·综述·

姜黄素及重复经颅磁刺激治疗脊髓损伤后中枢性疼痛的研究进展

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中枢性疼痛(central pain,CP)是中枢神经系统本身损伤或疾病所造成的自发痛和诱发痛,属于神经源性疼痛范畴。这种疼痛可以是单侧或是双侧,且与接触刺激诱发性疼痛和痛觉过敏有关[1]。CP 可发生在脊髓损伤(spinal cord injury,SCI)1 个月后任意时间且长期存在。全球每年有将近 250 万脊髓损伤患者,CP 发生概率高达 70%[2]。这种疼痛往往是长期存在且迁延不愈,临床上针对 CP 的治疗手段包括药物治疗、康复理疗、心理支持治疗及手术治疗等,其中以药物治疗和康复理疗占主导地位。姜黄素因无毒、价廉,具有抗炎、镇痛和神经保护等作用,逐渐成为 CP 治疗药物新宠。重复经颅磁刺激(repetitive transcranial magnetic stimulation,rTMS)是一种非介入性治疗手段,具有无创、无痛、操作简易及安全指数高等优点,能显著缓解药物难治性慢性神经病理性疼痛患者症状,在临床上具有广泛应用前景。本文就姜黄素及 rTMS 在治疗脊髓损伤后中枢性疼痛的作用及相关机制作一简要综述。

姜黄素治疗中枢性疼痛

目前研究显示传统中药姜黄素在抗氧化、抗炎、抗细胞凋亡、免疫调节、镇痛和神经保护等方面均有显著疗效[3],能调控脊髓损伤后多条信号通路,从多方面促进脊髓修复及治疗脊髓损伤后中枢性疼痛。

一、减轻活性氧和脂质过氧化对疼痛的影响

活性氧(reactive oxygen species,ROS)能促进兴奋性氨基酸(excitatory amino acid,EAA)释放并激活 N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid,NMDA)受体,通过激活脊髓胶质细胞等途径使细胞兴奋性发生改变,导致中枢敏化。姜黄素邻-甲氧基酚羟基上亚甲基的 H 位点可与自由基反应,直接清除自由基[4]。此外姜黄素能降低胶质细胞内中间丝蛋白胶质纤维酸性蛋白(glial fibrillaryacdic protein,GFAP)表达,同时还能降低脊髓组织中丙二醛(malondialdehyde,MDA)水平,提高脊髓组织中谷胱甘肽(glutathione,GSH)、过氧化物酶、超氧化物歧化酶(superoxide dismutase,SOD)及过氧化氢酶(catalase,CAT)活性,有助于缓解脊髓组织氧化应激损伤[5]。除了直接清除 ROS 外,姜黄素还能通过以下途径减少 ROS 产生:①抑制 NADH 氧化酶介导的氧化应激,NADH 氧化酶是产生 ROS 的主要酶,其中 NADH 氧化酶 2 过度表达和 ROS 过度产生在神经损伤、脊髓胶质细胞活化及疼痛过敏中具有重要作用。姜黄素能减少 NADPH氧化酶亚基 $p47^{phox}$ 和 $gp91^{phox}$ 表达,抑制 NADPH 氧化酶介导的氧化应激反应,减少脊髓组织中 ROS 产生,同时增加 SOD 含量[6]。②激活 Nrf2/ARE 信号通路,姜黄素能激活 Nrf2 信号通路,降低 MDA 水平,提高 SOD,同时还能影响 Bax/Bcl-2-Caspase-3 途径,抑制细胞凋亡[7]。如 González-Reyes 等[8]研究发现,姜黄素能激活 Nrf2/ARE 信号通路,提高抗氧化酶血红素氧合酶(hemeoxygenase,HO-1)、γ-谷氨酰半胱氨酸连接酶、谷胱甘肽-S-转移酶、GSH 和 SOD 水平,降低谷胱甘肽/谷胱甘肽二硫化物比值,从而减少 ROS 生成。

