石燕碱甲对大鼠辨别学习和再现过程的影响

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摘要 用Y型迷宫实验，能Hup 100–167 μg/kg 很明显促进大鼠在明暗分划学习过程，ip 36–167 μg/kg 对该反应的记忆再现有显著性差异。海藻酸盐也有上述增效作用，其结果表明海藻酸盐能促进记忆再现

关键词 石燕碱甲，辨别学习，再现过程

石燕碱甲（hyperzine A，Hup）是从石燕科

石燕藻属植物千层塔 Hyperzia serrata（Thunb.）Trev. 中分离到的生物碱。该实验已证实，Hup 是一种强大的，可逆肌酸磷酸酯酶抑制剂，它对 AChE 的抑制作用比毒扁豆碱（Phys）等强，而毒性则低于 Phys。Hup 近十余年来，有关中枢肌酸磷酸酯酶抑制作用的临床和记忆增强作用对学习，记忆的影响已日益引起高度关注。本文研究

Hup 对大鼠辨别学习过程和记忆再现的促进作用，及其初步分析作用机理。

学习、记忆实验 三等分 Y 型迷宫箱系自

制。隔断直径为 4 mm 的隔断。通过脉冲

流（脉冲流调节度为 120 mm，脉冲周期

1.2 s，20-28 V），每隔 15 s 次教学，示

示空间（不设电击），安全区（局部电击），安全区的定位偏斜或隔

隔位方式改变。大鼠受电击后从起始区直接

通过安全区为 “正确反应”，其余均视为 “错误反

应”。大鼠学习和记忆成绩分别以其学习过程测试

时间达到练 5 或 10 次电击为 “正确反应”（各 5 次

或 10 次）的所需的电击次数（又称实验次数），

表内大鼠在训练过程中，完在学习和记忆实验中。

1. 选择：室内饲养，将大鼠放入迷路箱

内，观察其自发动活 3 min，然后给予电击至

其自发动活停止，立即关闭电击，选

自发动活活跃，对电击反应敏感并逃避迅速者

作为实验用大鼠。

2. 学习方法 大鼠在迷路箱内的一侧静

置 5 min，按隔断处给予灯光条件刺激 5 s，

继而以电击至其逃避至安全区，灯光继续作

用 5 s，然后熄灯休息 45 s。接着给予第二次

测试，依次重复测试至 10/10 标准。若大鼠

连续 30 次仍未达到此标准即停止实验。

3. 记忆恢复实验按模拟隔断法训练

大鼠，选取达到 S/5 标准前尝试次数为 5-20

次的大鼠，休息 48 h 后，再次同法测试。
### Table 1. Effects of anticholinesterase agents on the memory retrieval of a visual discrimination in rats. Drug was administered 20 min before test. (S x SD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Rats</th>
<th>Trials to criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>ip 9 g</td>
<td>1</td>
<td>12.2 ± 2.4</td>
</tr>
<tr>
<td>Huperzine A</td>
<td>ip 8 g</td>
<td>12.4 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>neostigmine</td>
<td>IP 5 g</td>
<td>12.2 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>salinexine</td>
<td>ip 8 g</td>
<td>12.2 ± 0.9</td>
<td></td>
</tr>
</tbody>
</table>

Significant differences were observed between the control and the experimental groups (p < 0.05).

### Results

Huperzine A and neostigmine at the doses of 0.08 and 0.02 mg/kg (1/30 and 1/100 LD50) were significantly effective compared with the control. The learning efficiency of rats treated with these drugs was significantly higher than that of the control group, and the differences were significant (p < 0.05).

### Discussion

The results show that Huperzine A and neostigmine have a pronounced memory enhancement effect in rats. These findings are consistent with previous studies, indicating that these compounds may have potential therapeutic applications in the treatment of cognitive disorders.

However, further research is needed to elucidate the mechanisms underlying these effects and to determine the optimal dose and administration route for clinical use.
表 1. Effects of scopalamine (Scop), atropine (Atrop) and hydroxypropyl bromide (MA) on hippocampal A (Hup) -induced facilitation of memory retrieval of a visual discrimination. (x ± SD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Rate</th>
<th>Trials to criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mg/kg)</td>
<td>Training</td>
<td>Test**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS + NS</td>
<td>1 ml + 1 ml</td>
<td>30</td>
<td>12.4 ± 6.0</td>
</tr>
<tr>
<td>Hup + NS</td>
<td>0.1 ml</td>
<td>16</td>
<td>11.4 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>0.2 ml</td>
<td>16</td>
<td>11.4 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml</td>
<td>8</td>
<td>12.0 ± 3.0</td>
</tr>
<tr>
<td>Hup + Scop</td>
<td>0.1 ml</td>
<td>8</td>
<td>12.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>0.2 ml</td>
<td>8</td>
<td>12.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml</td>
<td>8</td>
<td>12.5 ± 3.0</td>
</tr>
<tr>
<td>NS + MA</td>
<td>1 ml + 1 ml</td>
<td>8</td>
<td>12.3 ± 3.0</td>
</tr>
<tr>
<td>Hup + MA</td>
<td>0.1 ml</td>
<td>8</td>
<td>12.5 ± 3.0</td>
</tr>
</tbody>
</table>

Drugs were injected 20 min before test. *p < 0.05, **p < 0.01 as compared with NS (saline) + NS group.

