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综 述

Tau磷酸化及其激酶在缺氧缺血性脑损伤中的作用机制研究进展

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摘 要：缺氧缺血性脑损伤(hypoxic-ischemic brain damage, HIBD)是导致中老年人残疾和新生儿高致残率、低生存率及长期身体功能缺陷的主要原因之一。HIBD主要病理表现为神经元损伤和髓鞘丢失。Tau蛋白是脑内重要的微管相关蛋白，存在于神经元和少突胶质细胞中，可调节多种细胞活动，如细胞分化成熟、轴突转运和维持细胞骨架结构。磷酸化是Tau的一种常见的化学修饰，在生理状态下，其参与调节Tau结构和功能，维持正常细胞骨架和生物学功能；在病理状态下，Tau磷酸化发生异常，使其结构改变并影响其功能，致Tau病(Tauopathy)发生。研究发现，脑缺氧缺血可使Tau磷酸化发生异常变化，参与HIBD的病理过程。同时，脑缺氧缺血可诱导氧化应激和炎症，多个具有调控Tau磷酸化作用的Tau蛋白激酶在此过程中被激活，并且Tau磷酸化异常与它们激活有关。因此，探索HIBD激活Tau蛋白激酶的具体分子机制，以及阐明它们与Tau异常磷酸化之间的关系，这对未来开展HIBD相关治疗的研究具有重要意义。本综述重点关注Tau磷酸化在HIBD中的作用机制，以及Tau蛋白激酶与Tau磷酸化之间的潜在关系，为HIBD的干预和治疗提供依据。

关键词：Tau；缺氧缺血性脑损伤；Tau蛋白激酶；Fyn；GSK3β；CDK5；MAPK；PKA

Research progress on the mechanisms of Tau phosphorylation and its kinases in hypoxic-ischemic brain damage

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Abstract: Hypoxic-ischemic brain damage (HIBD) is one of the main causes of disability in middle-aged and elderly people, as well as high mortality rates and long-term physical impairments in newborns. The pathological manifestations of HIBD include neuronal damage and loss of myelin sheaths. Tau protein is an important microtubule-associated protein in brain, exists in neurons and oligodendrocytes, and regulates various cellular activities such as cell differentiation and maturation, axonal transport, and maintenance of cellular cytoskeleton structure. Phosphorylation is a common chemical modification of Tau. In physiological condition, it maintains normal cell cytoskeleton and biological functions by regulating Tau structure and function. In pathological conditions, it leads to abnormal Tau phosphorylation and influences its structure and functions, resulting in Tauopathies. Studies have shown that brain hypoxia-ischemia could cause abnormal alteration in Tau phosphorylation, then participating in the pathological process of HIBD. Meanwhile, brain hypoxia-ischemia can induce oxidative stress and inflammation, and multiple Tau protein kinases are activated and involved in Tau abnormal phosphorylation. Therefore, exploring specific molecular mechanisms by which HIBD activates Tau protein kinases, and elucidating their relationship with abnormal Tau phosphorylation are crucial for future researches on HIBD related treatments. This review aims to focus on the mechanisms of the role of Tau phosphorylation in HIBD, and the potential relationships between Tau protein kinases and Tau phosphorylation, providing a basis for intervention and treatment of HIBD.

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Key words: Tau; hypoxic-ischemic brain damage (HIBD); Tau protein kinases; Fyn; GSK3β; CDK5; MAPK; PKA

缺氧缺血性脑损伤(hypoxic-ischemic brain damage, HIBD)，如中老年人的缺血性卒中和新生儿缺血缺氧性脑病，是导致成年人和新生儿高致残率、低生存率及长期身体功能缺陷的主要原因之一。HIBD主要是由于多种原因引起脑血流阻断造成脑部缺血缺氧性损伤，主要的病理表现为神经元死亡[1, 2]和脑白质损伤(white matter injury, WMI)，WMI包括轴突损伤和髓鞘丢失[3, 4]。HIBD发病机制未完全阐明，因此给相关药物治疗研究带来了更大的挑战。Tau蛋白是脑内一种重要的微管相关蛋白，在组装稳定微管结构和维持细胞骨架中起着重要的作用。Tau蛋白激酶如糖原合酶激酶3β (glycogen synthase kinase-3β, GSK3β)、细胞周期素依赖蛋白激酶5 (cyclin-dependent kinase 5, CDK5)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和酪氨酸蛋白激酶Fyn等具有磷酸化Tau蛋白的作用，并且Tau蛋白磷酸化易受多种因素影响发生异常，参与多种神经系统疾病发生。HIBD的病理过程与Tau磷酸化和其激酶密切相关。本综述重点关注Tau磷酸化及其激酶在HIBD中的作用机制研究进展，旨在为HIBD的干预和治疗提供依据。

