

•实验研究•

[文章编号] 1007-3949(2000)-02-0118-03

移植胚鼠弓状核细胞后对动脉粥样硬化形成的影响

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[关键词] 动脉粥样硬化; 弓状核; 移植; 细胞悬液; 大鼠;

[摘要] 为进一步证实毁损弓状核可诱发动脉粥样硬化的早期变化这一作用, 用毁损弓状核诱发动脉粥样硬化早期变化后, 重新植入胚鼠弓状核细胞悬液来观察动脉壁的变化是否能得以恢复。实验用新生 Wistar 大鼠 18 只, 按出生后 1、3、5、7、9 天皮下注射 10% 谷氨酸单钠 4 g/kg 体重, 共注射 5 次, 为毁损弓状核诱发动脉粥样硬化动物模型, 存活 30 天后, 取 6 只动物主动脉作为对照组 iv, 另 12 只动物分为实验组和对照组 ㊟。实验组在弓状核区重新植入 14 天胚鼠弓状核细胞悬液 5 μ L (细胞浓度为 1×10^{15} /L), 对照组 ㊟植入等量生理盐水继续存活 30 天后各取主动脉作电镜观察。结果发现: 对照组 iv 动物主动脉壁内皮细胞腔面可见微绒毛样突起, 内皮细胞核有些扭曲, 不规则, 内皮下层未见增厚; 对照组 ㊟动物内皮细胞变性、脱落, 内皮下层明显增厚, 出现许多大小不等的空泡和胶原纤维, 有巨噬细胞和平滑肌细胞迁入内皮下层, 这些变化是动脉粥样硬化发病的早期特征性病变; 实验组动物内皮细胞核完整, 内皮与内皮下层连接紧密, 偶尔可见内皮细胞核扭曲。实验证明, 在被毁损弓状核区重新植入胚鼠弓状核细胞后对动脉粥样硬化有明显恢复作用, 从而证实下丘脑弓状核对动脉粥样硬化的形成具有重要调控作用。

[中图分类号] R363.2

[文献标识码] A

Influence of Transplanted Embryonic Arcuate Nucleus in Destroyed Nucleus on Atherosclerosis

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MeSH Atherosclerosis; Arcuate Nucleus; Transplant; Cell Suspension; Rat

ABSTRACT **Aim** It has been proved in our previous work that destruction of arcuate nucleus could induce early atherosclerosis. In order to further research into the influence of hypothalamic arcuate nucleus on the development of atherosclerosis, this study was to investigate whether the transplantation of cell suspension of arcuate nucleus into the destroyed nucleus would act on the recovery of atherosclerosis. **Methods** Eighteen new born Wistar rats injected with monosodium glutamate (MSG) 4 g/kg hypodermically once every other day for 5 d were used as induced atherosclerosis model. After surviving for 30 d, six animals sacrificed with their aorta taken serve as control group iv. The other 12 animals were equally divided into experiment group and control group ㊟. The experimental group were transplanted with 5 μ L cell suspension (1×10^{15} /L) of arcuate nucleus from 14 d embryo and control group ㊟ were given equal volume of normal saline. After surviving for another 30 d, the aorta of these animals were made ultrathin section and investigated under electromicroscope. **Results** In control group iv (arcuate nucleus damaged by MSG for 30 d), microvillous projections of endothelial cells were observed on the luminal surface and the nuclei of the endothelial cells became twisted and irregular, but without thickening of subendothelial tissue. In control group ㊟ (arcuate nucleus damaged by MSG for 60 d), degeneration of endothelial cells could be seen and some endothelial cells had fallen off. The subendothelial tissue was evidently thickened with a few collagenous fibers, vesicles of various size and macrophage or smooth muscle cells migrated from blood and tunica media through the ruptured elastic intima, indicating characteristic changes of early atherosclerosis. In the experimental group (transplanted with embryonic arcuate nucleus), the endothelial cells remained intact, and connected tightly with subendothelial tissue, occasionally twisted nucleus could be seen. **Conclusions** This experiment indicate that transplanted arcuate nucleus in the destroyed nucleus has notably made the animal recovery from atherosclerosis and thereby confirms that hypothalamic arcuate nucleus has influence on development and/or control of atherosclerosis.

