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姜辣素对链霉素诱导糖尿病大鼠 ghrelin 表达及胃轻瘫的影响 *

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摘要 目的:探究姜辣素对链霉素诱导糖尿病大鼠胃肠功能的影响。**方法:**链霉素诱导糖尿病大鼠连续灌胃姜辣素(100, 200, 400 mg/kg)28天,检测胃部超氧化物歧化酶(SOD)和过氧化氢酶(CAT)活性、谷胱甘肽(GSH)和丙二醛(MDA)含量以及胃排空。结果:糖尿病大鼠 SOD、CAT 以及 GSH 水平降低 (SOD: 6.29± 1.03 vs. 3.41± 1.21; CAT: 27.43± 5.27 vs. 10.52± 2.37, GSH: 1091.27± 170.09 vs. 685.07± 75.24, P<0.05), MDA 水平增高 (9.79± 2.41 vs. 46.38± 12.59, P<0.05), 姜辣素灌胃后 SOD、CAT 以及 GSH 水平增高 (SOD: 3.41± 1.21 vs. 4.36± 1.01, 5.62± 1.18, 7.05± 1.48, 6.48± 1.82; CAT: 10.52± 2.37 vs. 15.27± 4.59, 19.29± 5.42, 23.79± 6.35, GSH: 10.52± 2.37 vs. 15.27± 4.59, 19.29± 5.42, 23.79± 6.35, P<0.05-0.01), MDA 水平降低 (46.38± 12.59 vs. 34.61± 9.27, 28.01± 8.34, 19.17± 5.19, P<0.05-0.01);糖尿病大鼠胃 ghrelin 水平下降 (381.26± 94.37 vs. 195.07± 57.42, P<0.01) 血浆 ghrelin 水平上升 (76.86± 21.81 vs. 108.83± 27.75, P<0.05) 胃 ghrelin mRNA 表达增多, 给予中高剂量姜辣素后胃 ghrelin 水平上升 (195.07± 57.42 vs. 301.43± 81.24, 328.93± 76.59, P<0.05~0.01) 胃 ghrelin mRNA 表达减少, 呈量效依赖关系;糖尿病大鼠胃排空降低 (82.24± 19.74 vs. 45.37± 11.23, P<0.01), 给予姜辣素后胃排空增强 (45.37± 11.23 vs. 52.43± 15.42, 49.89± 9.84, 74.39± 20.79, P<0.05-0.01)。**结论:**姜辣素通过抗氧化性改善糖尿病胃轻瘫。

关键词:姜辣素;糖尿病胃轻瘫;ghrelin;胃排空;氧化应激**中图分类号:**R-33; R587.2 **文献标识码:**A **文章编号:**1673-6273(2018)06-1067-06

The Effect of Gingerol on the Expression of Ghrelin and Gastroparesis in Gastric Tissues of Streptozotocin-induced Diabetic Rats*

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ABSTRACT Objective: Aim to investigate the effect of gingerol on gastrointestinal function in streptozotocin-induced diabetic rats.

Methods: Gingerol was administrated intragastrically at a dose of 100, 200 and 400 mg/kg/day to diabetic rats. After 28 dayst, assayed the activity of superoxide dismutase (SOD), catalase (CAT), the content of reduced glutathione (GSH), malondialdehyde (MDA) in gastric mucosa and gastric emptying. **Results:** The diabetic rats exhibited significant decreases in the above mentioned antioxidative enzymes activities and GSH level and exhibited a high level of MDA(SOD: 6.29± 1.03 vs. 3.41± 1.21; CAT: 27.43± 5.27 vs. 10.52± 2.37, GSH: 1091.27± 170.09 vs. 685.07± 75.24, MDA: 9.79± 2.41 vs. 46.38± 12.59, P<0.05). After administration of gingerol, SOD, CAT and GSH level increase (SOD: 3.41± 1.21 vs. 4.36± 1.01, 5.62± 1.18, 7.05± 1.48, 6.48± 1.82; CAT: 10.52± 2.37 vs. 15.27± 4.59, 19.29± 5.42, 23.79± 6.35, GSH: 10.52± 2.37 vs. 15.27± 4.59, 19.29± 5.42, 23.79± 6.35, P<0.05-0.01), MDA level decrease (46.38± 12.59 vs. 34.61± 9.27, 28.01± 8.34, 19.17± 5.19, P<0.05-0.01); After administration of gingerol, the parameters were ameliorated to a large extent; gingerol treatment dose-dependently augmented the ghrelin levels of stomach and plasma (195.07± 57.42 vs. 301.43± 81.24, 328.93± 76.59, P<0.05~0.01), which were earlier depleted in the diabetic control rats; the expression of ghrelin mRNA was decreased after gingerol treatment; the gastric emptying in gingerol treated diabetic rats (45.37± 11.23 vs. 52.43± 15.42, 49.89± 9.84, 74.39± 20.79, P <0.05-0.01) was notably accelerated compared with the diabetic control rats. **Conclusion:** The gingerol can against streptozotocin-induced gastroparesis possibly by its antioxidant property.

Key words: Gingerol; Diabetic gastroparesis; Ghrelin; Gastric emptying; Oxidative stress**Chinese Library Classification(CLC):** R-33; R587.2 **Document code:** A**Article ID:** 1673-6273(2018)06-1067-06

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前言

糖尿病，是一种常见的伴有高血糖慢性代谢紊乱性疾病，已经成为威胁人类健康的第三大杀手，仅次于肿瘤和心血管疾病^[1]。糖尿病患者多伴有消化系统异常^[2]，其中最常见的是胃轻瘫^[3-5]。糖尿病胃轻瘫患者胃排空减缓，胃运动下降^[6,7]。目前糖尿病胃轻瘫的治疗主要是以缓解症状为主^[8]。

有研究发现，30-50%的糖尿病患者受胃轻瘫困扰^[9]，糖尿病胃轻瘫的主要发病机制为高血糖引起的自主神经病变、激素水平改变以及肠神经系统功能障碍。Ghrelin 是一种主要由胃肠道粘膜分泌的脑肠肽，能够促进摄食和胃肠蠕动的作用。姜辣素是生姜提取物，主要成分有姜酚及姜烯酚，有研究发现，姜辣素具有抗炎、抗氧化、抗糖尿病及心血管疾病的作用^[10,11]。慢性高血糖导致葡萄糖氧化、蛋白质氧化以及脂质氧化、促进自由基产生从而导致氧化应激^[12,13]。目前关于姜辣素的抗氧化作用能否降低血糖，缓解糖尿病胃轻瘫及其机制的研究较少。

