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小檗碱与罗格列酮干预高脂饮食诱导大鼠非酒精性脂肪性肝炎的比较观察*

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摘要 目的:比较中药单体化合物小檗碱和噻唑烷二酮类药物罗格列酮对高脂饲料诱导大鼠非酒精性脂肪性肝炎(NASH)的干预作用,探讨小檗碱成为天然胰岛素增敏剂的可能性。**方法:**雄性 SD 大鼠 40 只,随机分为 4 组,采用连续饲喂高脂饲料的方法诱导大鼠 NASH,以预防给药的方式灌胃给予小檗碱(100 mg/kg 体重)和罗格列酮(20 mg/kg 体重),持续 8 周后取材。采用生化分析的方法检测大鼠血清胆固醇(CHO)、甘油三酯(TG)、高密度脂蛋白(HDL)、低密度脂蛋白(LDL)、空腹血糖(FPG)及空腹胰岛素(FINS)并计算胰岛素抵抗指数(HOMA-IR)。采用常规石蜡切片 HE 染色、冰冻切片油红 O 染色评估 NASH 的病理程度,用常规免疫组织化学方法检测了肝组织中 PPAR- γ 的表达。**结果:**小檗碱和罗格列酮均能较好的干预高脂饲料诱导大鼠 NASH 的病理过程。此外,二者均能改善大鼠胰岛素抵抗状态、上调肝组织中 PPAR- γ 的水平。**结论:**小檗碱和罗格列酮均能较好的改善高脂饲料诱导的大鼠 NASH 病理过程,二者共同的药理机制是改善胰岛素抵抗状态和上调肝组织中 PPAR- γ 的表达。该实验结果提示:小檗碱有望开发为具有胰岛素增敏作用的天然药物。

关键词:小檗碱;罗格列酮;非酒精性脂肪性肝炎;大鼠

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Comparison of the Efficacy between Berberine and Rosiglitazone in Non-alcoholic Steatohepatitis Rats Induced by High Fat Fiet*

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ABSTRACT Objective: The study was to compare the efficacy of berberine and rosiglitazone in the treatment of non-alcoholic steatohepatitis (NASH) rats induced by high fat diet, so as to investigate the possibility of substituting rosiglitazone. **Methods:** 40 Male SD rats were randomly divided into 4 groups (10 rats per group), i.e. the normal group (fed with normal diet), the NASH model group (fed with high fat diet), Rosiglitazone treatment group (20 mg/Kg body weight) and berberine treatment group (100 mg/Kg body weight). Drugs were adopted in the preventive intervention method for 8 weeks. The hepatic histopathology method was adopted to evaluate the drug therapeutic effect. The serum levels of cholesterol (CHO), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), fasting plasma glucose (FPG), and fasting insulin (FINS) were examined with biochemical method. And then, HOMA-IR was calculated to show insulin resistance. And PPAR- γ expression on hepatic tissue was detected by immunohistochemistry method. **Results:** The results showed berberine and rosiglitazone could improve the degree of hepatic histopathology. Furthermore, both drugs can improve insulin resistance, and up-regulate the level of PPAR- γ on hepatic tissue. **Conclusion:** Berberine and rosiglitazone could alleviate the pathological process in high fat diet induced NASH model possibly through improving insulin resistance, up regulating PPAR- γ expression. The results suggest that berberine is expected to be developed into a natural drug with insulin sensitization effect.

Key words: Berberine; Rosiglitazone; Non-alcoholic steatohepatitis; Rat

Chinese Library Classification(CLC): R95-3, R575.5 **Document code:** A

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前言

非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)是除外过量饮酒,肝细胞以脂肪变性、肝小叶弥漫性炎症或肝小叶中央静脉及肝血窦周围结缔组织增生为主要特征的临床

病理综合征^[1]。研究表明,NASH 预后不佳可增加肝硬化的发病率,是药物干预和治疗的关键时期,受到研究者的广泛关注^[2]。到目前为止,NASH 确切的病理机制尚未完全阐明,临床还未形成一致共识的治疗方案。越来越多的证据表明,胰岛素抵抗(insulin resistance, IR)及其诱发的脂肪代谢紊乱是 NASH 发