[基金项目] 国家自然科学基金(39660031)及江西省自然科学基金资助项目

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对动脉粥样硬化(atherosclerosis, As) 的研究已经历了一百多年, 但对其发病机理仍未完全明了。以往对 As 发病机理的研究, 基本上都是有是围绕血管本身病变的过程而提出的, 而对下丘脑血管中枢是否对 As 的形成具有调控作用很少有人提出过。70 年代前苏联 Zavodskaja 等^[1]用电长期刺激家兔下丘脑可引起高脂血症和 As 形成; 1983 年王天保等^[2]报道破坏下丘脑使冠状动脉粥样硬化加重; 1997 年日本 Nishida 等^[3]报道在特发糖尿病大鼠内, 通过损伤下丘脑可诱发 As 早期变化。在我们以前的研究工作中证实用不同方法毁损下丘脑弓状核后可诱发 As 早期病变^[4,5], 以及与 As 形成密切相关的物质(如总胆固醇、氧化型低密度脂蛋白、脂质过氧化物、一氧化氮等) 都发生了明显改变^[6,7]。为了进一步证实下丘脑弓状核对 As 形成的影响, 本文用毁损弓状核诱发 As 早期病变后, 重新植入胚鼠弓状核细胞悬液来观察 As 的变化是否得到恢复。力求为阐明下丘脑弓状核与 As 形成之间的关系提供有力证据。

1 材料与方法

选新生 Wistar 大鼠 18 只, 按出生后第 1、3、5、7、9 天背部皮下注射 10% 谷氨酸单钠(monosodium glutamate, MSG) 4 g/kg 体重, 共注射 5 次^[4], 为毁损弓状

核诱发 As 动物模型, 存活 30 天(喂饲大鼠普通饲料) 后, 取 6 只动物的主动脉作为对照组 iv, 另 12 只动物分为实验组和对照组 ⑤, 每组 6 只动物, 实验组按照 Pellegrino 图谱 A 系统, 固定于立体定位仪后, 向下丘脑弓状核区(坐标为 A 5. 6, L 和 R 0. 5, H 9. 0) 插入直径为 0. 1 mm 绝缘针管(针管的末端是非绝缘的), 植入 14 天胚鼠弓状核细胞 5 μ L(细胞浓度为 1×10^5 /L), 对照组 ⑤注入等量生理盐水, 两组动物在同一条件下继续存活 30 天(喂饲大鼠普通饲料) 后各取主动脉作电镜观察。

2 结果

对照组 iv(注射 MSG 后 30 d), 主动脉壁内皮细胞腔面可见微绒毛样突起, 内皮细胞核有些扭曲, 不规则, 内皮下层未见增厚(图 1, Figure 1); 对照组 ⑤(注射 MSG 后 60 d) 动物血管壁内皮细胞变性、脱落, 内皮下层明显增厚, 出现许多大小不等的空泡和增生的胶原纤维, 有巨噬细胞和平滑肌细胞迁入内皮下层, 这些变化是 As 早期的特征性病变(图 2, Figure 2); 实验组(注射 MSG 30 d 后植入胚鼠弓状核) 动物血管壁内皮细胞核完整, 内皮与内皮下层连接紧密, 偶尔可见内皮细胞核扭曲(图 3, Figure 3)。