1 Tau

1.1 Tau结构和分布

1975年，具有热稳定性的Tau蛋白被Weingarten等人通过磷酸纤维素上的离子交换色谱法从猪脑的微管蛋白分离出来[5]，其参与微管结构的装配与稳定[6]；Tau包含四个结构域，分别是N端结构域(N-terminal domain, NTD)、富含脯氨酸结构域(proline-rich region, PRR)、微管结合结构域(microtubule-binding domain, MTBD)和C端结构域(C-terminal domain, CTD) [7]，Tau蛋白不同区域对其功能发挥着不同的调节作用。野生型小鼠脑免疫荧光染色发现Tau蛋白不仅在神经元中表达，还在少突胶质细胞中高度表达[8]。之后又在中年大鼠和猴脑的海马和白质(胼胝体)中通过免疫荧光技术发现了Tau强烈表达于神经元和成熟的少突胶质细胞，而在少突胶质前体细胞、星形胶质细胞和小胶质细胞中不表达[9]。

1.2 Tau功能

Tau的主要功能是参与微管的组装和稳定其结构，以维持细胞骨架结构和促细胞生物学活动。有研究发现Tau的功能与其包含的多个结构域相关。体外研究显示，当截断CTD后，靠近N端的PRR多个位点如Thr205、Thr212、Ser214和Thr217磷酸化水平升高，Tau聚集增多[10]，影响其与微管结合，而CTD存在的Tau与微管稳定结合；当靠近C端的MTBD完全或部分缺失时，Tau表现出不能与微管结合或与微管结合程度降低[11, 12]，微管结构稳定性降低并影响其相关生物学功能。这表明CTD和MTBD两个结构域在Tau与微管结合过程中起正向调节作用。NTD也对Tau结合微管的过程具有调节作用。通过体外制造截断NTD的Tau构建体来观察其对Tau功能的影响，结果显示，NTD缺乏可增加Tau的PRR与微管结合能力，促进微管组装，而NTD存在时，PRR与微管结合能力下降，使Tau和微管功能失调，导致微管组装和稳定受影响[13]。另一项研究发现Tau内部存在NTD时可以使其发生液液相分离，Tau蛋白由液态变为不溶性的固体并发生病理性聚集[14]，影响其与微管组装导致Tau病(Tauopathy)发生。无NTD的Tau没有发生液液相分离和病理性聚集，微管稳定组装未受影响。这揭示了Tau的N端在微管结合过程中起负性调节作用，并有成为Tau病治疗靶点的可能。

Tau也具有参与轴突运输的功能并对其起重要作用。Tau与微管结合稳定微管结构，促进轴突物质运输，参与维持认知功能。研究发现，在神经系统疾病如阿尔茨海默病(Alzheimer's disease, AD)中，Tau可发生异常磷酸化，其构象变化，并与微管解离，微管结构损伤，使轴突运输受影响，致认知受损[15]。与微管解离的磷酸化Tau，发生错误折叠并聚集于轴突，使轴突内驱动蛋白-1 (kinesin-1)与运输物解离，使轴突运输受阻[16]；磷酸化Tau还可扰乱其与蛋白磷酸酯酶1 (protein phosphatase 1, PP1)相互作用而使轴突运输中断[17]。同时累积于轴突的磷酸化Tau损伤线粒体功能，使其不能满足轴突转运对能量的需求，致轴突运输受损，参与认知功能障碍[18]。

Tau还具有调节髓鞘形成的功能。髓鞘主要是由少突胶质细胞包裹轴突而形成，少突胶质细胞内Tau与Fyn结合后发生相互作用使Tau与微管结合，

稳定细胞骨架，促进少突胶质细胞突起生长与髓鞘碱性蛋白(myelin basic protein, MBP)转录，介导髓鞘形成[19]。在体外培养的少突胶质细胞中，截断少突胶质细胞内Tau的MTBD后，尽管其可与Fyn结合，但不与微管结合，使少突胶质细胞细胞骨架受损，影响突起生长以及MBP表达，进一步导致髓鞘形成失败[20]。相比之下，没被截断的Tau蛋白与Fyn结合发生相互作用，并结合微管，促进少突胶质细胞突起生长，促髓鞘形成。

可见，Tau蛋白功能对稳定中枢神经系统环境起有益作用，但Tau发生异常时，其功能改变也可起有害作用，促进神经系统疾病发生。总之，Tau蛋白在中枢神经系统生理和病理过程中发挥重要作用。

