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阿霉素注射剂量对肾病综合征大鼠脂蛋白脂酶和卵磷脂胆固醇酰基转移酶水平的影响*

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摘要 目的:探讨阿霉素注射剂量对肾病综合征(nephrotic syndrome, NS)大鼠脂蛋白脂酶和卵磷脂胆固醇酰基转移酶(Lecithin cholesterol acyltransferase, LCAT)水平的影响。**方法:**64只SD大鼠随机分为四组-对照组、小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组,四组大鼠经尾静脉一次性注射阿霉素0 mg/kg、2 mg/kg、4 mg/kg、8 mg/kg,检测造模后不同时间点大鼠肾脏脂蛋白脂酶和卵磷脂胆固醇酰基转移酶水平变化情况。**结果:**小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后7 d、14 d、21 d的体重与每日采食量、血肌酐与尿素氮都低于对照组($P<0.05$),24 h尿蛋白高于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后21 d、28 d的肾脏脂蛋白脂酶和卵磷脂胆固醇酰基转移酶相对表达水平低于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。**结论:**小剂量阿霉素可抑制大鼠肾脏脂蛋白脂酶和卵磷脂胆固醇酰基转移酶的表达,能快速有效建立肾病综合征大鼠模型,具有很好的模拟造模效果。

关键词:阿霉素;注射剂量;肾病综合征;大鼠模型;脂蛋白脂酶;卵磷脂胆固醇酰基转移酶

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Effect of Doxorubicin Injection Dose on the Levels of Lipoprotein Lipase and Lecithin Cholesterol Acyltransferase in Nephrotic Syndrome Rats*

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ABSTRACT Objective: To investigate the effects of doxorubicin injection on the levels of lipoprotein lipase and lecithin cholesterol acyltransferase (LCAT) in rats with nephrotic syndrome (NS). **Methods:** Sixty-four SD rats were randomly divided into four groups, namely: matched group, low-dose adriamycin group, medium-dose adriamycin group and high-dose adriamycin group. The four groups of rats were injected with adriamycin through the tail vein at one time at 0 mg/kg, 2 mg/kg, 4 mg/kg, 8 mg/kg, the changes in rat kidney lipoprotein lipase and LCAT levels were detected at different time points after modeling. **Results:** The body weight, daily feed intake, blood creatinine and urea nitrogen of the low-dose doxorubicin group, medium-dose doxorubicin group and high-dose doxorubicin group were lower than those of the matched group ($P<0.05$) at 7 d, 14 d, 21 d after modeling, the 24 h urine protein were higher than that of the matched group ($P<0.05$), and there were adose-dependence, the difference compared among the three groups were statistically significant ($P<0.05$). The relative expression levels of renal lipoprotein lipase and lecithin cholesterol acylase in the low-dose doxorubicin group, medium-dose doxorubicin group, and high-dose doxorubicin group were lower than those in the matched group at 21 d and 28 d after modeling ($P<0.05$). and there were dose-dependence, the difference compared among the three groups were statistically significant ($P<0.05$). **Conclusion:** A small dose of doxorubicin can inhibit the expression of lipoprotein lipase and LCAT in rat kidneys, and can quickly and effectively establish rat model of nephrotic syndrome with good simulation effect.

Key words: Adriamycin; Injection dose; Nephrotic syndrome; Lipoprotein lipase; Rat model; Lecithin cholesterol acyltransferase

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前言

NS是由多种原因引起肾小球基底膜通透性增高的临床疾

病,目前具体的发病机制未明确,涉及到免疫失调、基因表达异常、糖脂代谢异常等^[1,2]。NS多见于儿童及青少年,病变类型多为微小病变型NS,病理表现为弥漫性肾小球脏层上皮细胞

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足突消失或融合为主,多以糖皮质激素治疗为主,但是长期使用糖皮质激素对患者身心健康有一定的负面影响,为此早期预防与明确 NS 的发生因素具有重要价值^[3,4]。阿霉素肾病动物模型为比较常见与经典的 NS 模型,能够很难模拟人类慢性肾脏病的发生与发展过程,被广泛应用于肾病研究领域,当前对于注射剂量方面还有待商榷^[5]。NS 患者多伴有血脂代谢异常,主要表现为高密度脂蛋白胆固醇 (high-density lipoprotein cholesterol, HDL-C) 水平降低,使得胆固醇在动脉壁沉积,可导致机体出现血管粥样硬化^[6,8]。相关研究显示:血浆中大部分胆固醇酯的合成依靠 LCAT,具有抗动脉粥样硬化等作用,可参与胆固醇逆转运的血管内阶段,后者可调节动脉粥样硬化形成和发展^[9-11]。本文具体探讨了阿霉素注射剂量对 NS 大鼠脂蛋白脂酶和 LCAT 水平的影响,旨在进一步明确阿霉素的最佳造模使用剂量。

