花生四烯酸对兔主动脉环的缩血管作用

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提要　保留完整内皮的兔主动脉环对花生四烯酸(AA)呈收缩反应，并有量-效依赖关系(ED_{50} = 12 μmol/L)。去内皮主动脉对低剂量AA无反应而对SQ 26655呈良好收缩反应。吲哚美辛只能部分地抑制大剂量AA所致收缩反应；BW 755 c对其有强大抑制作用。内皮对AA所致主动脉收缩有重要作用，该收缩反应与环氧化酶及脂氧化酶途径代谢产物有关。

关键词　花生四烯酸；　吲哚美辛；　阿司匹林；去氧肾上腺素；　血管收缩；　主动脉；　内皮

动脉血管对AA呈松弛反应，该反应依赖血管内皮的存在[1-3]。AA引起犬股动脉血管松弛系由于AA在内皮细胞中转变成PGI_2所致[4]。血管内皮细胞能产生有强大缩血管作用的TXA_2[5]。那么，血管对外源性AA是否会呈收缩反应，内皮细胞在该反应中有什么作用。本文的目的是观察有完整内皮及去内皮的兔主动脉对AA的反应在性质上的区别；松弛状态和预先收缩的主动脉对AA的反应是否不同；AA的环氧化酶及其他途径代谢产物对该反应的影响；去内皮后血管平滑肌细胞的TXA_2受体的反应性是否改变。

材料和方法

新西兰兔，♀♂兼用，体重2.5±SD 0.5 kg。耳缘静注空气致死，取降主动脉，剔除结缔组织，剪成宽3 mm的主动脉环，配对地分到实验组及对照组。操作中避免牵拉和接触动脉内表面，以保证血管内皮完整。另组实验，以机械摩擦方法有目的地除去血管内皮[6]。用电子显微镜验证除内皮的效果。

动脉环悬挂于两个吊环之间，置于含有7 ml Krebs-Henseleit溶液的浴管中，pH 7.4，供以95% O_2 + 5% CO_2，37±1℃，负荷5.2 g。实验前标本在溶液中至少平衡90 min，通过UCJO型换能器测定张力变化，用Radio Shark TRS 80电子计算机记录。

AA溶于乙醇制成贮备液－20℃保存，用时制成钠盐溶液。去氧肾上腺素(苯福林)注射液用生理盐水稀释到适当浓度。SQ 26655及吲哚美辛溶于乙醇。BW 755 c溶于蒸馏水。以上药品来自Sigma。浴管溶液中乙醇终浓度不超过0.1%(vol/vol)。

结　果

处于松弛状态具有完整内皮的主动脉环对AA(1-100 μmol/L)呈收缩反应，该反应呈量-效依赖关系，ED_{50} = 12 μmol/L(见图1，2)。

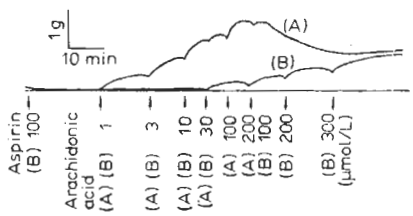

Fig 1. Rabbit aorta rings with intact intima showed contractile response to arachidonic acid (AA) in a dose-dependent manner. Aspirin (100 μmol/L) inhibited the contractile response induced by AA. (A) without aspirin, (B) with aspirin.

环氧化酶抑制剂吲哚美辛(10 μmol/L)及阿司匹林(100 μmol/L)可抑制AA引起的兔主动脉环收缩反应。低浓度AA(1－3 μmol/L)所致的收缩反应可被完全抑制，而高浓度(30 μmol/L)仍可引起强烈收缩反应。(见图2)

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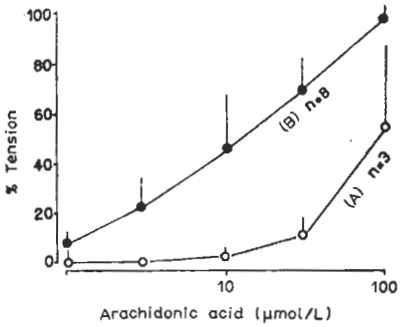

Fig 2. Dose-response curves for arachidonic acid in rings of rabbit aorta with intima in the presence (A) or absence (B) of indomethacin (10 μmol/L) $\bar{x}\pm SD$.