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生、发展的核心病理因素^[9]。鉴于此,胰岛素增敏剂,如噻唑烷二酮类药物(TZD)已经用于 NASH 的临床治疗。噻唑烷二酮是过氧化物酶体增殖物激活受体- γ (peroxisome proliferator-activated receptor- γ , PPAR- γ)的激动剂,二者特异性结合后可调控糖、脂代谢相关基因的表达,抑制炎症介质的合成,从而改善胰岛素抵抗状态,有效干预 NASH 的病理过程^[9]。

罗格列酮是人工合成的 TZD 类药物,临床研究显示,该药治疗 NASH 有效^[9]。然而,长期服用罗格列酮可能会诱发体重增加、水肿、贫血、女性骨质疏松、心力衰竭以及增加心血管病死亡风险等不良反应/副反应^[6,8],其安全性问题引起广泛关注,罗格列酮及相关复方制剂已在有些欧美国家和地区限制使用。为此,寻找和发现 TZD 的替代药物具有重要的现实意义。已有的研究表明:中药提取物小檗碱(Berberine)对脂肪性肝病有较好的治疗作用,其药理机制通常包括降糖、降脂、改善胰岛素抵抗、抗炎、抗氧化等多个环节^[9,10]。本文在前期研究的基础上,比较观察了小檗碱与罗格列酮对高脂饮食诱导 NASH 大鼠脂代谢、胰岛素抵抗及 PPAR- γ 蛋白表达的影响,期望为开发天然胰岛素增敏药物提供实验证据。

1 材料与方法

1.1 实验动物及高脂饲料订制

SD 大鼠 40 只,雄性,150 $\pm$ 10 g 体重(SCXK-京-2012-0001)购自北京维通利华实验动物有限公司。高脂饲料购自北京华康康生物科技股份有限公司(配方:88%基础饲料+10%猪油+2%胆固醇)。

1.2 试剂及耗材

甘油三酯(Triglyceride, TG)、总胆固醇(Cholesterol total,

CHO)、空腹血糖(Fasting plasma glucose, FPG)比色法试剂盒,购自中生北控股份有限公司。空腹胰岛素(Fasting insulin, FINS)放免法试剂盒,购自北京华英生物技术研究所。小檗碱购自南京泽朗医药科技有限公司;罗格列酮为葛兰素史克(天津)有限公司产品(批准文号:H20020475)。兔抗大鼠 PPAR- γ 一抗购自北京博奥森生物技术有限公司(Cat. Bs-4590R)。

1.3 动物分组及药物干预

实验动物随机分 4 组(10 只/组):正常对照组(常规饲料喂养、生理盐水灌胃模拟给药);NASH 模型组(依照本实验室常规方法^[11],饲喂高脂饲料、生理盐水灌胃);罗格列酮预防给药组(高脂饲料喂养、罗格列酮灌胃给药,20 mg/kg 体重);小檗碱预防给药组(高脂饲料喂养、小檗碱灌胃给药,100 mg/kg 体重)。实验持续 8 周。

1.4 血清中 TG、CHO、LDL 及 HDL 含量测定

采用比色法,经全自动生化分析仪按常规方法检测。

1.5 胰岛素抵抗水平测定

比色法检测血清中空腹血糖(FPG)的含量,放免法检测血清中空腹胰岛素(FINS)的浓度,根据公式计算 HOMA-IR 指数,即 $HOMA-IR = \text{空腹血糖}(\text{mmol/L}) \times \text{空腹胰岛素}(\text{mIU/L}) / 22.5$ 。

1.6 肝组织病理学检测及 NASH 病理诊断

常规石蜡包埋、石蜡切片(4 μm)及 HE 染色、光镜观察并摄片;冰冻切片(10 μm)行常规油红 O 染色、光镜观察并摄片。NASH 病理诊断标准采用 NAFLD 活动度积分^[12](NAFLD Activity Score, NAS)进行评估。

