DOI:10.16016/j.1000-5404.1996.03.023
第18卷第3期 第三军医大学学报 Vol,18,No.3
240 1996年6月 ACTA ACADEMIAE MEDICINAE MILITARIS TERTIAE Jun.1996

一氧化氮对内毒素血症大鼠肠道的保护作用

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提 要 用一氧化氮(NO)合酶底物左旋精氨酸和其特异性抑制剂硝基左旋精氨酸对比观察两者对内毒素血症大鼠肠道损伤的影响。结果表明抑制NO合成可加重内毒素引起的肠道微血管损伤和肠粘膜上皮损害,而促进NO合成则可减轻上述改变。提示在本实验条件下,NO对内毒素血症大鼠的肠道损伤有一定的保护作用。

关键词 一氧化氮;肠道;内毒素血症
中图法分类号 R826.65;R656

一氧化氮(NO)是近几年来发现的一种新的细胞信息分子,具有广泛的生物学作用[1]。文献[2,3]报道NO在内毒素/感染性休克中具有重要的病理生理意义。但目前有关NO的研究多集中在循环系统,而对其在组织损伤中的作用研究较少。笔者用NO合酶的底物左旋精氨酸(L-arg)和其特异性抑制剂硝基左旋精氨酸(LNNA)从正反两方面探讨NO对内毒素血症大鼠肠道损伤的影响。

1 材料与方法

1.1 动物分组及处理

健康Wistar大鼠118只,雌雄不拘,体重180~230 g,随机分为4组:①对照组(C,$n=6$):1 ml/kg生理盐水ip.;②内毒素血症组(L,$n=40$):10 mg/kg内毒素($O_{111}B_4$)ip.;③内毒素+LNNA组(LN,$n=32$):10 mg/kg内毒素+4 mg/kg LNNA ip.;④内毒素+L-arg组(LA,$n=40$):40 mg/kg L-arg+10 mg/kg内毒素ip..各组动物(除C组外)于给药后2、4、8、12和24 h分批活杀(每时相点8只),取血浆及肠组织待测。取24 h肠组织做病理检查(LN组因24 h全部死亡,故取12 h肠组织)。

1.2 测定指标及方法

血浆NO稳定代谢产物NO_2^-/NO_3^-按文献[4]方法经镉柱还原后,用Greiss试剂测定。肠组织二氨氧化酶(DAO)活性按文献[5]方法测定。伊文氏蓝(EB)及丙二醛(MDA)含量按常规方法测定。肠道病理学改变按常规石蜡包埋切片,光镜观察。

1.3 数据处理

所有数据以平均值±标准差($\bar{x}\pm s$)表示,用t检验进行统计分析。

2 结果

2.1 血浆NO_2^-/NO_3^-浓度改变(见附表)

L组血浆NO_2^-/NO_3^-浓度自2 h起明显高于C组($P<0.05\sim0.01$);LN组则明显低于C组($P<0.05$);LA组各时相点均显著高于C、L和LN组($P<0.05\sim0.01$)。

附表 血浆NO_2^-/NO_3^-的改变(μmol/L)

Table The changes of plasma NO_2^-/NO_3^- (μmol/L)

Groups	Time (h)				
	2	4	8	12	24
L	2.66±1.25^{+}	5.04±2.49^{++}	6.49±3.87^{++}	7.99±3.62^{++}	5.56±3.16^{+}
LA	2.41±1.04^{+}**	5.44±2.25^{++}**	9.02±2.75^{++}**	11.16±4.44^{++}**	9.23±3.70^{++}
LN	0.83±0.36$^{\#}$	0.96±0.47$^{\#\#}$	1.05±0.78$^{\#\#}$	1.35±0.85$^{\#\#}$	—
C	—	—	1.05±0.37	—	—

+:$P<0.05$ *vs* C,++:$P<0.01$ *vs* C;**:$P<0.01$ *vs* LN;#:$P<0.05$ *vs* L,##:$P<0.01$ *vs* L

2.2 肠组织EB含量改变(图1-A)

L组自8 h起明显高于C组($P<0.05$);LN组升高更为明显,4 h即明显高于C和L组($P<0.05$);而LA组升高则不明显,12 h还显著低于L组($P<0.05$)。

2.3 肠组织DAO活性改变(图1-B)

L组自4 h起DAO活性明显降低($P<0.05\sim0.01$);LA组仅24 h才显著低于C组($P<0.05$);LN组自2 h起DAO活性即明显低于C组($P<0.05\sim0.01$),4 h后还显著低于LA组($P<0.05$)。