本研究旨在研究姜辣素是否能够作用于 STZ 诱导糖尿病大鼠，减少氧化应激，缓解胃轻瘫，增加 ghrelin 表达，促进胃排空。

1 材料与方法

1.1 实验动物

雄性 Wistar 大鼠， 250 ± 20 g，室温 22 ± 2 °C，12/12 循环光照，饮食自由，所有动物实验均符合《青岛大学实验动物保护和使用管理办法》。

1.2 糖尿病模型制备

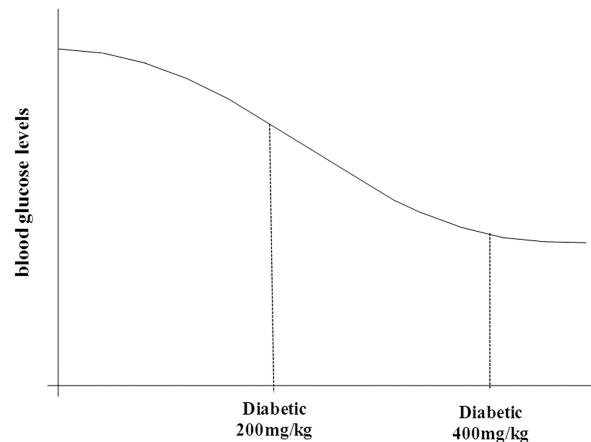
参考已有文献制备糖尿病大鼠模型^[14,15]。实验组大鼠给予高脂饮食饲养 4 周^[14]，对照组大鼠给予正常饲料，所有大鼠均饮水自由。高脂饮食饲养 4 周后，实验组大鼠禁食 12 小时后腹腔注射 1% 链霉素 (STZ, 35 mg/kg，溶于 0.1 M 柠檬酸缓冲液中)，注射后第 8 天再进行一次 35 mg/kg 链霉素注射。对照组注射方式及时间与实验组大鼠相同，仅注射同体积的柠檬酸缓冲液。实验组大鼠注射完成 72 h 后，大鼠禁食 12 h，进行口服糖耐量测试(葡萄糖，3.0 g/kg)。2 h 后测量大鼠血液中葡萄糖浓度、胰岛素水平及胰岛素抵抗 (IR)。选取血糖值高于 200 mg/dL 的大鼠做为实验组进行后续实验^[16]。对照组大鼠血浆胰岛素含量为 22.74 含量为岛素含 μ IU/mL, IR 为 5.1，实验组大鼠血浆胰岛素含量为 21.91 ± 5.62 μ IU/mL, IR 为 18.7。姜辣素从第二次注射链霉素后第八周开始灌胃，给药 28 天。

使用试剂盒检测血清胰岛素水平，胰岛素抵抗 (IR)^[17]= 空腹胰岛素水平 (μ IU/mL) \times 空腹血糖水平 (mmol/L) / 22.5。

1.3 实验设计

本研究分为两部分，第一部分分为 7 组每组 8 只大鼠：第 1 组，从正常大鼠中随机选取 8 只，给予生理盐水灌胃；第 2 组，从实验组大鼠中随机选取 8 只，给予生理盐水灌胃；第 3 组，从实验组大鼠中随机选取 8 只，给予姜辣素 100 mg/kg 灌胃；第 4 组，从实验组大鼠中随机选取 8 只，给予姜辣素 200 mg/kg 灌胃；第 5 组，从实验组大鼠中随机选取 8 只，给予姜辣素 400 mg/kg 灌胃；第 6 组，从对照组大鼠中随机选取 8 只，给予姜辣素 200 mg/kg 灌胃；第 7 组从实验组大鼠中随机选取 8

只，给予罗格列酮 2 mg/kg 灌胃。经过 28 天给药后，大鼠处死取胃，沿胃大弯剪开胃，生理盐水冲洗后，液氮浸泡后冻存于 -80 °C。



第二部分，实验分组与第一部分相同，给药结束后参照已有文献测量胃排空^[18]。蒸馏水加热至 80 °C 后加入甲基纤维素，配制成 1.5% 甲基纤维素溶液。溶液降温至 37 °C 后调整 pH 至 7.2，加入苯酚红 (1 mg/mL) 做为标准溶液。实验开始前大鼠禁食 18 h，给予大鼠经口灌胃 1.5 mL 甲基纤维素溶液，30 分钟后处死大鼠，结扎幽门和贲门后沿胃大弯剪开胃。收集胃内容物，使用 0.1 N NaOH 定容至 100 mL，室温静置 1 小时。取 5 mL 上清液加入 0.5 mL 20% 三氯乙酸，1007× g 离心 15 min 后，加入 4 mL 0.5 N NaOH，测量 560 nm 处吸光度，胃排空率计算公式：

$$\text{胃排空率\%} = \times 100\%$$

1.4 样本分析

分别参考已有文献对过氧化物歧化酶 (SOD) 活性^[19]、过氧化氢酶 (CAT) 活性^[20]、还原型谷胱甘肽 (GSH)^[21] 进行量化分析，脂类过氧化程度根据硫代巴比妥法测定的丙二醛 (MDA) 进行评估^[22]。血糖使用试剂盒检测。

1.5 ghrelin 及 ghrelin mRNA 测定

1.5.1 放射免疫法 (RIA) 测定 ghrelin 使用试剂盒测定 ghrelin 水平。在血液样本中加入 EDTA 和抑肽酶后冻存于 -80 °C。胃组织样本使用 PBS 清洗两次后在生理盐水中加热 5 min，使用滤纸吸干水分。分离粘膜并称重，最后加入 1 M 冷盐酸溶液匀浆。室温孵育 2 h 后，加入等体积 1 M NaOH, 4 °C 1790× g 离心 20 min，上清液冻存于 -70 °C。

RIA 法检测 ghrelin 水平，样本或标准液加入 ghrelin 抗体 4 °C 孵育 24 h，加入 125 I-ghrelin 后再 4 °C 孵育 24 h，加入用沉淀剂沉淀抗原抗体复合物 20 mg 活性炭，室温静置 45 min, 4 °C 1790× g 离心 20 min，取上清液在 g- 闪烁仪进行 5 min 放射性计数。

