基于CREB信号通路的脑卒中治疗中药研究进展

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摘要: cAMP反应元件结合蛋白 (cAMP response element binding protein, CREB) 是一种真核细胞生物核内蛋白质, 在各种器官中广泛表达, 其被激活后增加下游基因的转录活性, 促进相关基因的表达。CREB在神经元中的功能与许多细胞内过程有关, 如增殖、分化、生存、长期突触电位、神经发生和神经元可塑性。越来越多的研究结果证明, CREB功能影响脑卒中的发生和发展, 具有作为防治脑卒中新靶点的巨大潜力, 且部分中药及有效成分可以促进CREB的表达。因此, 本文将梳理归纳CREB信号通路在脑卒中病理生理学中的作用以及调节CREB表达的中药及有效成分的研究进展, 以期为未来天然药物防治脑卒中研发提供依据和参考。

关键词: 脑卒中; cAMP反应元件结合蛋白; 突触可塑性; 凋亡; 中药

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New advances in stroke therapy targeting the CREB signaling pathway and the potential for herbal interventions

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Abstract: cAMP response element binding protein (CREB) is an eukaryotic intranuclear protein widely expressed in a variety of organs, and its activation increases the transcriptional activity of downstream genes and promotes the expression of related genes. The neuronal function of CREB is related to many intracellular processes, such as proliferation, differentiation, survival, long-term synaptic potentials, neurogenesis and neuronal plasticity. Increasing evidence has demonstrated that CREB plays an important role in the stroke development and therefore, it may serve as a potential target for stroke therapy. Since some herbal medicines as well as their active ingredients regulate the CREB signaling, this article will summarize the role of CREB signaling pathway in stroke pathophysiology. The research progress of traditional Chinese medicine and its active ingredients modulating CREB activity will also be discussed, with the aim of providing the basis and reference for the future research and development of natural medicines against stroke.

Key words: stroke; cAMP response element binding protein; synaptic plasticity; apoptosis; traditional Chinese medicine

脑卒中是全球第二大死因。据估计, 全球每年因脑卒中造成的经济损失超过7 210亿美元[1]。当血管因血栓形成或狭窄而堵塞 (即缺血) 或血管因动静脉畸形或动脉瘤而破裂 (即出血) 时, 就会发生脑卒中。脑卒中具有高发病率、高致残率、高复发率和高死亡率的特点。仅在中国, 40岁及以上居民的脑卒中患病率

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平均每年增加0.24%[2]。到2030年, 脑卒中相关费用预计将达到240.67亿美元, 但可用的治疗选择仍然非常有限。cAMP反应元件结合蛋白 (cAMP response element binding protein, CREB) 是一种转录因子, 存在于大多数脑细胞中, 它参与神经元生长、细胞存活、突触可塑性、记忆控制和神经再生[3]。近期研究发现[4], CREB激活可通过调节神经炎症、凋亡及神经可塑性等多通路改善脑卒中后脑功能的恢复。中药可通过多途径多靶点发挥保护作用, 且已发现多种中药复方、单体通过调节CREB来发挥脑保护作用, 这提示CREB已成为干预脑损伤后恢复的潜在治疗靶标。

本文首先介绍了CREB的基本信息, 包括CREB的结构、功能和基因转录调节机制, 然后综述了CREB在脑卒中中相关机制的研究进展, 最后总结分析了近年来中成药和中药有效成分通过调控CREB相关机制而改善脑卒中后恢复的研究结果, 期望为以靶向CREB干预脑卒中提供参考。

1 CREB的结构及转录调节机制

CREB是一种真核生物细胞核内蛋白质, 其功能是调节基因转录。CREB由341个氨基酸残基构成, N端为甲硫氨酸, C端为天冬氨酸。CREB的二级结构有两个功能区, 其中C端富含碱性氨基酸, 含亮氨酸拉链结构 (b-zip-basic leucine zipper, bZIP) 为DNA结合域; N端富含酸性氨基酸, 负责调节CREB转录, 该区域包括含大量脯氨酸 (proline, PRO) 区和多激酶诱导结构域 (kinase inducible domain, KID) 等。PRO区将CREB的启动子结合部位和转录调节部位分隔开, 增加了分子柔性, 有助于更好地发挥转录调节功能[5]。