1.3 Tau亚型与HIBD

Tau基因位于17号染色体17q21的长臂上，编码Tau蛋白的基因包含了16个外显子，其中8个可以进行可变剪接[21]。由外显子2、3和10的交替剪接可形成6种Tau亚型：0N/3R、1N/3R、0N/4R、1N/4R、2N/3R和2N/4R，其中“R”表示MTBD重复的数量，“N”表示N端插入物的数量[22]。4R Tau比3R Tau更能够稳定地与微管结合，同时磷酸化也可以降低Tau与微管的亲和力，3R Tau在新生儿发育大脑丰富表达，4R Tau少量表达，随着大脑发育至成熟，4R Tau在成熟大脑中表达增加而3R Tau表达减少[23, 24]，维持微管和细胞骨架结构稳定，促进细胞正常发挥功能。这种不同亚型之间转化的机制尚未完全清楚，可能与不同阶段中Tau不同亚型的磷酸化程度不同和水平变化有关。由于3R Tau磷酸化程度比4R Tau高，高度磷酸化的3R Tau的稳定微管的活性比磷酸化程度低的4R Tau要弱得多，在小鼠大脑发育阶段中，4R Tau表达水平低而其磷酸化程度比成熟大脑中的4R Tau高，3R Tau高表达但其磷酸化程度高于成熟大脑3R Tau，随着发育的进展，高度磷酸化的3R Tau的数量和磷酸化水平逐渐降低，低程度磷酸化的4R Tau数量增加而其磷酸化水平也降低，并且这种变化可能与一种尚未确定的发育反应有关，该反应在Tau亚型变化的同时改变Tau的磷酸化水平[24]。

Tau蛋白的亚型可受脑缺氧缺血的影响而发生变化。在大鼠大脑中动脉闭塞(middle cerebral artery occlusion, MCAO)模型相关研究中，免疫荧光染色结果显示胼胝体区中少突胶质细胞内的3R Tau在脑缺氧缺血后明显增加，其微管发生动态变化，改变其突起方向，使其迁移至损伤区域，促再髓鞘化从而修复受损的轴突[23]。这种变化可能是对脑损伤作出的一种修复反应，为HIBD提供了一种新的治疗思路。未来仍需深入探究脑缺氧缺血致Tau亚型变化与其磷酸化之间的关系和具体机制。

1.4 Tau磷酸化

Tau蛋白的磷酸化是最早发现的Tau翻译后修饰[25]，Tau磷酸化水平发生改变影响其正常功能的发挥，甚至引起多种神经系统疾病。过度磷酸化的Tau蛋白可引起认知功能障碍[26–29]和脑白质中髓鞘损伤[30]，促进Tau病发展。Tau蛋白包含85个磷酸化位点(5个酪氨酸位点，45个丝氨酸位点和35个苏氨酸位点)[31, 32]，并且不同位点的不同程度的磷酸化与异常磷酸化参与调节Tau生理性功能，甚至引起Tau病。最近的一项研究发现Tau多个位点的磷酸化之间并非独立存在，而是存在相互依赖调节机制(site interdependence)。Stefanoska团队[33]在体内、外实验中将Thr205、Thr50、Thr69和Thr181等几个特定Tau磷酸化位点进行消融后，其他如Thr422、Ser404、Ser396、Ser181等多个位点的磷酸化水平明显降低，小鼠认知功能明显得到改善，并且确定了Thr205、Thr69、Thr181和Thr50为相互依赖调节机制的相关主位点。这揭示了Tau多个位点磷酸化之间存在相互依赖调节的关系，并且Tau逐渐过度磷酸化致Tau病发生与此有关。

Tau的多个位点如Thr205、Ser202和Ser396等可以被一些激酶如Fyn [34]和GSK3β [35]等磷酸化后参与微管系统稳态的破坏，使Tau蛋白从微管解离下来，形成神经纤维缠结(neurofibrillary tangles, NFT)沉积于神经元中并损伤神经元，使其数量减少，从而导致认知功能障碍[35–37]。在对AD转基因大、小鼠分别给予如姜黄素(Curcumin)[35]、双(乙基麦芽糖)氧化钒IV [Bis(ethylmaltolato)oxidovanadium (IV), BEOV] [38]、$A\beta_{3\text{-}10}$-KLH疫苗[39]、TNF-α抑制剂[40]、AZD0530 (Saracatinib) (Fyn抑制剂)[34]和S-腺苷蛋氨酸(S-adenosylmethionine, SAMe) [41]等药物之后，它们通过间接或直接作用使Tau多位点磷酸化水平下降，减少NFT数量，从而缓解神经元损伤，促认知功能恢复。

