fatal hip fractures: 16 years' follow-up of 674,000 Norwegian women and men [J]. Epidemiolog, 1995, 6(3): 299-305.
[8] Gao G, Zhang ZL, Zhang H, *et al*. Hip axis length changes in 10,554 males and females and the association with femoral neck fracture [J]. J Clin Densitom, 2008, 11(3): 360-366.
[9] Armstrong ME, Spencer EA, Cairns BJ, *et al*. Body mass index and physical activity in relation to the incidence of hip fracture in postmenopausal women [J]. J Bone Miner Res, 2011, 26(6): 1330-1338.
[10] Compston JE, Watts NB, Chapurlat R, *et al*. Obesity is not protective against fracture in postmenopausal women: GLOW [J]. Am J Med, 2011, 124(11): 1043-1050.
[11] Johansson H, Kanis JA, Odén A, *et al*. A meta-analysis of the association of fracture risk and body mass index in women [J]. J Bone Miner Res, 2014, 29(1): 223-233.
[12] Johansson H, Kanis J, Odén A, *et al*. High body mass index, adjusted for BMD, is a risk factor for fracture in women [C]. San Diego: ASBMR, 2011.
[13] Looker AC, Flegal KM, Melton LJ 3rd. Impact of increased overweight on the projected prevalence of osteoporosis in older women [J]. Osteoporos Int, 2007, 18(3): 307-313.
[14] Nielson CM, Srikanth P, Orwoll ES. Obesity and fracture in men and women: an epidemiologic perspective [J]. J Bone Miner Res, 2012, 27(1): 1-10.
[15] Premaor MO, Ensrud K, Lui L, *et al*. Risk factors for nonvertebral fracture in obese older women [J]. J Clin Endocrinol Metab, 2011, 96(8): 2414-2421.
[16] Premaor MO, Pilbrow L, Tonkin C, *et al*. Obesity and fractures in postmenopausal women [J]. J Bone Miner Res, 2010, 25(2): 292-297.
[17] Nielson CM, Marshall LM, Adams AL, *et al*. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS) [J]. J Bone Miner Res, 2011, 26(3): 496-502.
[18] Gnudi S, Sitta E, Lisi L. Relationship of body mass index with main limb fragility fractures in postmenopausal women [J]. J Bone Miner Metab, 2009, 27(4): 479-484.
[19] Compston JE, Flahive J, Hosmer DW, *et al*. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopausal women: The global longitudinal study of osteoporosis in women (GLOW) [J]. J Bone Miner Res, 2014, 29(2): 487-493.
[20] 邸彩霞. 2 型糖尿病患者腹腔内脏脂肪面积与骨密度的相关性研究 [D]. 石家庄: 河北医科大学, 2012.
[21] Amati F, Pennant M, Azuma K, *et al*. Lower thigh subcutaneous and higher visceral abdominal adipose tissue content both contribute to insulin resistance [J]. Obesity (Silver Spring), 2012, 20(5): 1115-1117.
[22] Orwoll E, Lambert LC, Marshall LM, *et al*. Endogenous testosterone levels, physical performance, and fall risk in older men [J]. Arch Intern Med, 2006, 166(19): 2124-2131.
[23] Cheng S, Massaro JM, Fox CS, *et al*. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study [J]. Diabetes, 2010, 59(1): 242-248.
[24] Grethen E, McClintock R, Gupta CE, *et al*. Vitamin D and hyperparathyroidism in obesity [J]. J Clin Endocrinol Metab, 2011, 96(5): 1320-1326.
[25] Sukumar D, Schlussel Y, Riedt CS, *et al*. Obesity alters cortical and trabecular bone density and geometry in women [J]. Osteoporos Int, 2011, 22(2): 635-645.
[26] Kanis JA, McCloskey EV, Johansson H, et al. Case finding for the management of osteoporosis with FRAX®-assessment and intervention thresholds for the UK [J]. Osteoporos Int, 2008, 19(10): 1395-1408.
[27] Premaor M, Parker RA, Cummings SR, *et al*. Predictive value of FRAX for fracture in obese older women [J]. J Bone Miner Res, 2013, 28(1): 188-195.
[28] Eastell R, Black DM, Boonen S, *et al*. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density [J]. J Clin Endocrinol Metab, 2009, 94(9): 3215-3225.

