中国病理生理杂志 2007 23 (12): 2336-2340 ISSN: 1000-4718 CN: 44-1187/R

论著

高同型半胱氨酸诱导血管内皮功能障碍促进微循环障碍和微血栓形成

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收稿日期 2007-4-18 修回日期 2007-8-26 网络版发布日期 2008-8-29 接受日期 2007-8-26

摘要 目的：采用蛋氨酸灌胃复制高同型半胱氨酸血症(hyperhomocysteinemia,HHcy)致内皮功能障碍,在此基础上，联合脂多糖（lipopolysaccharide，LPS）和角叉菜胶（carrageenan，Ca）造成大鼠体内广泛微血栓形成，观察血管内皮损伤和功能障碍对大鼠体内微血栓形成的促进作用。方法：①内皮损伤模型的建立。SD大鼠随机分为对照组（control）、内皮功能障碍组（HHcy）。HHcy组采用蛋氨酸灌胃4周复制HHcy致内皮功能障碍模型，对照组以等量纯净水灌胃。4 周后检测血浆同型半胱氨酸（homocysteine，Hcy）水平，并取大鼠胸主动脉段进行血管舒张功能检测，同时检测血浆一氧化氮（NO）和血管性假血友病因子（von Willebrand factor，vWF）水平，以评价血管内皮功能状况。②Ca/LPS诱导微血栓形成。SD大鼠随机分为对照组（control）、微血栓组（Ca/LPS）、内皮功能障碍加微血栓组（HHcy＋Ca/LPS）。Ca/LPS组大鼠腹腔注射Ca，16 h再腹腔注射LPS。注射LPS 20 h后心脏采血检测凝血功能和血小板计数，镜下观测肠系膜微循环，24 h大鼠颈动脉采血结束实验，检测血浆NO和vWF值。对照组腹腔注射等量生理盐水，检测指标同模型组。HHcy＋Ca/LPS组大鼠经蛋氨酸灌胃持续4周后，再按照上述方法注射Ca/LPS，观察内皮功能障碍对大鼠微循环障碍和微血栓形成的影响。结果： ①蛋氨酸灌胃4周导致HHcy,血浆vWF水平显著升高，NO水平降低，内皮依赖性血管舒张功能显著降低，提示血管内皮功能受损，大鼠内皮功能障碍模型复制成功。②Ca/LPS组肠系膜微循环可见广泛微血栓形成，注射LPS后20 h ，通过检测凝血指标可见血液处于高凝状态。而与之比较，HHcy＋Ca/LPS组微循环障碍进一步加强，血小板计数减少，血浆NO值降低，vWF升高；注射LPS 20 h后可见血液处于继高凝状态之后的消耗性低凝状态。结论： 蛋氨酸灌胃4周导致HHcy,诱导血管内皮功能障碍。联合Ca/ LPS 造模可建立微循环障碍和微血栓形成的动物模型，而内皮功能障碍能加速加重微循环障碍和微血栓形成。

关键词 内皮,血管 血栓形成 蛋氨酸 角叉菜胶 脂多糖类
分类号 Q463 R364.1

Hyperhomocysteinemia induces endothelial dysfunction and aggravates microcirculation dysfunction and microthrombosis

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Abstract

<FONT face=Verdana>AIM: To establish a microthrombus model by carrageenan (Ca)/ lipopolysaccharides (LPS) intraperitoneal injection in rats with hyperhomocysteinemia (HHcy) and endothelial dysfunction induced by L-methionine intake.
METHODS: ① Male Sprague Dawley rats were randomly divided into 2 groups: control and endothelial dysfunction (HHcy) groups.
 L-methionine was administered by gavage in HHcy group for total 4 weeks.Purified water was administered by gavage in control rats.Plasma Hcy,NO and vWF were examined and the thoracic aorta were excised after 4 weeks of L-methionine treatment to evaluate endothelial function.② Male Sprague Dawley rats were randomly divided into 3 groups to establish a microthrombus formation model with Ca/ LPS: control,microthrombus formation (Ca/LPS) and endothelial dysfunction plus mitoarothrombus formation (HHcy＋Ca/LPS) groups.Control rats were injected with normal saline (NS).Ca/LPS rats were intraperitoneally injected with carrageenan

(Ca) and followed by lipopolysaccharides (LPS) 16 h later.HHcy＋Ca/LPS rats were intragastric gavaged by L-methionine for total 4 weeks,and then were injected with Ca/LPS in the same way as Ca/LPS group.Cruor parameters and platelet count were detected at 20 h after LPS or NS injection and the mesentery microcirculation was monitored.Plasma NO and vWF were also detected at 24 h after LPS or NS injection.
RESULTS: ① Plasma Hcy concentrations and vWF level were significantly increased in HHcy group,while plasma NO content was significantly decreased compared with that in control group.Endothelial dependent relaxation (EDR) of aortic rings was significantly decreased in HHcy group,suggesting endothelial damage/dysfunction was induced by HHcy.② Mesentery capillary was obviously blocked by microthrombus in Ca/LPS rats and was blocked more seriously in HHcy＋Ca/LPS rats.Cruor parameter results suggested that Ca/LPS rats were in hypercoagulable phase and HHcy＋Ca/LPS rats were in hypocoagulable phase at 20 h after LPS injection.Platelet count and plasma NO content in HHcy＋Ca/LPS group were significantly decreased,while plasma vWF level was significantly increased compared with Ca/LPS group.
CONCLUSION: L-methionine intake induces severe HHcy and causes endothelial dysfunction in rats.Microcirculation dysfunction and microthrombosis can be caused by Ca/LPS intraperitoneal injection and may be aggravated by endothelial dysfunction.</FONT>

Key words Endothelium vascular Thrombosis Methionine Carrageenan Lipopolysaccharides

DOI: 1000-4718

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