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药物及靶向治疗在脊髓损伤中的治疗新进展 *

杨 鑫 祁 全△ 陶学强 张文龙 王金龙

(哈尔滨医科大学附属第一医院 黑龙江 哈尔滨 150001)

摘要: 脊髓损伤(spinal cord injury, SCI)是一种严重的损伤,它对患者的影响是相当持久的,SCI 治疗的难点主要是由于损伤后脊髓中的微环境不利于神经细胞的再生、轴突的生长和新突触的形成,从而影响了脊髓组织的修复。现在 SCI 治疗的策略就是要改善损伤脊髓微环境,减少不利因素, 从而促进脊髓结构修复和功能重建。本研究综述近年来逐渐发展起来的药物及靶向治疗方法,为 SCI 的新治疗提供参考依据,真正提高患者的生活质量。

关键词: 脊髓损伤;药物治疗;靶向治疗;新进展

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The Progress of Drugs and Target Therapy in the Treatment of Spinal Cord Injury*

YANG Xin, QI Quan, TAO Xue-qiang , ZHANG Wen-long, WANG Jin-long

(first affiliated hospital of Harbin medical university, Harbin, Heilongjiang, 151000, China)

ABSTRACT: Spinal cord injuries (spinal cord injury, SCI) is a serious damage, and its impact on patients is quite durable. SCI treatment is mainly due to the difficulty of microenvironment in the spinal cord after injury of nerve cells in the regeneration of axons, the growth and the formation of new synapses, which affects the spinal cord tissue repair. Now SCI treatment strategy is to improve the spinal cord injury microenvironment, and reduce adverse factors, so as to promote repair of spinal cord structure and functional reconstruction. This study summarized the targeted drugs and therapies in order to provide a reference basis for new treatment for SCI, and to really improve the quality of life.

Key words: Spinal cord injury; Drug treatment; Targeted therapy; The new progress

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前言

脊髓损伤(spinal cord injury,SCI)的最终神经学损害是由原发损伤和继发损伤两种机制引起的,原发损伤主要包括神经细胞坏死、轴索断裂等,是由创伤本身对神经细胞所造成的损伤;继发损伤主要包括水肿、局部缺血、炎性反应、脂质过氧化、兴奋性氨基酸的释放 / 神经细胞的凋亡等,一般发生在原发损伤后,伴有细胞内代谢和基因异常 。对于 SCI 的治疗方式目前较为集中在有细胞移植、基因治疗、针刺等[1-4]。药物治疗也是近年来较为关注的焦点。另外由于在 SCI 过程中,常伴有少突胶质细胞所释放的 Nogo-A 等相关抑制分子,同时可与 Nogo-66 受体结合防止轴突的再生及发展[5],因此靶向治疗也会成为日后 SCI 治疗的方向。故本研究对近年来主要开展的药物及靶向治疗进行综述,为更好地促进脊髓损伤患者有较高的生活质量提供依据。

1 药物治疗

1.1 糖皮质激素

皮质类固醇激素作为治疗 SCI 的经典药物,甲基强的松龙是其最具代表性的药物。激素对于神经系统有很好的保护作用,其治疗急性 SCI 的机制可能推测为;① 抑制炎性反应;② 降低氧自由基及脂质过氧化反应的活性;③ 抑制血管、前列腺素活性,增加脊髓的血流量,加速循环;④ 避免水肿;⑤ 分散细胞内 Ca^{2+} 的集中;⑥ 增强 Na^{+}-K^{+}-ATP 酶活性,加快脊髓冲动的传导[6-8]。MP 是人工合成的中效糖皮质激素,一般静注后 30 min 后在脊髓位存在峰浓度,有效治疗时间不长。现一般采用:先以 30 mg/kg 静脉冲击,后以 5.4 mg/(kg-h)维持 24 h,这对于患者运动和感觉功能的恢复作用明显。有研究提示, MP 对 SCI 后的神经保护可能仅在损伤早期起作用,控制较为容易。另有实验证明, 1 h 内给予急性 SCI 大鼠 MP (1.65 mg/kg 灌注),24 h 内连续给药[31.5 mg/(kg-h)灌注], 淋巴细胞水平可明显降低,伴有肺组织间质出血、肺部酸性细胞浸润、溃疡等不良反应,其中

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作者简介:杨鑫(1983-),男,医师,硕士,主要研究方向:脊髓损伤

△通讯作者:祁全(1972-),男,副主任医师,博士,主要研究方向:脊髓损伤

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对脾的作用最为明显。近来学者提出通过联合用药来降低并发症的发生率,但联合用药,特别对于本身有胃肠疾病者,注意采用奥美拉唑来对胃粘膜进行保护[9-13]。

1.2 促进神经元再生和降解胶质瘢痕的药物

1.2.1 **神经营养因子**(Neurotrophic factors, NT-Fs) NGF 作为神经再生微环境所必需,在神经系统中广泛分布,它可加速交感神经细胞的分化及成熟,催化突起生长为神经纤维,周围及交感神经的发育加速[14-16]。在 SCI 局部应用 NTF,可促进红核脊髓神经细胞的再生,避免细胞凋亡。胶质源性神经营养因子(GDNF)是新近发现的一个神经营养因子,它能够与 GFR-a1 受体、酪氨酸激酶 Ret 亚基结合,进一步激活其下游的各种蛋白酶而产生作用。