1 材料与方法

1.1 研究材料

清洁级健康雄性 64 只 SD 大鼠购自南京君科生物工程有限公司(批号:SCXK2021-83814),鼠龄 8~10 周,体重(220±25)g,饲养于本院实验动物中心。所有大鼠自由饮水与饮食。

1.2 动物分组与造模

32 只 SD 大鼠适应性喂养 1 周后随机平分为 4 组,即:对照组、小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组。四组大鼠经尾静脉一次性注射阿霉素 0 mg/kg、2 mg/kg、4 mg/kg、8 mg/kg,注射过程中严格预防感染。

1.3 观察指标

(1) 所有大鼠都在造模后 7 d、14 d、21 d 采用代谢笼接取 24 h 尿液测定尿蛋白,造模后≥7 d 尿蛋白含量>100 mg/24 h 代表 NS 模型建立成功。(2) 所有大鼠都在造模后 7 d、14 d、21 d 进行体重与采食量的测定。(3) 所有大鼠在造模后 7 d、14 d、21 d 经过腹腔抽取静脉血 0.2 mL 左右,上生化分析仪检测血肌酐与尿素氮含量。(4) 所有组别在造模后 21 d 与 28 d 分别处死 8 只大鼠,分离大鼠肾脏组织,研磨后进行低温蛋白小鼠 30 min, 12000 rpm 离心 10 min,取上层蛋白采用 BCA 法测定蛋白浓度,然后进行按 SDS-PAGE 凝胶电泳,半干法进行转膜到 PVDF 膜上,脱脂牛奶中封闭(室温)1 h 后置封口袋封闭孵育(4℃过夜)抗脂蛋白脂酶抗体和抗 LCAT 抗体,清洗 3 次后,孵育 1 h,清洗后 ECL 显影并拍照。

1.4 统计方法

本次研究统计软件为 SPSS22.00,计量数据以均数±标准差的形式表示(对比为 t 检验或方差分析),计数数据以百分比表示(对比为卡方分析或方差分析),检验水准为 $\alpha=0.05$ 。

2 结果

2.1 24 h 尿蛋白定量对比

小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组都造模成功,造模后 7 d、14 d、21 d 的 24 h 尿蛋白高于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。见表 1。

表 1 四组大鼠造模后不同时间点的 24h 尿蛋白定量对比(mg/24 h)

Table 1 Quantification of 24h urinary protein at different time points after moulding in four rats(mg/24 h)

Groups	n	7d	14d	21d
Matched group	8	35.15±3.28	35.29±4.99	35.29±5.01
Small dose group	8	134.09±12.49 ^a	135.22±14.44 ^a	134.52±12.48 ^a
Medium dose group	8	154.99±14.28 ^{ab}	155.09±14.26 ^{ab}	154.71±14.71 ^{ab}
High dose group	8	186.77±20.16 ^{abc}	187.09±18.57 ^{abc}	186.28±19.99 ^{abc}
<i>F</i>		29.483	30.144	28.533
<i>P</i>		0.000	0.000	0.000

Note: Compared with the control group, ^a $P<0.05$; compared with the low-dose group, ^b $P<0.05$; compared with the middle-dose group, ^c $P<0.05$.

2.2 体重与采食量变化对比

小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后 7 d、14 d、21 d 的体重与每日采食量都低于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。见表 2。

2.3 肾功能指标变化对比

小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后 7 d、14 d、21 d 的血肌酐与尿素氮含量高于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。见表 3。

2.4 脂蛋白脂酶和 LCAT 变化水平对比

小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模

后 21 d、28 d 的肾脏脂蛋白脂酶和 LCAT 相对表达水平低于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。见表 4。

3 讨论

NS 为泌尿系统的常见疾病,多发生于小儿,多为原发性,在病理上主要表现为弥漫性肾小球脏层上皮细胞足突消失与肾小球基本正常^[12,13]。目前 NS 的发病机制尚不明确,目前临床上多采用以糖皮质激素为主的综合治疗^[14,15]。阿霉素大鼠模型具有稳定性好、成功率高、造模简便等特点,目前作为该疾病的替代模型广泛应用于相关研究中^[16]。

