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白藜芦醇防治脑缺血再灌注损伤的作用机制研究进展

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摘 要

脑卒中是临床最常见的神经科疾病之一，也是成人致死和致残的第二大病因，其中近80%是缺血性脑卒中。尽快恢复脑组织的血流供应，目前被认为是最为有意义的治疗急性脑缺血的方法，但脑的缺血区恢复血流灌注后反而加重脑组织损伤，出现“二次”脑损伤，即脑缺血/再灌注损伤。有效干预脑缺血/再灌注损伤对治疗缺血性脑血管病意义重大。白藜芦醇是一种天然的植物抗毒素，主要存在于谷物，水果，蔬菜，干豆类和植物衍生饮料中，包括茶，咖啡和葡萄酒，白藜芦醇具有神经保护，心脏保护，肝肾肺保护，抗糖尿病，抗肥胖等多种作用。本文就白藜芦醇防治脑缺血再灌注损伤的作用机制进行研究。

关键词

白藜芦醇，脑缺血再灌注

Research Progress on the Mechanism of Resveratrol in the Prevention and Treatment of Cerebral Ischemia-Reperfusion Injury

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Abstract

Stroke is one of the most common neurological diseases in clinical practice and the second leading cause of death and disability in adults, with nearly 80% of them being ischemic stroke. Restoring blood supply to brain tissue as soon as possible is currently considered to be the most meaningful treatment for acute cerebral ischemia, but the restoration of blood perfusion in the ischemic area of the brain aggravates brain tissue injury, resulting in "secondary" brain injury, *i.e.*, cerebral ischemia/reperfusion injury. Effective intervention in cerebral ischemia/reperfusion injury is of great significance for the treatment of ischemic cerebrovascular disease. Resveratrol is a natural plant antitoxin, mainly found in cereals, fruits, vegetables, dried legumes and plant-derived beverages, including tea, coffee and wine. Resveratrol has a variety of beneficial effects such as cardioprotective, hepato-renal and lung-protective, anti-diabetic and anti-obesity.

Keywords

Resveratrol, Cerebral Ischemia-Reperfusion

1. 引言

据统计，中国 2017 年脑卒中患病治疗人数约 351 万例，其中发病亚型中近 80%是缺血性脑卒中[1]。缺血性脑卒中是由脑主要动脉的血流暂时或者持久减少引起的，缺血后，神经细胞正常的平衡以及跨膜离子梯度被破坏，从而引发细胞死亡过程：细胞凋亡、氧化应激、兴奋性毒性和炎症、免疫反应[2]。同时，神经元细胞、内皮细胞以及神经胶质细胞受到严重损害，且这些过程相互关联触发，形成恶性循环，最终导致脑坏死、凋亡、自噬[3]。脑组织对于缺血、缺氧的耐受性极差，因为它本身不能储存养分、能量和营养物质，必须依赖于血液的流动来保证养分及代谢产物的循环，尽快恢复脑组织的血流供应，拯救濒临死亡的脑组织，目前被认为是最为有意义的治疗急性脑缺血的方法。但研究显示，脑的缺血区恢复血流灌注后反而加重脑组织损伤，出现“二次”脑损伤，即脑缺血/再灌注损伤(cerebral ischemia/reperfusion injury) [4]。目前，唯一获得公认用于缺血性脑卒中急性期的药物为 1996 年美国食品药品监督管理局(FDA)批准的溶栓药物：组织纤溶酶原激活物 rTPA，但 3~4.5 小时的治疗“时间窗”限制了其在临床中的使用，该药物仅限于缺血发生后较短时间间隔内脑组织再灌注可以迅速恢复的病例[5]。同时组织型纤溶酶原激活剂(r-TPA)也不能改变再灌注损伤导致的终点事件[5]。可见，有效干预脑缺血/再灌注损伤，对治疗缺血性脑血管病具有极其重要的意义。

脑缺血/再灌注损伤的机制包括：一氧化氮的产生、炎症免疫反应、氧化应激反应(reactive oxygen species, ROS)、营养物质的缺乏、细胞凋亡、兴奋性氨基酸(excitatory amino acids, EAAs)的细胞毒性等。其中炎性、免疫反应作为重要因素一直是研究热点。脑缺血/再灌注损伤诱发的急性炎症、免疫反应涉及多种炎性介质、炎性细胞及炎性因子的参与。

白藜芦醇是一种广泛存在于虎杖、决明子、葡萄和花生等天然植物中的一种多酚类化合物，具有清除自由基、抗氧化等多种药理活性[6]。众所周知，在缺血性脑损伤之前用白藜芦醇进行预处理可以减少神经元损失并减少脑梗死体积[7] [8]。

2. 白藜芦醇通过 JAK/ERK/STAT 通路防治脑缺血再灌注损伤

脑缺血/再灌注损伤可诱发大量病理生理反应和保持高致死率[9]。缺血后血流的重建导致严重的脑损伤并导致活性氧的产生物种(ROS) [10]。不断积累细胞外谷氨酸增加钙内流，从而进一步触发几种细胞内反应并导致细胞死亡[11]。Janus 激酶、细胞外信号调节激酶和信号转录转导和激活因子(JAK/ERK/STAT)通路与细胞增殖、分化和存活有关[12]。该信号通路专用于基因表达的调节并作用于下游结合生长因子、细胞因子以及 ROS [12]。Cheng Chang 等人结果表明，白藜芦醇下调 p-JAK、p-ERK、p-STAT 和 p-JNK 表达和炎性细胞因子，通过调节大鼠的 JAK/ERK/STAT 信号通路，来防治脑缺血再灌注损伤，减少神经元丢失。