预先用去氧肾上腺素(0.1 μmol/L)使主动脉环处于收缩状态，然后给予AA(10 μmol/L)，未见松弛反应．相反，在原来收缩的基础上张力又增大．预先给予吲哚美辛(10 μmol/L)，对去氧肾上腺素所致收缩无影响，而对AA引起的收缩反应有明显抑制作用(见图3)．

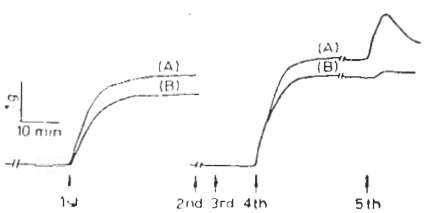

Fig 3. Additional contraction induced by arachidonic acid in the rings of rabbit aorta with intima precontracted with phenylephrine (PE),(A) an untreated ring, (B) a ring pretreated with indomethacin. lst ↑ and 4 th ↑ PE (0.1 μmol/L) was added to (A) and (B); 2nd ↑ the rings were washed with fresh medium; 3rd ↑ indomethacin (10 μmol/L) was added to (B); 5th ↑ arachidonic acid (10 μmol/L) was added to (A) and (B).

除去内皮的主动脉环对低浓度的AA(3 μmol/L)未显示任何反应，高浓度(30 μmol/L)仍可引起收缩反应(见图4)．

保留完整内皮和除去内皮的主动脉环对TXA_2受体激动剂SQ 26655均呈良好收缩反应，两者无明显差别(见图5)．

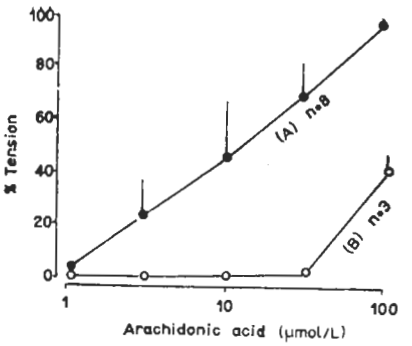

Fig 4. Dose-response curves for arachidonic acid in rings of rabbit aorta with (A) and without intima. $\bar{x}\pm SD$.

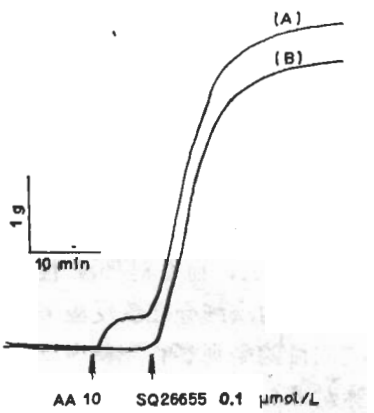

Fig 5. Comparison of SQ 26655 (0.1 μmol/L, TXA_2 receptor agonist) and arachidonic acid (10 μmol/L)-induced contractile response between rings of rabbit aorta (A) with and (B) without intima.

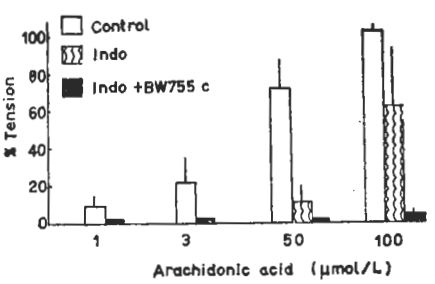

Fig 6. Inhibitory effects of indomethacin (10 μmol/L) and indomethacin (10 μmol/L) plus BW 755 c (30 μmol/L) on arachidonic acid-induced contraction in rabbit aorta rings.