CREB必须在被磷酸化成p-CREB后才能发挥其转录激活功能。CREB分子结构中KID的Ser133位点是最主要的磷酸化位点, 也是发挥其转录调节作用的关键位点。除此之外, CREB发挥转录作用尚需两个重要的辅助因子参与其转录调节功能的机制。辅助因子CREB结合蛋白 (CREB binding protein, CBP) 参与促进CREB的磷酸化, 并与CREB结合为复合物, 实现对基因转录的调节功能。另一个辅助因子cAMP调节的转录共激活因子 (cAMP-regulated transcriptional coactivator, CRTC) 或CREB调控转导子 (transducer of regulated CREB, TORC) 与CREB的bZIP结构域结合[6], 促使下游转录基因的激活, 增加相关基因的表达。

2 CREB信号通路在脑缺血中的作用

脑缺血再灌注损伤是一种病理生理级联反应, 初始损伤发生在缺血后几分钟内, 大脑血液供应中断, 神经元严重缺乏氧气和葡萄糖[7]。由于厌氧代谢和乳酸积累, ATP水平下降, 导致ATP依赖性离子转运功能障碍、线粒体钙过载、细胞肿胀和细胞死亡, 包括坏死、凋亡和自噬等不同机制的激活[8]。最终导致感觉和运动功能的损害, 从而加重损伤并恶化患者的预后。

2.1 线粒体氧化应激 缺血性脑卒中的特征是同时存在缺血性和再灌注相关性脑损伤, 导致神经元功能障碍和死亡。在正常生理情况下, 活性氧 (reactive oxygen species, ROS) 的产生主要来自还原型烟酰胺腺嘌呤二核苷酸磷酸 (nicotinamide adenine dinucleotide phosphate, NADPH) 氧化酶、线粒体呼吸链酶复合体、黄嘌呤氧化酶及蛋白激酶C等多种酶[9]。同时, 细胞内也存在一系列抗氧化物质, 如超氧化物歧化酶 (superoxide dismutase, SOD)、谷胱甘肽过氧化物 (glutathione peroxidase, GSH-Px)、过氧化氢酶 (catalase, CAT) 及谷胱甘肽 (glutathione, GSH) 等, 可清除多余的活性氧, 维持细胞稳定。急性缺血性脑卒中后ROS产生迅速增加, 破坏内源性抗氧化防御机制, 导致组织损伤。过度产生的ROS会直接损害细胞成分, 包括蛋白质、DNA、RNA和脂质, 导致自噬、凋亡和坏死[10]。

缺血再灌注诱导氧化磷酸化蛋白的翻译后修饰, 从而增加线粒体膜电位, 这种情况会导致ROS过度产生[11]。同时, 线粒体被报道为蛋白激酶A (protein kinase A, PKA)/CREB调节的ROS的主要来源[12]。研究发现[13], 激活PKA会触发CREB磷酸化并防止原代皮质神经元的线粒体功能障碍, 从而保护它们免受氧糖剥夺诱导的神经元损伤和死亡。Li等[14]研究发现细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) 也可激活CREB及内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 增强线粒体复合物呼吸链复合物I的活性, 减少氧化应激, 抑制线粒体细胞凋亡。同时有研究表明[15], 缺血性脑损伤可促进ERK和CREB的磷酸化, 以及增加其在脑损伤后的体内外mRNA的表达水平。通过调节ERK/CREB信号传导抑制神经元损伤和钙离子流入, 并在脑损伤后维持体内和体外线粒体膜电位, 从而减轻脑缺血/再灌注损伤。

2.2 细胞凋亡 细胞凋亡在缺血性脑卒中缺血诱导的神经元死亡中起至关重要的作用。在梗死核心, 兴奋性毒性和神经元坏死在几分钟内发生, 使得恢复血液和氧气供应的尝试几乎毫无价值[16]。然而, 缺血性半影中的许多休眠或半休眠神经细胞主要以细胞凋亡的形式发生延迟死亡。与不可逆的组织坏死不同, 细胞凋亡可以被抑制, 预防半影神经元凋亡并改善其功能障碍对于治疗缺血性脑卒中至关重要[8,17]。