3. 白藜芦醇通过磷脂肌醇 3-激酶/蛋白激酶 B (PI3K/Akt)信号通路防治脑缺血再灌注损伤

PI3K/Akt 信号通路是参与缺血性脑损伤神经保护的最重要的信号通路，参与缺血性脑损伤的炎症介质的表达变化，白藜芦醇可通过激活 PI3K/Akt 信号通路发挥抗炎活性[13]。雷军荣等使用 40 mg/kg 白藜芦醇可显著降低脑缺血再灌注大鼠的脑梗死体积和神经损伤评分，显著降低髓过氧化物酶(MPO)、TNF-α 的水平，上调 p-Akt 的表达，使用 Akt 抑制剂可阻断白藜芦醇的上述活性，提示白藜芦醇主要通过激活 PI3K/Akt 信号通路发挥抗炎活性[14]。

4. 白藜芦醇通过 KEAP1/Nrf2 信号通路防治脑缺血再灌注损伤

有研究表明，以核转录因子 E2 相关因子 2 (Nuclear factor erythroid 2-related factor, Nrf2)为核心的 Nrf2/ARE 通路在调控细胞炎症反应中起重要作用，Nrf2 在响应炎症刺激和阻止细胞/组织受到炎症损伤等方面发挥了巨大作用[15]。在静息条件下，Nrf2 位于细胞浆中，与胞浆蛋白伴侣 Keap1 结合而保持持续的泛素化状态。应激状态下，Keap1 通过半胱氨酸巯基残基的直接修饰而失活，Nrf2 从 Keap1 中释放，转运到细胞核内，与 ARE 结合形成 Nrf2/ARE 通路，激活下游的一系列抗炎或抗氧化酶蛋白的表达，包括总超氧化物歧化酶(SOD)、血红素氧合酶(HO-1)、谷胱甘肽-S-转移酶(GST)、过氧化氢酶(CAT)等[16] [17] [18] [19] [20]。中枢神经系统可以通过 Nrf2 过表达而增加 Nrf2/ARE 通路的活性，从而增加下游基因的表达来保护机体免受炎症损伤以及氧自由基的侵害[6]。众所周知，在缺血性脑损伤之前用白藜芦醇进行预处理可以减少神经元损失并减少脑梗死体积[21] [22]。研究表明，白藜芦醇通过与 Keap1 半胱氨酸的硫醇基团反应，增加 Nrf2 在细胞核的释放，增加 II 期解毒酶的表达，清除自由基并减轻组织损伤[7]，从而发挥药理作用。作为 Nrf2 激动剂，白藜芦醇对脑缺血再灌注后的神经系统损伤有显著的保护作用[8] [23] [24]。

5. 白藜芦醇通过上调沉默蛋白信息调节因子 1 (Sirt1)的表达防治脑缺血再灌注损伤

Sirt1 的表达能激活并增强细胞自噬，诱发神经保护作用[25]。He 等研究结果显示，白藜芦醇显著降低脑水肿和神经功能缺损评分，进一步上调 Sirt1 的表达，增加 LC3B-II/I 的比值，降低 p62 的水平，增强自噬的活性，并通过联合特异性自噬体干预发现，白藜芦醇通过诱导自噬来抑制 NLRP3 炎症小体的激活，表明白藜芦醇可通过上调 Sirt1 的表达增强细胞自噬，发挥脑缺血再灌注损伤的神经保护作用[25]。

6. 白藜芦醇通过调节多种炎症因子防治脑缺血再灌注损伤

越来越多的证据表明，缺血后大量炎症细胞、炎症细胞有助于发展治疗神经元损伤和脑梗塞。参与脑梗死的病理进程，调节免疫反应平衡，抑制炎症因子的分泌对减轻神经炎性损伤具有重要临床意义。有研究发现表明白藜芦醇可减轻脑缺血再灌注损伤通过抑制中性粒细胞浸润和 TNF-α。在炎症中，内源

性介质(细胞因子和趋化因子)和循环白细胞的募集参与其中。细胞因子是主要作用，在炎症条件下，介质和趋化因子作为二级介质吸引白细胞[26]。此外，激活星形胶质细胞和小胶质细胞产生细胞因子和趋化因子[27]。这些分子出现似乎与受损脑组织中的炎症细胞的积累有关。TNF-α、IL-1β 和 IL-6 是潜在的细胞因子缺血再灌注后启动炎症介质和炎症反应并诱导其他细胞因子表达的潜在细胞因子[28]。

7. 结语

白藜芦醇作为天然植物具有资源丰富、疗效好、副作用小的优点，可通过多种靶点治疗脑缺血再灌注的潜在药物[29]。白藜芦醇是一种天然的植物抗毒素，可保护脑缺血引起的损伤引起的神经元[30]和再预处理对脑缺血再灌注[31]。然而，其神经保护作用背后的机制是多因素的，目前尚未完全了解。虽然医学界进行了一系列动物模型、细胞培养的实验，但该领域的人体研究非常有限，需要更多的研究来阐明白藜芦醇的保护作用的机制及其对脑缺血再灌注的影响。希望本文能够为白藜芦醇的新药开发提供参考。

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