1.5.2 RT-PCR 使用 TRIzol 提取大鼠胃组织总 RNA。合成单链 cDNA 的逆转录酶为 superscriptTM II RNase H⁻。95 °C 孵育 10 min 后 42 °C 孵育 1 h，以合成的 cDNA 作为 PCR 模板，进行 35 次扩增 (95 °C × 15 s 变性, 65 °C × 10 s 退火, 72 °C × 15 s 延长)。Ghrelin 引物：5'-TTGAGCCCAGAGCACCAAGAAA-3' (正义链) 及 5'-AGTTGCAGAGGAGGCAGAACGCT-3' (反义链)。以

GAPDH 为内参, 5'-CGGCAAGTTAACGGCACAG-3' (有义链), 5'-ACTCCACGACATACTCAGCAC-3' (反义链)。使用 GeneAmp 5700 SDS 分析数据, 计算公式 $\Delta Ct = Ct_{\text{ghrelin}} - Ct_{\text{GAPDH}}$

1.6 统计分析

实验中数据以 $\bar{X} \pm \text{SEM}$ 表示, 数据的统计分析使用 Prism5.0, 用双因素方差分析(ANOVA)进行组间两两比较, $P < 0.05$ 为有统计学意义。

2 实验结果

2.1 姜辣素对血糖的影响

与对照组相比, STZ 诱导糖尿病大鼠血糖上升。糖尿病大鼠姜辣素治疗 28 天后, 未给与治疗的糖尿病大鼠相比, 血糖降低并呈剂量依赖性 (gingerol 100 mg/kg: 300.37 ± 37.19 vs. 237.45 ± 41.36 ; gingerol 200 mg/kg: 310.42 ± 45.27 vs. 218.36 ± 39.71 ; gingerol 400 mg/kg: 289.36 ± 41.34 vs. 151.64 ± 38.24 , $P < 0.05-0.01$)。正常大鼠给予姜辣素, 血糖未发生明显变化 ($P > 0.05$)。与糖尿病大鼠相比, 使用罗格列酮治疗后, 大鼠血糖明显下降 (338.27 ± 43.27 vs. 132.92 ± 36.59 , $P < 0.01$, 图 1), 并且罗格列酮对血糖的降低作用强于姜辣素 100 mg/kg 组 (237.45 ± 41.36 vs. 132.92 ± 36.59 , $P < 0.01$, 图 1) 和姜辣素 200 mg/kg 组 (237.45 ± 41.36 vs. 218.36 ± 39.71 , $P < 0.05$, 图 1)。

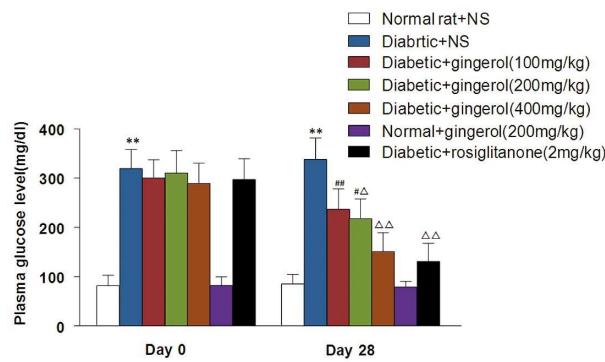


图 1 姜辣素对血糖的影响

Fig.1 Effect of gingerol on the blood glucose levels

** $P < 0.01$ vs. Normal rat+NS, # $P < 0.05$, ## $P < 0.01$ vs. Diabetic+rosiglitazone, $\Delta P < 0.05$, $\triangle P < 0.01$ vs. Diabetic+NS

2.2 姜辣素对 STZ 诱导糖尿病大鼠抗氧化酶活性、GSH 以及 MDA 水平影响

与未经治疗的糖尿病大鼠相比, 姜辣素中高剂量组大鼠 SOD、CAT 及 GSH 水平上升且呈量效依赖关系 (SOD: 3.41 ± 1.21 vs. 4.36 ± 1.01 , 5.62 ± 1.18 , 7.05 ± 1.48 , 6.48 ± 1.82 ; CAT: 10.52 ± 2.37 vs. 15.27 ± 4.59 , 19.29 ± 5.42 , 23.79 ± 6.35 ; GSH: 10.52 ± 2.37 vs. 15.27 ± 4.59 , 19.29 ± 5.42 , 23.79 ± 6.35 , $P < 0.05-0.01$, 图 2) 而 MDA 水平下降 (46.38 ± 12.59 vs. 34.61 ± 9.27 , 28.01 ± 8.34 , 19.17 ± 5.19 , $P < 0.05-0.01$, 图 2)。经罗格列酮治疗的糖尿病大鼠, 与未经治疗糖尿病大鼠相比, SOD、CAT、GSH 及 MDA 水平无明显改变 ($P > 0.05$)。正常大鼠给予姜辣素后 SOD、CAT、GSH 及 MDA 水平无明显改变 ($P > 0.05$)。

2.3 姜辣素对 STZ 诱导糖尿病大鼠血浆 ghrelin、胃 ghrelin 以

及 ghrelin mRNA 水平影响

与正常组相比, 糖尿病大鼠胃 ghrelin 水平明显下降 (381.26 ± 94.37 vs. 195.07 ± 57.42 , $P < 0.01$, 图 3.1 图 3.2), 但血浆 ghrelin 水平上升 (76.86 ± 21.81 vs. 108.83 ± 27.75 , $P < 0.05$, 图 3.2)。与未经治疗糖尿病大鼠相比, 使用姜辣素后胃 ghrelin 水平上升, 由 195.07 ± 57.42 上升至 301.43 ± 81.24 pg/mg (200 mg/kg, $P < 0.05$, 图 3.1 图 3.2) 以及 328.93 ± 76.59 pg/mg (400 mg/kg, $P < 0.01$, 图 3.1 图 3.2)。经过治疗后的糖尿病大鼠血浆 ghrelin 水平高于未经治疗糖尿病大鼠 ($P < 0.05-0.01$, 图 3)。