线粒体是多功能细胞器, 在生理和病理生理条件

下起着至关重要的作用。在缺血再灌注损伤的情况下, 线粒体不仅是ROS发生者, 而且还介导其他病理过程, 如细胞凋亡和坏死。此外, 一些调控因子也会引起线粒体膜通透性转换孔(mitochondrial permeability transition pore, mPTP) 的开放, 如B淋巴细胞瘤-2 (B-cell lymphoma-2, Bcl-2) 家族蛋白。Bcl-2相关X蛋白 (Bcl-2-associated X, Bax) 可以调控线粒体膜的通透性, 进而协助线粒体释放细胞色素C促进细胞凋亡。然而, Bcl-2可与Bax结合抑制细胞凋亡[18]。

相关研究表明, AMP活化蛋白激酶 [adenosine 5-monophosphate (AMP)-activated protein kinase, AMPK] 是一种重要的内源性防御因子, 通过缓解神经炎症, 减少氧化应激, 改善线粒体功能障碍和抑制细胞凋亡, 在缺血性脑卒中中发挥保护作用[19]。Liu等[20]研究发现, AMPK可刺激CREB磷酸化并进一步促进脑源性神经营养因子 (brain derived neurotrophic factor, BDNF) 的释放, 从而减少缺血半影神经元细胞凋亡, 促进细胞增殖。有研究发现激活ERK1/2/CREB/Bcl-2信号通路可提高细胞活力, 降低乳酸脱氢酶 (lactate dehydrogenase, LDH) 释放和细胞凋亡, 并减弱了ROS的产生和线粒体膜电位的丧失 (Δψm)。抑制ERK1/2信号通路则逆转了神经保护作用[21]。

2.3 神经炎症 脑卒中发作后几分钟至数小时发生的神经炎症和免疫反应与缺血性脑卒中后脑损伤的复杂病理学有关[22]。炎症起病急, 持续时间长, 从数天到数月不等, 因此从炎症的角度来看, 脑卒中后的干预和治疗窗口期较长[23]。许多研究表明, 中枢神经系统先天免疫细胞, 即小胶质细胞, 是第一个对缺血性损伤作出反应的炎症细胞, 并通过去除凋亡细胞和调节缺血性脑区域的炎症反应, 对缺血性脑卒中的预后做出关键贡献[24]。

研究发现, 氯离子运动和氯离子敏感信号通路有助于小胶质细胞存活和M2样极化, 从而减轻神经炎症和缺血性脑损伤, 这可能与激活血清/糖皮质激素调节激酶1 (serum/glucocorticoid regulated kinase 1, SGK1)-叉头框家族 (forkhead box O3, FOXO3a)/CREB信号通路有关[25]。同时, 有研究发现PKA/CREB信号通路也有助于调节小胶质细胞活化, 从而发挥神经保护作用[26]。过氧化物酶体增殖激活受体γ共激活因子1α (peroxisome proliferator-activated receptor-gamma coactivator 1α, PGC-1α) 是一种转录辅激活因子, 它能招募核受体或转录因子, 并调控细胞核和线粒体中下游基因的转录[27]。PGC-1α可抑制核因子κB (nuclear factor kappa-B, NF-κB) 通路, 减少炎症的发生[28]。CREB是调节PGC-1α表达的重要转录因子[29], 可以减少促炎因子的表达, 特异性抑制CREB会逆转抗炎作用[30]。

2.4 突触可塑性 脑缺血后神经功能的恢复主要依靠新形成的神经元向严重缺血病变的迁移, 如海马体的纹状体和颗粒层, 以取代坏死神经元。然而, 只有非常小一部分新生成的神经元可以分化为成熟的神经元[31]。除神经发生外, 脑卒中后神经功能的恢复还取决于同侧组织中已建立网络的神经可塑性, 包括轴突发芽、树突重塑和突触强化[8]。因此, 通过促进内源性神经发生和神经可塑性认为是治疗缺血性脑卒中的有希望的策略。

