Bronchial Hypersensitivity to Methacholine in Monkeys with Beta-Adrenergic Blockade

SUETSUGU MUE, TADAO ISE, SHUNSUKE SUZUKI, MASAHARU SUGIYAMA, TAKAO SASAKI and TAMOTSU TAKISHIMA

The First Department of Internal Medicine, Tohoku University School of Medicine, Sendai

MUE, S., ISE, T., SUZUKI, S., SUGIYAMA, M., SASAKI, T. and TAKISHIMA, T. Bronchial hypersensitivity to methacholine in monkeys with beta-adrenergic blockade. Tohoku J. exp. Med., 1975, 115 (4), 395-396 — In monkeys with beta-adrenergic blockade caused by administration of propranolol, we found that the conductance of the total respiratory system markedly decreased following intravenous administration of methacholine. The presence of beta-adrenergic blockade was judged from inotropic effect on the heart, levels of blood glucose and lactic acid, and the reaction of eosinophils after adrenalin injection.

bronchial hypersensitivity; beta-adrenergic blockade; monkey; methacholine

The possibility has been investigated that propranolol administration could change the response to adrenalin injection and the total respiratory conductance of monkeys. The animals were kept separate and were given the same solid feed, fruits and water with vitamins. 14 monkeys were studied: 5 crab eating monkeys (Macaca fascicularis), 5 Japanese monkeys (Macaca fuscata fuscata) and 4 pig-tailed monkeys (Macaca nemestrina). Weight ranged from 4.4 kg to 13.5 kg. Propranolol (5 mg each per kg of body weight) was given orally for 10 days (Ise 1974; Mue 1974). 13 or 14 hr after the last administration, the adrenalin response and the conductance of the total respiratory system were measured under anesthesia (ketamine hydrochloride). Adrenalin (60 μg per kg) was injected intramuscularly and methacholine (0.25% solution) intravenously. Among many responses to adrenalin, the heart rate, blood glucose and lactic acid, and peripheral eosinophils number were measured. Glucose was estimated with a Technicon Autoanalyzer, lactic acid by Lactate Test (made by Boehlinger Mannheim) and eosinophils number was calculated according to Hinkelman's method (Ise 1974; Mue 1974). The conductance of the total respiratory system was measured by the forced 3 Hz oscillation method using an endotracheal tube (Mead 1960). The endotracheal pressure and flow were recorded on a four channel direct-writing rectigraph (Sanei, Tokyo), together with electrocardiogram. The respiratory conductance was corrected by subtracting the endotracheal air flow resistance.

Without pretreatment with propranolol, the crab eating monkeys showed gradual increases in heart rate, blood glucose, and lactic acid, and a decrease in eosinophils number for 30 min after intramuscular injection of adrenalin (Table 1). These responses to adrenalin are similar to those in human beings. However, after the propranolol administration, these monkeys showed no increase in heart rate, blood glucose and lactic acid, and no decrease in the eosinophils number by 30 min after adrenalin injection. This means the complete formation of beta-adrenergic blockade as judged from the inotropic effect of adrenalin, metabolism of blood glucose and lactic acid, and the reaction of eosinophils (Szentivanyi 1968; Ise 1974; Mue 1974). In the Japanese monkeys, a beta-adrenergic blockade was observed, though not so definitively as in crab eating monkeys (Ise et al. 1975).

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TABLE 1. Effect of oral propranolol on adrenalin response of crab eating monkeys

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Before treating with propranolol</th>
<th>After treating with propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart rate</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>Crab eating</td>
<td></td>
<td>+73</td>
<td>+60</td>
</tr>
<tr>
<td>monkey</td>
<td></td>
<td>+41</td>
<td>+71</td>
</tr>
<tr>
<td>&quot;</td>
<td>6.2</td>
<td>+50</td>
<td>+57</td>
</tr>
<tr>
<td>&quot;</td>
<td>6.2</td>
<td>−9</td>
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</tr>
<tr>
<td>&quot;</td>
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<td>+54</td>
<td>+70</td>
</tr>
</tbody>
</table>

Fig. 1. The changes in respiratory conductance caused by methacholine injection in monkeys. o, control; •, after treated with propranolol.

Data were obtained from 13 monkeys and expressed as percentage increase or decrease with reference to the value before methacholine injection.

The results of the conductance measurements are shown in Fig. 1. Prior to the propranolol administration, the monkeys showed no change in conductance over a wide dose range. However, after propranolol, even a mild dose of methacholine given intravenously caused a marked drop in conductance.

Thus, the acquired bronchial hypersensitivity was demonstrated in those monkeys with beta-adrenergic blockade. As to the possibility that those are suitable for an experimental model of human bronchial asthma, the physiological, pharmacological and biochemical aspects await further studies.

References