收稿日期: 2014-02-12 **修回日期:** 2014-09-29 **编辑:** 辛欣

利鲁唑的神经保护作用及其机制的研究进展

韩国英[△], **李春燕**[※] (综述), **时海波, 殷善开** (审校)
(上海交通大学附属第六人民医院耳鼻咽喉科, 上海 200233)

中图分类号: R971 **文献标识码:** A **文章编号:** 1006-2084(2015)08-1353-04

doi: 10.3969/j.issn.1006-2084.2015.08.004

摘要: 利鲁唑(2-氨基-6-三氟甲氧基-苯并噻唑)属苯并噻唑类化合物, 具有明确的神经保护药理作用。它的主要作用是抑制多种受体和离子通道介导的谷氨酸突触传导和神经元超兴奋性, 提高神经营养因子的表达量, 保护神经元免受兴奋毒性损伤, 促进神经元的存活。该文就利鲁唑神经保护作用及其机制的相关研究进展进行综述。

关键词: 利鲁唑; 神经保护; 谷氨酸

Riluzole's Neuroprotective Effect and the Mechanisms *HAN Guo-ying, LI Chun-yan, SHI Hai-bo, YIN Shan-kai.* (*Department of Otorhinolaryngology, Shanghai Sixth People's Hospital, Shanghai* 200233, *China*)

Abstract: Riluzole(2-p-aminophenyl-6-substituent-benzothiazole) is a benzothiazole compound, which has definite neuroprotective effect. The main mechanisms underlying this effect are likely to be multifaceted, involving suppressing glutamate neurotransmission and neuronal hyperexcitation, promoting the expressing of nerve growth factors via the function of a variety of receptors and related ion channel, protecting neurons from toxicological damage. Here is to make a review of neuroprotective effect and mechanisms of riluzole to provide a basis for further study.

Key words: Riluzole; Neuroprotection; Gluamate

利鲁唑属苯并噻唑类化合物, 1995 年起作为处方药用于肌萎缩性脊髓侧索硬化的临床治疗, 而对其他的中枢神经系统疾病(如焦虑、抑郁及惊厥等)的临床前实验治疗效果也得到了广泛的关注和认可[1-2]。谷氨酸引起的兴奋毒性是这些中枢神经系统疾病的共同分子机制, 其显著的抗谷氨酸毒性的能力是利鲁唑神经保护作用的主要机制之一。现对利鲁唑的神经保护作用及其机制综述如下。

基金项目: 国家自然科学基金(81100718)

1　利鲁唑的神经元保护作用

大量的体外(突触体和脑片)和体内实验均证实利鲁唑对神经元损伤具有较强的保护作用。丙二酸二乙酯能抑制线粒体能量的产生及神经胶质细胞对谷氨酸的重摄取,利用它慢性处理新生大鼠脑皮质脑片,能造成大量大锥体神经元死亡,而利鲁唑(10 μmol/L)能显著抑制丙二酸二乙酯的毒性作用[3]。Nogradi 等[4]发现,成年大鼠脊髓腹根撕脱伤在腹根再植术治疗后仍有大量运动神经元死亡。而继腹根再植后联合应用利鲁唑治疗对运动神经元有良好的保护作用,并促进轴突再生进入撕脱的腹根。Wang 等[5]发现,耳蜗内或腹腔注射利鲁唑能保护豚鼠耳蜗毛细胞免受噪声损伤诱导的细胞调亡,其半数有效量为 17 μmol/L。在临床研究中利鲁唑对肌萎缩性脊髓侧索硬化[6]、帕金森病[7]等神经退行性疾病有明显的治疗作用,而其对抗抑郁和焦虑等精神疾病的研究也取得了可喜的进展[8]。在锂治疗中度躁狂抑郁症的前瞻性试验中 14 例患者治疗效果不明显,而联合服用锂和利鲁唑(171 mg/d)8 周后抑郁症状得到显著改善[1]。Sanacora 等[2]也发现,利鲁唑(95 mg/d)联合抗抑郁药物治疗 6~12 周后,难治性抑郁症患者的抑郁症状明显改善。

