doi: 10.13241/j.cnki.pmb.2022.23.006

芬太尼联合电针通过介导 HDAC2 途径调节糖尿病大鼠周围神经痛的作用机制研究 *

张银福 白 静△ 高 巍 王 乐 庞 芸 陈颖力

（西安交通大学第一附属医院麻醉科 陕西 西安 710089）

摘要 目的：探讨与研究芬太尼联合电针通过介导组蛋白去乙酰化酶 2（histone deacetylase 2，HDAC2）途径调节糖尿病大鼠周围神经痛的作用机制。**方法：**将建模成功的糖尿病周围神经痛大鼠（n=36）随机平分为三组 - 模型组、芬太尼组与电针组，芬太尼组、模型组分别经尾静脉泵注 1.0 μg/kg/min 芬太尼与等剂量的磷酸盐缓冲液 5 min，1 次 /d。电针组在芬太尼治疗的基础上给予电针治疗，1 次 /d，均共治疗 2 周。治疗第 1 周与第 2 周，对大鼠进行体重称重，采用双抗体酶联免疫夹心法测血清胰岛素浓度，动态足底触觉仪检测大鼠机械痛阈，免疫印迹检测 HDAC2 蛋白相对表达水平。**结果：**芬太尼组与电针组在治疗第 1 周、第 2 周的体重都明显高于模型组（*P*<0.05），电针组也明显高于芬太尼组（*P*<0.05）。芬太尼组与电针组在治疗第 1 周、第 2 周的血清胰岛素浓度都明显低于模型组（*P*<0.05），电针组也明显高于芬太尼组（*P*<0.05）。芬太尼组与电针组在治疗第 1 周、第 2 周的机械痛阈都明显高于模型组（*P*<0.05），电针组明显高于芬太尼组（*P*<0.05）。芬太尼组与电针组在治疗第 2 周、第 4 周的 HDAC2 蛋白表达水平明显高于模型组（*P*<0.05），电针组也显著高于芬太尼组（*P*<0.05）。**结论：**芬太尼联合电针在糖尿病周围神经痛大鼠的应用能提高机械痛阈，能提高大鼠体重，也可降低胰岛素浓度，其作用机制可能与促进 HDAC2 表达有关。

关键词：芬太尼；电针；糖尿病周围神经痛；机械痛阈；体重；胰岛素；组蛋白去乙酰化酶 2

中图分类号：R-33；R587.1；R614 **文献标识码：**A **文章编号：**1673-6273（2022）23-4430-05

Mechanism of Fentanyl Combined with Electroacupuncture in Regulating Peripheral Neuralgia in Diabetic Rats by Mediating HDAC2 Pathway*

ZHANG Yin-fu, BAI Jing△, GAO Wei, WANG Le, PANG Yun, CHEN Ying-li

(Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710089, China)

ABSTRACT Objective: To explore and study the mechanism of fentanyl combined with electroacupuncture in regulating peripheral neuralgia in diabetic rats by mediating histone deacetylase 2 (HDAC2) pathway. **Methods:** The successfully modeled diabetic peripheral neuralgia rats (n=36) were randomly divided into three groups - model group, fentanyl group and electroacupuncture group. The fentanyl group and model group were injected with 1.0 μg/kg/min fentanyl and equal dose of phosphate buffer for 5 min, once a day. The electroacupuncture group was given electroacupuncture on the basis of fentanyl treatment, once a day, for a total of 2 weeks. In the first week and the second week of treatment, the rats were weighed, and the serum insulin concentration was measured by double-antibody enzyme-linked immunosorbent assay, the mechanical pain threshold of rats was detected by dynamic plantar tactile instrument, and the relative expression level of HDAC2 protein was detected by western blotting. **Results:** The body weight of the fentanyl group and the electroacupuncture group were significantly higher than that of the model group in the first week and the second week of treatment (*P*<0.05), and the electroacupuncture group were also significantly higher than the fentanyl group (*P*<0.05). The serum insulin concentrations of the fentanyl group and the EA group were significantly lower than those of the model group in the first and second weeks of treatment (*P*<0.05), and the electroacupuncture group were also significantly higher than the fentanyl group (*P*<0.05). The mechanical pain thresholds of the fentanyl group and the electroacupuncture group were significantly higher than those of the model group at the first and second week of treatment (*P*<0.05), and the electroacupuncture group were significantly higher than the fentanyl group (*P*<0.05). The expression levels of HDAC2 protein in the fentanyl group and the EA group were significantly higher than those in the model group at the second and fourth week of treatment(*P*<0.05), and the EA group were also significantly higher than the fentanyl group (*P*<0.05). **Conclusion:** The application of fentanyl combined with electroacupuncture in rats with diabetic peripheral neuralgia can improve the mechanical pain threshold, increase the body weight of the rats, and reduce the concentration of insulin. The mechanism of action may be related to the promotion of HDAC2 expression.