与正常大鼠相比, 糖尿病大鼠胃 ghrelin mRNA 表达明显增多 ($P < 0.01$, 图 3.2)。与未经治疗的糖尿病大鼠相比, 经姜辣素 400 mg/kg 治疗后, 胃 ghrelin mRNA 表达减少 ($P < 0.05$, 图 3.2)。与正常大鼠相比, 给予姜辣素后胃 ghrelin mRNA 表达无改变 ($P > 0.05$), 与糖尿病组大鼠相比, 经罗格列酮治疗后, 胃 ghrelin mRNA 表达无改变 ($P > 0.05$)。

2.4 姜辣素对 STZ 诱导糖尿病大鼠胃排空影响

与正常大鼠相比, 糖尿病大鼠胃排空明显下降 (82.24 ± 19.74 vs. 45.37 ± 11.23 , $P < 0.01$, 图 4)。与糖尿病大鼠相比, 给予姜辣素治疗后胃排空上升, 呈明显量效依赖关系 (45.37 ± 11.23 vs. 52.43 ± 15.42 , 49.89 ± 9.84 , 74.39 ± 20.79 , $P < 0.05-0.01$, 图 4)。但是与糖尿病大鼠相比, 给予罗格列酮治疗后, 大鼠胃排空无明显改变 ($P > 0.05$)。与正常大鼠相比, 给予姜辣素后大鼠胃排空无明显改变 ($P > 0.05$)。

3 讨论

本研究发现, 使用 STZ 诱导糖尿病的大鼠经姜辣素治疗后糖尿病大鼠血糖降低, 并且糖尿病大鼠 SOD、CAT 及 GSH 水平上升且呈量效依赖关系而 MDA 水平下降, 血浆及胃 ghrelin 水平、胃 ghrelin 表达增强, 胃排空增强。

目前糖尿病动物模型普遍使用链霉素(STZ)诱导产生, 在实验中也观察到 STZ 诱导糖尿病大鼠血糖上升, 给予姜辣素后 STZ 诱导糖尿病大鼠血糖水平降低, 且呈量效依赖关系, 表明姜辣素能够降低血糖。

在本研究中发现糖尿病大鼠 SOD、CAT 以及 GSH 水平低于正常大鼠, 有研究发现 STZ 能够促进氧自由基(ROS)生成, 抑制氧自由基防御系统损伤胰岛 β 细胞损伤^[23-25], 氧化应激反应是人体重要的防御系统, 机体能够平衡 ROS 的生成和消除。在病理条件下, 如动脉粥样硬化、冠状动脉疾病、糖尿病以及癌症等, 氧自由基大量生成并且抗氧化反应受抑制。已经有研究表明氧化应激参与糖尿病及其并发症的发生发展^[26-27]。ROS 通常使生物膜脂质过氧化, 引起细胞内蛋白质变性, 损伤酶和 DNA, 导致细胞死亡^[28]。酶促抗氧化是第一道抗氧化防御系统, 与抗氧化剂一起保护机体免受自由基攻击^[29]。结合本研究结果推断糖尿病大鼠活性氧代谢产物的水平升高, 抗氧化作用受抑制, 产生大量 H_2O_2 、 O_2^- 及脂质氢过氧化物对组织产生损伤^[30]。经过姜辣素治疗的糖尿病大鼠表现出 SOD、CAT 以及 GSH 增多, 表明姜辣素能够清除自由基保护细胞对抗氧化应激, 这项发现与其他的研究结果相吻合^[31,32]。