1.7 PPAR- γ 免疫组织化学显色

石蜡切片行常规 SP 法免疫组织化学显色,光镜观察、摄

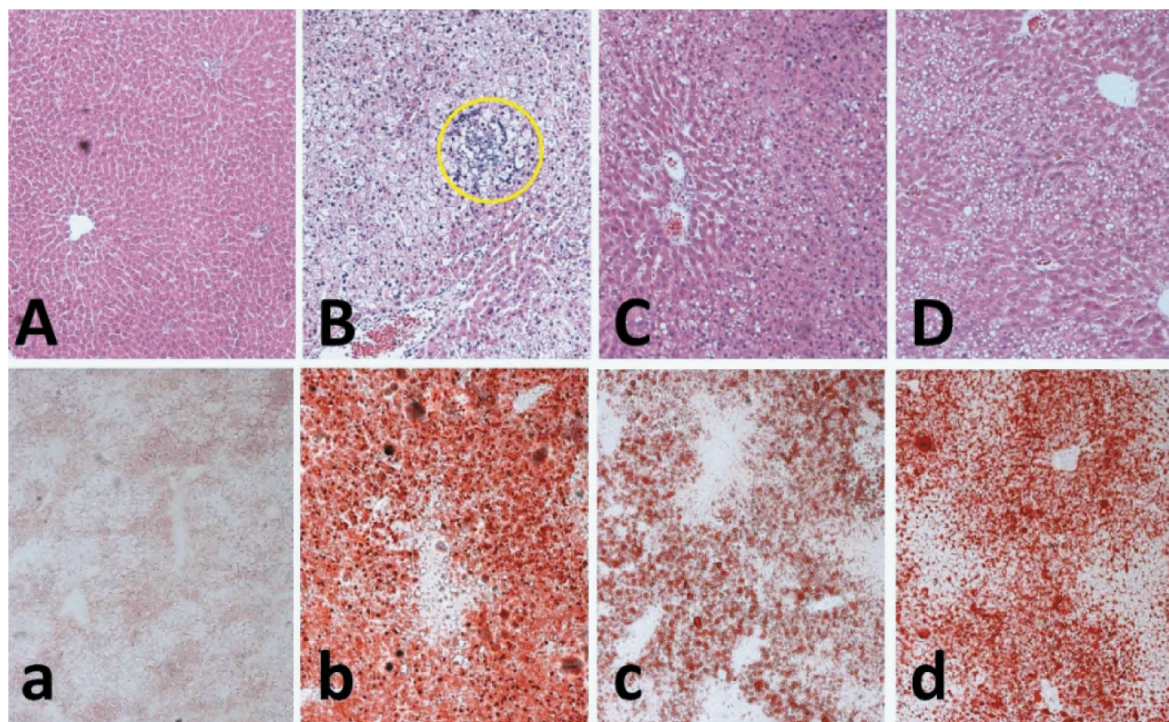


图 1 肝组织病理学检测结果, $\times 100$

Fig.1 The result of pathology in SD rat liver tissue($\times 100$)

注:A-D: 石蜡切片 HE 染色; a-d: 冰冻切片油红 O 染色;图 B 中圆圈内示炎症细胞聚集区。

Note: A-D: HE-stained in the paraffin section; a-d: Oil red O-stained in the frozen section. There is inflammatory lesions in the circle of Fig.B.

片、图像分析组织中 PPAR- γ 阳性反应的平均光密度值。

1.8 数据分析及统计学处理

定量数据采用 SPSS18.0 软件对血清生化指标检测结果进行统计学分析。不同组间差异以表示,对符合正态分布的计量资料组间比较采用独立样本 T 检验, $P < 0.05$ 表示差异有统计学意义, $P < 0.01$ 表示差异有显著统计学意义。

2 结果

2.1 动物行为学及病理评分结果

实验期间各组动物均无死亡。组织病理学观察, NASH 大鼠肝组织结构紊乱, 肝细胞脂肪样变性, 可见大量空泡化细胞, 肝门管区炎性细胞浸润明显(图 1-B); 油红 O 染色可见肝细胞中有大量脂肪滴(图 1-b)。罗格列酮和小檗碱预防给药组小鼠

肝组织脂肪空泡明显减少, 肝组织结构较清晰, 炎性细胞浸润不明显(图 1-C、D); 油红 O 染色可见肝细胞中脂肪滴显著减少(图 1-c、d)。病理评分结果显示, NASH 模型制备成功, 罗格列酮和小檗碱干预能显著改善小鼠 NASH 组织病理程度。

2.2 血清中 TG、CHO、HDL 及 LDL 水平检测结果

与正常组比较, NASH 模型大鼠血清中胆固醇 (CHO)、甘油三酯 (TG) 及低密度脂蛋白 (LDL) 水平显著增高 ($P < 0.05$ 或 $P < 0.01$), 高密度脂蛋白 (HDL) 水平则显著降低 ($P < 0.05$)。与模型组比较, 罗格列酮和小檗碱干预组大鼠血清中 CHO 及 TG 水平均显著降低 ($P < 0.05$ 或 $P < 0.01$); 而罗格列酮和小檗碱对 LDL 有降低趋势, HDL 升高趋势, 但差异未见统计学意义。结果见表 1。