Key words: Fentanyl; Electroacupuncture; Diabetic peripheral neuralgia; Mechanical pain threshold; Body weight; Insulin; Histone deacetylase 2

Chinese Library Classification（CLC）: R-33; R587.1; R614 Document code: A

Article ID: 1673-6273(2022)23-4430-05

* 基金项目：国家自然科学基金面上项目（81971290）

作者简介：张银福（1983-），男，本科，主治医师，研究方向：麻醉相关，电话：13474001003，E-mail：zyf08112022@163.com

△ 通讯作者：白静（1985-），女，本科，主治医师，研究方向：手术麻醉相关工作，电话：13319239072，E-mail：baijing8512@163.com

（收稿日期：2022-03-27 接受日期：2022-04-23）

前言

2 型糖尿病为糖尿病的主要类型，是以胰岛素抵抗和胰岛素分泌相对缺乏为特征的疾病[1,2]。糖尿病周围神经痛是糖尿病最常见的慢性并发症，具有病程长、病情反复等特点，可极大地影响糖尿病患者的生存质量[3]。当前对于糖尿病周围神经痛的治疗方法比较多，主要为对症治疗和支持治疗，包括溶血栓、降脂、合理饮食等[4,5]。芬太尼为临床上的常见麻醉药物之一，具有体内无蓄积、起效快等特点，临床常用于全麻诱导和全麻中维持镇痛。现代研究显示芬太尼具有降低炎症因子水平、保护缺血后组织损伤等作用[6]。糖尿病周围神经痛在中医上属于＂血痹＂、＂痿证＂、＂消渴＂、＂痹症＂等范畴，在中医治疗上多采用针刺治疗，特别是针刺治疗是在传统的针刺腧穴得气后在针上通以接近人体生物电的电流波，具有安全性好、对生理干扰小等特点[7,8]。电针治疗可以改善神经的传导功能，增加脊髓和外周神经的神经营养因子表达，改善神经组织的微血管环境，促进神经再生与修复[9]。组蛋白去乙酰化酶 2 是介导痛觉过敏持续现象的重要靶点，在细胞成熟和分化中发挥重要作用，可调节相关基因转录与表达[10,11]。本文探讨与研究了芬太尼联合电针通过介导 HDAC2 途径调节糖尿病大鼠周围神经痛的作用机制，以促进电针的应用。现报道如下。

1 材料与方法

1.1 主要研究材料

健康 6 周龄清洁级 SD 雄性大鼠购自上海斯莱克公司，饲养于本院实验动物中心（批号：88211442）。饲养条件：实验前适应环境 1 周，普通饲料喂养，自由饮水，温度 23.0~25.0 ℃，普通饲料喂养，模拟昼夜每 12 h 更换一次光照条件，自由饮水，实验前适应环境 1 周。

芬太尼购自湖北宜昌人福药业有限公司（批号：23781984），链脲佐菌素购自美国，兔抗 HDAC2 抗体购自美国 Cell Signaling Technology 公司，二抗购自美国 Jackson 公司，0.75 %盐酸布比卡因注射液购自上海禾丰制药有限公司，蛋白定量试剂盒与硝酸纤维素膜购自上海碧云天生物技术研究所。

