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脑梗死相关认知障碍机制

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[摘要] 脑梗死是脑卒中的常见类型, 发病率和致残率高, 且大多数脑梗死患者都存在不同程度的认知障碍。脑梗死相关认知障碍的表现形式和严重程度受多因素影响并相互作用, 其病理生理机制也非常复杂, 涉及周细胞变性、活性氧生成过量、谷氨酸生成过量和自噬过度激活等方面。脑梗死发生后, 周细胞生理功能异常, 激活神经炎症并促进炎性介质入脑; 周细胞脱离血管导致血脑屏障完整性被破坏; 虽能通过血管生成和胶质瘢痕形成缓解损伤, 但胶质瘢痕过度形成会抑制神经再生。过量活性氧引发氧化应激, 导致线粒体功能障碍、铁死亡及内皮型一氧化氮合酶/一氧化氮信号抑制, 损伤神经元。谷氨酸释放激增且清除不足导致细胞间隙谷氨酸过量堆积, 引发兴奋性毒性; 钙离子内流激活蛋白酶及凋亡途径, 导致神经元死亡。自噬被过度激活导致溶酶体膜通透性的改变及溶酶体腔内酶的外渗; 少突胶质细胞坏死引起严重脱髓鞘, 加重脑损伤; 促进受损线粒体自噬可改善线粒体损伤导致的认知功能障碍。

[关键词] 脑梗死; 认知障碍; 病理生理机制; 神经炎症; 突触功能障碍

Mechanisms of cognitive impairment associated with cerebral infarction

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ABSTRACT

Cerebral infarction is a common type of stroke with high incidence and disability rates, and most patients experience varying degrees of cognitive impairment. The manifestations and severity of post-infarction cognitive impairment are influenced by multiple interacting factors, and its pathophysiological mechanisms are highly complex, involving pericyte degeneration, excessive generation of reactive oxygen species (ROS), overproduction of glutamate, and overactivation of autophagy. After cerebral infarction, abnormal pericyte

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function activates neuroinflammation and facilitates the entry of inflammatory mediators into the brain; detachment of pericytes from blood vessels disrupts the integrity of the blood-brain barrier. Although angiogenesis and glial scar formation may alleviate injury, excessive scarring can inhibit neuronal regeneration. Excessive ROS trigger oxidative stress, leading to mitochondrial dysfunction, ferroptosis, and suppression of endothelial nitric oxide synthase/nitric oxide signaling, thereby damaging neurons. An excessive surge in glutamate release, coupled with insufficient clearance, results in its accumulation in the intercellular space, leading to excitotoxicity; the influx of calcium ions subsequently activates proteases and apoptotic pathways, causing neuronal death. Overactivation of autophagy alters lysosomal membrane permeability and results in leakage of lysosomal enzymes; oligodendrocyte necrosis then leads to severe demyelination, further exacerbating brain injury, although promoting the autophagic clearance of damaged mitochondria can ameliorate cognitive deficits arising from mitochondrial dysfunction.

KEY WORDS cerebral infarction; cognitive impairment; pathophysiological mechanisms; neuroinflammation; synaptic dysfunction

脑梗死即缺血性脑卒中,是最常见的卒中类型。脑梗死是多种原因导致脑部血流供应减少或血管闭塞进而引发的脑血管疾病,临床上常表现为血流闭塞区域相关神经功能损伤,并出现相应神经系统症状。相较于脑出血而言,脑梗死的生存率稍高,但更易导致神经系统相关功能缺损^[1],不仅可造成肢体残疾,还可导致认知障碍、抑郁等精神症状^[2]。

认知功能障碍是脑梗死常见的并发症,临床上表现为记忆、言语、执行、计算和理解等某一认知域或多认知域的受损^[3]。患者认知功能障碍表现与梗死涉及的具体部位区域和范围大小有关。当梗死发生在海马时,患者的空间定向、情景记忆、知识的学习和储存等可出现障碍^[4];当梗死发生在前额叶皮层时,患者的记忆、执行能力、注意力等认知功能会出现缺损^[5-6];此外,内侧前额叶皮层发生梗死导致的认知障碍的病程较长^[7]。随着时间的推移,脑梗死引起的认知障碍或逐渐好转,或缓慢进展,甚至发展为痴呆。其严重程度受多因素影响,包括患者的年龄、脑梗死起病时间、梗死部位和面积、神经元受损情况、侧支循环情况和其他大脑功能障碍^[8]。目前,脑梗死相关认知障碍的机制复杂且不明确,给该病的诊疗带来了难题。本文从周细胞变性、活性氧(reactive oxygen species, ROS)生成过量、谷氨酸生成过量、自噬过度激活等4个方面概述脑梗死后相关认知障碍的机制,旨在为脑梗死相关认知障碍的治疗提供新的思路。

