ANTI-SPASMOCENIC EFFECT OF CYPROHEPTADINE ON GUINEA-PIG ILEUM

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Summary: Antagonistic activity of cyproheptadine against common spasmogens, like acetylcholine, histamine, serotonin, bradykinin and angiotensin, was studied on isolated guinea-pig ileum. Cyproheptadine produced a reversible antagonism of non-competitive type and was most effective against serotonin. It was less potent against histamine, bradykinin and angiotensin and least potent against acetylcholine.

Key words: cyproheptadine, spasmogen, histamine, acetylcholine, bradykinin, guinea-pig ileum, serotonin, angiotensin II

INTRODUCTION

Cyproheptadine (CPH) is a well known antiserotonergic and antihistaminic drug (4,7). It also bears weak anticholinergic (7) and antibradykinin (2,3,6) properties. As most of the above reports on CPH-mediated antagonism come from varied biological systems, these may not be a true reflection of the potency and specificity of its antagonistic effects.

This study was undertaken to assess the antagonistic potency of CPH against five well known spasmogens, viz. serotonin, histamine, acetylcholine, bradykinin and angiotensin II, under identical conditions on the guinea-pig ileum.

MATERIAL AND METHODS

Normal healthy guinea-pigs of either sex weighing between 150-250 g were used. Ileum was removed surgically, after stunning the animals and immediately transferred to Tyrode solution.

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The guinea-pig ileum was set up in organ bath according to the method of Magnus as described by Perry (5). The contractile responses of the ileum in presence of different doses of the five spasmogens, were recorded on a kymograph using a simple isotonic lever. Time cycle of 3 to 5 min was followed.

Similarly, the dose-response curves for the spasmogens were also obtained in presence of different concentrations of CPH till the maximum contractile response of each spasmogen was reduced by more than 50 per cent. CPH was added to the bath 1 min prior to the addition of the agonists. The pD’2 values (1) of CPH against the spasmogens were obtained by plotting the per cent maximal response in each case against the log of molar concentrations of CPH. The values were expressed as negative log of the molar concentration of CPH producing 50 per cent reduction in maximal response.

Drugs used were: Cyproheptadine hydrochloride (Merck, Sharp and Dohme, FRG); acetylcholine bromide and histamine dihydrogen phosphate (Sigma Chemical Co., USA); bradykinin (BRS 640) and serotonin (5-hydroxytryptamine creatinine sulphate) Sandoz, Switzerland) and angiotensin II (Ciba, Bombay).

RESULTS

The dose response curves obtained with all the five spasmogens (acetylcholine-2 ng to 64 μg/ml; histamine - 10 ng to 100 μg/ml; bradykinin - 0.1 ng to 32 ng/ml; serotonin - 10 ng to 2.6 μg/ml; angiotensin II - 0.2 ng to 0.16 μg/ml) were shifted to

![Graph of percentage of maximum response vs log dose of CPH](image)

**Fig. 1:** Percentages of maximum response with acetylcholines on guinea-pig ileum in the presence of different concentrations of CPH (pD’2 = 6.05).
the right with increase in the concentration of CPH (0.1 μg to 0.5 μg/ml) and the maximum response was reduced in all the cases, indicating that the antagonism was of non-competitive type. The per cent of maximum response in presence of different concentrations of CPH gave a linear relationship (r=0.97) with the log of molar concentration of CPH (Fig. 1). The pD'2 values and slope of regression lines were also calculated from the graphs (Table I).

<table>
<thead>
<tr>
<th>Spasmogen</th>
<th>pD'2 value</th>
<th>Slope</th>
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<tbody>
<tr>
<td>Serotonin</td>
<td>9.15</td>
<td>1.73</td>
</tr>
<tr>
<td>Histamine</td>
<td>8.95</td>
<td>1.88</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>7.05</td>
<td>3.27</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>7.05</td>
<td>1.83</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>6.05</td>
<td>2.05</td>
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</tbody>
</table>

**DISCUSSION**

CPH antagonises the contractions induced by all the spasmogens at a fairly low concentration. The maximum response of all the agonists was supressed in the presence of CPH indicating that the antagonism was of non-competitive type. CPH was most potent against serotonin since its pD'2 value was highest (9.15) amongst the various spasmogens studied (Table I). The pD'2 values of CPH against the various agonists were in the following order:

Serotonin > Histamine > Bradykinin = Angiotensin II > Acetylcholine

Although CPH exhibited the same antagonistic activity against bradykinin and angiotensin II (pD'2=7.05), the slope of the regression line was considerably higher in the case of bradykinin (3.27) as against angiotensin (1.83). This indicates that CPH antagonises the action of bradykinin in a narrower concentration range as compared to angiotensin.

Thus, our findings are in agreement with that of Gomazkov and Shimkovich (2) who also observed that CPH was a more potent antagonist of serotonin and histamine than bradykinin. Since CPH produces a reversible antagonism of non-competitive type against all the spasmogens tested, it may be postulated that CPH interferes with the contraction of the tissue in a non-specific manner.

**REFERENCES**