NON-PARTICIPATION OF BLOOD-CEREBROSPINAL FLUID-BARRIER IN THE DEVELOPMENT OF TOLERANCE TO THE ANALGESIC EFFECT OF MORPHINE IN MICE

KOTOBUKI HANO, HIROSHI KANETO AND TAKEO KAKUNAGA

Department of Pharmacology, Faculty of Pharmacy, Osaka University, Toyonaka, Osaka

Received for publication May 13, 1964

Recently, Kase (1-2) put forward the remarkable hypothesis that the development of tolerance to morphine is due to the changes of blood-cerebrospinal fluid-barrier. This hypothesis was based on the experimental results that morphinized dogs lost their acquired tolerance to morphine by electrical shock or chemical seizures resulting from the alteration of blood-cerebrospinal fluid-barrier, and that repeated intracisternal injection of morphine into dogs failed to develop the tolerance.

However, since his experiments were done only with the antitussive effects of morphine it seemed worthwhile to investigate whether his hypothesis is applicable to other effects of morphine.

The male white mice of ddO strain weighing about 20 g were used in these experiments. Morphinized mice were made 1) by subcutaneous injections of morphine twice daily in increasing dose from 20 mg/kg to 80 mg/kg body weight or 2) by intracisternal injections of morphine daily increasing dose from 50 μg/kg to 150 μg/kg for 2 weeks. The control groups were given injections of saline for the same period.

Electroshock seizures were induced by applying 60 cps current of 15 mA for 0.2 sec to conjunctive sacs of mice. Metrazol shock was produced by injecting 60 mg/kg of Metrazol intraperitoneally into animals. Intracisternal injections were made as described by Horlington and Lockett (3). Analgesia was measured by both the D'Amour-Smith method and electric stimulation method.

In the first experiments, both control and subcutaneously morphinized mice were subjected to the Metrazol or electroshock. Twenty-four hours after the convulsion the analgesia caused by 5 mg/kg of subcutaneous morphine was evaluated.

REFERENCES

Differed from Kase's results, the convulsions produced by Metrazol or electroshock have effect neither on the analgesic action of morphine in control groups nor on the tolerance developed in morphinized groups.

In the next experiments, three groups of mice received subcutaneous injections of 5 mg/kg or intracisternal injections of 30 µg/kg of morphine. These doses were enough to produce complete analgesia in normal animals.

The results summarized in Table 1 show that both morphinized animals also had been tolerant to the analgesic effect of morphine administered by intracisternal route as well as that administered by subcutaneous route.

### Table I. A comparison of the analgesic effect of morphine in control and morphinized mice.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose of morphine (Route of inj.)</th>
<th>Analgesia (min-sec)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D'Amour-Smith method</td>
<td>Electric stimulation method</td>
</tr>
<tr>
<td>Control</td>
<td>5 mg/kg (s.c.)</td>
<td>975 ± 38.7 (30)</td>
<td>935 ± 45.3 (45)</td>
</tr>
<tr>
<td>Morphinized I</td>
<td></td>
<td>109 ± 24.2 (23)</td>
<td>128 ± 17.1 (40)</td>
</tr>
<tr>
<td>Morphinized II</td>
<td></td>
<td>321 ± 39.9 (25)</td>
<td>203 ± 15.1 (36)</td>
</tr>
<tr>
<td>Control</td>
<td>30 µg/kg (i.c.)</td>
<td>926 ± 34.9 (20)</td>
<td>960 ± 23.9 (46)</td>
</tr>
<tr>
<td>Morphinized I</td>
<td></td>
<td>170 ± 27.4 (25)</td>
<td>83 ± 9.0 (40)</td>
</tr>
<tr>
<td>Morphinized II</td>
<td></td>
<td>240 ± 48.7 (25)</td>
<td>169 ± 35.9 (40)</td>
</tr>
</tbody>
</table>

Morphinized I: subcutaneously morphinized, Morphinized II: intracisternally morphinized, ( ) Number of animals.

Apparently it is concluded from present results that blood-cerebrospinal fluid-barrier may not involved in the mechanisms of tolerance to the analgesic effect of morphine in mice.

These results lent further support to the idea that tolerance to the analgesic effect of morphine results in the cellular adaptation in the central nervous system (4-5).

Whether the discrepancy between Kase's results and ours may be due to the difference of the animal species or to the difference of the action of morphine is not clear at present.

REFERENCES


SIGNIFICANCE OF CALCIUM ION IN THE MORPHINE ANALGESIA

KOTOBUKI HANO, HIROSHI KANETO AND TAKEO KAKUNAGA

Department of Pharmacology, Faculty of Pharmacy, Osaka University, Toyonaka, Osaka

Received for publication May 16, 1964

At the 35th and 36th Annual Meeting of Japanese Pharmacological Society, we have reported the inhibition of potassium stimulated oxygen uptake of cerebral cortex slices by morphine and the...

羽野 勝・金戸 洋・角永 武夫