MODIFICATION OF TRICYCLIC ANTIDEPRESSANT ANALGESIA BY CALCIUM CHANNEL BLOCKERS

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Abstract: The influence of calcium channel blockers (CCB) on the analgesic activity of tricyclic antidepressants (TCA) was examined using hot plate (thermal) and writhing (chemical) method. Intraperitoneal injections of TCA, imipramine and amitriptyline or CCB viz: verapamil, nifedipine, nicardipine and cinnarizine per se produced analgesia. The analgesic effect of TCA was further enhanced by prior treatment with CCB. The increase in TCA analgesia could not be ascribed to unitary mechanism but could possibly be mediated by opioid and/or nonopioid systems. These results clearly provide an evidence that a combination treatment of CCB and TCA may permit reduction of the TCA doses while treating chronic pain of organic origin.

Key words: calcium channel blockers tricyclic antidepressants analgesia

INTRODUCTION

There is now substantial evidence to indicate that tricyclic antidepressants (TCA) produce analgesia (1,2) and are used to alleviate chronic pain (13), but their precise mechanism appears to be quite complex and unclear. Similarly, calcium has an important physiological in the control of pain either through direct action or through modulation of endogenous substances (4,5) and calcium channel blockers (CCB) have been reported to produce analgesic effects in mice (6). TCA used clinically in chronic pain leads to severe side effects. So an attempt to investigate the combined analgesic effect of CCB and TCA in mice has been made.

METHODS

Male NIH mice weighing 20-25 gm maintained under 12 hour light dark cycle were used. Two analgesic tests were used: the hot plate test and writhing test. In hot plate test, the surface temperature was maintained at 50±1°C (7) throughout the experiment. Animals showing reaction time between 10-15 sec for licking of hind paw and or jumping (whichever occurred first) were used for experiments and a cut off time of 60 sec was used to avoid tissue injury (7) and the percent analgesia was calculated (8) and the mean percent analgesia was computed for a representative group.

% Analgesia = \frac{\text{Test latency} - \text{Control latency}}{\text{60} - \text{Control latency}} \times 100

The writhing syndrome was elicited by administration of acetic acid (10 mg/kg, 1%, I.P) and the number of writhes displayed from 5 min to 15 min were recorded. Analgesia was represented by percentage inhibition of writhes and was calculated according to the formula, \% inhibitor of writhes = \frac{S - T}{S} \times 100. Where S is the number of writhes in control and T is the number of writhes in drug treated animals (6).

Drugs: imipramine hydrochloride (IMA) and amitriptyline hydrochloride (AMT) (Torrent Labs) cinnarizine, nifedipine, verapamil and nicardipine (Sigma Chemical Co., U.S.A.). Cinnarizine and nifedipine were suspended in 5% gum acacia, whereas all other drugs solutions were prepared in 0.9% NaCl. All the drugs were administered intraperitoneally in a volume of 0.1 ml per mouse.

Treatment protocol: The various TCA and CCB were administered individually and in combination at the dose of 20 mg/kg respectively in hot plate method.

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For writhing test only IMA (10 mg/kg) was used individually and in combination with verapamil 5 mg/kg and nicardipine 10 mg/kg. In both the tests, CCB were given 30 min prior to TCA administration and the response was noted at next 30 min. Statistical analysis of the results was done by upaired test and P<0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Tricyclic antidepressants and calcium channel blockers if given individually produced significant analgesia in both the tests. However, when given together, the analgesic effect was greater than either of them given alone (Table I and II). In hot plate test IMA analgesia was increased from 15.5% to 26.22%, while in writhing method % inhibition of writhes was raised from 60.5% to 85.36% by verapamil and nicardipine. The mechanism by which CCB increase

<table>
<thead>
<tr>
<th>Treatment</th>
<th>dose mg/kg, i.p.</th>
<th>n</th>
<th>% Inhibition of writhes (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>10</td>
<td>8</td>
<td>60.5±3.02*</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5</td>
<td>10</td>
<td>27.4±1.88*</td>
</tr>
<tr>
<td>Verapamil + Imipramine</td>
<td>5</td>
<td>8</td>
<td>85.36±2.28*</td>
</tr>
<tr>
<td>Imipramine</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>10</td>
<td>9</td>
<td>26.68±1.6*</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>10</td>
<td>7</td>
<td>82.07±1.8*</td>
</tr>
<tr>
<td>Imipramine</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant at P<0.001 when compared with (*) vehicle control and (a) imipramine alone respectively.

TCA analgesia are not fully clear. The analgesic action of TCA is linked to their direct activity on the structure of central nervous system (CNS) mediating pain perception, independent of their effects on mood and by blocking of alpha-2 adrenoceptors and or amine re-uptake (9). The CCB also inhibit alpha-2 adrenoceptors at nor-adrenergic axon terminals in CNS (10,11). It has been reported that the analgesic properties of antidepressants might be mediated by an interaction with opiate receptors in brain (12). Similarly a close relation ship between CCB and µ opiate receptors has been demonstrated (13).

The increase of TCA analgesia could also be ascribed to their calcium channel blocking activity or altered calcium disposition, and because this effect is shared by all CCB, EDTA, EGTA and lanthanum which by decreasing calcium cellular availability show antinociceptive activity (14, 15). The intracerebroventricular injection of calcium is reported to produce hyperalgesia (4). The exact mechanism responsible for the additive analgesic effect of TCA and CCB remains to be elucidated.

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REFERENCES