2　利鲁唑神经保护机制

2.1　利鲁唑抑制神经元超兴奋及兴奋毒性

2.1.1　利鲁唑抑制谷氨酸能突触传递　在谷氨酸突触传递过程中,突触前神经元由前膜电压依赖性钠通道开放引发去极化,继而前膜电压依赖性钙通道开放,钙离子内流并引发突触小泡内谷氨酸释放至突触间隙。谷氨酸与突触后受体结合,受体开放,介导钠离子、钙离子和钾离子(尤其是钠离子)内流,突触后膜产生去极化,诱发突触后神经元发放动作电位。既往研究证实,利鲁唑能从突触前、突触间隙及突触后受体三个方面拮抗谷氨酸兴奋毒性。

2.1.1.1　触前机制　大量研究证实,利鲁唑能显著抑制多种生物体中枢神经系统突触前谷氨酸释放[9-10]。在大鼠慢性坐骨神经痛模型实验中[11],腹腔注射利鲁唑(6~12 mg/kg)能显著减少福尔马林诱导的脊髓背角神经元谷氨酸的释放。

钙离子是突触释放过程中的关键因素,因此钙离子通道及突触前钙离子浓度的变化将影响正常的突触活性。利鲁唑可通过阻断突触前电压门控性钙通道,从而减少钙离子内流及细胞内钙离子浓度,抑制神经元的突触活性。Stefani 等[12]报道,利鲁唑能抑制新生及成熟大鼠皮质神经元高电压(high voltage activated, HVA)激活和低电压激活钙电流。其最大抑制幅度分别为 20% 和 12%。在 IMR32 神经母细胞瘤细胞和培养的胚胎大鼠运动神经元中,利鲁唑(100 ~ 1000 μmol/L)通过阻断 L 型 HVA 钙离子通道和细胞内储存钙的释放减少细胞内钙浓度[13]。此外,ω-agatoxin-IVA(蜘蛛毒提取物),P/Q 型 HVA 钙离子通道的特异性拮抗剂,可阻断利鲁唑(1 μmol/L)对大鼠大脑皮质突触体谷氨酸释放的抑制作用[10]。这些研究提示,阻断 P/Q 型 HVA 和低电压激活钙离子通道可能是利鲁唑抑制突触前谷氨酸释放的重要机制。

此外,据研究蛋白激酶 C 激活能上调 N-甲基-*D*-天冬胺酸(N-methyl-*D*-aspartate, NMDA)受体的表达和功能[14-15]。利鲁唑已被研究证实能直接抑制蛋白激酶 C 的活性,从而抑制突触前膜 NMDA 受体对递质释放的易化作用,减少谷氨酸的释放[16-17]。

2.1.1.2　利鲁唑增加突触间隙谷氨酸的重摄取　神经末梢释放至突触间隙的谷氨酸可被位于神经末梢和神经胶质细胞膜上的高亲和力谷氨酸转运体重摄取,以终止其突触传递效应。Fumagalli 等[18]发现,利鲁唑(0.01~100 μmol/L)能有效增加稳定表达于人胚肾细胞 293 的三大谷氨酸转运体的活性:谷氨酸/天冬氨酸转运体、兴奋性氨酸转运体 1 和谷氨酸转运体 1,并且这种效应具有剂量依赖性,在大鼠实验中观察到利鲁唑(0.1~1 μmol/L)能增加脊髓突触体谷氨酸的重摄取[19]。而在之后的一项研究表明[20],在野生型和 G93A SOD1 转基因大鼠中,更高浓度的利鲁唑(10~300 μmol/L)才有此效应。此外,近期研究发现[21],利鲁唑能上调突触间隙中负责清除谷氨酸的星形细胞谷氨酸转运体数量和活性。利鲁唑通过增加谷氨酸转运体摄取,加快突触间隙对谷氨酸的除,从而使突触后膜受体激活减少,继之抑制谷氨酸突触传递功能。