1.2 糖尿病周围神经痛大鼠模型的建立

所有高糖高脂饲料大鼠给予自制高糖高脂饲料喂养 8 周，8 周后腹腔注射 1 %的 35 mg/kg 的链脲佐菌素。持续给药后 2 周，在空腹状态下在早上 7:30-8:30 采尾静脉血测空腹血糖值和血清胰岛素浓度。糖尿病周围神经痛大鼠建模成功标准：空腹血糖≥16.7 mmol/L 且胰岛素敏感指数（ISI）较实验前下降在原来值的 1/2 及其以上。

1.3 大鼠分组与治疗

将建模成功的糖尿病周围神经痛大鼠（n=36）随机平分为三组 - 模型组、芬太尼组与电针组。芬太尼组、模型组分别经尾静脉泵注 1.0 μg/kg/min 芬太尼与等剂量的磷酸盐缓冲液 5 min，1 次 /d。电针组在芬太尼治疗的基础上给予电针治疗，选取环跳、阳陵泉等虚伪，进针 4-6 mm，留针 30 min，电针频率：低强度 1 mA、连续波、低频率 2 Hz，1 次 /d。

所有大鼠都连续治疗 2 周。

1.4 观察指标

1.4.1 体重测量 所有大鼠都在治疗第 1 周与第 2 周进行大鼠体重的称重。

1.4.2 血清胰岛素浓度检测 所有大鼠都在治疗第 1 周与第 2 周予以尾静脉采血，静置 2 h 后，2000 rpm 离心 10 min，取上层血清，采用双抗体酶联免疫夹心法测血清胰岛素浓度。

1.4.3 大鼠机械痛阈测量 所有大鼠在治疗第 1 周与第 2 周采用动态足底触觉仪检测大鼠机械痛阈，共检测 5 次，每次最大值和最小值去除后取平均值。

1.4.4 免疫印迹检测 HDAC2 蛋白表达 各组大鼠在治疗第 2 周与第 4 周分别处死 6 只，暴露硬膜，切开硬膜，取出腰 L4 段脊髓组织，研磨过滤后，12000 rpm 离心 10 min，取上清组织进行蛋白定量。取 20 μg 蛋白进行 SDS-PAGE 电泳，转膜后，封闭 1 h。加入兔抗 HDAC2 抗体（1：1000）孵育过夜，洗涤 3 次后，加入二抗孵育 1 h，然后进行曝光，以 β-actin 作为内参，检测 HDAC2 蛋白相对表达水平。

1.5 统计方法

使用 SPSS 22.00 对实验结果进行统计学处理，计量资料以均数± 标准差表示，两两对比为 t 检验，多组间对比为方差分析，方差不齐时采用 Dunnett's T3 检验，检验水准为α=0.05。

2 结果

2.1 大鼠体重变化对比

芬太尼组与电针组在治疗第 1 周、第 2 周的体重都明显高于模型组，电针组也明显高于芬太尼组（P<0.05）。见表 1。

表 1 三组大鼠治疗不同时间点的体重变化对比(g)

Table 1 Comparison of weight change of three rats at different time points (g)

Groups	n	Week 1 of treatment	Week 2 of treatment
Model group	6	195.33± 11.38^{ab}	207.38± 12.47^{ab}
Fentanyl group	6	210.84± 17.39^{a}	221.48± 18.83^{a}
Electric needle group	6	254.94± 16.09	312.48± 14.09
F		19.282	25.702
P		<0.001	<0.001

Note: Compared with the model group, ^{a}P<0.05; compared with the fentanyl group, ^{b}P<0.05. The same below.