CREB是一种分子开关, 可控制中枢神经系统中的突触可塑性和记忆形成。CREB的激活促进BDNF转录, BDNF调节神经元的存活和生长, 在大脑各个区域的突触传递和可塑性中起作用。MR-409是生长激素释放激素的有效合成激动类似物, 长期使用MR-409可显著减少缺血性损伤和海马萎缩。此外, MR-409可以刺激内源性神经发生, 改善短暂性大脑中动脉闭塞诱导的神经可塑性丧失。这与Akt/CREB和BDNF/TrkB通路的激活密切相关[32]。α7烟碱型乙酰胆碱受体 (α7 nicotinic acetylcholine receptor, α7nAChR) 属于烟碱型乙酰胆碱受体, 在中枢神经系统中广泛表达。缺血性脑卒中慢性期的α7nAChR上调可减少脑缺血性损伤, 改善了神经功能恢复。α7nAchR可以通过多种方式上调BDNF的表达, 并激活下游cAMP/PKA/CREB的表达, 这对于脑卒中后轴突可塑性至关重要[33]。

以上研究表明, CREB作为转录因子, 可调控线粒体氧化应激、细胞凋亡、神经炎症及突触可塑性改善脑卒中后的恢复。其机制可能涉及BDNF/TrkB、Bax/Bcl-2等多个靶点 (图1)[4]。

3 CREB信号通路在脑出血中的作用

脑出血占全球所有脑卒中的10%～15%, 具有高死亡率、高发病率的特征[34]。脑创伤后存在有序的时间和空间病理演变, 即原发性和继发性脑损伤。在初始损伤之后, 脑出血的继发性脑损伤可导致不良结果, 暂无有效的治疗方法[35]。神经炎症在继发性脑损伤的发病机制中起关键作用, 不受控制的神经炎症可导致额外的脑损伤[36]。

炎性小体介导的细胞焦亡被认为是多种神经系统疾病中炎症诱导神经元细胞死亡的重要机制[37]。趋化因子受体5 (C-C chemokine receptor type 5, CCR5) 是一种跨膜G蛋白偶联受体, 在炎症反应期间参与白细胞募集到组织损伤区域, 并已被证明是抗炎治疗的可行靶标。据报道, CREB蛋白是参与CCR5信号传导的

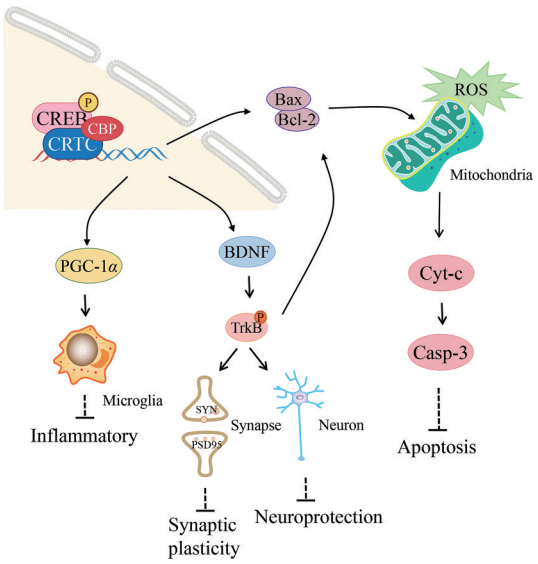

Figure 1 Downstream regulatory mechanisms of cAMP response element binding protein (CREB). Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; ROS: Reactive oxygen species; PGC-1α: Peroxisome proliferators-activated receptor γ coactivator 1 alpha; BDNF: Brain-derived neurotrophic factor; TRK: Tropomyosin receptor kinase; SYP: Synaptophysin; PSD95: Postsynaptic density protein 95; Cyt-c: Cytochrome c; Casp3: Caspase-3. Modified from Chowdhury MAR[4]

下游途径蛋白之一[38]。应用CCR5的特异性拮抗剂maraviroc (MVC)可通过激活小鼠脑出血后的PKA/CREB信号通路来减轻神经功能障碍, 并减少核苷酸结合寡聚化结构域样受体蛋白3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)依赖性神经元焦亡[39]。髓系细胞触发受体2 (triggering receptor expressed on myeloid cells 2, TREM2)已被证明通过调节神经炎症, 促进吞噬作用和细胞存活, 在神经退行性疾病和脑卒中中发挥神经保护作用。Akt/CREB/BDNF轴已被证明通过预防神经炎症、氧化应激、细胞凋亡和线粒体功能障碍, 对神经变性具有神经保护作用[40]。有趣的是, Akt是TREM2的下游靶标[41]。Yan等[42]研究发现, TREM2及其下游Akt/CREB/BDNF信号通路可能在脑创伤后发挥神经保护作用, TREM2耗竭可逆转这种保护作用, 这说明CREB可能通过调控神经炎症成为治疗脑出血的潜在靶点。