表 1 大鼠血清中 CHO、TG、LDL 及 HDL 含量统计结果 ($\bar{X} \pm S$, $n=10$)
Table 1 The content of CHO, TG, LDL, HDL in the SD rat serum ($\bar{X} \pm S$, $n=10$)

组别(Group)	CHO (mmol/L)	TG (mmol/L)	LDL (mmol/L)	HDL (mmol/L)
正常组(The normal group)	1.68 $\pm$ 0.19	0.56 $\pm$ 0.04	0.16 $\pm$ 0.02	1.41 $\pm$ 0.13
模型组(The model group)	2.81 $\pm$ 0.79**	1.65 $\pm$ 0.02**	0.81 $\pm$ 0.42*	0.96 $\pm$ 0.02*
罗格列酮 (The rosiglitazone group)	1.77 $\pm$ 0.01#	0.58 $\pm$ 0.02##	0.60 $\pm$ 0.14	1.11 $\pm$ 0.16
小檗碱(The berberine group)	2.07 $\pm$ 0.22#	0.56 $\pm$ 0.05##	0.54 $\pm$ 0.38	1.08 $\pm$ 0.26

注: * 与空白组比较, $P < 0.05$; ** 表与空白组比较, $P < 0.01$; # 与模型组比较, $P < 0.05$; ## 与模型组比较, $P < 0.01$ 。

Note: * represent compared with the normal group of rat, $P < 0.05$; ** represent compared with the normal group of rat, $P < 0.01$;

represent compared with the normal group of rat, $P < 0.05$; ## represent compared with the normal group of rat, $P < 0.01$ 。

2.3 大鼠胰岛素抵抗指数检测结果

根据已有的资料, 胰岛素抵抗指数 (HOMA-IR) 可通过空腹血糖及空腹胰岛素值间接推算。检测数据表明: 与正常对照组比较, NASH 模型组 HOMA-IR 值显著增高 ($P < 0.05$); 与模型组比较, 罗格列酮和小檗碱预防组 HOMA-IR 值均显著降低 ($P < 0.05$), 结果见表 2。

2.4 肝组织 PPAR- γ 蛋白表达免疫组织化学显色结果

与正常对照组比较, NASH 模型组大鼠肝组织中 PPAR- γ 蛋白表达呈下调趋势, 图像分析结果表明差异显著 ($P < 0.01$); 与模型组比较, 罗格列酮和小檗碱干预组 PPAR- γ 蛋白表达呈显著上调的趋势, 图像分析结果表明差异显著 ($P < 0.01$), 结果见图 2。

表 2 大鼠血清中空腹血糖 (FPG)、空腹胰岛素 (FINS) 含量及 HOMA-IR 指数 ($\bar{X} \pm S$, $n=10$)
Table 2 The content of FPG, FINS, HOMA-IR in the SD rat serum ($\bar{X} \pm S$, $n=10$)

组别(Group)	FPG (mmol/L)	FINS (mIU/L)	HOMA-IR
正常组(The normal group)	3.51 $\pm$ 0.67	16.67 $\pm$ 4.00	2.56 $\pm$ 0.50
正常组(The normal group)	3.51 $\pm$ 0.67	17.09 $\pm$ 2.40	3.72 $\pm$ 2.18*
罗格列酮(The rosiglitazone group)	2.24 $\pm$ 1.17#	12.74 $\pm$ 2.49	1.20 $\pm$ 0.53#
小檗碱(The rosiglitazone group)	2.09 $\pm$ 0.68#	15.77 $\pm$ 3.02	1.53 $\pm$ 0.75#

注: * 与空白组比较, $P < 0.05$; # 与模型组比较, $P < 0.05$ 。

Note: *: Compared with the normal group of rat, $P < 0.05$; #: compared with the normal group of rat, $P < 0.05$ 。

3 讨论

小檗碱又称黄连素, 是一种常见的异喹啉季铵型生物碱, 广泛存在于小檗科、毛茛科、芸香科等药用植物, 如黄柏、黄连、南天竹、三颗针等, 植物资源丰富、分布广泛, 具有较好的开发利用价值。现代药理学研究表明: 小檗碱治疗窗大、没有细胞毒和致突变等毒副作用, 临床广泛应用于急性胃肠炎、细菌性痢疾等消化道感染以及外用于眼结膜炎及化脓性中耳炎等疾病