与正常大鼠相比糖尿病大鼠脂质过氧化产物 MDA 水平明显增高, 推断糖尿病大鼠体内抗氧化剂减少。细胞膜脂质过

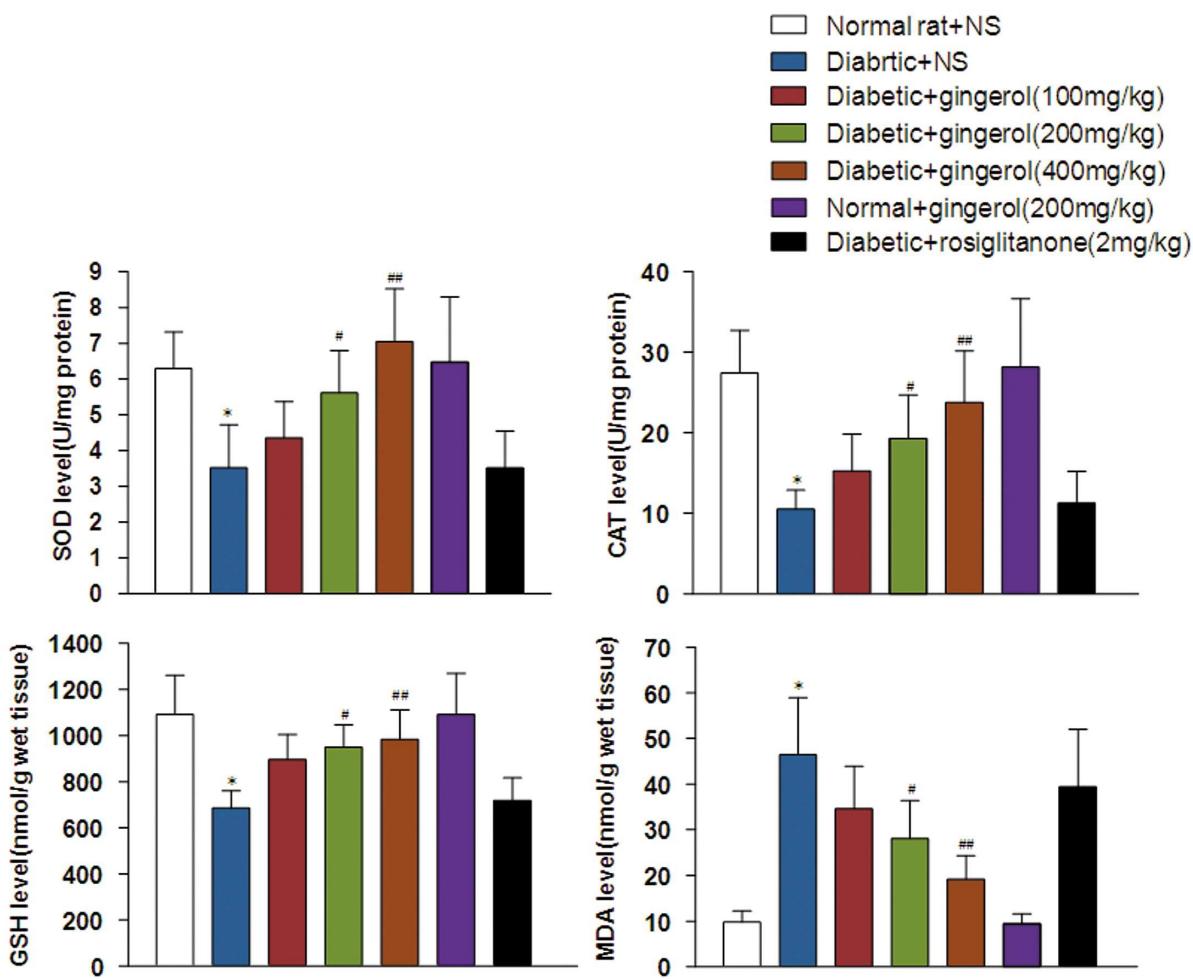


图 2 姜辣素对 STZ 诱导糖尿病大鼠抗氧化酶活性、GSH 以及 MDA 水平影响

Fig. 2 Effects of gingerol on enzymatic antioxidant activity and GSH and MDA contents in stomachs of normal and STZ induced diabetic rats.

*P<0.05 vs. Normal rat+NS group, #P<0.05, ##P<0.01 vs. Diabetic+NS group

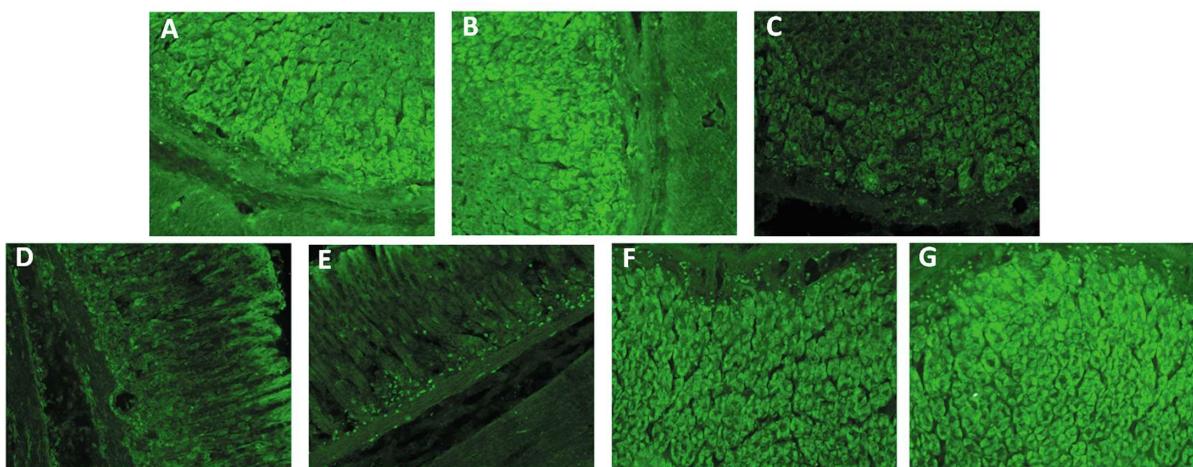


图 3.1 姜辣素对 STZ 诱导糖尿病大鼠胃 ghrelin 的影响

A, 正常大鼠 + 生理盐水; B, 正常大鼠 + 姜辣素 200 mg/kg; C, 糖尿病大鼠 + 罗格列酮 2 mg/kg; D, 糖尿病大鼠 + 姜辣素 100 mg/kg; E, 糖尿病大鼠 + 姜辣素 200 mg/kg; F, 糖尿病大鼠 + 姜辣素 400 mg/kg; G, 正常大鼠 + 姜辣素 200 mg/kg

Fig. 3.1 Effect of gingerol on stomach ghrelin of stomachin STZ-induced diabetic rats

A, Normal rat + NS; B, Normal rat + gingerol 200 mg/kg; C, Diabetic + rosiglitazone 2 mg/kg; D, Diabetic + gingerol 100 mg/kg; E, Diabetic + gingerol 200 mg/kg; F, Diabetic + gingerol 400 mg/kg; G, Normal rat + gingerol 200 mg/kg