4 中药调控CREB治疗缺血性脑卒中

中医在治疗脑卒中方面历史悠久, 具有独特的优势[43], 是治疗缺血性脑卒中新药开发的重要来源之一。西药治疗脑卒中靶点单一, 并且多数西药都有不同程度的耐药性, 不良反应明显, 可引起胃肠、肝肾等不同程度的损伤。此外, 大量研究表明, 中草药可作为西药的补充和替代来预防和治疗心脑血管疾病。中药通过多成分、多途径、多靶点及其不良反应少在治疗脑卒中中发挥功效[44,45]。

4.1 线粒体氧化应激 黄芪和川芎是广泛使用的中药, 具有抗氧化的作用。Tang等[15]使用小鼠大脑中动脉闭塞/再灌注模型和原代大鼠大脑皮质神经元的氧糖剥夺/再氧合模型评估黄芪与川芎联用对脑损伤的保护作用。实验结果表明, 二者联用可显著改善神经功能缺损, 减少梗死体积, 抑制神经元损伤和钙离子流入, 并在脑损伤后维持体内和体外线粒体膜电位。此外, 黄芪与川芎治疗显著增加了ERK和CREB的磷酸化, 并增加其在脑损伤后的体内外mRNA表达水平。黄芪甲苷IV (astragaloside IV, AST-IV)是黄芪的关键生物活性成分, 在中医中广泛用于治疗脑血管疾病[46]。另有研究通过原代大鼠大脑皮质神经元的氧糖剥夺/再氧合模型进行缺血性损伤的体外模拟, 这导致PKA失活和CREB磷酸化降低、细胞活力降低和神经元凋亡增加。经AST-IV治疗后, OGD诱导的线粒体和细胞损伤被逆转, PKA和CREB磷酸化增强, 从而保护暴露于OGD的神经元免受损伤和死亡[13]。

4.2 细胞凋亡 脉络宁口服液是以脉络宁注射液为基础的中成药, 在临床上广泛用于脑卒中的治疗。连续灌胃14天脉络宁口服液可明显降低大脑缺血/再灌注大鼠模型梗死体积和神经功能缺损, 抑制神经元细胞凋亡, 促进神经元存活和神经保护。进一步研究发现, 脉络宁口服液可激活CREB/BDNF通路促进的缺血性脑卒中恢复期的神经保护[47]。青蒿素是一种传统中药, 几十年来一直被用作临床上的抗疟疾药物。除了抗疟作用外, 青蒿素及其衍生物还被报道具有神经保护作用, 可能在预防和治疗脑部疾病方面具有潜在的应用[48,49]。Peng等[21]研究发现青蒿素改善了MCAO动物的神经和行为结果, 促进了抓握力和运动功能的恢复。此外, 青蒿素治疗显著抑制细胞凋亡、氧化应激和神经炎症的分子指标, 激活ERK1/2/CREB/Bcl-2信号通路。蒿甲醚是一种青蒿素衍生物, 具有比青蒿素更高的抗疟疾活性。这种化合物可以很容易地穿过血脑屏障, 在临床上更频繁地使用[50]。研究发现, 蒿甲醚通过刺激ERK1/2-p90RSK-CREB信号通路减少细胞损伤, 从而在预防脑缺血性损伤方面发挥关键作用[51]。研究证明, 淫羊藿苷II是一种潜在的天然磷酸二酯酶5 (phosphodiesterase 5, PDE5)抑制剂, 可通过降低PDE5的活性和激活PKG/CREB/BDNF/TrkB信号通路减少神经元凋亡, 防止OGD/R诱导的原发性海马神经元损伤[52]。此外, 银杏内酯也可作为新型外在调节剂, 激活Akt/CREB信号通路, 防止体内和体外脑缺血/再灌注损伤[53]。