吲哚美辛对高浓度 AA 引起的收缩反应有一定抑制作用，但收缩反应的幅度仍然很大。在吲哚美辛存在下，脂氧化酶抑制剂 BW 755c (30 μmol/L)对 AA 引起的收缩有强大抑制作用(见图 6)。

讨　论

实验证明松弛状态或预先用去氧肾上腺素收缩的兔主动脉对 AA 的反应在性质上是相同的，即呈收缩反应。该结果与文献(7)报道"AA 引起兔主动脉松弛"不同。是否本实验所用负荷较大而没观察到那样微小的松弛反应，有待探讨，但应指出，许多资料支持我们的结论。AA 在内皮细胞中可转变成 PGI_2 和 TXA_2[8]，前者虽有舒血管活性，但兔主动脉对其不敏感[9]，后者有缩血管活性。此外，实验表明兔主动脉有脂氧化酶代谢途径产物生成，绝大多数该途径产物具有缩血管活性[10,11]。本实验结果与上述文献是一致的。

去内皮主动脉丧失了对低浓度 AA(μmol/L)的反应性；只有带完整内皮的主动脉对 AA 呈量-效依赖关系的收缩反应。结果提示内皮细胞与 AA 引起的兔主动脉收缩有关，内皮细胞暴露于 AA 能产生刺激血管平滑肌收缩的物质。吲哚美辛能完全抑制低浓度 AA 所致兔主动脉收缩，证明生成的致收缩物质为 AA 的环氧化酶代谢途径产物。

去内皮主动脉对低浓度 AA 无反应，是否去内皮的操作损害了平滑肌细胞对 AA 的反应性。为此，比较了保留完整内皮和除去内皮的主动脉对 TXA_2 受体激动剂的反应，结果两者均呈良好收缩反应。去内皮只影响对 AA 的反应，而对 SQ 26655 的作用无妨碍，这不仅为解释内皮细胞对 AA 引起收缩反应的重要性提供了旁证，而且也证明去内皮后平滑肌上的 TXA_2 受体反应性没有改变。

环氧化酶抑制剂不能完全抑制高浓度 AA 对主动脉的收缩作用，很可能该收缩反应有相当大一部分来自环氧化酶途径以外的代谢产物。在吲哚美辛存在下，BW 755 c 能阻断高浓度 AA 所致的兔主动脉收缩。文献(12)指出，除血小板，白细胞及肺等，不是所有组织都存在脂氧化酶，而我们的实验结果提示兔主动脉壁也具有脂氧化酶，该酶代谢途径的产物能引起兔主动脉收缩。只有在高浓度 AA 的情况下，脂氧化酶途径产物才能生成。看来兔主动脉中脂氧化酶对底物 AA 不如环氧化酶敏感。

总之，兔主动脉内皮对 AA 引起的主动脉平滑肌收缩有重要作用。该收缩反应取决于 AA 的环氧化酶和脂氧化酶通路的代谢产物。

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Vasoconstrictive effect of arachidonic acid on aortic ring of rabbit

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ABSTRACT It has been demonstrated that rings of rabbit thoracic aorta with intact endothelium contracted in response to arachidonic acid (AA) in a dose-effect dependent manner (ED_{50} = 12 μmol/L). The contractile response by AA was inhibited by cycloxygenase inhibitor, indomethacin 10 μmol/L. Rings of rabbit aorta in precontracted state affected by phenylephrine Showed an additional contraction in response to AA.

Rabbit aorta without endothelium did not show any response to AA (1 μmol/L). Aorta with or without endothelium contracted to the same extent in response to thromboxane A_2 receptor agonist, SQ 26655 (0.1 μmol/L). The contraction caused by AA 10 μmol/L was not completely inhibited by indomethacin or aspirin, but was inhibited by a lipoxygenase inhibitor, BW 755 c 30 μmol/L.

We conclude that the intact endothelium of aorta is greatly responsible for the contraction of smooth muscle of rabbit aorta by AA, and the contraction of aorta by AA is mediated by cycloxygenase and lipoxygenase metabolites.

KEY WORDS arachidonic acids; indomethacin; aspirin; phenylephrine; vasoconstriction; aorta; endothelium

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