·基础研究·

利拉鲁肽对糖尿病肾病大鼠NOD样受体热蛋白结构域相关蛋白3表达的影响

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【摘 要】 目的 探讨利拉鲁肽是否通过抑制NOD样受体热蛋白结构域相关蛋白3(NLRP3)的活化在糖尿病肾病(DN)中发挥肾脏保护作用。**方法** 22只4周龄的Wistar品系雄性大鼠随机分为正常对照组($n=6$)、利拉鲁肽组($n=8$)和生理盐水组($n=8$)。利拉鲁肽组予利拉鲁肽200 μg/(kg·d)皮下注射,生理盐水组予等体积的生理盐水皮下注射,正常对照组不做任何处理,共治疗4周。治疗结束后检测大鼠体质量、24 h尿总蛋白定量(UTP)、空腹血糖(FBG)、甘油三酯(TG)、胆固醇(TC)、血尿素氮(BUN)、血肌酐(SCr)等生化指标,各组大鼠肾组织进行苏木素-伊红染色(HE),光镜下观察肾组织病理形态学改变,Western blot检测肾组织中NLRP3炎症小体相关蛋白表达,酶联免疫吸附试验(ELISA)检测血清白细胞介素-18(IL-18)及血清白细胞介素-1β(IL-1β)的水平。采用SPSS 26.0统计软件和Graph Prism 9.0软件进行分析及绘图。计量资料多组间比较采用单因素方差分析,组内两两比较采用Tukey检验。**结果** 利拉鲁肽组大鼠FBG、UTP、BUN、SCr、TC、TG等生化指标水平较生理盐水组改善($P<0.01$)。肾脏组织病理切片提示正常对照组肾小球、肾小管结构正常;生理盐水组可见肾小球体积增大、结构紊乱,系膜外基质增多,基底膜增厚明显;利拉鲁肽组大鼠肾脏病理变化减轻。Western blot检测提示经过利拉鲁肽的干预,NLRP3炎症小体相关蛋白的表达明显低于生理盐水组;ELISA检测提示生理盐水组IL-18、IL-1β水平明显增加,经利拉鲁肽干预后,IL-18、IL-1β水平下降。**结论** 利拉鲁肽可改变糖尿病肾病大鼠的疾病进程,这可能与利拉鲁肽抑制NLRP3炎症小体的激活有关。

【关键词】 糖尿病肾病;利拉鲁肽;NOD样受体热蛋白结构域相关蛋白3
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Effects of liraglutide on NOD-like receptor pyrin domain containing 3 expression in rat model of diabetic nephropathy

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【Abstract】 Objective To investigate whether liraglutide plays a protective role in diabetic nephropathy (DN) by inhibiting the activation of NOD-like receptor pyrin domain containing 3 (NLRP3). **Methods** Twenty-two male Wistar rats (4 weeks old) were randomly divided into normal control group ($n=6$), liraglutide group ($n=8$) and normal saline group ($n=8$). After DN model was established, the rats of the liraglutide group were subcutaneously injected with 200 μg/(kg·d) liraglutide, those from the normal saline group were subcutaneously injected with same volume of normal saline, and those of the normal control group received no treatment. After 4 weeks' treatment, body mass, 24 h urinary total protein (UTP), fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), blood urea nitrogen (BUN), serum creatinine (SCr) and other biochemical indexes were detected. Hematoxylin-eosin (HE) staining was used to observe the pathological changes of renal tissue. The expression of NLRP3 inflammasome-related proteins in renal tissue was measured by Western blot, and the serum levels of interleukin-18 (IL-18) and interleukin-1β (IL-1β) were detected by enzyme-linked immunosorbent assay (ELISA). SPSS statistics 26.0 and Graph Prism 9.0 software were used for analysis and mapping. One-way ANOVA was employed for intergroup comparison for measurement data, and Tukey test was adopted for intra-group comparison. **Results** Liraglutide intervention improved the levels of FBG, UTP, BUN, SCr, TC and TG when compared with those in normal saline group ($P<0.01$). Pathological observation displayed that normal structure of glomeruli and tubules were

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observed in the normal control group, increased glomerular volume and structure, extramembranous matrix, and significant thickening in basement membrane were seen in the normal saline group, and the pathological changes of the kidneys were alleviated in the liraglutide group. Western blot assay indicated that the protein expression levels of NLRP3 inflammasome-related proteins were significantly lower in the liraglutide group than the normal saline group. The results of ELISA showed that the levels of IL-18 and IL-1β were significantly increased in the normal saline group, but decreased after liraglutide intervention. **Conclusion** Liraglutide alters disease progression in DN rats, which may be related to its inhibition of NLRP3 inflammasome activation.