1 周细胞变性

在生理状态下,周细胞的主要生理功能包括脑血流量(cerebral blood flow, CBF)的调控、血脑屏障(blood-brain barrier, BBB)的维持、血管生成、瘢痕的形成及炎症细胞的运输5个方面^[9]。当脑梗死发生后,周细胞收缩变性,功能出现异常,挤压脑微血管,使微血管长期处于收缩状态,大脑持续处于缺血/缺氧状态,进一步加重脑损伤^[10],导致认知障碍发生^[6]。

周细胞是激活神经炎症的重要介质。一方面,周细胞能够促使神经胶质细胞转变为促炎表型,分泌一系列炎症相关细胞因子,如白细胞介素(interleukin, IL)-1 β 、IL-6和肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)等,引发强烈的炎症级联反应^[11-12],炎症因子破坏BBB,促使炎性介质通过主动运输(直接)或通过迷走神经刺激(间接)进入大脑,破坏脑白质纤维结构及损害胆碱能通路,信息传递出现阻碍,致使认知障碍的发生^[13]。Duan等^[14]的研究也证实了这一观点。另一方面,周细胞表达的细胞间黏附分子-1(intercellular cell adhesion molecule-1, ICAM-1)与白细胞上的整合素配体相互作用,募集白细胞完成炎性介质的迁移,将炎性信号传递给神经元,导致神经元之间相互缠结,引起突触功能障碍,最终导致认知障碍^[15](图1)。

研究^[16]发现:脑梗死发生后周细胞脱离毛细血管,降解紧密连接蛋白(tight junctions proteins, TJs)和黏附连接蛋白(adherens junctions proteins, AJs),

破坏内皮细胞间的紧密连接, 导致BBB完整性被破坏, β -淀粉样蛋白(amyloid β -protein, A β)清除率降低并异常沉积在脑实质中, 影响突触传递, 甚至加重炎症级联反应, 进一步促进认知障碍的发展^[17]。Liu等^[18]通过对72例脑梗死/短暂性脑缺血发作后出现认知障碍的患者追踪随访, 发现A β 的沉积明显加重并加速认知衰退。Jolivel等^[19]也提出了类似的观点。

周细胞通过促进血管生成和瘢痕形成减轻脑损

伤, 缓解脑梗死造成的认知障碍。在脑梗死状态下, 周细胞被募集并迁移至脑梗死区域, 不仅参与血管生成, 缓解了梗死周围区域的缺血状态, 还在梗死与非梗死区域之间形成胶质瘢痕, 防止神经元进一步的丢失^[20]。虽然胶质瘢痕的形成有助于防止脑损伤的进一步加重, 但胶质瘢痕过度形成会抑制轴突再生, 阻碍神经元的恢复^[21]。

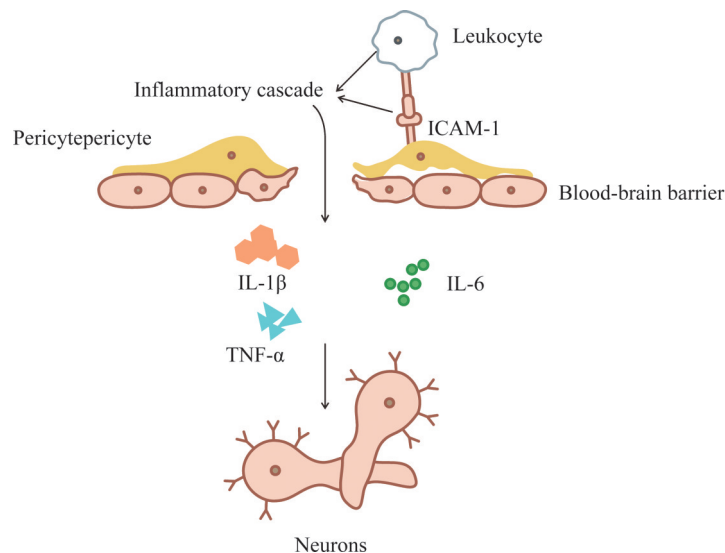


图1 周细胞变性激活神经炎症导致认知障碍

Figure 1 Pericyte degeneration activates neuroinflammation leading to cognitive impairment