2 Tau磷酸化与HIBD

目前对Tau磷酸化的研究大多数集中在AD中，

尽管在HIBD中的研究较少，但仍然有证据发现Tau蛋白磷酸化水平在HIBD过程中发生变化并参与损伤过程。

2.1 Tau磷酸化与HIBD后的神经元损伤

脑缺氧缺血致神经元凋亡与Tau磷酸化升高有关。多个研究团队分别在对HIBD的动物模型进行相关研究，结果发现脑缺氧缺血后皮层区和海马区Tau多个位点如Thr205 [42–45]、Ser202 [42, 44–48]、Ser396 [43, 49]、Thr231 [48, 50, 51]、Ser199 [46, 47]、Ser262 [52, 53]、Ser356 [53]、Ser214 [48]和Ser402 [48]的磷酸化水平升高，并且与凋亡的神经元共定位。这提示Tau磷酸化参与神经元凋亡。神经元内Tau磷酸化水平在缺氧缺血后升高，其微管稳定性降低和细胞骨架受损，改变神经元形态，促进神经元发生凋亡[49]。一项新研究发现，脑缺氧缺血后24 h、48 h和72 h，Tau的位点Thr231磷酸化水平随时间的增加而升高，使Tau构象逐渐发生变化(即由生理性的反式磷酸化Tau转变为病理性的顺式磷酸化Tau)[51]，促进神经元凋亡。同时，此研究还发现，顺式磷酸化Tau还可通过神经元轴突散播到其他神经元并诱导其损伤和凋亡[51]。这表明脑缺氧缺血初期脑损伤逐渐加重与Tau磷酸化水平以时间依赖性升高有关。

脑缺氧缺血损伤轴突也与Tau磷酸化升高有关。相关体内实验的结果显示，在脑缺氧缺血时磷酸化的Tau聚集于神经元轴突中，其通过破坏轴突内微管结构，使轴突线性结构改变与长度变短，加重轴突损伤和变性，同时也阻碍轴突运输[49, 50, 52]。

Tau是HIBD的一个潜在的治疗靶点[54]。多个研究团队在相关体内实验中分别使用多种药物如拉莫三嗪(Lamotrigine, LTG)[45]、外源性胰岛素样生长因子1 (insulin-like growth factor 1, IGF-1)[43]和三花汤(Sanhua Decoction, SHD)[46]后，Tau磷酸化水平明显降低，神经元损伤缓解，促进脑损伤恢复(表1)。但这些药物降低Tau磷酸化的具体机制尚未明确，后续值得进一步探索。

2.2 Tau磷酸化与HIBD后的髓鞘损伤

脑白质区的Tau磷酸化水平也受脑缺氧缺血的影响而发生变化。MCAO模型的相关实验结果发现，与假手术组相比，损伤组的脑白质胼胝体区Tau位点Thr205 [55]和Ser202 [55]以及Thr396 [49]磷酸化水平升高，并与少突胶质细胞共定位，同时出现条索状的髓鞘形态结构受损，并伴有髓鞘MBP减少。出乎意料的是，损伤的胼胝体区中少突胶质细胞数量并未因损伤而减少，反而增多。研究表明这些增多的少突胶质细胞是少突胶质前体细胞，一部分是脑缺血缺氧后损伤的轴突向少突胶质前体细胞发送信号，上调其内部Tau表达，促进细胞骨架稳定，使它们迁移至损伤区并分化成熟来修复已损伤的髓鞘[49, 56–58]，促进轴突再髓鞘化。另一部分是由于脑缺氧缺血阻碍了损伤区的少突胶质前体细胞的分化成熟，使其聚集在损伤处[59]。此机制也与磷酸化Tau有关，主要是一方面与脑内代谢物清除系统损伤致磷酸化Tau堆积于少突胶质细胞内有关[49]；另一方面与磷酸化Tau可通过神经元传播至少突胶质细胞内部聚集有关[60]，双方因素综合作用下损伤少突胶质细胞，进一步导致髓鞘丢失，参与认知功能损伤。然而，Tau磷酸化致髓鞘缺氧缺血性损伤之间的机制仍未完全明确，少突胶质前体细胞具有促进损伤后修复的作用，有望成为HIBD的一种潜在的治疗策略。

3 Tau激酶与HIBD

缺氧缺血性损伤过程中，脑缺氧缺血使Tau磷酸化水平变化的机制虽然尚未完全阐明，但目前也取得了比较大的研究进展。据报道，脑缺氧缺血可通过多种途径如HIF-α/Ngb/ROS通路[50]、天冬酰胺内肽酶(asparagine endopeptidase, AEP)/蛋白磷酸酶2A (protein phosphatase 2A, PP2A)通路[53]和损伤Glymphatic系统(一种脑代谢废物清除机制)[49]诱导Tau磷酸化水平升高，参与脑损伤。那么Tau激酶是否在此病理过程中同样扮演重要角色？Tau蛋白激酶分为三组：(1)丝氨酸/苏氨酸脯氨酸定向激酶，如GSK3β，CDK5， MAPK和其他应激激活激酶；(2)丝氨酸/苏氨酸非脯氨酸定向激酶，如DYRK1A，蛋白激酶A (protein kinase A, PKA)，钙调素依赖蛋白激酶II (Calmodulin-dependent protein kinase II, CaMKII)和CK1；(3)酪氨酸激酶，如Fyn，Yes，Lyn和Src [32, 61]。其中，部分激酶可受缺氧缺血影响调节Tau磷酸化水平(图1)。