【Key words】 diabetic nephropathy; liraglutide; NLRP3

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糖尿病肾病(diabetic nephropathy,DN)是慢性肾脏病(chronic kidney disease,CKD)和终末期肾病(end stage renal disease,ESRD)的最常见原因,并且与增加心血管疾病发病率和死亡率的风险直接相关[1]。作为糖尿病最严重的微血管并发症之一,DN是一种由多种炎症因子介导的代谢性疾病,高血糖、脂质代谢紊乱、氧化应激、晚期糖基化终末产物等多种因素贯穿于疾病的整个进程[2]。NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor pyrin domain containing 3,NLRP3)炎症小体被认为是调控炎症产生的分子开关。NLRP3炎症小体由NLRP3、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a caspase recruitment domain,ASC)及天冬氨酸特异性半胱氨酸蛋白酶1(cysteinyl aspartate specific protease-1,caspase-1)组成,激活的NLRP3炎症小体可以通过裂解caspase-1分泌成熟白细胞介素-18(interleukin-18,IL-18)和IL-1β等多种炎症因子产生炎症级联反应[3]。

利拉鲁肽是一种长效的胰高血糖素样肽-1(glucagon-like peptide,GLP-1)受体激动剂。研究发现,利拉鲁肽除具有良好的降血糖作用,还具有抗氧化应激和减轻机体炎症的作用[4]。GLP-1可以调节肾脏和血管多个部位的炎症,还可以激活环磷酸腺苷-蛋白激酶A(cyclic adenosine monophosphate-protein kinase A,cAMP-PKA)通路,保护肾脏免受炎症损伤[5]。本研究旨在观察利拉鲁肽调节NLRP3炎症小体与肾脏保护作用的关系,以期为临床治疗DKD提供新的理论依据。

1 材料与方法

1.1 研究对象与试剂

1.1.1 实验动物 4周龄健康雄性Wistar大鼠(SPF级),体质量180~200 g,购自北京斯贝福生物技术有限公司,动物许可证号:SCXK(京)2019-0010,饲养于环境温度恒定为(22±2)℃,湿度为50%~60%的动物房中,定期更换垫料,自由饮水及进食。

1.1.2 主要试剂 链脲佐菌素(streptozotocin,STZ)购自索莱宝生物科技有限公司;利拉鲁肽购自诺和诺德公司;血清肌酐(serum creatinine,SCr)、血尿素氮(blood urea nitrogen,BUN)、尿总蛋白定量(urine total protein,UTP)、血清总胆固醇(total cholesterol,TC)和血清甘油三酯(triglyceride,TG)测定试剂盒购自南京建成生物技术研究所;IL-18和IL-1β酶联免疫吸附试验(enzyme-linked immuno sorbent assay,ELISA)试剂盒购自江苏泽雨生物技术有限公司;NLRP3、ASC、caspase-1一抗、羊抗兔二抗均购自北京博奥森生物技术有限公司。

1.2 方法

1.2.1 DN大鼠模型建立及分组 22只健康雄性Wistar大鼠,采用单纯随机抽样方法分为正常对照组($n=6$)和糖尿病肾病组($n=16$),正常对照组大鼠给予普通饲料喂养,糖尿病肾病组大鼠给予高糖高脂饲料喂养。喂养4周后糖尿病肾病组大鼠禁食不禁水12 h,次日清晨称体质量,腹腔注射现配的STZ 30 mg/kg溶液,72 h后尾静脉取血测量大鼠随机血糖,3次随机血糖≥16.7 mmol/L,即糖尿病大鼠模型成功。继续予高糖高脂饲料喂养12周,将大鼠分别置于代谢笼内收集各组大鼠24 h尿液,尿蛋白>20 mg即视为糖尿病肾病大鼠模型成功建立。将造模成功的大鼠随机分为利拉鲁肽组($n=8$)和生理盐水组($n=8$),利拉鲁肽组大鼠予200 μg/(kg·d)利拉鲁肽皮下注射,生理盐水组大鼠予相同体积生理盐水皮下注射,正常对照组大鼠不予任何处理,共治疗4周。