ICAM-1, a cell surface adhesion molecule expressed by pericytes, interacts with integrin ligands on leukocytes, thereby recruiting leukocytes to complete the migration of inflammatory mediators and triggering the inflammatory cascade. The shedding of pericytes disrupts the blood-brain barrier, allowing inflammatory mediators to enter and leading to intertwined neurons, synaptic dysfunction, and ultimately cognitive impairment. ICAM-1: Intercellular adhesion molecule 1; IL: Interleukin; TNF- α : Tumor necrosis factor- α .

2 ROS生成过量

ROS生成过量是脑梗死患者发生认知障碍的重要因素^[22-23]。当患者出现脑梗死后, 其大脑的局部缺血组织处于缺血/缺氧状态, 促使脑组织产生大量的ROS^[24], 当ROS产生的量超过机体内源性抗氧化剂和抗氧化酶的保护清除能力时, 会激活氧化应激反应^[25]。动物实验^[23]发现氧化应激与认知功能障碍的发生有关。Zhang等^[22]的研究也同样证明神经保护剂通过抑制氧化应激来改善认知功能。一方面, 氧化应激会导致线粒体功能障碍^[26]和蛋白质错误折叠沉积^[27], 影响神经元完整性和基因表达, 进而通过引起海马树突结构的变化影响认知能力^[28]。当线粒体功能出现障碍时, 过量的ROS产生、钙超载、细胞色素

C释放和凋亡通路激活等一系列异常的生理过程也会随之出现, 从而导致DNA损伤和caspase依赖性凋亡细胞死亡, 进一步加重脑损伤^[29-30](图2)。另一方面, 氧化应激会介导细胞铁依赖性的死亡, 即铁死亡^[31]。研究^[32]表明, 在氧葡萄糖剥夺/再灌注(oxygen-glucose deprivation/reoxygenation, OGD/R)诱导的神经元损伤的模型中, 抑制铁死亡可以改善神经元的损伤及脑梗死相关的认知障碍。铁死亡过程也会通过介导过度金属铁的酶促反应产生可溶性和脂质ROS^[33], 而过量的ROS可通过过度氧化脂质和蛋白质、破坏DNA等方式破坏生物分子的结构和功能, 从而引起细胞坏死、神经元损伤, 最终导致认知障碍^[34]。氧化应激通过抑制脑血管内皮细胞中的内皮型一氧化氮合酶/一氧化氮(endothelial nitric oxide synthase/nitric

oxide, eNOS/NO)信号, 阻碍脑源性神经营养因子的合成, 从而抑制突触可塑性和神经再生, 降低机体记忆和大脑学习能力, 最终导致认知障碍的发生^[35]。

在脑梗死发生后, 体内内源性抗氧化剂如谷胱甘肽和抗氧化酶如谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)、超氧化物歧化酶(superoxide dismutase, SOD)^[36]、过氧化氢酶等^[34]被耗尽, 抗氧化相关因子也被下调, 从而导致认知障碍。研究发现, 增强抗氧化相关因子如核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)等的表达水平可以减轻ROS对认知能力的损伤, 保护神经元活性^[37], 从而改善脑梗死相关的认知障碍^[38]。

3 谷氨酸生成过量

谷氨酸是中枢神经系统中重要的兴奋性神经递质。在正常生理条件下, 谷氨酸的产生和清除处于

动态平衡, 以维持细胞外液中较低的谷氨酸水平。在脑梗死的病理条件下, 由于氧和葡萄糖的大量消耗, 释放谷氨酸的量远远大于清除的量。过量的谷氨酸积累在细胞间隙中, 不能被能量依赖性突触的突触前膜重新摄取^[39], 因此神经元和神经胶质细胞上的N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体^[40]、 α -氨基-3-羟基-5-甲基-4-异唑(α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA)受体被过度刺激^[41], 继而出现一系列继发的神经损伤, 即兴奋性毒性。受体过度刺激引发神经元内 Ca^{2+} 内流^[42], 一方面, 激活蛋白激酶和核酸内切酶, 导致神经细胞中核酸、蛋白质等重要物质降解, 使得神经元变性或死亡; 另一方面, 激活并增强 Ca^{2+} 依赖的凋亡途径, 进一步促使神经元死亡, 脑组织萎缩, 出现认知功能下降(图2)。此外, 也有研究^[43]表明这种兴奋性毒性导致白质疏松症等脑部病理变化, 最终导致认知功能障碍。

