Antidepressant activity of fosinopril, ramipril and losartan, but not of lisinopril in depressive paradigms of albino rats and mice

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Fosinopril, ramipril and losartan significantly decreased the duration (sec) of immobility in forced swim test and were comparable to amitriptyline. The duration of immobility were significantly decreased in fosinopril, ramipril and losartan in the tail suspension test and were comparable to amitriptyline. Only losartan significantly increased the rearing number of entries, time spent (sec) in open arm and in light area in comparison to control animals. Fosinopril and ramipril and not lisinopril showed significant antidepressant activity while losartan showed a significant antidepressant and anxiolytic activity. Present findings suggest that these drugs could be better antihypertensives in hypertensive patients with co-morbidity like depression or anxiety.

Keywords: Anxiety, Depression, Fosinopril, Lisinopril, Losartan, Ramipril

Physiological depression and anxiety when become severe and chronic lead to a variety of psychiatric disorders. Quite often such mood disorders could be secondary to a number of cardiovascular and endocrinal disorders1,2 requiring treatment with two drugs, one for physical or metabolic and the other for associated mental disorder. Logically, a single drug that can control the physical and associated mental illness would be an ideal agent for the treatment of such co-morbid conditions.

Interestingly, angiotensin converting enzyme (ACE) inhibitors like captopril3, perindopril4 and ceronapril5 have been reported to possess antidepressant activity in experimental animals. Similarly losartan, an angiotensin II receptor blocker has also been reported to possess antidepressant activity in experimental animals. Moreover captopril7, 8 and enalapril8 have been reported to control not only blood pressure but also improve the depressed mood and cognition in hypertensive patients. In addition captopril9,10, enalapril11 and losartan11,12 have been shown experimentally to exert anxiolytic activity both in normotensive and hypertensive rats.

Due to the common mechanism of action, other ACE inhibitors used clinically could be expected to possess antidepressant and anxiolytic activity like captopril and enalapril. A report regarding quinapril13 indicates that all ACE inhibitors may not share antidepressant and anxiolytic activity and such activities are not probed with other ACE inhibitors used clinically. It is therefore planned to investigate the effect of widely used, chemically heterogeneous ACE inhibitors14 with varying lipophilicity15 viz. fosinopril, ramipril and lisinopril for their antidepressant and anxiolytic activity in male Wistar rats and Swiss mice.

Materials and Methods

Animals—Male adult Wistar rats and Swiss mice, weighing between 150-250 g and 20-30 g respectively, were obtained from the central animal house of the institute and were kept in the laboratory for about 10 days in 12:12 hr L:D cycle. Throughout the experiment the animals were fed with laboratory chow (Amrut Brand) and water ad libitum. Animals receiving alprazolam orally were fasted overnight prior to the day of experiment and experiments were conducted between 09.00-14.00 hrs.

The study was approved by Institutional Animal Ethical Committee formed as per the guidelines of CPCSEA, New Delhi.

Drugs and doses—Amitriptyline (Inj. Typtin, Sterfil Labs Ltd), alprazolam (Tablets Alprax, Torrent Ltd), lisinopril (Tablets Lipril, Lupin Ltd) and losartan (Tablets Angizaar, Carsynoa, Microlabs) were
purchased locally. Fosinopril and ramipril were obtained as generous gift samples from Cipla Ltd.

Rat and mice equivalent doses in mg/kg body weight of clinical doses were calculated as mg/kg body weight with the help of the table cited earlier and were 27.0 for amitriptyline (AMT), 0.045 for alprazolam (AZM), 1.8 for fosinopril (FSL), 0.23 for ramipril (RML), 1.8 for lisinopril (LSL), 10.0 for losartan (LTN); while the corresponding doses for mice were 7.8 for AMT, 0.52 for FSL, 0.06 for RML, 0.52 for LSL, and 2.88 for LTN. All the drugs except AZM were dissolved in distilled water while AZM was suspended in 2% gum acacia. All drugs were freshly prepared and were administered in a single ip dose in the volume of 0.5 ml to groups of mice (n=6, in each) and 1.0 ml to groups of rats (n=6, in each), while the corresponding doses for mice were 7.8 for AMT, 0.52 for FSL, 0.06 for RML, 0.52 for LSL, and 2.88 for LTN. All the drugs except AZM were dissolved in distilled water while AZM was suspended in 2% gum acacia. All drugs were freshly prepared and were administered in a single ip dose in the volume of 0.5 ml to groups of mice (n=6, in each) and 1.0 ml to groups of rats (n=6, in each), while alprazolam suspension was given orally in the volume of 1 ml to the rats. Equal volumes of either gum acacia 2% suspension or normal saline were administered through corresponding route to the control group.