1.2.2 标本获取与保存 每周称量大鼠体质量,每2周尾静脉取血,血糖仪测量大鼠空腹血糖(fasting blood glucose,FBG)。第4周治疗结束前一天代谢笼收集各组大鼠24 h尿液,所有大鼠禁食不禁水12 h,以3%戊巴比妥钠50 mg/kg腹腔注射麻醉,麻醉后开腹,于腹主动脉采血3~5 ml,室温下静置15 min后离心(3 000转/min,15 min),取上清液,标

记分装后于-80℃冰箱冻存。取出大鼠双侧肾脏，去除包膜及结缔组织，生理盐水充分灌洗，滤纸吸干水分，称重，计算肾指数（双侧肾质量总和/体质量×100%）；肾脏组织于矢状面平分为两部分，一部分于4%多聚甲醛固定液中固定 24 h，常规酒精梯度脱水，石蜡包埋，4 μm 厚连续切片，苏木素-伊红（hematoxylin-eosin，HE）染色，中性树胶封片，光学显微镜下观察肾脏组织形态；另一部分分装于冻存管，于-80℃冰箱保存备用。

1.3 观察指标

（1）肾功能测定：血液离心取上清液，严格按照试剂盒说明书操作，测定血清 SCr 和 BUN 水平。（2）血脂测定：血液离心取上清液，严格按照试剂盒说明书操作，测定血清 TC、TG 水平。（3）IL-18 和 IL-1β 水平测定：采用 ELISA 法检测血清 IL-18、IL-1β 水平，严格按照实验说明书操作。（4）NLRP3、ASC、caspase-1 蛋白的表达：采用 Western blot 法检测。将 0.1 g 肾脏组织在液氮中研磨至肉眼无可见颗粒，加入 500 μl 蛋白裂解液，冰上充分裂解，离心（离心力 146 843 *g*，4℃，5 min），取上清液。二喹啉甲酸（bicinchoninic acid，BCA）法进行蛋白浓度测定。进一步行十二烷基硫酸钠-聚丙烯酰胺凝胶（sodium dodecyl sulfate-poly acrylamide gel electrophoresis，SDS-PAGE）电泳，将蛋白转移至聚偏二氟乙烯（polyvinylidene flooride，PVDF）膜上，5%脱脂奶粉封闭 1 h，TBST 洗涤 3 次，每次 10 min；分别加入 NLRP3、ASC、caspase-1 一抗，4℃孵育过夜，TBST 洗涤 3 次，每次 10 min；加入二抗孵育 1 h，TBST 洗涤 3 次，每次 15 min，增强型化学发光（enhanced chemiluminescence，ECL）试剂盒显色，ImageJ 分析 NLRP3、ASC、caspase-1 蛋白灰度值。

1.4 统计学处理

采用 SPSS 26.0 统计软件和 Graph Prism 9.0 软件进行分析及绘图。计量资料以均数±标准差（$\bar{x}\pm s$）表示，多组间比较采用单因素方差分析，组内两两比较采用 Tukey 检验。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 大鼠一般情况

糖尿病肾病组大鼠精神萎靡，毛发粗糙，颈部毛发出现红棕色，进食、饮水、尿量均增多，垫料味道大且潮湿。利拉鲁肽组 2 只大鼠血糖不达标，予以剔除，实验期间生理盐水组 2 只大鼠死亡，可能由于血糖过高所致急性并发症。

2.2 3 组大鼠体质量、肾重及肾指数比较

与正常对照组比较，生理盐水组大鼠体质量降低，肾重、肾指数升高，差异均有统计学意义（$P<0.01$）；利拉鲁肽组大鼠体质量差异无统计学意义（$P>0.05$），肾重、肾指数升高，差异有统计学意义（$P<0.01$）。与生理盐水组比较，利拉鲁肽组大鼠体质量升高，肾重下降，差异有统计学意义（$P<0.01$），肾指数差异无统计学意义（$P>0.05$；表 1）。

表 1 3 组大鼠体质量、肾重及肾指数比较

Table 1 Comparison of body mass, kidney weight and renal index among three groups of rats （$n=6$, $\bar{x}\pm s$）

Group	Body mass (g)	Kidney weight (g)	Renal index (%)
Normal control	588.02±21.05	2.75±0.75	0.47±0.04
Normal saline	522.50±15.68**	3.90±0.22**	0.69±0.05**
Liraglutide	563.82±12.21##	3.45±0.36**##	0.66±0.09**
F	23.57	29.93	22.80
P value	<0.01	<0.01	<0.01

Compared with normal control group, ** $P<0.01$; compared with normal saline group, ## $P<0.01$.

