saline (pH 5.1−5.5), and sulpiride (Koei Chemicals) was dissolved in a 0.9% saline together with a small amount of 0.1 N hydrochloric acid (pH 5.0−5.8). The drugs
Table 1. Effects of minaprine and sulpiride injected into the medial amygdaloid nucleus on the duration of immobility

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (µg/µl)</th>
<th>N</th>
<th>Duration of immobility (sec) (Mean±S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>—</td>
<td>9</td>
<td>183.7±8.7</td>
</tr>
<tr>
<td>Minaprine</td>
<td>10</td>
<td>6</td>
<td>215.6±15.6</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>9</td>
<td>135.2±5.2**</td>
</tr>
<tr>
<td>Vehicle</td>
<td>—</td>
<td>10</td>
<td>183.3±13.3</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>20</td>
<td>8</td>
<td>201.5±14.0</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>9</td>
<td>243.9±9.0***</td>
</tr>
</tbody>
</table>

Minaprine (10, 50 µg/µl) and sulpiride (20, 50 µg/µl) were injected 5 min before the test into both sides of the medial amygdaloid nucleus. Each value is the mean for 6–10 animals. The significance of differences from the control was assessed statistically using the two-tailed Student’s t-test. ***P<0.01.

were injected 5 min before the test into both sides of the medial amygdaloid nucleus, in a volume of 2 µl each, through a 0.35-mm diameter needle inserted into the guide cannula, in unrestrained and unanesthetized rats.

Minaprine at 10 µg/µl and sulpiride at 20 µg/µl had no effect on the duration of immobility in rats forced to swim, when injected into the medial amygdaloid nucleus (Table 1). Minaprine at 50 µg/µl injected into the medial amygdaloid nucleus significantly reduced the duration of immobility. On the other hand, sulpiride at 50 µg/µl remarkably enhanced the duration of immobility.

It was reported that minaprine reduced the duration of immobility in the forced swimming test when injected intraperitoneally (6). Furthermore, minaprine injected into the lateral ventricle also reduced the duration of immobility (K. Biziere et al., unpublished data). The site of action of minaprine is most interesting, in the present study, minaprine injected into the medial amygdaloid nucleus reduced the duration of immobility. We had already noted that the medial amygdaloid nucleus might play an important role in the selective reducing effect of tricyclic antidepressants and ECS on the duration of immobility in rats forced to swim (3, 5). The anti-immobility effect of minaprine was caused by a prolongation of escape-directed behavior, such as is seen with tricyclic antidepressants. These results may indicate that the medial amygdaloid nucleus is involved in the suppressive effects of not only tricyclic antidepressants but also those of minaprine.

Sulpiride injected into the medial amygdaloid nucleus enhanced the duration of immobility, which is opposite of what is seen with tricyclic antidepressant and minaprine, and the behavioral pattern noted after sulpiride administration was similar to that of neuroleptics (1, 2, 10). Sulpiride blocks the action of D2 receptors, whereas minaprine has dopamine-stimulant properties (11). It is well-known that the activation of the central catecholaminergic system is responsible for the reduction in the duration of immobility induced by antidepressants (12, 13). Thus, the findings on minaprine and sulpiride in rats forced to swim may be explained by the opposite effect of the catecholaminergic system. However, sulpiride is effective in depressive illnesses. The brain sites, except for the medial amygdaloid nucleus, may be involved in the antidepressive effect of sulpiride.

Therefore, the characteristics of the effects of tricyclic antidepressants and minaprine in rats forced to swim may be similar, whereas the effect of sulpiride differs from that of tricyclic antidepressants.

References
3. 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