3.1 GSK3β与Tau磷酸化

糖原合酶激酶-3 (glycogen synthase kinase-3, GSK3)是一种普遍表达和具有活性的激酶，可磷酸化多种底物的丝氨酸和苏氨酸位点[62]。它被发现于上世纪80年代，Embi团队从兔骨骼肌中将其提取出来[63]；由19号染色体和3号染色体上的不同基因编码，GSK-3有两种细胞亚型：GSK3α (51 kDa)和

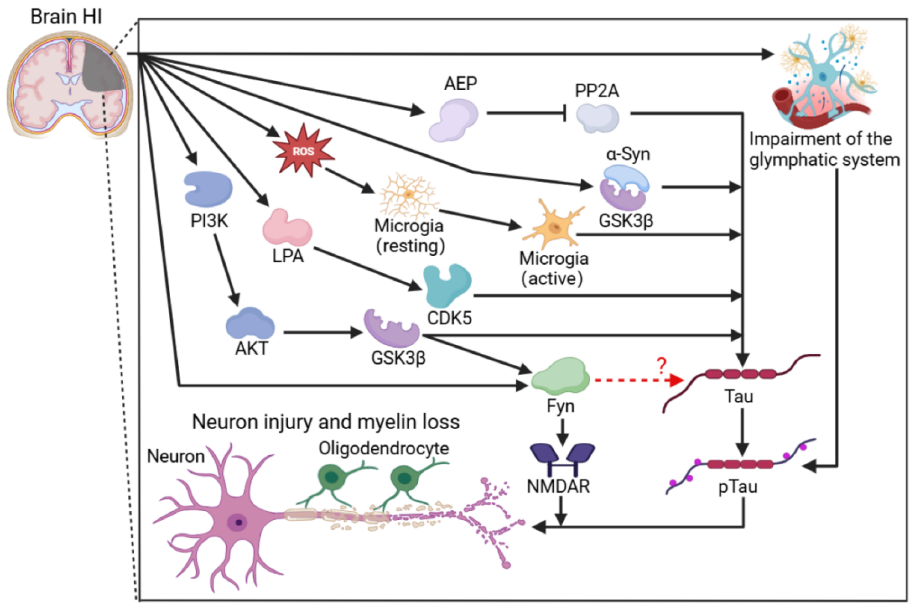

图 1. 脑缺氧缺血诱导Tau磷酸化水平升高的机制

Fig. 1. Mechanism of Tau high phosphorylation level induced by brain hypoxia-ischemia (HI). The elevation of Tau phosphorylation can be induced by brain HI through various mechanisms, including in signaling pathways such as PI3K/AKT/GSK3β pathway, LPA/CDK5 pathway, APE/PP2A pathway, ROS/microglia pathway, Fyn/NMDAR pathway; and other mechanisms such as the increased interaction of GSK3β and α-Syn, as well as the impairment of the glymphatic system. This further aggravated hypoxic-ischemic brain damage, including neuronal axon injury and loss of myelin formed by oligodendrocytes. However, whether phosphorylation of Tau can be elevated by Fyn in HIBD still remains unclear. ROS: reactive oxygen species; AEP: asparagine endopeptidase; PP2A: protein phosphatase 2A; α-Syn: α-Synuclein; LPA: lysophosphatidic acid; CDK5: cyclin-dependent kinase 5; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; GSK3β: glycogen synthase kinase-3β; NMDAR: *N*-mythly-*D*-aspartate receptor; HIBD: hypoxic-ischemic brain damage.

GSK3β (47 kDa) [62, 64–66]，其在大脑中广泛表达[66]。

多数相关研究的蛋白免疫印迹结果显示，海马区和皮层区中除了出现Tau多个位点如Ser396 [67–70]、Thr231 [71]、Ser202 [47, 70]、Ser404 [70]、Ser199 [47, 70]和Ser262 [72]磷酸化水平升高，还均有检测到GSK3β活性在缺氧缺血后出现升高(Ser9磷酸化降低)[47, 67–72]。这提示Tau磷酸化升高与脑缺氧缺血激活GSK3β有关，并且GSK3β可通过一些途径调节Tau磷酸化水平。大鼠MCAO模型的相关实验数据表明，脑缺氧缺血24 h后GSK3β可通过PI3K/AKT途径被激活，使Tau磷酸化水平升高，并且GSK3β在伤后28 d仍可保持激活状态，Tau磷酸化水平仍高于正常组，并且脑损伤进程也未停止[47]。这说明在脑损伤过程中GSK3β可长时间保持激活，使Tau长时间维持高磷酸化水平并加重脑损伤。另一项在小鼠MCAO模型的体内实验结果发现，脑缺氧缺血后激活的GSK3β通过与α-突触核蛋白(α-synuclein, α-Syn)发生相互作用，使Tau蛋白磷酸化水平升高，参与脑损伤过程。在给小鼠静脉注射GSK3β抑制剂后，Tau磷酸化降低，脑损伤减轻[73]。