2.3 3 组大鼠 SCr、BUN、UTP、TC、TG 及血糖水平比较

与正常对照组相比，生理盐水组大鼠 FBG、UTP、SCr、BUN、TC、TG 明显升高，利拉鲁肽组大鼠 FBG、UTP、SCr、BUN 明显升高，差异均有统计学意义（$P<0.01$）。与生理盐水组相比，利拉鲁肽组大鼠 FBG、UTP、SCr、BUN、TC、TG 明显下降，差异均有统计学意义（$P<0.01$；表 2）。

表 2 3 组大鼠生化指标比较

Table 2 Comparison of biochemical parameters among three groups of rats （$n=6$, $\bar{x}\pm s$）

Group	FBG (mmol/L)	UTP (mg)	SCr (μmol/L)	BUN (mmol/L)	TC (mmol/L)	TG (mmol/L)
Normal control	5.83±1.69	5.24±0.40	20.61±1.28	5.32±0.46	0.92±0.22	0.97±0.20
Normal saline	28.25±1.70**	25.94±1.67**	40.93±2.92**	13.49±1.00**	2.05±0.34**	2.01±0.33**
Liraglutide	20.27±2.07**##	21.87±0.74**##	30.27±1.12**##	7.79±0.55**##	1.16±0.22##	1.20±0.42##
F	84.07	148.60	162.51	207.09	26.30	20.48
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

FBG: fasting blood glucose; UTP: urine total protein; SCr: serum creatinine; BUN: blood urea nitrogen; TC: total cholesterol; TG: triglyceride. Compared with normal control group, ** $P<0.01$; compared with normal saline group, ## $P<0.01$.

2.4 3组大鼠 IL-1β、IL-18 水平比较

结果显示,生理盐水组大鼠血清 IL-1β、IL-18 水平较正常对照组显著升高;经利拉鲁肽干预后,IL-1β、IL-18 水平明显下降,差异均有统计学意义($P<0.01$;表3)。

表3 3组大鼠 IL-1β 与 IL-18 水平比较

Table 3 Comparison of serum IL-18 and IL-1 β expression among three groups of rats (pg/ml, $n=6$, $\bar{x}\pm s$)

Group	IL-18	IL-1β
Normal control	27.15±3.97	20.87±1.01
Normal saline	90.26±2.82**	55.53±0.89**
Liraglutide	44.38±2.43**##	42.85±0.98**##
F	104.50	83.16
P value	<0.01	<0.01

IL-18: interleukin-18, IL-1β: interleukin-1β. Compared with normal control group, ** $P<0.01$; compared with normal saline group, ## $P<0.01$.

2.5 3组大鼠 NLRP3 炎症小体蛋白表达情况比较

Western blot 检测结果显示,生理盐水组 NLRP3 蛋白表达量较正常组明显增加,而经过利拉鲁肽干预后,NLRP3 蛋白表达量有所下降;生理盐水组凋亡相关斑点样蛋白 ASC 表达量较正常组明显增加,利拉鲁肽干预后,ASC 蛋白表达下降;生理盐水组 caspase-1 蛋白表达量较正常组明显增加,经过利拉鲁肽的干预,caspase-1 蛋白下降。研究结果显示,利拉鲁肽干预可明显改善糖尿病肾病大鼠肾脏组织中 NLRP3 炎症小体的表达,从而改善糖尿病肾病大鼠疾病的进展(图1)。

2.6 利拉鲁肽对 DN 大鼠肾脏病理变化的影响

肾组织 HE 染色光学显微镜下观察显示,与正常对照组相比,生理盐水组出现肾小球体积增大、结构紊乱,系膜外基质增多,基底膜增厚明显,利拉鲁肽组大鼠肾脏病理变化减轻(图2)。

3 讨 论

糖尿病现已成为一个全球性的健康问题,DN 是糖尿病常见的微血管并发症。DN 是糖尿病患者发病和死亡的主要原因,其在1型和2型糖尿病患者中患病率分别为30%和50%[6]。目前尚无治疗 DN 的特异性药物,而现有的治疗效果尚不能令人满意,全球近1/2的 DN 患者需要肾脏替代治疗[7]。一项荟萃分析提示,GLP-1 受体激动剂对2型糖尿病的肾脏结局具有有益影响[8]。本研究使用高糖高脂饮食联合 STZ 制备 DN 大鼠模型,观察利拉鲁肽对 DN 大鼠肾脏功能的保护作用,结果显示持续高血糖状态下,肾小球硬化、肾小管扩张或萎缩、细胞外基质过度蓄积、间质纤维化等各种病理改变,引起肾脏结构及功能上的改变,促进 DN 的发生与发展。一项临床研究发现,患有3期慢性肾脏病的超重糖尿病患者,经过利拉鲁肽治疗18周后,肾小球滤过率增加,尿白蛋白显著减少[9]。本研究亦发现,利拉鲁肽治疗后,DN 大鼠体质量、24 h 尿量、血