1.2.2 **神经节苷脂**(Ganglioside, GM-1) GM-l 作为唾液酸的一种,广泛分布于哺乳动物细胞膜,在中枢神经系统含量较高,对急性期神经损伤的修复及神经再生的作用尤为明显。GM-1 通过降低兴奋性氨基酸的毒性,牵制脂质过氧化反应,增强并促进细胞膜 Na^+-K^+-ATP 酶的活性,平衡细胞内外离子,同时调控多种炎性因子及其表达,降低或减轻 SCI 后神经细胞凋亡。

1.2.3 **降解胶质瘢痕药物** SCI 后瘢痕的形成可抑制神经轴突的生长。胶质瘢痕细胞可通过物理屏障作用、分泌硫酸软骨素(CSPGs),阻止神经元轴突生长等机制来阻碍神经元轴突的生长。

1.3 雌激素

流行病学调查结果表明;男性患 SCI 的概率高于女性,且神经恢复程度较差,可能的机制主要是因为雌激素可能有保护 SCI 后的神经细胞的作用。据推测,雌激素是利用雌激素受体(ER) 的介导活化作用来实现对而发挥 SCI 后的神经细胞的保护作用的。

1.4 抗氧化剂和氧自由基清除剂

褪黑激素(Melatonin, MT)广泛存在于机体,作为神经内分泌较为重要的物质,其具有脂水双溶性,可以透过各种生物膜清除自由基,抑制 TNF, 恢复损伤脊髓的正常功能。甚至有报道指出,MT 比 MP 具有更高的神经保护功能[21-24]。多酚类化合物白黎芦醇以其抗氧化、抗炎来降低受损脊髓乳酸脱氢酶活性,将脊髓损害的程度降至最低,更好地起到保护神经功能的作用。

1.5 其他药物

当 IL-2 生成量有所降低时,免疫抑制剂环孢素 A 可利用此来避免患者机体免疫细胞的浸润,降低或延缓细胞凋亡率。抗炎药物如 酶联蛋白 A1(Ac2-26)等。中药在 SCI 治疗中也占有一定的地位,中药提取物对患者机体具有改善微循环、抗氧、降低脊髓继发损伤等功效,且中药对症治本、价格低廉、毒副作用级不良反应小,市场前景较好。

2 靶向治疗

近几年,有些学者设计出针对 NgR 的拮抗性肽 NEP-1、NgR/NgR DNA 蛋白疫苗等尝试治疗动物 SCI[25,26]。髓鞘相关抑制因子(Myelin-associated growth inhibitors, MAGI)受体拮抗剂多肽 NEP1-40 是近年来研究较为广泛的靶向治疗因子,中枢神经再生困难之一是其内在的髓鞘相关抑制因子(MAIs)的存在,Nogo-A 蛋白、髓鞘相关糖蛋白、少突胶质细胞髓鞘糖蛋白是三个经典的 MAIs,基于 RADA-FGL 多肽自组装支架材料的 NEP1-40 缓释体系的构建目前也是修复脊髓损伤较为热门的研究,现将其目前的进展进行阐述。

2.1 MAGI 受体拮抗剂

SCI 发生后,神经轴突再生受到影响,其中 MAGI 最为明显,其作用机制主要是与 Nogo66 受体结合,进而发挥生物学效应,神经轴突的再生受到抑制[27-29]。抗 NgR DNA 疫苗 体内外实验证实 NgR DNA 诱导的 CD-8 T 细胞介导细胞免疫应答可修复损伤的 SCI。SCI 大鼠试验结果显示,利用生物素化的葡聚糖胺(BDA)行顺行标记的大鼠皮质脊髓束,经 NgR 蛋白免疫的大鼠,3/4 的个体其神经纤维可再生。

2.2 多肽 NEP1-40

体外实验表明,NEP1-40 可以阻止或降低中枢神经系统髓鞘或 Nogo-66 对轴突的抑制,在胸段脊髓半横切大鼠蛛网膜下腔注射 NEP1-40,SCI 大鼠的皮质脊髓束的再生以及行为学评估改善较为明显[30-32],运动功能恢复颇佳。

3 小结与展望

SCI 是一种严重的损伤,其治疗的难点主要是损伤后脊髓中的微环境破坏了神经细胞的再生、轴突的生长,从而使得脊髓组织的修复受到抑制。尽管 SCI 治疗的方法较多,但以 NgR 为靶点的治疗方式在众多方法中的优势较为明显。关于与 NgR 结合的两种抑制分子在体内的相互作用、NgR 亚型在 SCI 中的作用机制等问题,需进一步深入的研究。另外,髓鞘相关蛋白并不是唯一的抑制轴突生长的胞外因素,诸如硫酸软骨素多糖等均可对这些细胞外的抑制因素产生作用,如何与促再生因子共同调控轴突的生长,也是相关工作者目前需要着力的关键。本研究通过综述近年来逐渐发展起来的药物及靶向治疗方法,为 SCI 的新治疗提供参考依据,真正提高患者的生活质量。

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