2.2 大鼠血清胰岛素浓度变化对比

芬太尼组与电针组在治疗第 1 周、第 2 周的血清胰岛素浓度都明显低于模型组，电针组也明显高于芬太尼组（P<0.05）。见表 2。

表 2 三组大鼠治疗不同时间点的血清胰岛素浓度变化对比(mIU/L)

Table 2 Comparison of changes in serum insulin concentration at different time points in three groups of rats (mIU/L)

Groups	n	Week 1 of treatment	Week 2 of treatment
Model group	6	83.22± 3.28[ab]	83.82± 4.14[ab]
Fentanyl group	6	65.20± 4.48[a]	51.84± 5.09[a]
Electric needle group	6	43.20± 2.87	23.87± 3.10
F		24.884	29.114
P		<0.001	<0.001

2.3 大鼠机械痛阈变化对比

芬太尼组与电针组在治疗第 1 周、第 2 周的机械痛阈都明显高于模型组，电针组明显高于芬太尼组（*P*<0.05）。见表 3。

表 3 三组大鼠治疗不同时间点的机械痛阈变化对比(g)

Table 3 Comparison of mechanical pain threshold changes at different time points (g)

Groups	n	Week 1 of treatment	Week 2 of treatment
Model group	6	18.38± 0.33[ab]	18.09± 0.84[ab]
Fentanyl group	6	21.98± 1.47[a]	25.98± 1.57[a]
Electric needle group	6	25.69± 2.22	31.82± 2.18
F		11.372	15.025
P		<0.001	<0.001

2.4 HDAC2 蛋白表达水平变化对比

芬太尼组与电针组在治疗第 2 周、第 4 周的 HDAC2 蛋白表达水平明显高于模型组，电针组也显著高于芬太尼组（*P*<0.05）。见表 4。

表 4 三组大鼠治疗不同时间点的 HDAC2 蛋白表达水平变化对比

Table 4 Comparison of HDAC2 protein expression levels at different time points

Groups	n	Week 1 of treatment	Week 2 of treatment
Model group	6	1.67± 0.21[ab]	1.68± 0.17[ab]
Fentanyl group	6	2.37± 0.14[a]	3.17± 0.27[a]
Electric needle group	6	3.78± 0.28	5.10± 0.23
F		24.932	31.472
P		<0.001	<0.001

3 讨论

糖尿病周围神经痛为 2 型糖尿病常见并发症导致的神经性疼痛，具有致残率高、致死率高、治疗费用高、治疗难度大等问题[12]。目前糖尿病周围神经痛模型制备的方法众多，高糖高脂饮食联合链脲佐菌素法具有制备成本较低、制备周期较短、成功率高、制备简单等优点，当前临床上的应用比较多[13,14]。糖尿病周围神经痛主要表现为四肢远端出现的自发性疼痛、触诱发痛、感觉过敏为其特征，芬太尼可以降低糖尿病大鼠体内异常升高的丙二醛、乳酸脱氢酶水平，升高活性氧活性，清除机体过多的氧自由基，从而发挥镇痛作用[15]。本研究显示芬太尼组与电针组在治疗第 1 周、第 2 周的体重都明显高于模型组，电针组也明显高于芬太尼组（*P*<0.05）；芬太尼组与电针组在治疗第 1 周、第 2 周的血清胰岛素浓度都明显低于模型组，电针组也明显高于芬太尼组（*P*<0.05），表明芬太尼联合电针可有效提高糖尿病周围神经痛大鼠的体重，也可降低胰岛素浓度。从机制上分析，电针治疗当前也常用于治疗疼痛和运动系统损伤的治疗，可抑制感觉神经及运动神经。同时电针的应用可引起中枢内吗啡肽释放，降低机体的氧化应激水平[16,17]。

目前糖尿病周围神经痛的发病机制尚不明确，无菌性慢性炎症、慢性高血糖、继发血脂代谢紊乱是糖尿病周围神经痛致病的重要因素。特别是长期高血糖、血脂紊乱导致营养神经的血管管腔变窄与管腔脂质沉积，可减慢神经血流速度，从而影响神经的血供，从而诱发神经功能障碍的发生[18,19]。芬太尼可以通过降低机体炎症反应缓解糖尿病周围神经痛引起的损伤，可缓解心肌组织损伤，抑制心肌细胞凋亡[20,21]。本研究显示芬太尼组与电针组在治疗第 1 周、第 2 周的机械痛阈都明显高于模型组，电针组明显高于芬太尼组（*P*<0.05），表明芬太尼联合电针