GSK3β被认为是HIBD的治疗靶点[74]。研究人员尝试在脑缺氧缺血相关动物模型中分别使用氯化铝(lithium chloride, LiCl) [68, 70]、尼莫地平(Nimodipine) [69]、人参皂苷Rd (Ginsenoside Rd) [47]、美金刚(Memantine) [71]和神经营养素(Neurotropin, NTP) [67]等多种药物后，实验结果显示，与损伤组动物相比，给药组动物脑内GSK3β活性显著降低，Tau多个位点磷酸化水平明显下降，神经元凋亡、轴突损伤和认知功能等脑损伤表现得到显著改善(表1)。

3.2 Fyn与Tau磷酸化

Fyn (59 kDa)是Src家族激酶的一种非受体酪氨酸激酶，由位于染色体6q21上的基因编码，具有537个氨基酸残基[66]；Fyn-B、Fyn-T和Fyn-Delta7是Fyn的三个亚型[75]，其有六个结构域[66, 76]，其中SH2与SH3被证实在Fyn与其他蛋白质如Tau等相互作用中起到重要作用[66, 77–79]。Tyr420和Tyr531是

Fyn的两个关键的残基[80]，两个位点分别磷酸化和去磷酸化具有调节Fyn活性的作用[78, 80, 81]。Fyn在大脑中广泛表达与分布，并参与调节轴突引导、神经元迁移、少突胶质细胞成熟和髓鞘形成等多种脑活动[78, 80]。

重要的是，Fyn也参与调控Tau蛋白磷酸化的过程。大量研究证实，在AD转基因小鼠模型中将Fyn敲除或使用AZD0530 (Fyn抑制剂)抑制Fyn后，实验组小鼠脑内出现Tau蛋白的多个位点如Thr205、Ser202、Ser396、Ser404、Ser199和Thr231等的磷酸化水平降低和Tau蛋白过磷酸化后聚集形成的NFT减少，从而缓解Tau病的发展。而未加Fyn抑制剂的小鼠脑中Tau蛋白磷酸化水平明显升高，NFT数量增多，小鼠出现更严重的认知功能障碍[34, 82, 83]。还有研究发现Fyn还可以通过激活Pyk2激酶进一步致Tau蛋白磷酸化[77]，加重Tau病发生。

在小鼠[84, 85]和大鼠[86]HIBD模型中的相关研究结果显示，胼胝体区和海马神经元内中，Fyn表达和活性在脑缺血缺氧后比正常组明显升高[86]，这提示了HIBD也与Fyn异常激活有关。这些研究还发现激活的Fyn可磷酸化其下游因子*N*-甲基-*D*-天冬氨酸受体(*N*-methyl-*D*-aspartate receptors, NMDAR)使其激活，后再通过增加钙蛋白酶活性使大量钙内流，介导脑损伤[84–86]。体内注射PP2 (Fyn抑制剂)后，HIBD表现明显改善[85, 86]。这进一步证实了Fyn参与HIBD。另外，一项在小鼠MCAO模型的相关研究结果中发现，损伤的小鼠脑内上调的Fyn和其激活的NMDAR转录因子cAMP反应元件结合蛋白(cAMP response element-binding protein, CREB)与Tau磷酸化升高的神经元发生共定位[44]。此研究虽然未证实Tau磷酸化升高与Fyn的具体关系，但此结果也提示了缺氧缺血后脑内Tau磷酸化升高可能与Fyn激活NMDAR有关。后续需进一步探究Tau磷酸化与Fyn介导兴奋性损伤之间的关系，以提供更多的证据证明Fyn是HIBD的一个潜在治疗靶点[80] (表1)。

3.3 CDK5与Tau磷酸化

CDK5是一种丝氨酸/苏氨酸脯氨酸定向激酶，具有调节细胞有丝分裂周期和调控其多种底物磷酸化和去磷酸化的作用。细胞周期蛋白相关激活剂p25、p35和p39可激活CDK5 [87–89]。在多个神经系统疾病如AD和帕金森病(Parkinson's disease, PD)的相关研究结果表明，CDK5是脑中Tau的主要激酶之一，在病理状态下可被p25过度激活，使Tau蛋白过度磷酸化，诱导其结构出现错误折叠，导致神经发生病理变化，当CDK5被抑制后，Tau磷酸化降低，减轻其对神经系统的毒性作用[90, 91]。