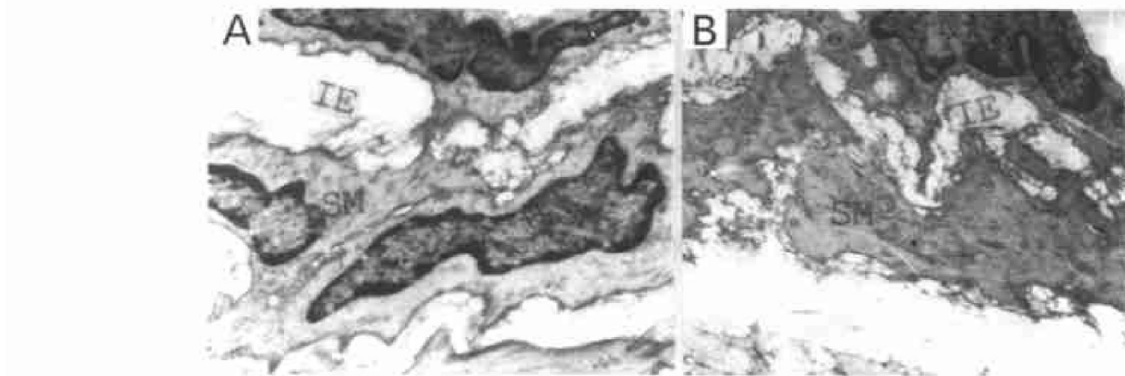


图 1. 对照组 iv 动物注射谷氨酸单钠后 30 天的电镜观察

Figure 1. Electron micrograph (EM) of 30 d after arcuate nucleus being damaged by MSG. Short projections on the luminal surface of endothelial cells are present, the nuclei of the endothelial cells become twisted. A: $\times 6\ 000$; B: $\times 6\ 000$

3 讨论

我室从 1994 年开始对 As 发病的“中枢机理”进行了一些探索性研究, 用不同方法毁损下丘脑弓状核后主动脉壁内皮细胞发生变性, 细胞核肿胀, 内皮下层增厚并出现空泡, 可见有平滑肌细胞向内皮下层迁移, 这些变化是 As 早期发病的特征性病变^[4,5]。此外, 血液中与 As 形成密切相关的物质也发生变

化, 如毁损弓状核后总胆固醇(TC)、氧化型低密度脂蛋白(ox-LDL)和脂过氧化物(LPO)均升高, 而一氧化氮(NO)则下降, 与用药物诱发 As 的变化极为相似^[6,7]。从我们以前的研究结果来看, 下丘脑弓状核对 As 形成可能具有重要影响。

