强啡肽对离体动脉电场刺激诱发收缩的抑制效应

孙凤艳  张守方  张玲玲  丁桂平

<上海第一军医大学临床药理研究所，神经药理病区，上海 200032>

摘要

目的：观察阿片受体拮抗剂kappa类药物对离体电刺激诱发的血管收缩的抑制效果。

方法：用离体大鼠血管全段，置于Krebs液中，并添加0.5% CO_2和pH 7.4，移至测张机，每10 min记录血管张力变化，以促进血管张力的稳定。电刺激为125-30 V，脉冲宽度为5 ms，频率为1 600 Hz，每2 s记录一次，共进行6次记录。

结果：与电刺激前相比，电刺激后血管张力显著升高，而使用阿片受体拮抗剂kappa类药物后，血管张力明显下降，表明kappa类药物对离体电刺激诱发的血管收缩有显著的抑制作用。

结论：kappa类药物对离体电刺激诱发的血管收缩有明显的抑制作用，为临床治疗血管疾病提供了一种新的思路。
Fig. 1.  Inhibitory effects of dynorphin, + and enkephalin on contraction of rabbit ear arteries (A) and dog mesenteric arteries (B) induced electrically.

别为(± SD): 85.24% (p<0.001), 35.5% (p>0.001), 50 ± 29% (p>0.05). 28 ± 3% (p>0.05) 31 ± 8% (p>0.05). 对狗肱动脉上段的抑制率为 D₁₇, 59 ± 27% (p<0.001). ET-1. 60 ± 32% (p<0.001) 与 MT-5. 58 ± 28% (p<0.01). 而 DAME 和 DAME 失去作用意义. 但通过加敏收缩药的测试, 证明不显著, 以上激动剂的 IC₅₀ 如表 1.

阿片受体受体拮抗剂 NAL 对 D₁₇, DAME 和 MT-5 的抑制效果的抑制率分别为 23% (p<0.05), 52% (p<0.05) 和 75% (p<0.001). 同时, 对血管电场刺激收缩的抑制效果及 NAL 的部分抑制作用的记录图, D₁₇, 对去甲肾上腺素引起的收缩的作用 D₁₇,0.033 (mM) 能抑制, 也能抑制 NE (0.65 - 0.4 μM) 引起的收缩.

讨 论

本文报告了受体激动剂 D₁₇, 3 μM DAME 激动剂 DAME 和 DAME, 内源性 μ 受体激动剂 MT-5, 3 μM 与 ET 对血管舒张的作用. 对血管作用, D₁₇, 的抑制效果最强, DAME 中, 而 DAME 激动剂无明显作用. 而对支配血管作用, 也是 D₁₇, 的抑制效果最强, MT 与 DAME 另起作用. 由此可知, 除血管外还有 μ 和 δ 受体. 基于没有 μ 受体, 胺类药物中对有 μ 和 δ 受体, 从而对血管作用. 造出部分不改变功能的药物的种类不同. 其他受体也被认为与血管收缩.

NAL 同样作用于三种受体的拮抗剂 DAME, 作用效果分别为 50 μM 与 5 μM 的 NAL, 各种受体对血流有影响. μ 受体, 引起 NAL 与 NAL 4 μM 的 DAME, 5 μM 的 DAME, 3 μM 的 DAME, 3 μM 的 DAME.

在放射性分析中, DAME 仅减少. μ 受体 ET 与血流扩张膜的结合. 实验中, DAME 也影响血流的收缩, 提示血流上没有能与 DAME 结合的 μ 受体. 然而, DAME 明显

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Rabbit ear artery</th>
<th>Dog mesenteric artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynorphin-₁₇</td>
<td>0.055 ± 0.023 (n=7)</td>
<td>0.51 ± 0.26 (n=8)</td>
</tr>
<tr>
<td>Enkephalin</td>
<td>&gt;1 (n=5)</td>
<td>0.32 ± 0.16 (n=4)</td>
</tr>
<tr>
<td>DAME</td>
<td>1 (n=2)</td>
<td>1 (n=1)</td>
</tr>
<tr>
<td>DAME</td>
<td>&gt;1 (n=8)</td>
<td>&gt;1 (n=6)</td>
</tr>
<tr>
<td>Met-enkephalin</td>
<td>&gt;1 (n=2)</td>
<td>1 (n=1)</td>
</tr>
</tbody>
</table>
Fig 2. Effect of dynorphin, β or substance P on stimulation (25 V, 5-6 Hz, train of 5 pulses, 1 ms in pulse for 2.5 min) induced contraction of dog mesenteric artery and its response to norepinephrine. The final concentrations of dynorphin, β (D) and substance P (NAL) were 1 μM.

The effect of an axonally retained substance caused by sympathetic nerve activity is similar to that of a small local anesthetic, and it is effective even when the nerve is damaged. This suggests that dynorphin and substance P are released locally in the sympathetic nerve and act on the blood vessels. The effect of substance P is stronger in the presence of norepinephrine, suggesting that substance P enhances the effect of norepinephrine. This effect is not observed when the same dose of norepinephrine is applied to the artery, indicating that substance P acts directly on the blood vessels.

Inhibitory effects of dynorphin on electric field stimulation induced contraction of blood vessels in vitro

SUN Feng-yun, ZHANG An-zhong, ZHANG Lin-mei, YU Gui-hua

Dep't Acupuncture Research, Laboratory of Neuropharmacology, Shanghai First Medical College, Shanghai 200020

ABSTRACT The direct effects of opiate peptides on blood vessels were observed on rabbit ear arteries and dog mesenteric arteries isolated. The contraction of rabbit ear arteries induced by electric field stimulation was markedly inhibited by dynorphin, β - a kappa agonist, with an IC₅₀ of 0.083 μM (n = 7). Substance P - enkephalin was less effective (IC₅₀ = 1 μM, n =

Inhibitory effects of dynorphin on electric field stimulation induced contraction of blood vessels in vitro
and D-Ala³-D-Leu⁴-ENK, a delta agonist, or metenkephalin, a mu agonist, was ineffective with concentrations as high as 1 µM (n = 6 and 3, respectively). The stimulation-induced contraction of dog mesenteric arteries was reduced by dynorphin₁₋₇ (IC₅₀ = 0.51 µM, n = 8) and metenkephalin (IC₅₀ = 1.9 µM, n = 7), but was not affected by D-Ala²-Met⁵-ENK or D-Ala²-D-Leu⁴-ENK in concentrations up to 1 µM (n = 6 and 5, respectively).

Naloxone reversed effects of these opioid peptides with very different potencies, the order of the potencies was: metenkephalin > D-Ala²-Met⁵-ENK > dynorphin.

Dynorphin₁₋₇ (5 µM, n = 11) did not alter the basal tension of blood vessels, nor the contraction induced by norepinephrine (0.06–0.4 µM), both contractions were markedly inhibited by phenolamine, an α-adrenergic blocker.

These results suggest that opioids can directly act on opiate receptors (mainly kappa subtype) of blood vessel. Dynorphin reduces the stimulation-induced contraction of blood vessels probably by a presynaptic inhibition of norepinephrine release from nerve terminals.

**KEY WORDS**: blood vessel, endorphin receptor, enkephalins, dynorphin, norepinephrine