对啮齿动物MCAO模型的研究结果显示，缺氧缺血使CDK5活性升高，后者诱导神经元内Tau位点Thr205、Ser202、Thr231、Ser214、Ser396和Ser422磷酸化水平升高，Tau出现错误折叠参与神经元凋亡[92, 93]。在这些研究中还发现MCAO组小鼠脑内CDK5的特异性激活因子p25水平也高于假手术组，这提示缺氧缺血激活CDK5与p25有关。这也提示了缺氧缺血与CDK5激活存在间接关系。将体外培养的原代皮层神经元进行糖氧剥夺后，蛋白印迹和免疫荧光染色检结果发现，缺氧缺血激活CDK5从而磷酸化Tau的同时，还出现溶血磷脂酸(lysophosphatidic acid, LPA)水平升高[42]。随后，研究人员分别使用LPA抑制剂和CDK5抑制剂验证CDK5磷酸化是否受LPA调控，实验结果显示CDK5活性受LPA抑制剂的影响，LPA不受CDK5抑制剂影响，而两个抑制剂均使Tau磷酸化水平下降和神经元凋亡缓解[42]。此结果进一步证明了CDK5活性可受LPA调控，从而磷酸化Tau，促神经元凋亡。另一个团队的相关实验结果还发现，缺氧缺血可通过CK2/AKT/GSK3β途径激活CDK5，引起脑白质区少突胶质细胞内线粒体完整性受损和细胞数量丢失，不能形成髓鞘，导致神经元轴突受损[94]。但该研究未报道Tau磷酸化水平是否受其调节。上述数据表明脑缺氧缺血改变Tau磷酸化与CDK5激活有关。因此，CDK5在Tau病中是一种有吸引力的治疗靶点，研发其抑制剂也有望成为HIBD的一个潜在治疗策略，这对于研究神经系统疾病中Tau磷酸化的调控机制具有重要意义。

3.4 MAPK与Tau磷酸化

MAPK是一组能被细胞外刺激激活的丝氨酸-苏氨酸蛋白激酶。MAPK除了具有调节细胞生物学过程的功能，其还是调控Tau磷酸化的激酶之一，并且Tau磷酸化变化受MAPK激活的影响。先前对AD病理进程的相关研究结果发现，多个Tau磷酸化位点如Thr205/Ser202、Ser262/Ser356、Ser396/Ser404、Ser214和Thr231位点磷酸化水平升高均与MAPK激活有关，磷酸化Tau发生错误折叠堆积，引起神经变性[95]。其中，p38是MAPK的一员，在调控Tau磷酸化中具有重要作用。在AD患者体内相关研究结果显示，在病理情况下p38过度激活可

表1. 缺氧缺血性脑损伤中Tau、Fyn和GSK3β的潜在靶向治疗策略

Table 1. Potential pharmacological therapeutic strategy targeting Tau, GSK3β and Fyn in hypoxic-ischemic brain damage

Strategy	Name	Animal model	Method of treatment	Effect to Tau	Tau phospho-sites	Effect to brain damage	Reference
Inhibition of p-Tau							
	Sanhua Decoction	Rat MCAO model	Intragastric administration	Reduced phosphorylation level of Tau	Ser199/202	Promoting neurogenesis	[46]
	Exogenous insulin-like growth factor 1	Rat MCAO model	Intravenous administration	Reduced phosphorylation level of Tau	Thr205/ Ser396	Diminished neuron injury	[43]
	Lamotrigine	Rat MCAO model	Intraperitoneal administration	Reduced phosphorylation level of Tau	Ser202/ Thr205	Diminished neuron injury	[45]
Inhibition of GSK3β							
	Ginsenoside Rd	Rat MCAO model	Intraperitoneal administration	Reduced phosphorylation level of Tau	Ser199/202, PHF-1	Diminished neuron injury	[47]
	LiCL	Rat HIBD model	Intragastric administration	Reduced phosphorylation level of Tau	Ser396	Diminished neuron injury	[68, 70]
	Nimodipine	Rat model of CCH	Intragastric administration	Reduced phosphorylation level of Tau	Ser396	Diminished neuron injury and myelin loss	[69]
	Neurotropin	Rat model of CCH	Intragastric administration	Reduced phosphorylation level of Tau	Ser396	Diminished neuron injury	[67]
	Memantine	Rat MCAO model	Intraperitoneal administration	Reduced phosphorylation level of Tau	Thr231	Diminished neuron injury	[71]
Inhibition of Fyn							
	PP2 (Tocris)	Rat HIBD model	Intraperitoneal administration	Lack	Lack	Diminished neuron injury and myelin loss	[86]

In this Table, previous *in vivo* studies demonstrated hypoxic-ischemic brain damage can be attenuated by inhibiting p-Tau, Fyn and GSK3β respectively. Among them, inhibition of GSK3β showed the indirect effect to alleviate HIBD through reducing Tau phosphorylation. However, inhibition of Fyn contributed to the mitigation of HIBD, but its effect on Tau phosphorylation is still unknown. MCAO: middle cerebral artery occlusion; CCH: chronic cerebral hypoperfusion; PP2: 4-amino-5-(4-chlorophenyl)-7-(t-butyl) pyrazolo [3, 4-d] pyramidine; HIBD: hypoxic-ischemic brain damage.