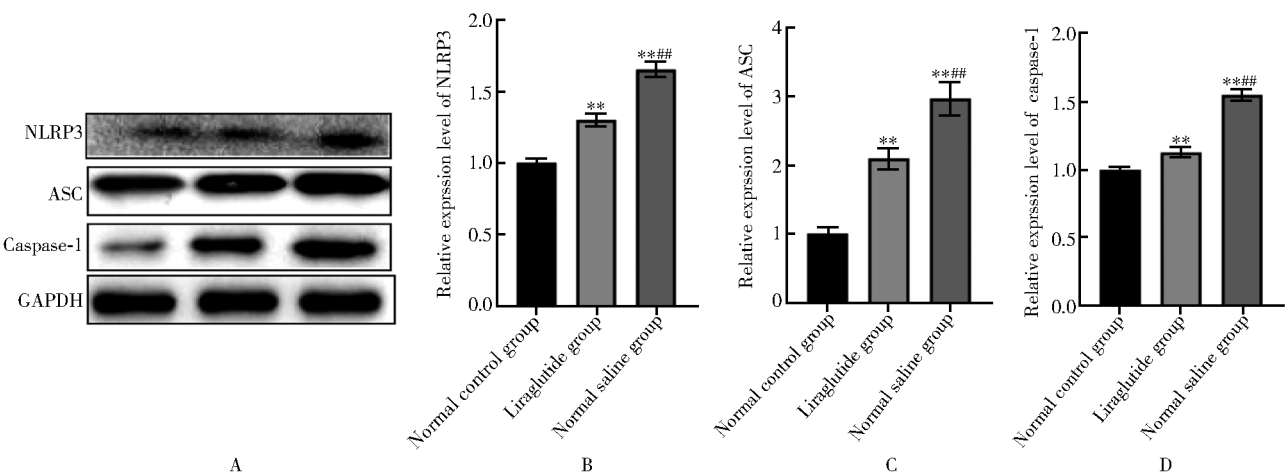
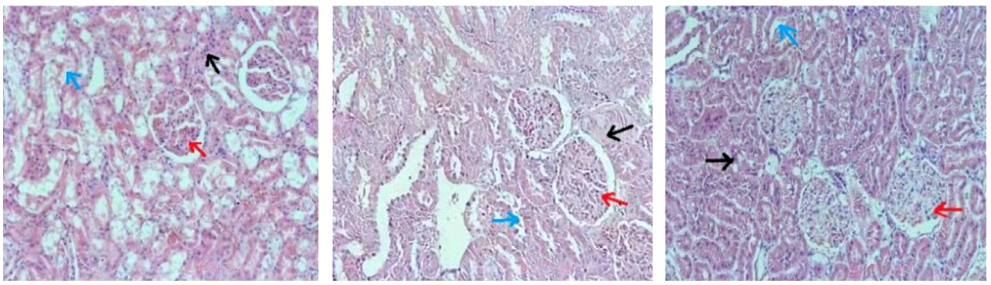


图1 3组大鼠 NLRP3 炎症小体相关蛋白表达情况比较

Figure 1 Comparison of NLRP3 inflammasome-associated protein expression among three groups

A: protein levels of NLRP3, ASC and caspase-1 in renal tissue were detected by Western blot; B, C, D: statistical analysis results. NLRP3: NOD-like receptor pyrin domain containing 3; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain; caspase-1: cysteinyl aspartate specific protease-1; GAPDH: glyceraldehyde-3-phosphate dehydrogenase. Compared with normal control group, ** $P<0.01$; compared with normal saline group, ## $P<0.01$.



A B C

图 2 3 组大鼠肾组织光镜图片

Figure 2 Light microscopic findings of renal tissue of rats in three groups (HE ×200)

A: renal tissue of normal control group, shows clear glomerular structure, a small amount of renal interstitium around renal tubules; B: renal tissue of normal saline group, shows increased glomerular volume, mesangial cell proliferation, tubular cell vacuolar degeneration, interstitial inflammatory infiltration; C: renal tissue of liraglutide group, shows glomerular volume decreased, mesangial cell proliferation decreased, mesangial matrix increased. Red arrow indicates glomerulus; blue arrow indicates renal tubules; black arrow indicates renal mesenchyme.