Behavioral studies—a) Antidepressant activity studies were carried out in rats using forced swim test paradigm as described earlier. Briefly, male adult rats weighing 160-180 g were plunged into a vertical plexiglass cylinder (40 cm height 18 cm diam) containing 15 cm of water column maintained at 25°C and left there for 5 min. The duration of immobility in seconds as indicated by the animal floating motionless in the water making only those movements necessary to keep its head above water was noted. Animals were trained for 15 min, 24 hours prior to the experiment. After the experiment, the animals were then allowed to dry for 15 min before returning to their individual cages. Group mean of immobility time was calculated in treated and control animals.

b) Tail suspension test was carried out in mice as described earlier. The mouse pretreated with drug/vehicle was suspended from the hook hanging at the center of a horizontal rod placed on 2 metallic stands kept 35 cm apart. An adhesive tape stuck 2 cm proximal to the tail tip was used to suspend the animal through the hook hanging about 35 cm distance from the ground. Immobility time in seconds was recorded by assessing motionless hanging of the mice over a period of 6 min.

c) Anxiolytic activity was studied using elevated plus maze as described earlier.

The plus maze apparatus consists of two open (50 × 10 cm) and two side-closed arms (50 × 10 × 40 cm) without roof, elevated 50 cm from the floor. The pretreated animals were placed individually for 5 min at the center of the elevated plus maze facing the head towards an open arm. The number of entries into the open or closed arm and the time spent in each arm were recorded. At the same time, number of rears in the open arm was recorded.

The percentage of the number of entries (against the total number of entries both in open and closed arms) and time spent in the open arm were calculated for each group. Similarly mean number of rears (standing on the hind limbs) for each group was calculated.

d) Light–dark arena: It consists of a wooden box (50 × 30 × 35 cm) placed on a table, 1 m above floor level. A partition with a gap of 7.5 × 7.5 cm at the centre of its lower border was fixed to separate 2/5th of the base from the remaining 3/5th. The smaller 2/5th chamber was painted black and the other one (3/5th of the base) was painted white on all four sides. The chamber painted black was illuminated with red light while the other chamber was brightly illuminated with a 100 W light source located 17 cm above the box. Pretreated rats were placed in the centre of the bright area. The number of rearings, entries into and time spent in light area were recorded over a period of 5 min. The mean number entries and rears and percentage of time spent were calculated for each group.

The effect of all the drugs used in the present study, on locomotor activity was tested using actophotometer (M/S INCO)

Statistical analysis—The results were analyzed by one-way ANOVA followed by Dunnet’s test using Graph pad prism software and P ≤ 0.05 was considered significant.

Results

Forced swim test and tail suspension test—The mean duration of immobility in the FSL, RML and LTN treated groups were significantly (P<0.01, <0.05) reduced as compared to that of the control group and was comparable to that of AMT. However LSL failed to show antidepressant activity in both the paradigms (Table 1).

Elevated plus maze—The mean number of entries into the open arm in the control and treated groups though did not significantly differ, the mean of
percentage entries into open arm was significantly increased in the LTN ($P \leq 0.05$) and AZM ($P \leq 0.01$) treated animals. Similarly the mean number of rears and percentage of time spent in the open arm was significantly increased in the LTN ($P \leq 0.05$) and AZM ($P \leq 0.01$) treated animals (Table 2).

**Light dark arena**—The mean number of rears and percentage of time spent in the light area in the LTN and AZM treated group was significantly increased ($P < 0.05$, $\leq 0.01$) when compared to that of control group (Table 2).

**Discussion**

The findings of the present study in both the models of depression viz. forced swim test and tail suspension test clearly indicate that FSL, RML and LTN have significant antidepressant activity, comparable to that of AMT. The antidepressant activity of LTN observed in the present study agrees with an earlier report\(^6\) however, to the best of our knowledge the antidepressant activity of FSL and RML is being reported for the first time.

Dysregulated hypothalamopituitary adrenal axis (HPA)\(^22\) leading to increased cortisol levels and decreased BDNF level\(^23\) have been implicated with depressive disorders and restoration of normalcy of HPA axis by captopril has been correlated with its antidepressant activity in a hypertensive patient\(^7\). Involvement of glucocorticoids in the pathogenesis of depression has been confirmed in an experimental study\(^24\). Antidepressant activity of captopril has also been reported to be mediated through enkephalin\(^7\) and ACE inhibitors used in the present study could be acting in the same way as captopril.

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**Table 1**—Effect of various treatments on depression paradigms
[Values are mean ± SE from 6 animals in each group]

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Dose (mg/kg)</th>
<th>Immobility time (sec)</th>
<th>Treatment Groups</th>
<th>Dose (mg/kg)</th>
<th>Immobility time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>1 ml</td>
<td>0.5 ml</td>
<td>Rat</td>
<td>176 ± 5.26</td>
<td>218.7 ± 12.25</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>27</td>
<td>7.8</td>
<td>Mice</td>
<td>142 ± 3.19**</td>
<td>159.7 ± 2.33**</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1.8</td>
<td>0.52</td>
<td>Forced swim test in rats</td>
<td>143.5 ± 3.74**</td>
<td>153.2 ± 2.94**</td>
</tr>
<tr>
<td>Ramipril</td>
<td>0.225</td>
<td>0.065</td>
<td>Tail suspension test in mice</td>
<td>158.8 ± 3.46*</td>
<td>163.5 ± 3.35**</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.8</td>
<td>0.52</td>
<td></td>
<td>165.7 ± 3.46*</td>
<td>203.2 ± 3.87</td>
</tr>
<tr>
<td>Losartan</td>
<td>10</td>
<td>2.88</td>
<td></td>
<td>148.3 ± 3.39</td>
<td>158.2 ± 3.87</td>
</tr>
</tbody>
</table>