阿霉素是一种高效发泡剂,也属广谱抗肿瘤抗生素^[17]。采

表 2 四组大鼠造模后不同时间点的体重与采食量变化对比(g)

Table 2 Comparison of weight and intake at different time points after moulding in four rats (g)

Groups	n	Weight			Daily intake		
		7 d	14 d	21 d	7 d	14 d	21 d
Matched group	8	317.94±28.88	351.49±33.33	392.74±24.68	27.09±1.57	27.44±2.21	27.09±2.68
Small dose group	8	290.88±18.83 ^a	292.87±19.48 ^a	299.88±20.18 ^a	22.88±2.22 ^a	22.19±3.09 ^a	22.47±2.76 ^a
Medium dose group	8	276.09±20.71 ^{ab}	277.93±12.58 ^{ab}	277.98±13.37 ^{ab}	19.09±1.47 ^{ab}	19.66±2.56 ^{ab}	19.45±2.00 ^{ab}
High dose group	8	254.01±19.48 ^{abc}	255.20±12.77 ^{abc}	254.29±13.33 ^{abc}	16.89±4.22 ^{abc}	16.26±3.22 ^{abc}	16.59±2.74 ^{abc}
<i>F</i>		18.024	21.488	24.988	8.882	8.113	8.913
<i>P</i>		0.000	0.000	0.000	0.001	0.004	0.001

Note: Compared with the control group, ^a*P*<0.05; compared with the low-dose group, ^b*P*<0.05; compared with the middle-dose group, ^c*P*<0.05.

表 3 四组大鼠造模后不同时间点的体重与采食量变化对比(g)

Table 3 Comparison of weight and intake at different time points after moulding in four rats (g)

Groups	n	Urea nitrogen(mmo/L)			Serum creatinine (μmol/L)		
		7 d	14 d	21 d	7 d	14 d	21 d
Matched group	8	6.28±0.33	6.27±0.24	6.29±0.33	57.82±2.58	57.29±3.11	57.29±4.10
Small dose group	8	6.64±0.33 ^a	6.67±0.28 ^a	6.65±0.17 ^a	60.29±3.11 ^a	60.33±2.77 ^a	60.82±5.67 ^a
Medium dose group	8	6.90±0.14 ^{ab}	6.92±0.16 ^{ab}	6.91±0.22 ^{ab}	63.28±2.67 ^{ab}	63.55±5.19 ^{ab}	63.58±4.55 ^{ab}
High dose group	8	7.19±0.22 ^{abc}	7.19±0.13 ^{abc}	7.20±0.16 ^{abc}	68.98±4.28 ^{abc}	68.28±5.16 ^{abc}	68.44±4.17 ^{abc}
<i>F</i>		9.823	9.991	9.142	11.733	12.472	11.778
<i>P</i>		0.000	0.000	0.001	0.000	0.000	0.000

Note: Compared with the control group, ^a*P*<0.05; compared with the low-dose group, ^b*P*<0.05; compared with the middle-dose group, ^c*P*<0.05.

表 4 四组大鼠造模后不同时间点的肾脏脂蛋白脂酶和 LCAT 变化水平对比

Table 4 Comparison of change levels of renal lipase and lecithin cholesterol acyltransferase at different time points after moulding in the four four rats

Groups	n	LPL		LCAT	
		21 d	28 d	21d	28 d
Matched group	4	4.29±0.33	4.33±0.21	3.87±0.14	3.88±0.22
Small dose group	4	2.74±0.25 ^a	2.77±0.18 ^a	2.38±0.22 ^a	2.37±0.17 ^a
Medium dose group	4	1.67±0.13 ^{ab}	1.69±0.22 ^{ab}	1.28±0.11 ^{ab}	1.29±0.18 ^{ab}
High dose group	4	0.87±0.11 ^{abc}	0.88±0.02 ^{abc}	0.76±0.03 ^{abc}	0.77±0.06 ^{abc}
<i>F</i>		32.193	31.003	28.934	28.115
<i>P</i>		0.000	0.000	0.000	0.000

Note: Compared with the control group, ^a*P*<0.05; compared with the low-dose group, ^b*P*<0.05; compared with the middle-dose group, ^c*P*<0.05.