讨论

左旋-麦角碱或许与学习，记忆功能密切相关。抗胆碱药对学习，记忆过程有促进作用，抗胆碱药，麦角碱类药物在视觉识别有促进作用。Hup 对 AChE 有选择性抑制作用，且对 AChE 的抑制作用比 MA 低。本文结果表明 Hup 在 1/10 的 MA 的 LD50 可以抑制大鼠学时一反馈反应的记忆过程，而麦角碱类药物对 1/10 的 LD50 测量才有效，故 Hup 的作用效果优于麦角碱类，因此可以认为 Hup 促进学习，记忆再现可被抗胆碱药 Scop。Atrop 以及 icv 静脉内 AChE 合成抑制剂使胆碱能传递，而用于外伤的 MA 则对 Hup 的作用无影响，这些结果表明，Hup 促进学习，记忆再现是通过脑内 AChE 的抑制，使 ACh 含量升高，达到激活血脑屏障通透性系统的功能有关。

作者之一：黄永元实验结果表明在视觉空间分辨的异常过程之后，也有报道在大鼠重复盆饲实验中，未观察到有任何影响**，与本文结果不一致，对于视觉空间分辨的研究结果，很难对此进行分析。我们在重复盆饲时观察到控制组未影响到时间因素，说明实验后的影响在不同实验中，虽然不同的实验方法和程序系是不包含一致的实验结果。

表 2. Reversal effect of hemicholinium-3 (HC-3) on hippocampal (Hup)-induced facilitation of memory retrieval of a visual discrimination. (x ± SD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Rate</th>
<th>Trials to criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mg/kg)</td>
<td>Training</td>
<td>Test**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS + NS</td>
<td>10 μl + 1 ml</td>
<td>6</td>
<td>11 ± 6.0</td>
</tr>
<tr>
<td>Hup + NS</td>
<td>0.1 ml</td>
<td>6</td>
<td>10 ± 6.0</td>
</tr>
<tr>
<td>HC-3 + NS</td>
<td>20 μl</td>
<td>6</td>
<td>11 ± 6.0</td>
</tr>
</tbody>
</table>

HC-3 was injected 30 min before test, a dose of Hup was administrated 10 min after HC-3, *p < 0.05, **p < 0.01 as compared with NS + NS control.
Techniques and basic experiments for the study of brain and behavior. 1st ed. Amsterdam: Elsevier, 1987: 115-61
Effects of huperzine A on learning and retrieval process of discrimination performance in rats

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ABSTRACT Huperzine A (Hup), a new alkaloid isolated from Huperzia serrata (Thunb.) Trev., has powerful and reversible anticholinesterase activity. Rats were placed on an electrified grid in a Y-maze and learned to run into the light arm (safe area). The criterion of learning or retrieval was met after they had chosen the light arm 10 trials in succession. Hup injected intraperitoneally with 100-167 μg/kg 20 min before training caused a significant decrease in the number of trials to criterion. Facilitation of retrieval was also produced dose-dependently at doses of 36-167 μg/kg ip. Scopolamine 0.2 mg/kg sc, atropine 5 mg/kg sc or hemicholinium 20 μg/10 μl icv antagonized the positive effects of Hup 0.1 mg/kg on retrieval process, but methyl-atropine (2 mg/kg sc) did not. Under the same conditions, physostigmine at doses of 80-180 μg/kg ip improved learning and retrieval processes, but quaternary cholinesterase inhibitor neostigmine (30 μg/kg, ip) did not.

Our results suggested that the facilitation actions of Hup were due to an effect on the central cholinergic system, especially the muscarinic system. Since M-receptor blockers reversed the actions of Hup, but their quaternary nitrogen derivatized methyl-atropine, which did not pass the blood-brain barrier, was inactive.

Besides, the preliminary clinical studies showed that Hup, the first nootropic compound in China, did improve short-term and long-term memory in patients of cerebral arteriosclerosis with memory impairment.

KEY WORDS huperzine A, physostigmine, scopolamine, atropine, hemicholinium 3; discrimination learning, memory, rats