升高Tau磷酸化和毒性NFT的产生，介导AD发病[96]。抑制p38活性后，Tau磷酸化减少，神经损伤缓解[97]。这些病理特征都表明未来需要进一步研究MAPK家族信号通路在Tau磷酸化中的调控机制，有助于提供治疗Tau病的潜在途径。

MAPK参与缺氧缺血影响Tau磷酸化过程的相关研究较少。脑缺氧缺血可扰乱体内氧化和抗氧化平衡导致发生氧化应激。体外研究的实验结果显示，急性氧化应激期p38 (一种应激活化蛋白激酶，是MAPK家族的亚类之一)的磷酸化水平升高，同时Tau的Ser396、Ser202和Ser199位点磷酸化水平也升高[98, 99]。这表明氧化应激升高Tau磷酸化水平与MAPK激活有关。研究还发现，使用具有抗氧化作用的多聚糖蛋白(spinosin, SPI)抑制氧化应激后，Tau磷酸化水平随着p38活化受抑制而下降，细胞损伤缓解[98, 99]。可见，MAPK活化对氧化应激影响Tau磷酸化极其重要，Tau磷酸化水平变化与MAPK激活呈正相关。然而，氧化应激激活MAPK的具体信号转导机制仍未完全清楚，Tau磷酸化与MAPK之间的具体调控关系仍需进一步研究。

3.5 PKA与Tau磷酸化

PKA又称依赖于cAMP的蛋白激酶A，由一个调节亚基和催化亚基组成，其中催化亚基包含ATP

结合位点、肽结合位点和催化位点，并对蛋白磷酸化调节有重要作用[100]。PKA是Tau的激酶之一，PKA催化亚基可受ATP/ADP比率调节而影响其对Tau磷酸化的调控作用。AD相关研究发现，在病理状态下，ATP合成受阻可影响PKA催化亚基与ATP结合率，扰乱其调节Tau磷酸化，导致Tau异常磷酸化，异常磷酸化的Tau蛋白易发生聚集，使海马神经元受其毒性影响出现树突棘和轴突丧失、线粒体损伤和细胞膜完整性受损，最终导致细胞死亡[101, 102]。

与AD研究结果不同的是，PKA在HIBD中可能具有神经保护作用。脑缺氧缺血可引起炎症反应，PKA活性可受炎症影响而发生变化。在脂多糖(lipopolysaccharide, LPS)诱导炎症的小鼠模型中，Tau磷酸化水平升高、神经元死亡增多的同时，PKA活性下降，而CAMKII活性升高[103]，提示缺氧缺血使Tau磷酸化升高可能与CAMKII激活有关，而活性降低的PKA可能没有参与此过程。另一项体内实验结果显示，尽管脑缺氧使Tau磷酸化水平升高致动物认知功能受损，但PKA活性也是出现降低[104]。然而，PKA与Tau磷酸化之间究竟存在一个什么样的调控关系？据报道，PKA可通过磷酸化Ser214位点来保护Tau的其他位点如Thr212、Thr205和Ser202免受GSK3β磷酸化，从而阻止Tau发生病理构象，维持微管结构和防止神经细胞损伤[105]。这也提示PKA在脑缺氧缺血中具有潜在的神经保护作用的可能，但其保护机制有待进一步研究。

4 总结与展望

Tau蛋白作为参与组成和稳定微管结构的重要部分，缺血缺氧可导致其磷酸化水平升高，并且HIBD病理进程与Tau蛋白磷酸化变化密切相关。缺氧缺血影响Tau磷酸化水平的分子机制极为复杂，现有的研究发现缺氧缺血使Tau多个位点磷酸化升高，这与多个Tau蛋白激酶如GSK3β、Fyn、CDK5、MAPK和PKA等的异常激活有关，脑缺氧缺血产生的氧化应激和炎症也在其中起调节作用。然而，这些Tau蛋白激酶在脑缺氧缺血中的异常激活机制、它们之间相互调控关系以及对Tau磷酸化调控的分子机制仍未完全清楚。这在研究HIBD相关治疗策略道路上造成了一些障碍。因此，未来还需进一步研究Tau磷酸化在HIBD中的病理作用，Tau蛋白激酶在其中的作用和异常激活的机制，以及研发激酶的抑制剂，这些研究有望为HIBD临床治疗策略提供新的研究思路和依据。

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