二、抑制炎性因子释放及炎症反应

炎症反应是机体局限或消灭损伤因子、清除或吸收坏死组织和细胞并修复损伤的防御性反应,但过度炎症反应会带来严重伤害,如脊髓损伤后过度炎症反应会造成进一步损伤和继发性疼痛。Chen 等[9]研究发现鞘内注射姜黄素能缓解完全弗氏佐剂(complete Freund's adjuvant,CFA)诱导的关节机械痛过敏、热痛觉过敏和脊髓神经炎性痛,其作用机制主要是抑制脊髓组织中炎性介质释放及星型胶质细胞、小胶质细胞激活,弱化 GFAP mRNA 表达。姜黄素还能抑制其他原因造成脊髓损伤后继发中枢性疼痛的炎性介质(如诱导型一氧化氮合酶和 Cox-2)表达。姜黄素能通过抑制 HAT 家族 p300/CBP 活性,减少 NF-κB 下游产物 Cox-2 表达,在抑制中枢性疼痛中发挥重要作用[10-11]。此外姜黄素还能抑制瞬时受体电位香草醛亚家族 1(transient receptor potential cation channel subfamily V member1,TRPV-1)敏化,TRPV-1 与缓激肽受体 B1 和大麻素受体 CB1 活性密切相关,TRPV-1、B1、CB1 活化都会促进脊髓损伤后中枢性疼痛发生,其中 CB1 活化能抑制丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)信号通路,激活基质金属蛋白酶-9(matrix metalloprotein,MMP-9)活性。姜黄素 KMS4034 能抑制 TRPV-1 敏化来缓解神经性疼痛,同时还能降低降钙素基因相关肽(calcitonin gene related peptide,CGRP)表达[2,12]。

三、抑制小胶质细胞激活

相关研究发现,小胶质细胞激活也有助于脊髓损伤后中枢性疼痛发展,Hains 等[13]向脊髓挫伤大鼠鞘内注射小胶质细胞抑制剂-米诺环素后,其痛阈值明显提高,脊髓背角神经元反应性降低。姜黄素抑制小胶质细胞激活可能作用于以下两个方面:①抑制 ERK1/2/p38 通路,姜黄素能抑制 Aβ42 在小胶质细胞中诱导的 ERK1/2 和 p38 磷酸化,此外还能抑制白介素-1β、白介素-6 和肿瘤坏死因子-α 蛋白表达[14]。②抑制趋化因子受体(CX3C chemokine receptor 1,CX3CR1)表达,小胶质细胞中 CX3CR1 对脊髓炎症反应进展至关重要,且直接参与脊髓损伤后中枢性疼痛发展。姜黄素通过抑制核因子-κB(nuclear factor-κB,NF-κB)抑制剂激活酶(IκBα kinase,IKK)和 AKT 活化,从而

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抑制 NF-κB 激活,降低 CX3CR1 在脊髓背角及背根节中的表达,从而缓解坐骨神经慢性束缚损伤诱导的神经源性疼痛[15]。

重复经颅磁刺激治疗中枢性疼痛

rTMS 是利用重复磁刺激产生的感应电流刺激大脑运动皮质,从而达到神经调控目的。rTMS 治疗 SCI 后 CP 的效果主要与刺激部位、刺激频率、刺激持续时间等参数有关,而多次 rTMS 刺激可使镇痛效果持续更长时间。

rTMS 作用于大脑运动皮质以及邻近结构,能对 SCI 后 CP 发生进展进行多方面调控,从而起到镇痛作用,并且 rTMS 作用疼痛部位相邻皮质区的疗效较作用于疼痛部位相应运动皮质区明显[16];此外 rTMS 还可通过改变大脑皮质兴奋性和调控神经递质水平产生镇痛效果。Gustin 等[17]采用 rTMS 刺激脊髓损伤患者初级运动皮质,发现能抑制患者丘脑及脊髓神经元兴奋。目前研究发现长时间连续 θ 波脉冲刺激比“经典”高频重复经颅磁刺激能产生更显著的镇痛作用[18]。前额叶背外侧皮质(orsolateral prefrontal cortex,LPFC)是除初级运动皮质外rTMS 另一主要作用位点。Borckardt 等[19]研究报道,部分慢性神经疼痛患者经 rTMS 刺激后,其疼痛症状明显改善,痛阈值有所提高,然而其具体生物学机制尚未明确。最近有研究表明,rTMS 只对 957TT 基因型患者具有镇痛作用,这将为以后临床选择治疗群体带来指导意义[20]。