2.4 肠组织MDA含量改变(图1-C)

L组和LN组肠组织MDA均明显升高,LN组更为明显,4 h后明显高于L组($P<0.05$);LA组各时相点均低于LN组

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用，同时引起肠道出血及粘膜上皮脱落。上述结果均说明NO对肠道具有保护作用，其机理目前认为可能与NO抑制白细胞聚集和抗自由基作用有关[11]。

有学者认为使用NO抑制剂有利于脓毒症的治疗，其依据是抑制NO可升高血压，但他们的研究对NO抑制对组织损伤的影响涉及很少[2,12]。我们的实验结果表明抑制NO不仅加重肠道损伤，且对动物的转归不利（另文报道）；而且近年来较多文献报道抑制NO虽可升高血压，但对休克的转归均有不利影响[13,14]。由此可见，关于NO抑制剂对休克的利弊尚有争议，但其原因不清楚，尚待进一步研究。

参考文献

1 Kuo PC, Schroeder RA. The emerging multifaceted roles of nitric oxide. Ann Surg, 1995; 221: 220

2 Mitada C, Hirata Y, Ichikawa K *et al*. Effects of nitric oxide synthase inhibitor on hemodynamic changes and O_2 delivery in septic dogs. Am J Physiol, 1995; 268: H2017

3 Palmer RMJ. The discovery of nitric oxide in the vessel wall: a unifying concept in the pathogenesis of sepsis. Arch Surg, 1993; 128: 396

4 Hegesh E, Shiloah J. Blood nitrates and infantile hemoglobinemia. Clin Chim Acta, 1983; 125: 107

5 Hosada N, Nishi M, Madagawa M *et al*. Structural and functional alterations in the gut of parenterally enterally fed rats. J Surg Res, 1989; 47: 129

6 Star RA. Nitric oxide. Am J Med Sci, 1993; 306: 348

7 Forstermann U, Closs EI, Pollock JS *et al*. Nitric oxide synthase isozymes: characterization, purification, molecular cloning, and functions. Hypertension, 1994; 23 [part 2]: 1121

8 Bragg LE. Intestinal diamine oxidae levels reflect ischemia injury. J Surg Res, 1991; 50: 228

9 Kubes P, Granor N. Nitric oxidc modulates microvascular permeability. Am J Physiol, 1992; 262: H611

10 Hutcheson IR. Whittle BJR, Boughton-Smith NK. Role of nitric oxide in maintaining vascular integrity in endotoxin-induced acute intestinal damage in the rat. Br J Pharmacol, 1990; 101: 815

11 Cooke JP, Tsao PS. Cytoprotective effects of nitric oxide. Circulation, 1993; 88: 2451

12 Schilling J, Cakmakeci M, Battig U *et al*. A new approach in the treatment of hypotension in human septic shock by NG-monomethyl-L-arginine, an inhibitor of the nitric oxide synthase. Intensive Care Med, 1993; 19: 227

13 Minnard EA, Shou J, Naama H *et al*. Inhibition of nitric oxide synthesis is detrimental during endotoxemia. Arch Surg, 1994; 129: 142

14 Fukatsu K, Saito H, Fukushima R *et al*. Detrimental effects of a nitric oxide synthase inhibitor (N-ω-nitro-L-arginine-methyl-ester) in a murine sepsis model. Arch Surg, 1995; 130: 410

（收稿：1995-09-24；修回：1996-05-27）

（编辑 仇玉福）

Study of protective effects of nitric oxide on intestines during endotoxemia in rats

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Abstract The protective effects of nitric oxide (NO) on endotoxin-induced intestinal damages were observed in rats after the rats with endotoxemia were treated with L-arginine, the substrate of NO synthase, and LNNA, a specific inhibitor of NO synthase. Plasma NO_2^-/NO_3^-, intestinal content of Evan's blue (EB) and malondialdehyde (MDA) and the activity of diamine oxidase (DAO) were determined. It was found that the intestinal content of EB and MDA was increased, the activity of DAO decreased and the intestinal mucosal damages intensified which implies that the endotoxin-induced damages of intestinal microvascular permeability and intestinal mucosa were aggrevated because of the inhibition of NO synthesis. The administration of L-arginine promoted the synthesis of NO and the endotoxin-induced intestinal damages were attenuated markedly. It is believed that NO exerts protective effects on the intestines during endotoxemia.

Key words nitric oxide; intestine; endotoxemia

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