在糖尿病周围神经痛大鼠的应用能提高机械痛阈。从机制上分析，电针对慢性疼痛具有镇痛作用，具有较好的效果和较少的不良反应[22,23]。电针是将针刺入腧穴得气后，可准确控制治疗参数，通过接近受刺动物生物电的微量电流，从而改善机体的机械痛阈[24-26]。

对于患病时间较长的糖尿病患者而言，糖尿病周围神经痛是最为常见并发症，可影响患者的生存质量，特别是部分患者因为长期慢性疼痛的刺激与困扰甚至会出现负性情绪[27,28]。HDAC2 可以在细胞质和细胞核间穿梭，可调节染色体重组过程，在痛觉过敏的诱导和维持过程中发挥重要作用[29,30]。HDAC2 的高表达可激活相关基因转录，促使各种通路的转录因子的表达，从而调节机体疼痛状况[31-33]。本研究显示芬太尼组与电针组在治疗第 2 周、第 4 周的 HDAC2 蛋白表达水平明显高于模型组，电针组也显著高于芬太尼组（$P<0.05$），表明芬太尼联合电针在糖尿病周围神经痛大鼠的应用能促进 HDAC2 表达。不过由于经费问题，本研究样本数量较少，且没有设置空白组，可能会对结果产生一定误差，将在后续研究中探讨。

总之，芬太尼联合电针在糖尿病周围神经痛大鼠的应用能提高机械痛阈，能提高大鼠体重，也可降低胰岛素浓度，其作用机制可能与促进 HDAC2 表达有关。

参 考 文 献（References）

[1] Alyoubi R A, Alshareef A A, Aldughaither S M, et al. Efficacy and safety of mirogabalin treatment in patients with diabetic peripheral neuropathic pain: A systematic review and meta-analysis of randomised controlled trials[J]. Int J Clin Pract, 2021, 75(5): e13744

[2] Basu P, Maier C, Basu A. Effects of Curcumin and Its Different Formulations in Preclinical and Clinical Studies of Peripheral Neuropathic and Postoperative Pain: A Comprehensive Review [J]. Int J Mol Sci, 2021, 22(9): 114-118

[3] Bhandari R, Sharma A, Kuhad A. Novel Nanotechnological Approaches for Targeting Dorsal Root Ganglion (DRG) in Mitigating Diabetic Neuropathic Pain (DNP)[J]. Front Endocrinol (Lausanne), 2021, 12 (3): 790747

[4] 王纪鹰,杨篷,孙文善,等.以疾病为中心的糖尿病周围神经病变的个体化诊疗模式的临床探讨 [J]. 中华糖尿病杂志, 2021, 13(11): 1021-1025

[5] Viel E, Eerdekens M, Kandaswamy P. Treatment Impact on Patient-Reported Outcomes in Peripheral Neuropathic Pain: Comparing Single Intervention With Topical High-Concentration Capsaicin to Daily Oral Pregabalin[J]. Pain Physician, 2021, 24(6): 453-463

[6] Wang A, Shi X, Yu R, et al. The P2X (7) Receptor Is Involved in Diabetic Neuropathic Pain Hypersensitivity Mediated by TRPV1 in the Rat Dorsal Root Ganglion [J]. Front Mol Neurosci, 2021, 14 (8): 663649

[7] Yang J, Yang X, Zhao D, et al. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy[J]. J Diabetes Investig, 2021, 12(5): 828-836

[8] Ye D, Fairchild T J, Vo L, et al. Painful diabetic peripheral neuropathy: Role of oxidative stress and central sensitisation [J]. Diabet Med, 2022, 39(1): e14729

[9] Abrams R M C, Pedowitz E J, Simpson D M. A critical review of the capsaicin 8% patch for the treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet in adults [J]. Expert Rev Neurother, 2021, 21(3): 259-266

[10] Alkhudhayri S, Sajini R, Alharbi B, et al. Investigating the beneficial effect of aliskiren in attenuating neuropathic pain in diabetic Sprague-Dawley rats [J]. Endocrinol Diabetes Metab, 2021, 4 (2): e00209

[11] Casale R. Capsaicin 179-mg cutaneous patch in the treatment of post-surgical neuropathic pain: a scoping review of current evidence and place in therapy [J]. Expert Rev Neurother, 2021, 21 (10): 1147-1158