4.3 神经炎症 人参和银杏叶均被广泛用于治疗神经退行性疾病, 研究发现人参和银杏叶在临床应用中具有协同作用, 它们可改善人类生理和认知功能的各个方面[54]。Zhao 等[55]研究采用网络分析和动物实验研究共同探讨人参和银杏叶提取物 (combination of *P. ginseng* and *G. biloba* extracts, CGGE) 治疗缺血性脑卒中的潜在机制。实验结果表明, 口服 CGGE 可以通过抑制 NLRP3 炎症小体的活性来减少炎症反应, 并通过 CAMK4/CREB 途径来维持谷氨酸 (glutamic acid, Glu) γ-氨基丁酸 (gamma-aminobutyric acid, GABA) 的平衡。拟人参皂苷 F11 (pseudoginsenoside F11, PF11) 是从西洋参中分离出的一种有效成分。大量研究证实, PF11 对中枢神经系统和心血管系统的疾病有很多有益的影响[56], 特别是其对短暂和永久性大脑中动脉闭塞的大鼠缺血性脑损伤的有益作用[57,58]。Liu 等[59]证明静脉注射 PF11 可以改善缺血诱导的神经元组织病理损伤和细胞内蛋白水解, 这与激活 Akt-CREB 通路有关。

4.4 突触可塑性 人参皂苷 Rb1 (ginsenoside Rb1, GRb1) 是人参中主要活性成分之一。越来越多的研究表明, 人参皂苷具有促进暴露于谷氨酸的神经突触生长和分支的能力, 以及促进神经挤压损伤大鼠模型中的周围神经再生[60]。最近的研究表明, GRb1 通过刺激轴突再生和脑修复来改善脑卒中后的功能恢复, 其潜在的机制可能是上调 cAMP/PKA/CREB 通路的表达[61]。此外, 研究发现红景天苷 (salidroside, Sal) 也可通过调节 cAMP/PKA/CREB 途径抑制炎症和细胞凋亡, 促进树突生长, 改善与突触可塑性相关的基因发挥神经保护活性[62]。三七皂苷 R1 (notoginsenoside R1, R1) 是从三七中分离出的主要成分, 是一种植物雌激素, 在缺血性脑卒中大鼠模型中发挥许多神经保护作用。Zhu 等[63]研究揭示了 R1 对缺血性脑卒中长期恢复的影响, 该研究采用体内体外模型评估 R1 对缺血性脑卒中后神经发生和长期功能恢复的影响。实验结果表明, 造模后腹腔注射 R1 可显著恢复神经功能, 并刺激神经发生和少突胶质细胞生成, 进一步研究表明, R1 可能通过激活 BDNF/Akt/CREB 信号传导发挥神经保护和促神经发生作用。

目前靶向 CREB 的中草药如表 1[15,47,55,64-67]、表 2[18,21,40,51,59,61-63,68,69]总结所示。

5 总结与展望

除 CREB 介导的线粒体氧化应激、细胞凋亡、神经炎症、突触可塑性外, CREB 调节血管新生可能是治疗脑卒中的另一个重要靶点。众所周知, 血管生成是缺血中必不可少的组织反应, 通过建立缺血后的血管通路以尽快恢复氧和糖的供应, 这很可能决定神经元能否存活。这个过程依赖于内皮细胞增殖、迁移和毛细管形成, 这可以改善脑卒中后的长期残疾[70]。

Table 1 Traditional Chinese medicine regulating CREB signaling to treat ischemic stroke. a: Middle cerebral artery occlusion/reperfusion, MCAO/R; b: Permanent middle cerebral artery occlusion, pMCAO; c: Microsphere induced cerebral embolism; d: Oxygen glucose deprivation/rehydration, OGD/R; iv: Intravenous injection; ip: Intraperitoneal injection; ig: Intragastric administration