姜黄素联合 rTMS 治疗中枢性疼痛

姜黄素联合 rTMS 治疗 CP 给 SCI 患者带来新的希望,两者协同治疗将有助于进一步缓解 SCI 后顽固性 CP 病情。相关的协同治疗机制包括以下方面。

一、共同抑制中枢敏化

SCI 后脊髓神经中枢下行抑制作用减弱或完全消失,神经元持续性异常放电和脊髓背角突触传递效率持续性增强,导致周围神经刺激反应性增强、痛阈降低,引起疼痛。患者中枢敏化的重要原因包括 EAA 释放堆积,激活 Ga^{2+}通道,随之激活蛋白激酶 C(protein kinase C,PKC),引起突触前、后 NMDA 受体磷酸化,神经元兴奋性增强,可见有效抑制 EAA 释放将有助于缓解疼痛。Somers 等[21]研究发现在高频 rTMS 作用下,慢性神经损伤大鼠脊髓背角内 EAA 含量下降,脊髓中枢兴奋性降低,CP 得以缓解。姜黄素也具有类似作用,如有研究证实姜黄素能抑制大鼠前额叶神经末梢 Glu 释放,其机制可能是调制电压依赖性 Ca^{2+}入口,抑制 ERK1/2 磷酸化和突触囊泡相关蛋白 synapsin I 表达,从而增强突触囊泡胞吐作用,减少 Glu 释放,抑制中枢组织兴奋性[22]。相关靶向治疗研究发现姜黄素能通过减少 Ca^{2+}内流、阻断 AKAP79 从细胞膜到细胞质的易位以减轻 Glu 诱导的兴奋毒性[23]。因此在 rTMS 干预基础上联用姜黄素将进一步抑制中枢异常兴奋,提高 CP 治疗效果。

rTMS 的作用机制可能还涉及对突触后膜 NMDA 受体的影响。据报道 rTMS 联合使用 NMDA 受体拮抗剂时,对中枢长时程增强效应的抑制作用减弱,提示 rTMS 作用效应可能具有 NMDA 受体依赖性特点[24]。而姜黄素通过与 Ca^{2+}竞争蛋白激酶 C(proteinkinaseC,PKC)上的调节区,能抑制 NMDA 介导的细胞内 Ca^{2+}升高及中枢敏化[25-26],同时抑制 NMDA 受体下游钙/钙调蛋白依赖性蛋白激酶 II(calcium/calmodulin dependent protein kinase II,CaMKII)活性,其参与了病理性谷氨酸盐释放和中枢异常兴奋[27]。

二、提高痛阈

rTMS 能增加机体压力疼痛阈值,可能涉及所有参与疼痛管理的神经结构活性变化,如丘脑、前扣带皮质、第二躯体感觉皮质、中脑导水管周围灰质以及 GABA 能受体重塑等[28]。而姜黄素则通过影响信号通路来提高痛阈。SCI 后 JNK 通路活化,c-Jun 磷酸化,从而促使星形胶质细胞释放单核细胞趋化蛋白-1(monocyte chemotactic protein 1,MCP-1)作用于 CC 趋化因子受体 2(CC chemokine receptor 2,CCR2),并且 MCP-1 可直接激活背角神经元 NMDA 受体,增加疼痛敏感性[29]。Liu 等[30]报道姜黄素通过抑制 JNK 和 NF-κB 信号通路来降低 MCP-1 水平,从而提高疼痛阈,缓解 CP 症状。

三、神经保护作用

Li 等[31-32]联合采用电针及 rTMS 干预脑梗死大鼠时发现,治疗组大鼠 Caspase-3 水平明显下降,bcl-2 基因 mRNA 水平显著升高,提示 rTMS 能抑制神经元细胞凋亡。姜黄素也具有类似作用,如姜黄素能通过抑制 JNK 信号通路,裂解神经元中 Caspase-3,解除 MPTP/MPP(+)诱导的多巴胺神经元毒性,抑制神经元死亡[33]。此外姜黄素还能通过 PI3K/MAPK 信号传导途径增加调节激活正常 T 细胞表达和分泌因子(regulated upon activation normal T cell expressed and secreted,RANTES)在原代培养星形胶质细胞中的表达,RANTES 是由星形胶质细胞和小胶质细胞分泌的趋化因子,也是调节 T 细胞表达和分泌的趋化因子,具有神经保护作用[34],同时姜黄素对脊髓神经祖细胞(spinal cord neural progenitor cells,SC-NPCs)增殖具有双相作用,如低浓度姜黄素能促进 SC-NPCs 增殖[35]。可见 rTMS 与姜黄素联用能进一步发挥神经保护作用。