氧化反应增强导致大量脂质氢过氧化物的形成, 导致细胞膜结构破坏及功能损伤^[33]。而使用姜辣素治疗后 MDA 水平降低^[31]。

使用姜辣素治疗的糖尿病大鼠抗氧化能力增强, MDA 水平降低, 表明姜辣素能够增强糖尿病大鼠的抗氧化能力。

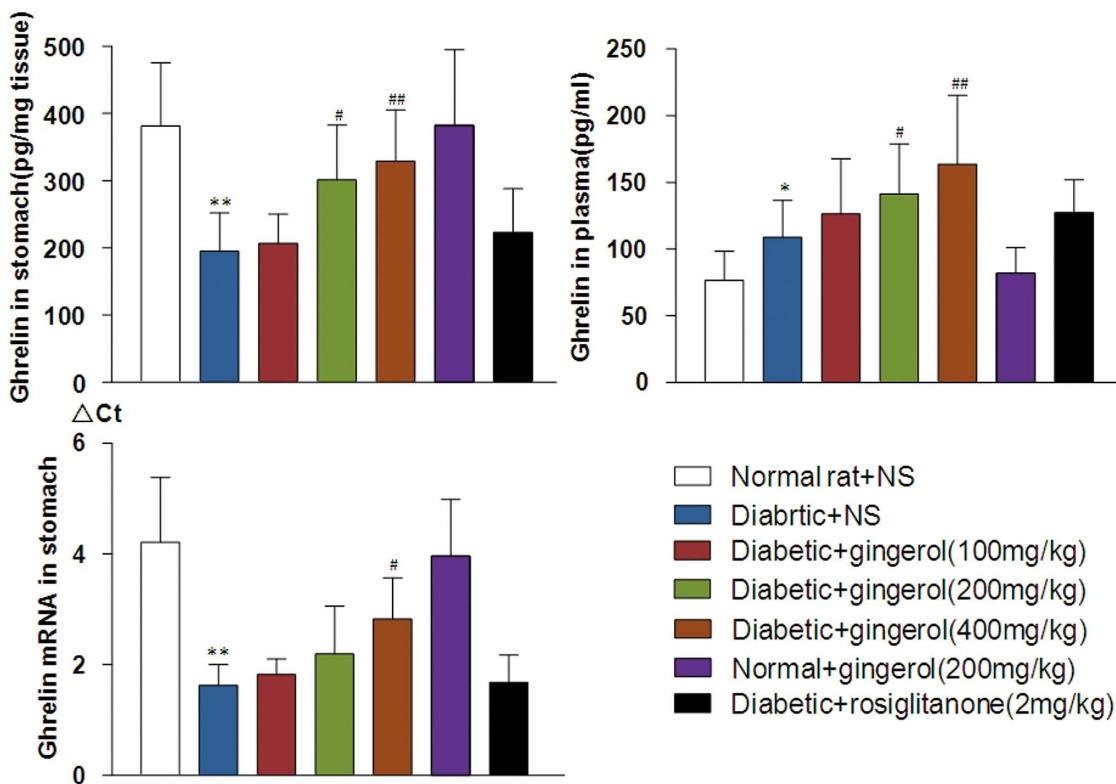


图 3.2 姜辣素对 STZ 诱导糖尿病大鼠血浆 ghrelin、胃 ghrelin 以及 ghrelin mRNA 水平影响

Fig 3.2 Effect of gingerol on plasma ghrelin, stomach ghrelin and ghrelin mRNA of stomach in STZ-induced diabetic rats

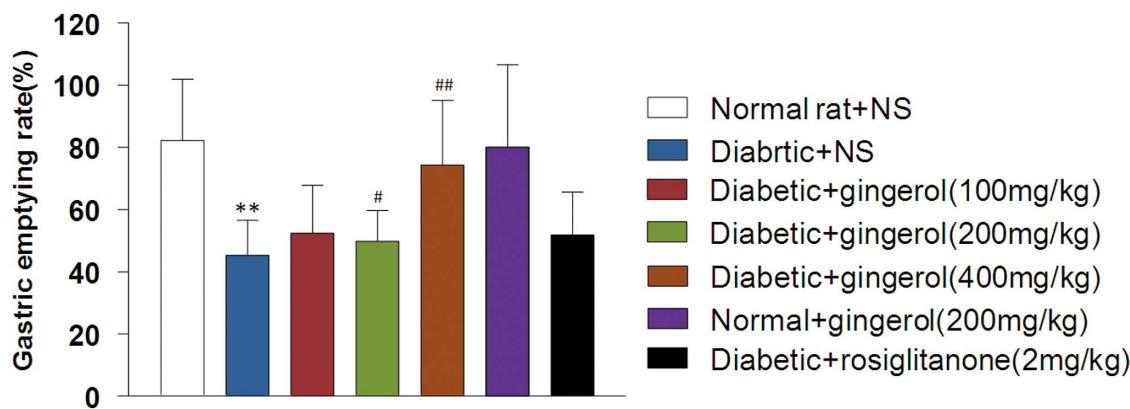
 $*P < 0.05$, $**P < 0.01$ vs. Normal rat+NS group, $#P < 0.05$, $##P < 0.01$ vs. Diabetic+NS group

图 4 姜辣素对 STZ 诱导糖尿病大鼠胃排空影响

Fig 4 Effect of gingerol on gastric emptying rate in STZ-induced diabetic rats

 $**P < 0.01$ vs. Normal rat+NS group, $#P < 0.05$, $##P < 0.01$ vs. Diabetic+NS group

本研究观察到糖尿病大鼠经姜辣素治疗后胃 ghrelin 水平上升, 血浆 ghrelin 水平下降, 但是血浆 ghrelin 水平依然高于正常大鼠。表明, 姜辣素可能能够促进糖尿病大鼠胃 ghrelin 的合成及释放。有趣的是, 研究中还观察到经过姜辣素治疗后的糖尿病大鼠, 胃 ghrelin mRNA 的表达减少。表明在机体负能量平衡状态下, 胃 ghrelin mRNA 表达受抑制, ghrelin 的表达及分泌减少。但是目前的研究并不能完全解释 ghrelin 及 ghrelin mRNA 间的表达差异, 未来将对此进行进一步研究。

本研究发现使用姜辣素治疗的糖尿病大鼠胃排空增强。有研究发现静脉注射 ghrelin 能够增强糖尿病胃轻瘫患者胃排空^[34]。Ghrelin 是一种促生长激素分泌素, 人类以及大鼠的胃均能

够表达 ghrelin^[35]。在人类及啮齿动物, ghrelin 能够刺激生长激素释放, 促进摄食^[36], 促进胃排空^[37], 在饥饿、恶病质或厌食症等机体负能量平衡状态下, 血浆 ghrelin 水平上升^[38-41]。有研究表明胃底 A 样细胞能够分泌 ghrelin^[42]。本研究发现 STZ 诱导糖尿病大鼠血浆 ghrelin 水平以及胃 ghrelin mRNA 表达水平升高, 但是胃 ghrelin 降低。糖尿病大鼠血浆 ghrelin 水平上升而胃 ghrelin 水平下降可能是由于胃分泌 ghrelin 后大量释放至血液。

综上所述, 本研究发现, STZ 诱导糖尿病大鼠经姜辣素治疗后能够改善胃肠功能, 抑制氧化损伤。未来仍需要深入研究在糖尿病中姜辣素抗氧化作用的机制, 以便为治疗糖尿病及其并发症提供新策略。

参考文献(References)