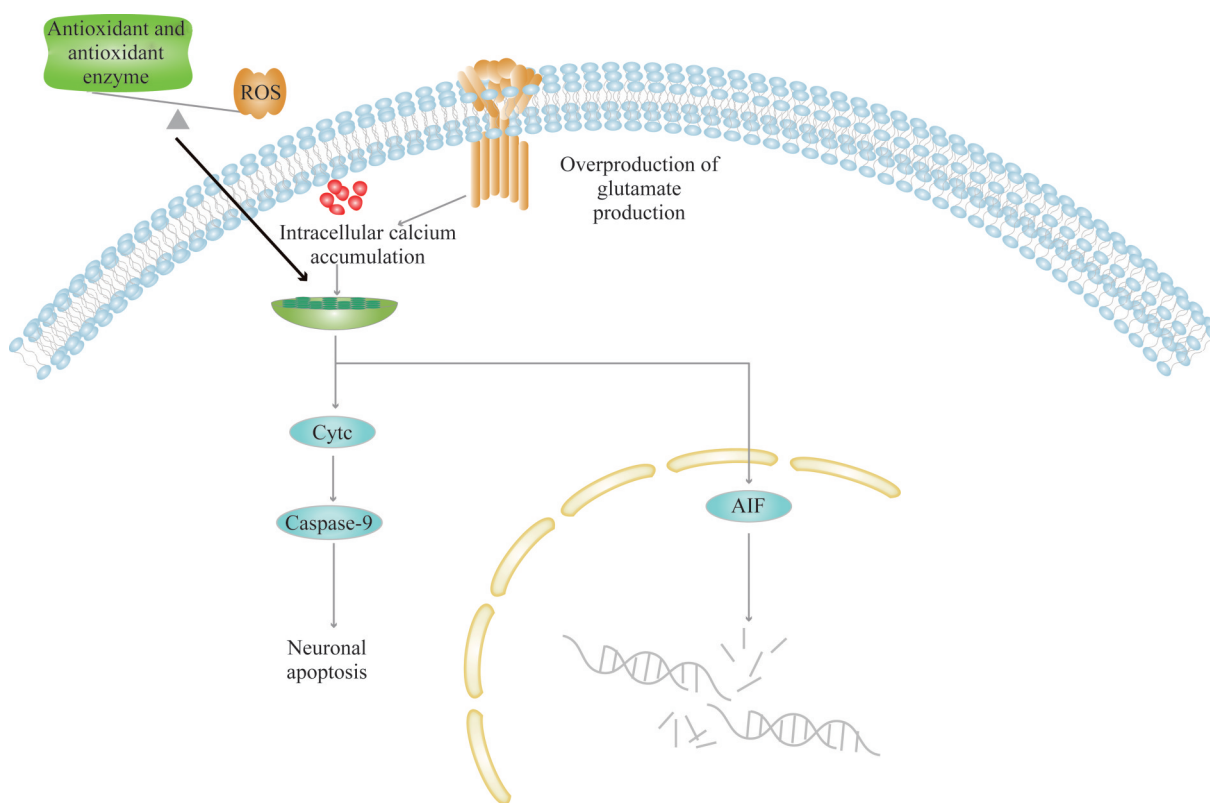


图2 ROS生成过量及谷氨酸生成过量导致的神经元死亡形式

Figure 2 Forms of neuronal death caused by excessive ROS generation and glutamate production

Under pathological conditions of ischemic stroke, the depletion of oxygen and glucose leads to excessive glutamate release and insufficient clearance, resulting in its accumulation in the extracellular space. The impairment of energy-dependent reuptake triggers overactivation of NMDA and AMPA receptors, causing Ca^{2+} influx into neurons and activating protein kinases and apoptotic pathways. ROS: Reactive oxygen species; NMDA: N-methyl-D-aspartate; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AIF: Apoptosis-inducing factor.