[12] Chen E Y, Beutler S S, Kaye A D, et al. Mirogabalin as a Novel Gabapentinoid for the Treatment of Chronic Pain Conditions: An Analysis of Current Evidence [J]. Anesth Pain Med, 2021, 11 (6): e121402

[13] Crasto W, Altaf Q A, Selvaraj D R, et al. Frequency Rhythmic Electrical Modulation System (FREMS) to alleviate painful diabetic peripheral neuropathy: A pilot, randomised controlled trial (The FREMSTOP study)[J]. Diabet Med, 2022, 39(3): e14710

[14] Deguchi T, Takatsuna H, Yokoyama M, et al. A Cross-Sectional Web Survey of Satisfaction with Treatment for Pain in Participants with Suspected Diabetic Peripheral Neuropathic Pain in Both Feet[J]. Adv Ther, 2021, 38(8): 4304-4320

[15] 陈佳丽,张茂表,陆嘉辉,等.脊髓活性氧激活自噬参与调节 2 型糖尿病神经病理性疼痛[J].中国疼痛医学杂志, 2020, 26(01): 27-34

[16] Freynhagen R, Argoff C, Eerdekens M, et al. Progressive Response to Repeat Application of Capsaicin 179 mg (8% w/w) Cutaneous Patch in Peripheral Neuropathic Pain: Comprehensive New Analysis and Clinical Implications[J]. Pain Med, 2021, 22(10): 2324-2336

[17] Hoffmann T, Kistner K, Joksimovic S L J, et al. Painful diabetic neuropathy leads to functional Ca (V)3.2 expression and spontaneous activity in skin nociceptors of mice[J]. Exp Neurol, 2021, 346: 113838

[18] 潘玉琴,陆红荧,周可轶,等.应激性高血糖与急性自发性脑出血患者术后并发症和早期预后的相关性研究 [J]. 现代生物医学进展, 2019, 19(03): 461-464

[19] Jensen T S, Karlsson P, Gylfadottir S S, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management[J]. Brain, 2021, 144(6): 1632-1645

[20] Jin H Y, Moon S S, Calcutt N A. Lost in Translation Measuring Diabetic Neuropathy in Humans and Animals[J]. Diabetes Metab J, 2021, 45(1): 27-42

[21] Kessler J A, Shaibani A, Sang C N, et al. Gene therapy for diabetic peripheral neuropathy: A randomized, placebo-controlled phase III study of VM202, a plasmid DNA encoding human hepatocyte growth factor[J]. Clin Transl Sci, 2021, 14(3): 1176-1184

[22] Liao C, Zhou H, Chen H, et al. Patterns of Nerve Fibre Impairments and Neuronal Activation in Male Diabetic Rats With and Without Mechanical Allodynia: A Comparative Study [J]. Can J Diabetes, 2022, 46(2): 157-164

[23] Ma L, Ju P, Wang W, et al. Microglial Activation of GLP-1R Signaling in Neuropathic Pain Promotes Gene Expression Adaption Involved in Inflammatory Responses [J]. Neural Plast, 2021, 8 (14): 9923537

[24] Raghu A L B, Parker T, Aziz T Z, et al. Invasive Electrical Neuro-

modulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis[J]. Neuromodulation, 2021, 24(1): 13-21

[25] Düzova H, Nazıroğlu M, iğ B, et al. Noopept Attenuates Diabetes-Mediated Neuropathic Pain and Oxidative Hippocampal Neurotoxicity via Inhibition of TRPV1 Channel in Rats [J]. Mol Neurobiol, 2021, 58(10): 5031-5051

[26] Fan X M, Ren Y F, Fu X, et al. Gabapentin has Longer-Term Efficacy for the Treatment of Chronic Pelvic Pain in Women: A Systematic Review and Pilot Meta-analysis [J]. Pain Ther, 2021, 10 (2): 1673-1689

[27] Ferreira N, Gonçalves N P, Jan A, et al. Trans-synaptic spreading of alpha-synuclein pathology through sensory afferents leads to sensory nerve degeneration and neuropathic pain [J]. Acta Neuropathol Commun, 2021, 9(1): 31-35