2.1.1.3　利鲁唑对突触后受体的直接影响　应用放射性配体结合技术的研究证明[22-23],利鲁唑(100 μmol/L)与NMDA、非 NMDA 谷氨酸受体和代谢型谷氨酸受体的 NMDA 没有结合位点。Sankaranarayanan 等[24]发现,利鲁唑(100 μmol/L)能抑制放射性配体与 NMDA 或代谢型谷氨酸受体的 NMDA 位点的结合,但作用并不显著。这些研究表明,利鲁唑与谷氨酸受体无结合位点,同时对于谷氨酸与其受体的结合有直接抑制作用但作用有限。此外,有研究观察到[25],利鲁唑(10 μmol/L)不影响脊髓神经元中自发的兴奋性突触后电流和外源性谷氨酸激活的突触后电流的幅度,提示其不改变突触后谷氨酸受体的敏感性。然而,有研究证实[26],20 和 30 μmol/L 利鲁唑能分别减小舌下运动神经元和纹状体棘状神经元外源性谷氨酸激活的谷氨酸受体电流的幅度。这些研究结果不一致的原因可能与其药物浓度和神经元种类等的差异有关。

2.1.2　利鲁唑对神经元兴奋性调节的其他通路

2.1.2.1　利鲁唑抑制持续性钠电流　在多种神经元中已证实[25,27-28],利鲁唑能显著减少神经元的持续放电而并不改变其静息膜性能,如静息膜电位或输入电阻。低浓度利鲁唑(0.1~1 μmol/L)能增加神经元放电阈值,稳定非开放状态的电压依赖性钠通道,而较高浓度利鲁唑(2~10 μmol/L)可完全阻断神经元动作电位的发放。与此同时,大量研究报道低浓度(<10 μmol/L)利鲁唑即可显著抑制神经元的持续性钠电流,并且利鲁唑对持续性钠电流的抑制作用与其对神经元持续性放电的作用具有相似的剂量关系,提示利鲁唑主要通过抑制持续性钠电流来减少神经元的连续放电,降低神经元兴奋性[29-31]。

2.1.2.2　利鲁唑抑制钙依赖性钾通道　钙依赖性钾通道受电压和钙离子的双重调控,通道开放可增加动作电位之后的后超极化幅度和时程。有研究报道[32],利鲁唑能增加钙依赖性钾通道开放概率,加大神经元后超极化,抑制其紧张式自发放电的产生和频率,从而降低神经元兴奋性。

2.1.2.3　利鲁唑增强突触后氨基丁酸受体的反应性　早期的研究显示,利鲁唑(100 μmol/L)对突触后 GABAA, GABAB 或甘氨酸受体并无高亲和力,且利鲁唑并没有竞争这些受体

的放射性配体结合位点。随后有研究则发现[33-34]，利鲁唑(30~300 μmol/L)增加海马神经元和人胚肾细胞 293 细胞中外源性 GABA 诱导的抑制性突触后电流幅度，并具有剂量依赖性。提示利鲁唑可增强 GABA 受体的敏感性，加强突触后 GABA 抑制作用，降低神经元兴奋能力。

2.2 利鲁唑提高神经营养因子的表达量 神经生长因子、胶质细胞源性神经营养因子和脑源性神经营养因子均属于神经营养因子家族，是一类由神经所支配的组织和星形胶质细胞产生的，具有促进神经元的发育、分化、生长和存活作用的蛋白质。Mizuta 等[35]发现，在培养的小鼠星形胶质细胞中，利鲁唑(100 μmol/L)能上调这三类营养因子的信使 RNA 表达水平。

Caumont 等[36]研究发现，在培养的大鼠神经胶质瘤细胞中，通过调节促丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)信号通路上细胞外相关激酶的转录，利鲁唑(1 μmol/L)能上调胶质细胞源性神经营养因子信使 RNA 和蛋白表达水平。腹腔注射利鲁唑(19 mg/kg)引起成年小鼠齿状回神经元和海马 CA3 区的脑源性神经营养因子表达量增加，这种效应是通过 N 型钙通道和腺苷 A1 受体介导的 p38MAPK 的活化来完成的[37]。这些实验证实在体和离体条件下利鲁唑(1~100 μmol/L)均能增加神经营养因子的表达量，促进神经元的存活。神经元和神经胶质细胞 MAPK 信号通路在利鲁唑的作用机制中具有重要意义，如何激活 MAPK 信号通路和调节下游神经营养因子表达的机制仍不清楚。