4 自噬过度激活

在正常的生理活动中, 自噬是一种机体自我保护的过程。大脑缺血/缺氧时, 神经元的自噬过程在脑梗死中起双重作用。研究^[44-45]表明: 大脑缺血/缺氧时, 自噬被过度激活, 破坏海马神经元的自噬通量, 导致溶酶体膜通透性改变及溶酶体腔内酶外渗, 自噬小体无法与溶酶体结合进行底物降解, 加重脑损伤, 出现认知障碍(图3)。而当自噬被抑制就可以起到神经保护的作用。在缺血/缺氧性脑损伤模型的新生大鼠中, 微管相关蛋白1轻链3-II(microtubule-associated protein 1 light chain 3-II, LC3-II)表达增加, 提示缺血/缺氧诱导神经元过度自噬, 进一步加重脑损伤并在青春期诱发认知和记忆障碍。给予新生大鼠大脑中注入自噬抑制剂3-甲基腺嘌呤(3-methyladenine, 3-MA)后, LC3-II蛋白的表达下调, 从而减少神经元的死亡, 减轻脑损伤^[46]。

脑梗死发生时, 大脑中的其他细胞和细胞器也

会发生自噬, 加重或减轻认知障碍的程度^[47]。在正常的生理情况下, 少突胶质细胞维持神经元轴突和神经元功能的完整性^[48]。而当大脑缺血/缺氧过度激活自噬时, 少突胶质细胞坏死, 引起严重脱髓鞘, 导致神经冲动传导减慢, 记忆和认知形成的通路受阻, 最终出现认知功能障碍^[49]。反之, 线粒体损伤会加重缺血/缺氧导致的脑损伤, 因此激活线粒体自噬可保护神经, 从而改善认知障碍。线粒体自噬不仅能降解受损的线粒体, 还能防止由线粒体DNA突变引起的细胞损伤^[50]。Fan等^[51]的研究表明, 在脑梗死模型大鼠中, RGD1564534通过竞争性结合miR-101a-3p上调*DUSP1*基因的表达, 促进受损线粒体自噬并减弱NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎症小体活性, 从而缓解脑白质和小血管损伤, 改善大鼠的认知功能障碍。Zhong等^[52]的研究中通过调节脑梗死状态下大鼠的褪黑素也能得出此结论。

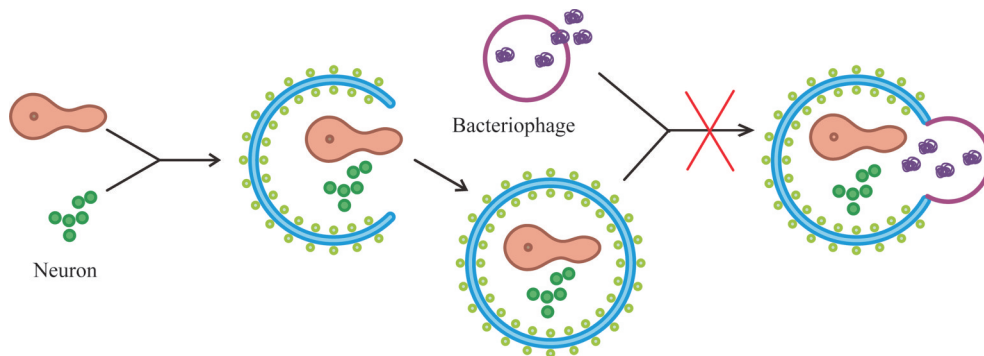


图3 神经元自噬过度激活

Figure 3 Neuronal autophagy hyperactivation

In cases of cerebral ischemia and hypoxia, autophagy is excessively activated. This disruption disrupts the autophagic flux of hippocampal neurons, leading to alterations in lysosomal membrane permeability and the leakage of lysosomal enzymes. Consequently, autophagosomes fail to fuse with lysosomes for substrate degradation, exacerbating brain damage and cognitive impairment.

5 结 语

脑梗死患者常合并认知功能障碍。脑梗死相关的认知障碍与周细胞变性、ROS生成过量、谷氨酸生成过量、自噬过度激活4种病理生理改变有关(图4), 但该疾病致病的根本机制仍不明确。现有研究主

要证明了某种机制与疾病发生发展之间存在关联, 但这些机制间的因果关系尚不清楚。换言之, 氧化应激、兴奋性毒性、自噬过度激活、周细胞变性都是可能导致该疾病和/或其进展的潜在因素。所以, 为了充分明确脑梗死相关认知障碍的精确机制及各因素间的因果关系, 未来无疑需要进行更多研究。