Herb	Dose	Disease target	Function	Subject	Ref
MaiLuoNing KouFuYe	6 mg·kg^{-1} (ig), 0.7/1.4/2.8 mg·mL^{-1}	CREB/BDNF	Apoptosis	SD rats[a], PC-12 cell[d]	[47]
HouShiHeiSan	5.25/10.5 g·kg^{-1} (ig)	ERK1/2/CREB	Apoptosis	SD rats[b]	[64]
Black Bamboo Rhizome	1.35/4.5 g·kg^{-1} (ig)	CREB/BDNF	Apoptosis	SD rats[a]	[65]
Angelica sinensis	0.5/1 g·kg^{-1}	p90RSK/CREB/BDNF	Apoptosis	SD rats[a]	[66]
CGGE	15/35 mg·kg^{-1} (ig)	CAMK4/CREB	Neuroinflammation	SD rats[c]	[55]
Astragalus membranaceus and Ligustrazine	10 mg·mL^{-1} (ip), 0.2 mg·mL^{-1} Ast, 120 μmol·L^{-1} Lig	NR2B-ERK/CREB	Mitochondrial function	C57BL/6 mice[a], primary neuron[d]	[15]
Danhong injection	1/2 mg·kg^{-1} (iv), 2.5−40 μL·mL^{-1}	BDNF/Akt/CREB	Synaptic plasticity	SD rats[a], PC-12 cell[d]	[67]

Table 2 Traditional Chinese medicine ingredients regulating CREB signaling to treat ischemic stroke

Active ingredient	Dose	Disease target	Function	Subject	Ref
Altemisinin	3/6/18 mg·kg^{-1} (ig), 12.5/25/50 μmol·L^{-1}	ERK1/2/CREB/Bcl-2	Apoptosis	C57BL/6 mice[a], PC-12 cell[d], Primary neuron[d]	[21]
Aretemether	5/10/20 mg·kg^{-1} (ig), 30 μmol·L^{-1}	ERK1/2-p90RSK-CREB	Apoptosis	C57BL/6 mice[a], PC-12 cell[d], primary neuron[d]	[51]
Icariside II	12.5/25/50 μmol·L^{-1}	PKG/CREB/BDNF/TrkB	Apoptosis	Primary hippocampus neuron[d]	[40]
Eudesmol	100 mg·kg^{-1} (ig)	TRPC6/CREB	Apoptosis	SD rats[a]	[68]
PF11	3/6/12 mg·kg^{-1} (iv), 10/30/100 μmol·L^{-1}	Akt-CREB	Neuroinflammation	SD rats[b], primary neuron[d]	[59]
AST-IV	6.25/12.5/25 μmol·L^{-1}	PKA/CREB	Mitochondrial function	Primary neuron[d]	[18]
GRb1	24 mg·mL^{-1} (ip)	cAMP/PKA/CREB	Axon regeneration	C57BL/6 mice[a]	[61]
R1	10/20/40 mg·kg^{-1} (ip)	BDNF/Akt/CREB	Neurogenesis	SD rats[a], PC-12 cell[d]	[63]
Sal	25/50/100 mg·kg^{-1} (ip)	cAMP/PKA/CREB	Synaptic plasticity	SD rats[a], PC-12cell[d]	[62]
Resveratrol	2 mg·kg^{-1} (ip)	ERK-CREB	Neuroprotection	SD rats[a]	[69]

PDE抑制剂已安全有效地用于临床, 并可增加细胞内环核苷酸的浓度。这些分子激活下游介质, 包括控制神经元兴奋性和生长反应的CREB蛋白。Rolipram是一种PDE4抑制剂, 可激活CREB通路, 促进缺血边界区微血管密度升高, 刺激血管生成[71,72]。研究发现, CREB转录共激活因子CRTC2在内皮细胞中表达, 缺血条件下在内皮细胞中被激活, 维持内皮屏障功能。内皮细胞特异性CRTC2敲除小鼠在体外表现出血管生成减少, 内皮功能障碍[73]。此外, 有研究表明, CREB激活可促进前列腺癌的神经内分泌分化和血管生成, 抑制CREB则会抑制体内神经内分泌分化和血管生成[74]。同时, 也有研究表明缺氧可诱导CREB介导内皮细胞迁移和增殖, 而CREB基因沉默可逆转这种效果。CREB还可调节血管平滑肌细胞表型和新内膜形成[75]。以上研究发现为CREB调控血管新生治疗脑卒中提供研究基础。

综上所述, CREB及其信号转导通路参与了多种细胞信号的传导作用, 在脑卒中中扮演着重要的角色, 但是目前的研究对CREB在神经系统疾病中的作用尚未完全阐明, 因此仍具有进一步深入探讨的价值和意义, 希望将来可以为神经系统疾病提供新的治疗靶点。

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