- [1] KingH, AubertRE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections [J]. *Diabetes Care*, 1998, 21(9): 1414-1431
- [2] BytzerP, TalleyNJ, LeemonM, et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults [J]. *Arch Intern Med*, 2001, 161 (16): 1989-1996
- [3] Mohammad MK, Pepper DJ, Kedar A, et al. Measures of Autonomic Dysfunction in Diabetic and Idiopathic Gastroparesis [J]. *Gastroenterology Res*, 2016, 9(4-5): 65-69
- [4] Scheinberg N, Salbu RL, Goswami G, et al. Treatment of Diabetic Autonomic Neuropathy in Older Adults with Diabetes Mellitus [J]. *Consult Pharm*, 2016, 31(11): 633-645
- [5] Walk D. Using Random Forest Methods to Identify Factors Associated with Diabetic Neuropathy: A Novel Approach[J]. *Pain Med*, 2017, 18 (1): 1-2
- [6] Crimmins S, Smiley R, Preston K, et al. Increased Expression of Pyloric ER β Is Associated With Diabetic Gastroparesis in Streptozotocin-Induced Male Diabetic Rats[J]. *Gastroenterology Res*, 2016, 9(2-3): 39-46
- [7] Bharucha AE, Daley SL, Low PA, et al. Effects of hemin on heme oxygenase-1, gastric emptying, and symptoms in diabetic gastroparesis[J]. *Neurogastroenterol Motil*, 2016, 28(11): 1731-1740
- [8] Lacy BE, Crowell MD, Mathis C, et al. Gastroparesis: Quality of Life and Health Care Utilization [J]. *J Clin Gastroenterol*, 2016 [Epub ahead of print]
- [9] Lin G, Zhang J, Li L, et al. Effect of electroacupuncture on gastric interstitial cells of Cajal in a rat model of diabetic gastroparesis [J]. *Exp Ther Med*, 2016, 1(6): 2489-2494
- [10] Natale JJ. Reviewing current and emerging antiemetics for chemotherapy-induced nausea and vomiting prophylaxis [J]. *Hosp Pract* (1995), 2015, 43(4): 226-234
- [11] Yang Y, Kinoshita K, Koyama K, et al. Structure-antiemetic-activity of some diarylheptanoids and their analogues [J]. *Phytomedicine*, 2002, 9(2): 146-152
- [12] Jemil I, Nasri R, Abdelhedi O, et al. Beneficial effects of fermented sardinelle protein hydrolysates on hypercaloric diet induced hyperglycemia, oxidative stress and deterioration of kidney function in wistar rats[J]. *J Food Sci Technol*, 2017, 54(2): 313-325
- [13] Oikonomidis IL, Kiosis EA, Brozos CN, et al. Reference intervals for serum reactive oxygen metabolites, biological antioxidant potential, and oxidative stress index in adult rams [J]. *Am J Vet Res*, 2017, 78 (3): 274-278
- [14] Wang Y, Qi X, Wang C, et al. Effects of propofol on myocardial ischemia-reperfusion injury in rats with type-2 diabetes mellitus [J]. *Biomed Rep*, 2017, 6(1): 69-74
- [15] Dai Y, Yang F, Zhou N, et al. A post-weaning fish oil dietary intervention reverses adverse metabolic outcomes and 11 β -hydroxysteroid dehydrogenase type 1 expression in postnatal overfed rats[J]. *Br J Nutr*, 2016, 116(9): 1519-1529
- [16] MahmoudAM, AshourMB, Abdel-MoneimA, et al. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats[J]. *J Diabetes Complications* 2012, 26(6): 483-490
- [17] Li XG, Lin XJ, Du JH, et al. Combination of methylprednisolone and rosiglitazone promotes recovery of neurological function after spinal cord injury[J]. *Neural Regen Res*, 2016, 11(10): 1678-1684
- [18] Abid S, Jafri W, Zaman MU, et al. Itopride for gastric volume, gastric emptying and drinking capacity in functional dyspepsia [J]. *World J Gastrointest Pharmacol Ther*, 2017, 8(1): 74-80
- [19] Ishihara Y, Tsuji M, Kawamoto T, et al. Involvement of reactive oxygen species derived from mitochondria in neuronal injury elicited by methylmercury[J]. *J Clin Biochem Nutr*, 2016, 59(3): 182-190
- [20] AebiH. Catalase in vitro [J]. *Methods Enzymol*, 1984, 105 (8): 121-126
- [21] Xiong Y, Wang CJ, Tao T, et al. A miniaturized fiber-optic colorimetric sensor for nitrite determination by coupling with a microfluidic capillary waveguide [J]. *Anal Bioanal Chem*, 2016, 408 (13): 3413-3423
- [22] Kanazawa K, Sakamoto M, Kanazawa K, et al. Lipid peroxides as endogenous oxidants forming 8-oxo-guanosine and lipid-soluble antioxidants as suppressing agents [J]. *J Clin Biochem Nutr*, 2016, 59 (1): 16-24
- [23] de Morais H, de Souza CP, da Silva LM, et al. Anandamide reverses depressive-like behavior, neurochemical abnormalities and oxidative-stress parameters in streptozotocin-diabetic rats: Role of CB1 receptors[J]. *Eur Neuropsychopharmacol*, 2016, 26(10): 1590-1600
- [24] Sharma H, Mendiratta SK, Agarwal RK, et al. Evaluation of anti-oxidant and anti-microbial activity of various essential oils in fresh chicken sausages[J]. *J Food Sci Technol*, 2017, 54(2): 279-292
- [25] Raoufi S, Baluchnejadmojarad T, Roghani M, et al. Antidiabetic potential of salvianolic acid B in multiple low-dose streptozotocin-induced diabetes[J]. *Pharm Biol*, 2015, 53(12): 1803-1809
- [26] Boshra V, Atwa A. Effect of cerebrolysin on oxidative stress-induced apoptosis in an experimental rat model of myocardial ischemia [J]. *Physiol Int*, 2016, 103(3): 310-320
- [27] Yue XD, Wang JY, Zhang XR, et al. Characteristics and Impact Factors of Renal Threshold for Glucose Excretion in Patients with Type 2 Diabetes Mellitus[J]. *J Korean Med Sci*, 2017, 32(4): 621-627
- [28] Castillo-Castañeda PC, Gaxiola-Robles R, Labrada-Martagón V, et al. Oxidative damage to proteins related to metals and antioxidant defenses in breastmilk[J]. *Nutr Hosp*, 2017, 34(1): 59-64
- [29] Koyuncuoğlu T, Vızdıklar C, Üren D, et al. Obestatin improves oxidative brain damage and memory dysfunction in rats induced with an epileptic seizure[J]. *Peptides*, 2017, 90(1): 37-47
- [30] Yan H, Wang D, Ding TB, et al. Comparison of lens oxidative damage induced by vitrectomy and/or hyperoxia in rabbits [J]. *Int J Ophthalmol*, 2017, 10(1): 6-14
- [31] Gupta SC, Patchva S, Koh W, et al. Discovery of gingerol, a component of golden spice, and its miraculous biological activities[J]. *Clin Exp Pharmacol Physiol*, 2012, 39(3): 283-299

(下转第 1097 页)