用尾静脉一次性注射造模具有成模较快、无需手术、操作简单等特点。但是采用高剂量阿霉素的组容易发生血管外渗时,可导致局部组织出现化学性损伤^[18]。本研究经尾静脉一次性注射盐酸阿霉素进行造模,结果显示小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组都造模成功,造成成功率为 100.0%,造模后 7 d、14 d、21 d 的 24 h 尿蛋白高于对照组 (*P*<0.05),且存在剂量依赖性,三组间对比差异有统计学意义 (*P*<0.05),表明小剂量阿霉素的应用可成功建立 NS 大鼠模型,与上述研究结论相符。结合 Roschewski M^[19]和 Yarmohammadi F^[20]等研究分析:阿霉素经人体吸收后在体内药物代谢酶的作用下,形成

半醌自由基,从而产生过氧化作用,破坏滤过膜结构和功能,对肾脏造成损伤,诱发肾小球上皮细胞脂质过氧化反应,从而诱发形成 NS。

NS 在临床上多表现为高胆固醇血症、蛋白尿、低蛋白血症等,可导致个体的体重与每日进食量减少,伴随有肾功能下降^[21]。本研究显示小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后 7 d、14 d、21 d 的体重与每日采食量都低于对照组 (*P*<0.05),且存在剂量依赖性,三组间对比差异有统计学意义 (*P*<0.05);小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后 7 d、14 d、21 d 的血肌酐与尿素氮含量高于对照

组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$)。结合 Chojnowski A 等^[22]研究分析:阿霉素毒性较强,一次性给药剂量较大易引起毒性反应,导致实验动物死亡,采用小剂量阿霉素造模减轻了阿霉素的毒性反应,可模拟 NS 机体的病情状况,因此可成功建立模型。

血浆胆固醇中 $\geq 70.0\%$ 为胆固醇酯,在血液中可以游离形态与结合形态存在^[23,24]。其中脂蛋白酯酶在血浆中起催化作用,可将卵磷脂分子中的不饱和脂肪脂酰基转移给的胆固醇羟基上,生成胆固醇酯、溶血卵磷脂^[25]。脂蛋白酯酶也能水解乳糜微粒中的甘油三酯,将乳糜微粒转化为富含胆固醇酯及载脂蛋白 E 的残粒,有利于促进胆固醇的转化与排泄^[26]。脂蛋白酯酶在极低密度脂蛋白及高密度脂蛋白形成中起关键作用,有利于机体将多余胆固醇逆向转运到肝脏,可以从多靶点调节胆固醇代谢网络,具有综合性的调脂作用^[27]。LCAT 基因全称为 4200 bp,包含 6 个外显子和 5 个内含子,蛋白又 416 个氨基酸残基组成^[28]。LCAT 的组成包括脯氨酸、亮氨酸、谷氨酸、天冬氨酸、甘氨酸等,属于 α/β - 水解酶折叠家族,由 β 折叠链组成环状。LCAT 对维持胆固醇稳态及调节胆固醇转运具有重要价值,LCAT 水平与高密度脂蛋白胆固醇呈正相关,与三酰甘油呈负相关,可催化高密度脂蛋白胆固醇的游离胆固醇酯化,可抑制机体动脉粥样硬化的形成^[29,30]。本研究显示小剂量阿霉素组、中剂量阿霉素组与高剂量阿霉素组造模后 21 d、28 d 的肾脏脂蛋白酯酶和 LCAT 相对表达水平低于对照组($P<0.05$),且存在剂量依赖性,三组间对比差异有统计学意义($P<0.05$),表明小剂量阿霉素在 NS 大鼠的应用就可抑制肾脏脂蛋白酯酶和 LCAT 的表达。当前也有研究表明,阿霉素可以损伤肾脏近曲小管,扩张粒体和溶酶体囊,使近曲小管上皮细胞肿胀、扭曲,导致细胞核发生一定的损伤。但是当使用阿霉素剂量较大时常可导致模型动物的生存力减弱,增加致死率^[31,32]。本研究也存在一定的不足,没有进行细胞学分析和肾脏病理学观察,将在后续研究中展开进一步研究。

综上所述,小剂量阿霉素可抑制大鼠肾脏脂蛋白酯酶和 LCAT 的表达,能快速有效建立 NS 大鼠模型,具有很好的模拟造模效果。

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