如果这一结果进一步得到证实的话, 对中枢发病机理的假说将提供重要证据。因此, 为了进一步证实下丘脑弓状核对 As 的形成是否具有重要影响,

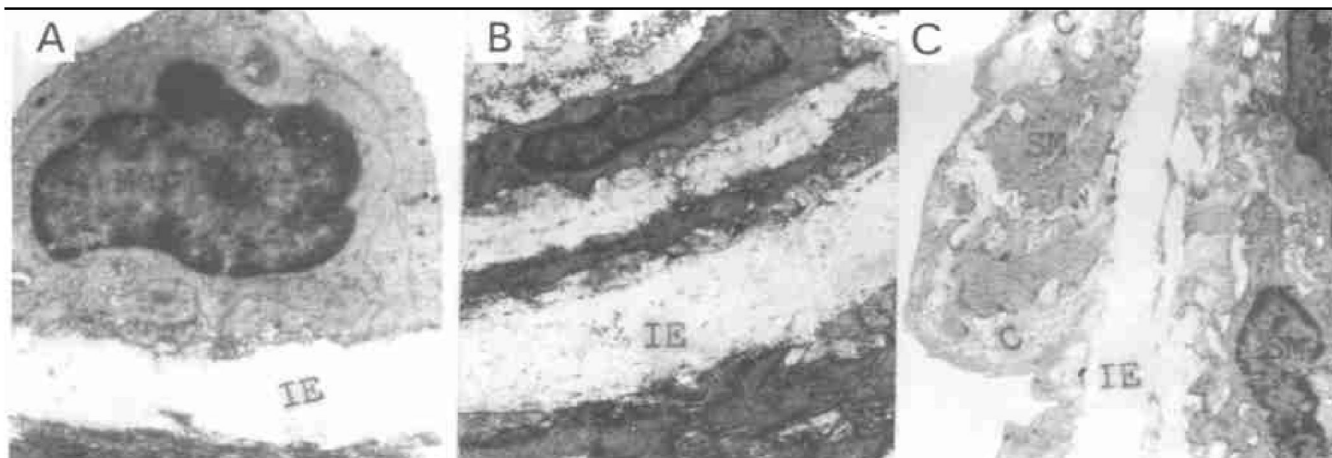


图 2. 对照组 ①动物注射谷氨酸单钠 60 天后电镜观察

Figure 2. EM of 60 d after arcuate nucleus being damaged by MSG. Egeneration of endothelial cells could be seen and some as the endothelial cells had fallen off. The subendothelial tissue was evidently thickened with macrophages or smooth muscle cells migrated from blood and tunica media. A: $\times 9\ 000$; B: $\times 4\ 800$; C: $\times 3\ 000$.

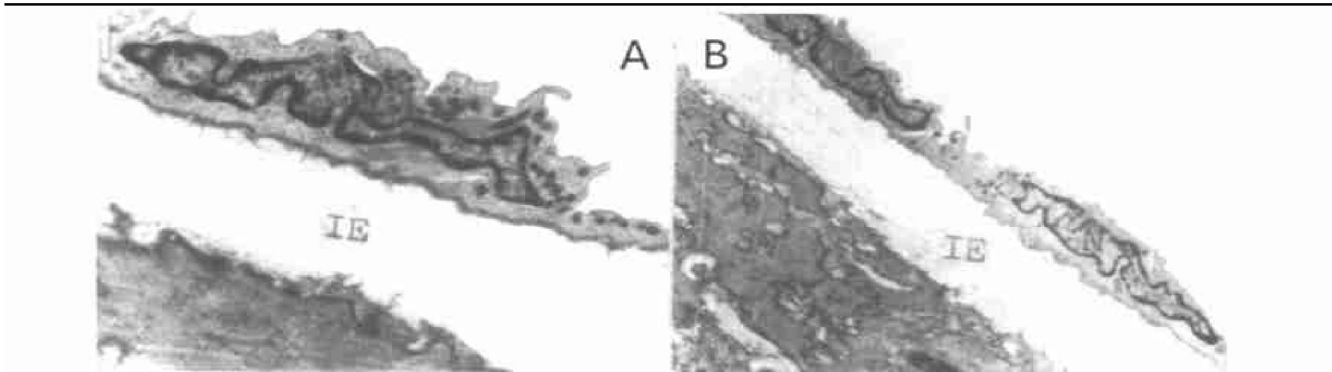


图 3. 实验组动物注射谷氨酸单钠 30 天后植入胚鼠弓状核的电镜观察

Figure 3. EM of transplanted with embryonic arcuate nucleus after arcuate nucleus being damaged by MSG for 30 d. The endothelial cells remained intact, and connected tightly with subendothelial tissue, occasionally twisted nucleus could be seen. A: $\times 9\ 000$; B: $\times 3\ 600$.

本文用毁损弓状核诱发 As 早期病变后,重新植入胚鼠弓状核细胞悬液来观察 As 变化是否得到恢复。本文结果表明注射 MSG 后 30 d,对照组主动脉血管壁内皮细胞腔面可见微绒毛样突起,内皮细胞核有些扭曲,不规则,内皮下层未见明显增厚;注射 MSG 后 60 d 对照组,内皮细胞变性、脱落,内皮下层明显增厚,出现许多大小不等的空泡和胶原纤维,有巨噬细胞和平滑肌细胞迁入内皮下层,这些变化是 As 早期特征性病变;实验组(注射 MSG 30d 后植入胚鼠弓状核),内皮细胞核完整,内皮与内皮下层连接紧密,偶尔可见内皮细胞核扭曲。本文结果证明在被毁损弓状核区重新植入胚鼠弓状核对 As 有明显恢复作用,从而为证实下丘脑弓状核对 As 的形成具有重要调控作用提供了可靠证据,但其调控是通过何种物质来实现?其通路如何?需进一步深入研究。

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(此文 1999- 08- 08 收到, 2000- 04- 26 修回)

(此文编辑 胡必利)