四、改善皮质及局部血液循环

rTMS 能介导丘脑网状核(thalamic reticular nucleus,TRN)功能并抑制丘脑兴奋性,其可能机制是 SCI 后 TRN 区血流量减少,GABA 含量降低,对丘脑抑制作用减弱,rTMS 能改善 TRN 区尤其是体感刺激区域血流量,达到治疗 CP 目的[36]。脊髓损伤部位常发生缺血再灌注(ischemia reperfusion,IR),此时黄嘌呤氧化酶生成增多,中性粒细胞聚集活化,线粒体损伤,儿茶酚胺自氧化增加都可导致 ROS 产生及堆积,造成局部组织缺血甚至坏死,引起疼痛。姜黄素通过清除 ROS 并提高呼吸电子传递链复合蛋白 I 活性,抑制线粒体膜上通透性转换孔的开放及细胞色素 C 的释放来减轻 IR 对线粒体的损伤[37],改善局部组织血液循环,从而发挥 CP 治疗作用。

五、拮抗负性刺激

NO 是强烈炎性介质,当高水平表达时具有神经毒性作用,诱导型一氧化氮合酶增多是 SCI 后慢性炎症反应重要的初级表现形式,诱导型一氧化氮合酶抑制剂已被证实能有效减轻炎症反应及疼痛过敏。相关研究发现,实验大鼠经 rTMS 作用后其大脑皮质及海马回 NO 水平明显增高,在一定程度上影响了治疗效果[38]。而姜黄素能限制一氧化氮合酶表达,如 Jiang 等[39]在体外培养的星型胶质细胞中发现,姜黄素能抑制脂多糖和一氧化氮合酶表达,减少 ROS 产生。

结语

SCI 后 CP 的发生机制尚未明确,目前临床上综合治疗手段并不能完全缓解患者疼痛。姜黄素具有降低中枢敏化、抗炎、抗氧化、抗细胞凋亡、保护神经等多种药理作用,且副反应小,有望成为新一代治疗 SCI 后 CP 的主要临床用药。rTMS 因其无创、无痛、安全系数高等优点将成为 SCI 后 CP 康复理疗的热门治疗手段。科学联合采用姜黄素及 rTMS 将给 SCI 患者康复带来希望。至于上述疗法的确切生物学作用机制还有待更多实验证明。

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·外刊撷英·

Concussed athletes more prone to injury

BACKGROUND AND OBJECTIVE Previous studies have demonstrated that athletes who sustain a concussion have a higher risk of sustaining another serious injury during the 21 days after return to play. This study employed a large database of patients who had presented to the emergency department with concussion, to better understand the rate of subsequent injuries.

METHODS Patient data were collected from the Umea Injury Data Base in northern Sweden, the only hospital within a 120km radius. Data were collected concerning participants in four contact sports, (ice hockey, soccer, handball and floorball), who were treated for concussion between 1995 and 2009. Data were reviewed for injuries treated 24 months before through 24 months after the index concussion. A control group of athletes with an ankle sprain, but no concussion, was used for comparison.

RESULTS Between 1995 and 2009, 4,961 concussions were documented, of which 699 occurred during the participation in the sports identified. These athletes were compared to 1,259 athletes without concussion. Compared to the control group, those with concussion had a higher risk of injury in the 24 months after the index concussion (OR 1.72), as well as in the 24 months before the injury (OR 1.98). This was not true for the athletes with ankle injury.

CONCLUSION This study found that, while athletes who suffer a concussion are more likely to sustain injuries during the two years after the concussion, this risk is no greater than during the two years before the concussion.

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