[28] Filimonova T, Karakulova Y. Tropomyosin receptor kinase B-mediated signaling in integration of neuropathic pain and obesity in diabetic polyneuropathy[J]. Einstein (Sao Paulo), 2021, 19: eAO6256

[29] Rice A S C, Dworkin R H, Finnerup N B, et al. Efficacy and safety of EMA401 in peripheral neuropathic pain: results of 2 randomised, double-blind, phase 2 studies in patients with postherpetic neuralgia and painful diabetic neuropathy[J]. Pain, 2021, 162(10): 2578-2589

[30] Santos D F S, Donahue R R, Laird D E, et al. The PPARγ agonist pioglitazone produces a female-predominant inhibition of hyperalgesia associated with surgical incision, peripheral nerve injury, and painful diabetic neuropathy[J]. Neuropharmacology, 2022, 205(14): 108907

[31] Tian J, Song T, Wang H, et al. Intrathecal Injection of SIRT1-modified Human Mesenchymal Stem Cells Alleviates Neuropathic Pain in Rat[J]. J Mol Neurosci, 2021, 71(5): 972-980

[32] Todorovic M S, Frey K, Swarm R A, et al. Prediction of Individual Analgesic Response to Intravenous Lidocaine in Painful Diabetic Peripheral Neuropathy: A Randomized, Placebo-controlled, Crossover Trial[J]. Clin J Pain, 2021, 38(2): 65-76

[33] Tsymbalyuk O, Gerzanich V, Mumtaz A, et al. SUR1, newly expressed in astrocytes, mediates neuropathic pain in a mouse model of peripheral nerve injury[J]. Mol Pain, 2021, 17(14): 6603-6615

（上接第 4505 页）

[19] Lunetta C, Lizio A, Tremolizzo L, et al. Serum irisin is upregulated in patients affected by amyotrophic lateral sclerosis and correlates with functional and metabolic status [J]. J Neurol, 2018, 265 (12): 3001-3008

[20] Zhang J, Zhang W. Can irisin be a linker between physical activity and brain function[J]. Biomol Concepts, 2016, 7(4): 253-258

[21] Zhang Y, Mu Q, Zhou Z, et al. Protective Effect of Irisin on Atherosclerosis via Suppressing Oxidized Low Density Lipoprotein Induced Vascular Inflammation and Endothelial Dysfunction [J]. PLoS One, 2016, 11(6): e0158038

[22] Li DJ, Li YH, Yuan HB, et al. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia [J]. Metabolism, 2017, 68(3): 31-42

[23] Patel YJ, Payne Smith MD, de Belleroche J, et al. Hsp27 and Hsp70 administered in combination have a potent protective effect against FALS-associated SOD1-mutant-induced cell death in mammalian neuronal cells[J]. Brain Res Mol Brain Res, 2005, 134(2): 256-274

[24] 王宇萍, 蒋建东. 热休克蛋白 70 的结构和功能 [J]. 中国细胞生物学学报, 2010, 32(2): 305-313

[25] Ikwegbue PC, Masamba P, Oyinloye BE, et al. Roles of Heat Shock Proteins in Apoptosis，Oxidative Stress，Human Inflammatory Diseases, and Cancer[J]. Pharmaceuticals（Basel）, 2017, 11(1): 2

[26] 冼珊, 邱嘉茗, 谢欢欢, 等. 肌电图对肌萎缩侧索硬化症的早期诊断价值[J]. 现代电生理学杂志, 2018, 25(1): 3

[27] 靳娇婷, 胡芳芳, 陈乔依, 等. 肌萎缩侧索硬化症患者针电极肌电图肌肉选择的优化 [J]. 西安交通大学学报（医学版）, 2020, 41(6): 831-836

[28] Momenzadeh S, Zamani S, Dehghan F, et al. Comparative proteome analyses highlight several exercise-like responses of mouse sciatic nerve after IP injection of irisin [J]. Eur J Neurosci, 2021, 53 (10): 3263-3278