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Bradykinin-Induced Immediate Skin Reactions and $H_1$-Blockade

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Introduction
Skin reactivity to bradykinin (BK) has been studied in the past by different investigators using a range of techniques. In these studies, the agonist BK was injected intra-dermally (i.d.) at various concentrations (expressed in µg or µl) and volumes, and different skin parameters were measured: itch, wheal and/or erythema. When $H_1$ antihistamines were tested, these drugs were different or given at different doses and the skin parameters were measured at different times after drug intake [1-4].

Under such conditions, it is rather difficult to make reliable comparisons between the different available experiments. The aim of the present paper is double: (1) to express the available data in a standardized table that allows easier critical analysis and (b) to compare the published data with new results obtained in healthy subjects and atopies following skin challenge with BK administered i.d. or by pricking (P) in two double-blind crossover randomized studies.

Results and Discussion
According to the literature, it is rather difficult to state whether or not BK can act as a histamine-releasing agent in vivo in humans. Only a few clinical pharmacology studies in humans are available, and they tend to demonstrate that the BK-induced skin reactions are not affected by $H_1$ blockade. These studies were carried out in healthy subjects as well as atopies. As can be seen from table 1, only two investigators demonstrated an inhibition by previous $H_1$ blockade of BK-induced itch (Hägermark) and BK-induced wheal (our own data). In these studies, the volume injected in the skin was low (prick or 10 and 20 µl). All the other studies are negative as far as $H_1$ blockade is concerned, regardless of the drugs used, the amounts of BK injected and the concentrations. In these negative studies, the volumes injected in the skin are higher: 50-100 µl.

It is interesting to note that the mean wheal area observed after BK administration into the skin is very small (7 mm2) when the P technique is used despite the very high concentration of the agonist (21.2 mg/ml). When BK is injected i.d. in a small volume (10 µl), the resulting wheal also remains very small, i.e. 30 mm2. If the volume is increased while the concentration remains similar, the resulting wheal becomes much larger and reaches 100 mm2. At the same time, this larger wheal becomes insensitive to $H_1$, blockade. Many years ago, Shelley and Arthur [5]...
observed that it is essential to inject volumes less than 0.05 ml to elicit experimental itch. It may be hypothesized that larger volumes injected i.d. induce some tissue damage accompanied by a local release.

Table 1. Summary of experiments conducted to date with BK

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Volume</th>
<th>Amount injectedit.d.</th>
<th>g</th>
<th>M Concentration/µl</th>
<th>nM</th>
<th>Parameters measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greaves and Shuster 1967</td>
<td>lOOµl</td>
<td>lOµg 9.4 nM 100.Ong 0.09 nM</td>
<td>I9l</td>
<td>absent</td>
<td>chlorpheniramine i.m. 8 mg ineffective</td>
<td></td>
</tr>
<tr>
<td>Hägermark 1974[2]</td>
<td>20 µl</td>
<td>1.8 µg 1.7 nM 90.0 ng</td>
<td>0.08 nM</td>
<td>not measured</td>
<td>levopromazine p.o. 5 mg chlorcyclizine p.o. 25 mg inhibition</td>
<td></td>
</tr>
<tr>
<td>Rihoux and Fadel 1994</td>
<td>prick technique</td>
<td>21.2 µg 20 nM 7</td>
<td>not measured</td>
<td>cetirizine p.o. lOmg 80% inhibition</td>
<td>i.m. = Intramuscular; p.o. = by mouth. of various mediators that may interact with BK itself, leading to the formation of a nonspecific wheal phenomenon.</td>
<td></td>
</tr>
</tbody>
</table>

Another hypothesis to explain the inhibiting effect of cetirizine on BK-induced wheal could be the existence in this drug of unexpected pharmacological activities not linked to the H, receptor: either a direct inhibiting effect on BK receptors for instance, or a modulating effect on G proteins involved in the signalling pathway linked with BK receptor activation. These hypotheses are under investigation.

References


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