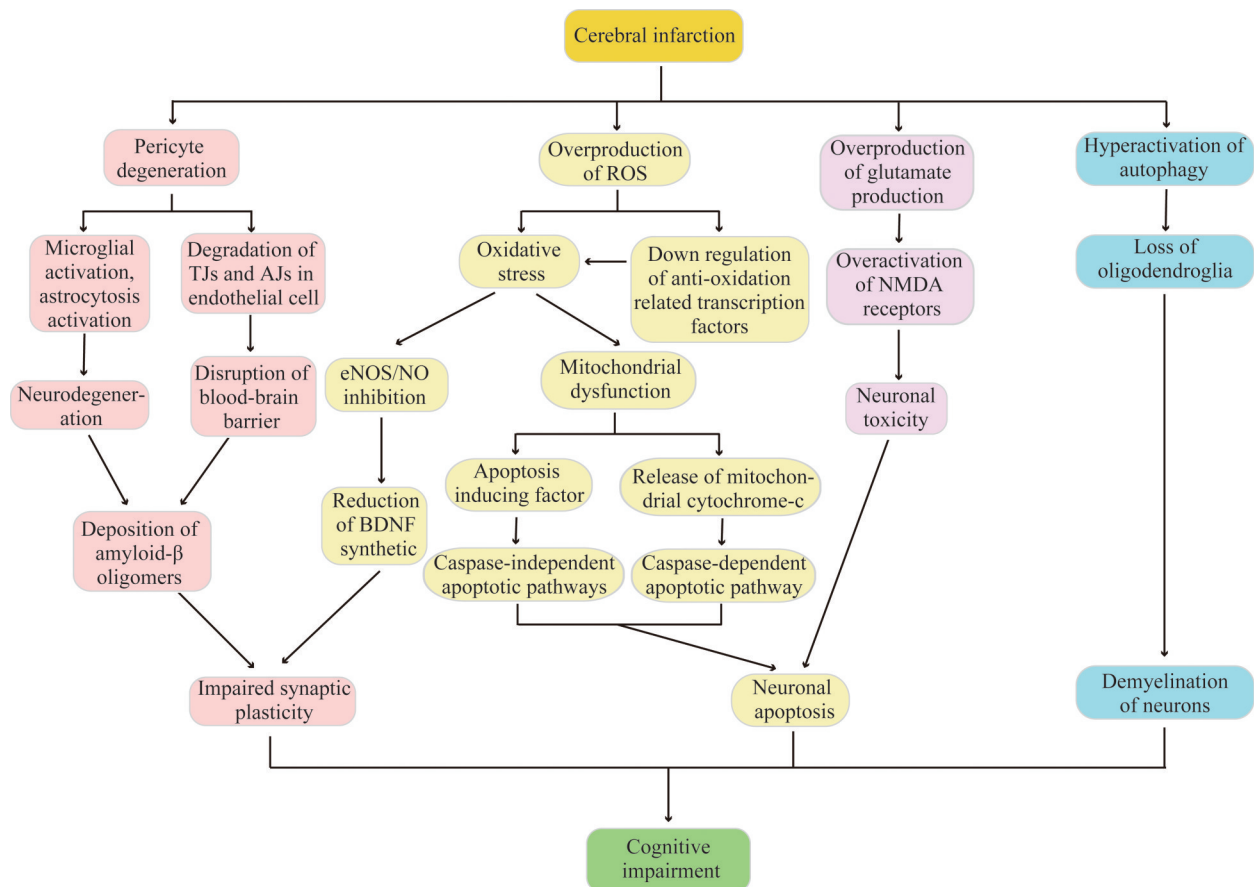


图4 脑梗死相关认知障碍的机制

Figure 4 Molecular mechanism of cerebral infarction related cognitive impairment

The schematic diagram illustrates the molecular mechanisms underlying cognitive impairment following cerebral infarction. These mechanisms include pathophysiological changes such as pericyte degeneration, excessive ROS generation, excessive glutamate production, and excessive activation of autophagy. TJs: Tight junctions proteins; AJs: Adherens junctions proteins; ROS: Reactive oxygen species; NMDA: *N*-methyl-D-aspartate; eNOS/NO: Endothelial nitric oxide synthase/nitric oxide; BDNF: Brain-derived neurotrophic factor.

作者贡献声明: 尹晴 文献检索, 图例制作, 论文设计、撰写与修改; 杨利 论文设计、指导及修改。所有作者阅读并同意最终的文本。

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