3 小 结

利鲁唑对谷氨酸突触传递的抑制效应在其神经保护作用机制中具有重要意义，作用位点涵盖了突触前、突触间隙及突触后。利鲁唑对谷氨酸突触传递的抑制能直接降低神经元超兴奋，而利鲁唑抑制持续性钠电流、增强钙依赖性钾电流、增加突触后 GABA 受体的反应性的能力同样对降低神经元超兴奋具有协同作用，从而保护神经元免受兴奋毒性损伤。此外，利鲁唑对神经营养因子基因及蛋白表达水平的调节作用将促进神经元的发育、分化、生长和存活。这些研究对了解利鲁唑的神经保护作用提供了重要线索，而对利鲁唑已知及潜在作用机制更深入的探索将为该药在临床上的应用提供更多帮助。

参考文献

[1] Zarate CA Jr, Quiroz JA, Singh JB, *et al*. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression [J]. Biol Psychiatry, 2005, 57(4): 430-432.

[2] Sanacora G, Kendell SF, Levin Y, *et al*. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms [J]. Biol Psychiatry, 2007, 61(6): 822-825.

[3] Van Westerlaak MG, Joosten EA, Gribnau AA, *et al*. Differential cortico-motoneuron vulnerability after chronic mitochondrial inhibition in vitro and the role of glutamate receptors [J]. Brain Res, 2001, 922(2): 243-249.

[4] Nogradi A, Szabo A, Pinter S, *et al*. Delayed riluzole treatment is able to rescue injured rat spinal motoneurons [J]. Neuroscience, 2007, 144(2): 431-438.

[5] Wang J, Dib M, Lenoir M, *et al*. Riluzole rescues cochlear sensory cells from acoustic trauma in the guinea-pig [J]. Neuroscience, 2002, 111(3): 635-648.

[6] Debove C, Zeisser P, Salzman PM, *et al*. The Rilutek (riluzole) Global Early Access Programme: an open-label safety evaluation in the treatment of amyotrophic lateral sclerosis [J]. Amyotroph Lateral Scler Other Motor Neuron Disord, 2001, 2(3): 153-158.

[7] Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease [J]. Parkinsonism Relat Disord, 2002, 8(4): 271-276.

[8] Zarate CA, Manji HK. Riluzole in psychiatry: a systematic review of the literature [J]. Expert Opin Drug Metab Toxicol, 2008, 4(9): 1223-1234.

[9] Jehle T, Bauer J, Blauth E, *et al*. Effects of riluzole on electrically evoked neurotransmitter release [J]. Br J Pharmacol, 2000, 130(6): 1227-1234.

[10] Wang SJ, Wang KY, Wang WC. Mechanisms underlying the riluzole inhibition of glutamate release from rat cerebral cortex nerve terminals (synaptosomes) [J]. Neuroscience, 2004, 125(1): 191-201.

[11] Coderre TJ, Kumar N, Lefebvre CD, *et al*. A comparison of the glutamate release inhibition and anti-allodynic effects of gabapentin, lamotrigine, and riluzole in a model of neuropathic pain [J]. J Neurochem, 2007, 100(5): 1289-1299.

[12] Stefani A, Spadoni F, Bernardi, G. Differential inhibition by riluzole, lamotrigine, and phenytoin of sodium and calcium currents in cortical neurons: implications for neuroprotective strategies [J]. Exp Neurol, 1997, 147(1): 115-122.

[13] Wang JL, Lee KC, Tang KY, *et al*. Effect of the neuroprotective agent riluzole on intracellular Ca^{2+} levels in IMR32 neuroblastoma cells [J]. Arch Toxicol, 2001, 75(4): 214-220.

[14] Scott DB, Michailidis I, Mu Y, *et al*. Endocytosis and degradative sorting of NMDA receptors by conserved membrane-proximal signals [J]. J Neurosci, 2004, 24(32): 7096-7109.

[15] Hawkins LM, Prybylowski K, Chang K, *et al*. Export from the endoplasmic reticulum of assembled N-methyl-d-aspartic acid receptors is controlled by a motif in the c terminus of the NR2 subunit [J]. J Biol Chem, 2004, 279(28): 28903-28910.

[16] Noh KM, Hwang JY, Shin HC, *et al*. A novel neuroprotective mechanism of riluzole: direct inhibition of protein kinase C [J]. Neurobiol Dis, 2000, 7(4): 375-383.