的治疗。近年来, 有临床研究表明: 小檗碱治疗非酒精性脂肪性肝病有很好的治疗作用^[13]。动物及细胞实验结果提示其可能的药理机制包括: 改善血脂紊乱、糖代谢异常^[14,15]; 调节 PPAR(α 、 γ) 基因转录及蛋白表达^[16,17]; 调节肝脏脂联素受体表达^[18]; 改善胰岛素抵抗、氧化应激及内质网应激等^[19,20]。因此, 小檗碱及其制剂有望作为一类新型抗非酒精性脂肪性肝病的天然药物得到深度开发。

迄今为止, NASH 的发病机制尚未完全阐明, 学术界广泛

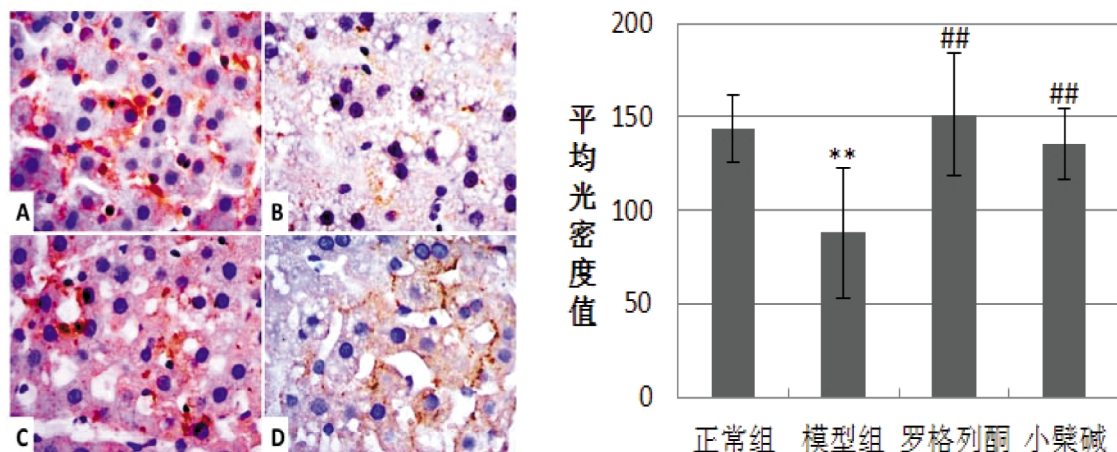


图2 肝组织石蜡切片 PPAR- γ 免疫组化显色结果, $\times 400$

Fig.2 Immunohistochemical Result of PPAR- γ in rat liver tissue, $\times 400$

注: ** 与空白组比较, $P < 0.01$; ## 与模型组比较, $P < 0.01$ 。

Note: **: compared with the normal group of rat, $P < 0.01$; ##: compared with the normal group of rat, $P < 0.01$.

认可的“二次打击”学说认为,该病的核心病理机制是胰岛素抵抗,进而肝组织出现脂质过氧化、氧自由基损伤、线粒体功能障碍以及炎症细胞因子增多等病理过程^[2]。针对胰岛素抵抗的病理环节,西医临床常采用胰岛素增敏剂,如噻唑烷二酮类,改善 NASH 患者的糖脂代谢。然而,该治疗方案的有效性尚缺乏大量临床数据证实;另一方面,噻唑烷二酮类药物的副作用也极大的限制了临床推广应用。为此,从天然药物中发现和开发噻唑烷二酮类的替代药物成为研究者关注的热点。

本实验在课题组前期研究的基础上,观察了小檗碱与罗格列酮干预高脂饮食诱导大鼠 NASH 的药效,比较了二者对血脂、胰岛素抵抗和 PPAR- γ 蛋白表达的调节作用,结果提示:小檗碱可显著改善高脂饮食导致的大鼠血脂紊乱及胰岛素抵抗状态,其药理机制可能为通过促进 PPAR- γ 蛋白表达,从而调节糖、脂代谢,改善肝脏脂沉积和炎症反应,阻断脂肪性肝病的病理进程。综合已有的文献资料,小檗碱有望开发为新型胰岛素增敏剂,其进一步的药理机制需要深入探讨。

在未来的研究中,课题组计划采用分子对接技术研究小檗碱与 PPAR- γ 蛋白可能发生偶联的位点,同时引进 PPAR- γ 基因敲除小鼠深入研究小檗碱干预 NASH 的分子机制。

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