One-way ANOVA followed by Dunnet’s test. $P$ values: *$<0.05$, **$<0.01$ (vs control group)

**Table 2**—Effect of various treatments on anxiety paradigms
[Values are mean ± SE from 6 animals in each group]

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Dose (mg/kg)</th>
<th>Elevated plus maze</th>
<th>Light dark arena</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of open arm entries</td>
<td>Number of total arm entries</td>
</tr>
<tr>
<td>Gum acacia</td>
<td>1.0ml</td>
<td>2.67 ± 0.67</td>
<td>9.83 ± 0.28</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.045</td>
<td>3.67 ± 0.95</td>
<td>7.5 ± 0.36</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1.8</td>
<td>3 ± 0.57</td>
<td>8.67 ± 1.36</td>
</tr>
<tr>
<td>Ramipril</td>
<td>0.225</td>
<td>2.5 ± 0.22</td>
<td>7.33 ± 0.33</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.8</td>
<td>2.17 ± 0.60</td>
<td>6.16 ± 1.47</td>
</tr>
<tr>
<td>Losartan</td>
<td>10</td>
<td>4.83 ± 1.80</td>
<td>9.16 ± 0.94</td>
</tr>
</tbody>
</table>

One-way ANOVA followed by Dunnet’s test. $P$ values: *$<0.05$, **$<0.01$ (vs control group)
It is unlikely that ACE antagonists used in the present study augment central synaptic norepinephrine (NE) level in order to exert antidepressant activity, since angiotensin II itself is said to augment the synaptic NE release\textsuperscript{14}.

Lack of antidepressant activity in rats treated with lisinopril could be explained on the basis of its poor lipophilicity\textsuperscript{15}, despite its passage through blood brain barrier. It is well known that, the lipophilicity is one of the determinants of tissue penetration by drug molecules to exert pharmacological actions.

In the present study only LTN, an angiotensin receptor blocker, in the dose of 10 mg/kg but not 5 mg/kg showed significant anxiolytic activity in both the models of anxiety (elevated plus maze and light dark arena) and was comparable to that of AZM. These findings of the present study are in agreement with an earlier report\textsuperscript{17} wherein LTN was reported to produce dose dependent anxiolytic activity in hypertensive rats, while its anxiolytic activity was observed only with a higher dose (10 mg/kg) in normotensive rats\textsuperscript{11}.

Increased central norepinephrine (NE) is often implicated with anxiety. Anxiolytic activity of LTN in hypertensive rats has been attributed to its selective blockade of AT\textsubscript{1} (anxiogenic) receptors leading to suppressed NE release\textsuperscript{5,26,27}.

All the three ACE inhibitors viz. FSL, RML and LSL used in the present study, failed to show significant anxiolytic activity and there is paucity of information regarding their influence on anxiety. However, captopril and enalapril have been reported to exert anxiolytic activity in hypertensive rats but not in normotensive ones\textsuperscript{1,25}. The lack of anxiolytic activity of FSL, RML and LSL in the present study could be explained on the basis of normotensive rats being used and the present findings agree with an earlier report wherein enalapril failed to produce anxiolytic activity in normotensive rats.

The anxiolytic effect of renin angiotensin system antagonists could be attributed to increased central GABA activity, since angiotensin II has been reported to decrease central GABA activity\textsuperscript{28}. It is difficult to explain why ACE inhibitors used in the present study failed to show anxiolytic activity. However, except AZM none of the treatments significantly changed locomotor behavior. This finding indirectly indicates insignificant changes in central GABA activity and that probably explains the lack of their anxiolytic activity. Though, anxiolytic activity is mediated through central GABAergic mechanisms, central sympathetic over activity is also involved in anxiogenesis.

Captopril has been reported to relieve the signs of depression in a hypertensive patient with recurrent unipolar major depression and improved the quality of life in hypertensive individuals\textsuperscript{30}. The observed antidepressant and anxiolytic activity of LTN; antidepressant activity of FSL and RML indicate that, these drugs can improve the quality of life in hypertensive individuals. These drugs may be preferred to treat hypertensive patients with mood disorders, provided the present findings could be extrapolated to humans. Such patients need the treatment with an antihypertensive and an antidepressant. When these drugs particularly LTN is used as an antihypertensive might reduce the dosage requirement of potentially toxic antidepressants and the same needs clinical evaluation.

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References