脂、血糖均明显降低,SCr、BUN、UTP 等生化指标明显改善,然而对 DN 大鼠摄食量无明显影响,提示利拉鲁肽具有肾脏保护作用。肾脏纤维化是所有 CKD 的最终途径,它会导致进行性肾损伤,比肾小球损伤更能加快肾功能衰竭,而且目前尚无特异性治疗方法。Xu 等[10]研究发现利拉鲁肽通过增加存活因子葡萄糖调节蛋白 78(glucose-regulated protein 78,GRP78)的表达减轻肾细胞凋亡,可有效改善血管平滑肌细胞从合成表型向收缩表型的转化,从而减少高糖环境诱导的肾纤维化。本研究结果显示,DN 大鼠肾脏重量增加,肾小球肥大导致肾脏大小和重量增加,是早期 DN 的形态学标志。肾脏组织 HE 染色结果显示,利拉鲁肽组大鼠肾脏肾小球形态更规则,肾小管水肿减轻;相反生理盐水组大鼠表现出明显的病理变化,包括肾小球形态不规则,肾小管水肿伴部分坏死,说明利拉鲁肽可对 DN 发挥保护作用。

NLRP3 炎症小体参与多种慢性肾脏疾病的发生与发展[11]。在 DN 患者肾组织活检及 DN 大鼠肾组织中均可以观察到 NLRP3 炎症小体的激活[12,13]。本研究中,DN 组大鼠肾脏组织中 NLRP3、caspase-1、ASC 蛋白表达高于正常对照组,血清 IL-18 和 IL-1β 水平也显著升高,与 Feng 等[14]研究结果一致。Fu 等[15]研究显示,在体外培养肾小球系膜细胞,经高糖刺激一段时间后,NLRP3 和 caspase-1 蛋白的表达明显增加,并随着刺激时间的延长而增加。Qiu 等[16]研究显示,在 2 型糖尿病患者中,尿白蛋白排泄率与血清和尿液中 IL-18 的水平之间存在独立相关性,并且血清和尿液中 IL-18 的水平与蛋白尿的程度呈正相关,表明这些炎症标志物可能是 DN 发展的独立危险因素。IL-1β 水平升高可导致肾近端小管上皮细胞增殖,内皮细胞通透性增加,诱导细胞间黏附因子-1(intercellular adhesion factor-1,ICAM-1)、转化生长因子-β1(transforming growth factor-β1,TGF-β1)和钙黏蛋白的表达,影响肾小球血流动力学变化,从而进一步加重肾脏损害。Sakai 等[17]研究表明,抑制 DN 患者体内 NLRP3 炎症小体的激活和表达可以改善患者的肾功能,延缓肾脏病理变化。NLRP3 炎症小体通过诱导 IL-1β 和 IL-18 产生将糖尿病肾脏代谢反应与促炎级联反应的激活联系起来。江思瑜等[18]研究发现,利拉鲁肽可以抑制 TOLL 样受体 4/髓样分化初级反应蛋白 88(TOLL like receptor 4/myeloid differentiation primary response protein 88,TLR4/MyD88)先天免疫信号转导通路,降低促炎因子的表达,发挥肾脏保护作用。Kawanami 等[19]研究发现,利拉鲁肽还可激活环磷酸腺苷-蛋白激酶 A(cyclic adenosine monophosphate-protein kinase A,cAMP-PKA)通路,减少肾脏活性氧的产生,抑制 NLRP3 炎症小体的激活,进而减轻肾脏内皮细胞炎症所致损伤,同时抑制 TGF-β 及其下游信号通路,减弱肾小管上皮-间质转化(renal tubular epithelial-mesenchymal transition,EMT),预防和修复肾小管间质纤维化。本研究结果与此一致,经过利拉鲁肽干预后,大鼠肾脏组织中 NLRP3 炎症小体蛋白表达下降,其下游炎症因子 IL-18、IL-1β 也下降,说明利拉鲁肽可能抑制了 NLRP3 炎症小体的激活,从而发挥对 DN 大鼠肾脏保护作用。

综上,DN 中存在 NLRP3 炎症小体的激活,利拉鲁肽可能通过抑制 NLRP3 炎症小体的表达,延缓 DN 的病情进展。NLRP3 炎症小体可能成为防治 DN 的新靶点,未来需要我们深入研究其具体作用机制。

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