[17] Lamanauskas N, Nistri A. Riluzole blocks persistent Na^+ and $Ca2^+$ currents and modulates release of glutamate via presynaptic NMDA receptors on neonatal rat hypoglossal motoneurons in vitro [J]. Eur J Neurosci, 2008, 27(10): 2501-2514.

[18] Fumagalli E, Funicello M, Rauen T, *et al*. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1 [J]. Eur J Pharmacol, 2008, 578(2-3): 171-176.

[19] Azbill RD, Mu X, Springer JE. Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes [J]. Brain Res, 2000, 871(2): 175-180.

[20] Dunlop J, Beal McIlvain H, She Y, *et al*. Impaired spinal cord glutamate transport capacity and reduced sensitivity to riluzole in a transgenic superoxide dismutase mutant rat model of amyotrophic lateral sclerosis [J]. J Neurosci, 2003, 23(5): 1688-1696.

[21] Carbone M, Duty S, Rattray M. Riluzole elevates GLT-1 activity and levels in striatal astrocytes [J]. Neurochem Int, 2012, 60(1): 31-38.

[22] Debono MW, Le Guern J, Canton T, *et al*. Inhibition by riluzole of electrophysiological responses mediated by rat kainate and NMDA receptors expressed in Xenopus oocytes [J]. Eur J Pharmacol, 1993, 235(2/3): 283-289.

[23] Doble A. The pharmacology and mechanism of action of riluzole [J]. Neurology, 1996, 47(6 Suppl 4): S233-241.

[24] Sankaranarayanan A, Raman G, Busch C, *et al*. Naphtho [1,2-d] thiazol-2-ylamine (SKA-31), a new activator of KCa2 and KCa3.1 potassium channels, potentiates the endothelium-derived hyperpolarizing factor response and lowers blood pressure [J]. Mol Pharmacol, 2009, 75(2): 281-295.

[25] Tazerart S, Viemari JC, Darbon P, *et al*. Contribution of persistent

sodium current to locomotor pattern generation in neonatal rats [J]. J Neurophysiol, 2007, 98(2): 613-628.
[26] Bellingham MC. Pre- and postsynaptic mechanisms underlying inhibition of hypoglossal motor neuron excitability by riluzole [J]. J Neurophysiol, 2013, 110(5): 1047-1061.
[27] Centonze D, Calabresi P, Pisani A, *et al*. Electrophysiology of the neuroprotective agent riluzole on striatal spiny neurons [J]. Neuropharmacology, 1998, 37(8): 1063-1070.
[28] Kuo JJ, Siddique T, Fu R, *et al*. Increased persistent Na(+) current and its effect on excitability in motoneurones cultured from mutant SOD1 mice [J]. J Physiol, 2005, 563(Pt 3): 843-854.
[29] Pieri M, Carunchio I, Curcio L, *et al*. Increased persistent sodium current determines cortical hyperexcitability in a genetic model of amyotrophic lateral sclerosis [J]. Exp Neurol, 2009, 215(2): 368-379.
[30] Cramer NP, Li Y, Keller A. The whisking rhythm generator: a novel mammalian network for the generation of movement [J]. J Neurophysiol, 2007, 97(3): 2148-2158.
[31] Lamas JA, Romero M, Reboreda A, *et al*. A riluzole- and valproate-sensitive persistent sodium current contributes to the resting membrane potential and increases the excitability of sympathetic neurones [J]. Pflugers Arch, 2009, 458(3): 589-599.
[32] Cao YJ, Dreixler JC, Couey JJ, *et al*. Modulation of recombinant and native neuronal SK channels by the neuroprotective drug riluzole [J]. Eur J Pharmacol, 2002, 449(1/2): 47-54.
[33] Jahn K, Schlesinger F, Jin LJ, *et al*. Molecular mechanisms of interaction between the neuroprotective substance riluzole and GABA(A)-receptors [J]. Naunyn Schmiedebergs Arch Pharmacol, 2008, 378(1): 53-63.
[34] He Y, Benz A, Fu T, *et al*. Neuroprotective agent riluzole potentiates postsynaptic GABA(A) receptor function [J]. Neuropharmacology, 2002, 42(2): 199-209.
[35] Mizuta I, Ohta M, Ohta K, *et al*. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes [J]. Neurosci Lett, 2001, 310(2/3): 117-120.
[36] Caumont AS, Octave JN, Hermans, E. Specific regulation of rat glial cell line-derived neurotrophic factor gene expression by riluzole in C6 glioma cells [J]. J Neurochem, 2006, 97(1): 128-139.
[37] Katoh-Semba R, Kaneko R, Kitajima S, *et al*. Activation of p38 mitogen-activated protein kinase is required for in vivo brain-derived neurotrophic factor production in the rat hippocampus [J]. Neuroscience, 2009, 163(1): 352-361.