- Du Wei-qiang. Serum CD73 and apel in levels in patients with diabetic retinopathy and the clinical significance [J]. Journal of Hainan Medical University, 2017, 23(4): 570-573
- [19] Benyamine A, Magalon J, Cointe S, et al. Increased serum levels of fractalkine and mobilisation of CD34+CD45- endothelial progenitor cells in systemic sclerosis[J]. Arthritis Res Ther, 2017, 19(1): 60
- [20] 王伟超,张洁,王虹,等.社区中老年糖尿病患者泪液和血清肿瘤坏死因子 α 及血清糖化血红蛋白与糖尿病视网膜病变的关系 [J].中国全科医学, 2015, 18(35): 4288-4292
- Wang Wei-chao, Zhang Jie, Wang Hong, et al. Relationship Between the Levels of Tear Fluid TNF- α , Serum TNF- α and Serum HbA1c and Diabetic Retinopathy in Middle-aged and Elderly Diabetes Patients [J]. Chinese General Practice, 2015, 18(35): 4288-4292
- [21] 陈家欣,林如海.血清中期因子联合总胆红素在糖尿病视网膜病变中的诊断价值[J].中国糖尿病杂志, 2017, 25(2): 121-124
- Chen Jia-xin, Lin Ru-hai. Diagnostic value of serum midkine combined with total bilirubin for diabetic retinopathy [J]. Chinese Journal of Diabetes, 2017, 25(2): 121-124
- [22] Gómez-Díaz RA, Gutiérrez J, Contreras-Rodríguez A, et al. Association of V249I and T280M variants of fractalkine receptor CX3CR1 with carotid intima-media thickness in a mexican population with type 2 diabetes [J]. Gac Med Mex, 2017, 153(1): 49-56
- [23] Chew EY. Dietary Intake of Omega-3 Fatty Acids From Fish and Risk of Diabetic Retinopathy[J]. JAMA, 2017, 317(21): 2226-2227
- [24] 肖雪娜,王心捷.糖尿病患者血清 CA199 水平升高与糖化血红蛋白及糖尿病视网膜病变的关系[J].河北医科大学学报, 2015, 36(6): 695-698
- Xiao Xue-na, Wang Xin-jie. The relationship between elevated serum CA199 level and glycosylated hemoglobin and diabetic retinopathy in patients with diabetes mellitus [J]. Journal of Hebei Medical University, 2015, 36(6): 695-698
- [25] Ma Y, Yue Y, Ma Y, et al. Structural Basis for Apelin Control of the Human Apelin Receptor[J]. Structure, 2017, 25(6): 858-866
- [26] Yang P, Read C, Kuc RE, et al. Elabala/Toddler Is an Endogenous Agonist of the Apelin APJ Receptor in the Adult Cardiovascular System, and Exogenous Administration of the Peptide Compensates for the Downregulation of Its Expression in Pulmonary Arterial Hypertension[J]. Circulation, 2017, 135(12): 1160-1173
- [27] Du JH, Li X, Li R, et al. Elevation of serum apelin-13 associated with proliferative diabetic retinopathy in type 2 diabetic patients [J]. Int J Ophthalmol, 2014, 7(6): 968-973
- [28] Zhang P, Yi LH, Meng GY, et al. Apelin-13 attenuates cisplatin-induced cardiotoxicity through inhibition of ROS-mediated DNA damage and regulation of MAPKs and AKT pathways [J]. Free Radic Res, 2017, 51(5): 449-459
- [29] Soualmia H, Midani F, Hadj-Fradj S, et al. The A445C Variant in Apelin Receptor and Diabetic Retinopathy in Tunisian Patients [J]. Clin Lab, 2017, 63(2): 379-383
- [30] Tien T, Zhang J, Muto T, et al. High Glucose Induces Mitochondrial Dysfunction in Retinal Müller Cells: Implications for Diabetic Retinopathy[J]. Invest Ophthalmol Vis Sci, 2017, 58(7): 2915-2921

(上接第 1072 页)

- [32] Kim YE, Hwang CJ, Lee HP, et al. Inhibitory effect of punicalagin on lipopolysaccharideinduced neuroinflammation, oxidative stress and memory impairment via inhibition of nuclear factor-kappaB [J]. Neuropharmacology, 2017, 117(1): 21-32
- [33] Badgugar PC, Pawar NN, Chandratre GA, et al. Fipronil induced oxidative stress in kidney and brain of mice: protective effect of vitamin E and vitamin C [J]. Pestic Biochem Physiol, 2015, 118(2): 10-18
- [34] Wang L, Murphy NP, Stengel A, et al. Ghrelin prevents levodopa-induced inhibition of gastric emptying and increases circulating levodopa in fasted rats[J]. Neurogastroenterol Motil, 2012, 24(5): e235-e245
- [35] Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach [J]. Nature, 1999, 402(3): 656-660
- [36] Trippel TD, Holzendorf V, Halle M, et al. Ghrelin and hormonal markers under exercise training in patients with heart failure with preserved ejection fraction: results from the Ex-DHF pilot study[J]. ESC Heart Fail, 2017, 4(1): 56-65
- [37] Goswami C, Shimada Y, Yoshimura M, et al. Motilin Stimulates Gastric Acid Secretion in Coordination with Ghrelin in *Suncus murinus*[J]. PLoS One, 2015, 10(6): e0131554-e0131560
- [38] Sagheb MM, Azarpira N, Mokhtary M. The effect of ghrelin on Kiss-1 and KissR gene transcription and insulin secretion in rat islets of Langerhans and CRI-D2 cell line[J]. Iran J Basic Med Sci, 2017, 20(1): 36-40
- [39] Esposito A, Criscitiello C, Gelao L, et al. Mechanisms of anorexia-cachexia syndrome and rational for treatment with selective ghrelin receptor agonist[J]. Cancer Treat Rev, 2015, 41(9): 793-797
- [40] Zhou L, Cheng YP. Effect of Electroacupuncture on Expression of Ghrelin and mRNA Expression of Its Receptor in Functional Dyspepsia Rats [J]. Chinese Journal of Integrated Traditional and Western Medicine, 2016, 36(3): 322-326
- [41] Tschöp M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents[J]. Nature, 2000, 407(1): 908-913
- [42] Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans[J]. Endocrinology, 2000, 141(11): 4255-4261