收稿日期: 2014-05-04　**修回日期:** 2014-08-29　**编辑:** 伊姗

Periaxin 与腓骨肌萎缩症 4F 亚型

任页玫[△](综述), 石亚伟[※](审校)
(山西大学生物技术研究所 教育部化学生物学与分子工程重点实验室, 太原 030006)

中图分类号: R746　**文献标识号:** A　**文章编号:** 1006-2084(2015)08-1356-03

doi: 10.3969/j.issn.1006-2084.2015.08.005

摘要: Periaxin 是施万细胞特异表达的一种蛋白, 在维持髓鞘稳定性方面起重要作用, 该基因突变将导致脱髓鞘型常染色体隐性遗传的腓骨肌萎缩症 4F 亚型发生。从分子遗传学角度探讨腓骨肌萎缩症 4F 亚型发病的机制已成为目前研究的热点。从 periaxin 的分布、结构与功能开展研究, 寻找与其相互作用的蛋白质并揭示其互作的生物学意义, 从蛋白质水平上研究腓骨肌萎缩症的发病机制具有重要意义。

关键词: 腓骨肌萎缩症 4F 亚型; Periaxin; 结构; 功能

Periaxin and Charcot-Marie-Tooth Disease Subtype 4F

REN Ye-mei, SHI Ya-wei. (Key Laboratory of Chemical Biology and Molecular Engineeringof Ministry of Education, Institute of Biotechnology of Shanxi University, Taiyuan 030006, China)

Abstract: Periaxin is expressed by myelinating Schwann cells, which plays an essential role in stabilization of the myeline sheath. Periaxin mutations cause autosomal recessive, demyelination neuropathy, Charcot-Marie-Tooth 4F(CMT4F) subtype. Molecular genetics mechanism of CMT4F subtype has been one of the hot spots in the research field. The study of periaxin distribution, structures and functions, finding the interacting proteins with periaxin will reveal its biological function, and lay the foundation for the research of CMT pathogenesis on the protein level.

Key words: Charcot-Marie-Tooth disease 4F; Periaxin; Structure; Function

腓骨肌萎缩症又称为 Charcot-Marie-Tooth 病(CMT)是一类最常见的遗传性周围神经单基因遗传病, 具有明显的临床和遗传异质性, 发病率约 1/2500, 多数呈常染色体显性遗传。CMT 的临床主要特征是四肢远端进行性的肌无力和萎缩性感觉障碍, 腱反射减弱或消失、轻到中度远端感觉减退, 典型者双下肢呈倒立酒瓶状或称鹤立腿[1]。近十几年内, 将近 30 个不同的 CMT 遗传位点被定位, 20 个基因相继被克隆, 这些基因在维持周围神经轴索、髓鞘的结构完整性和功能完整性、线粒体功能、细胞信号转导等方面发挥重要作用。将 CMT 的为数众多的致病基因组成一个微芯片系统, 可揭示维持施万细胞-轴突完整结构的分子组织和维持周围神经正常功能必须的生物分子的种类和数量。现对 Periaxin 与 CMT4F 进行综述。

1　CMT4F

周围神经系统发育时, 轴突是否被有髓鞘施万细胞包裹, 以及包裹的厚度、长度均会影响神经信号转导, 越厚越长则传导速度越快。施万细胞和神经元为彼此提供整个发育过程中生存及分化的调节。影响施万细胞中任何一种类型的基因突变导致的遗传缺陷都可使神经元和施万细胞间通讯发生紊乱而引起 CMT 发生。根据临床特征、周围神经电生理和病理特点, CMT 分为脱髓鞘型和轴突型两大类。神经电生理检查表明脱髓鞘型 CMT 正神经传导速度减慢(<38 m/s), 周围神经传导速度减缓, 神经活检

基金项目: 国家自然科学基金(31170748)