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缺血性脑卒中后脑水肿的发病机制及治疗进展

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摘　要

缺血性脑卒中已成为全球死亡和残疾的主要原因。脑水肿是缺血性脑卒中的严重并发症，会引起颅内压升高，神经系统症状迅速恶化，形成脑疝，是脑卒中后不良结局的重要危险因素。迄今为止，脑卒中后脑水肿的详细机制尚不清楚。这限制了预防和治疗策略以及药物开发的进展。本文就脑水肿的分类、病理特点、缺血性脑卒中后脑水肿的发生机制与水通道蛋白4、SUR1-TRPM4通道、基质金属蛋白酶9、microRNA、脑静脉回流、炎症反应的关系进行综述。综述了脑卒中后脑水肿治疗新药的研究进展。因此，本文综述为进一步研究和临床治疗缺血性脑卒中后脑水肿提供参考。

关键词

缺血性脑卒中，脑水肿，机制，治疗

The Pathogenesis and Treatment Progress of Cerebral Edema after Ischemic Stroke

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Abstract

Ischemic stroke is associated with increasing morbidity and has become the main cause of death and disability worldwide. Cerebral edema is a serious complication arising from ischemic stroke. It causes an increase in intracranial pressure, rapid deterioration of neurological symptoms, and

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formation of cerebral hernia, and is an important risk factor for adverse outcomes after stroke. To date, the detailed mechanism of cerebral edema after stroke remains unclear. This limits advances in prevention and treatment strategies as well as drug development. This review discusses the classification and pathological characteristics of cerebral edema, the possible relationship of the development of cerebral edema after ischemic stroke with aquaporin 4, the SUR1-TRPM4 channel, matrix metalloproteinase 9, microRNA, cerebral venous reflux, inflammatory reactions. It also summarizes research on new therapeutic drugs for post-stroke cerebral edema. Thus, this review provides a reference for further studies and for clinical treatment of cerebral edema after ischemic stroke.

Keywords

Ischemic Stroke, Brain Edema, Mechanism, Treatment

1. 引言

由于脑卒中的高发病率和死亡率，给社会和家庭带来了沉重的负担。缺血性脑卒中占所有脑卒中病例的约 76% [1]。恶性脑水肿(Malignant brain edema, MBE)是脑卒中的严重并发症，死亡率高达 80%。即使在不危及生命的卒中患者中，脑水肿的严重程度也是预后不良的危险因素[2]。脑卒中后脑水肿是脑卒中恶性进展的重要原因，并与不良结局相关。本文就脑水肿的分类、病理特点、各种分子的作用及其机制、脑卒中后发生脑水肿的治疗新药物等方面进行综述，为脑水肿的进一步研究和临床治疗提供依据。

2. 脑水肿的分类及病理特征

脑卒中后脑水肿的病理机制根据分子病理生理分为三组：细胞毒性水肿、离子性水肿和血管源性水肿[3]。脑卒中后细胞毒性水肿迅速发生，其次是离子性水肿、血管源性水肿，然后是混合性水肿[4]。其中细胞毒性水肿和血管源性水肿是相互依存的[5]。

血脑屏障(blood-brain barrier, BBB)与脑水肿密切相关。它是一种高度选择性的细胞复合物，位于脑部血管和间质之间[6]。它由脑微血管内皮细胞、基膜、周细胞、星形胶质细胞以及紧密连接组成[7]。它含有向中枢神经系统(CNS)提供营养的转运蛋白、参与脑内离子稳态的离子转运蛋白以及阻止化合物进入大脑的外排转运蛋白[6]。当脑缺血时可引起血脑屏障的破坏，进而导致各种化学物质、液体及血源性细胞通过受损的血脑屏障进入脑实质，破坏大脑的水和离子稳态，最终导致脑水肿。

2.1. 细胞毒性水肿

细胞毒性水肿是脑水肿病理过程的第一步。在脑缺血缺氧早期，Na/K-ATP 酶的损伤和离子渗透梯度的变化导致渗透作用的发生，主要是钠离子、氯离子和水从外部转移到内部，为离子型水肿和血管源性水肿的形成提供驱动力[8]，最终导致细胞肿胀，这种病理的改变在星形胶质细胞中尤为明显[9]。

水可以通过三种方式流入星形胶质细胞。首先，通过脂质双分子层的简单扩散可以导致大量水的流入[10]。其次，水由渗透梯度驱动，通过跨膜水通道，后者包括水通道蛋白(AQP)家族和一些星形胶质细胞转运蛋白，如 SGLT1、GLUT1 和 GLUT2 [11]。此外，在星形胶质细胞表达的一些离子转运体的驱动

下，水可以与离子一起转运。这些转运蛋白，如 NKCC1 和谷氨酸转运蛋白 EAAT1，可以通过每次转运作用转移固定数量的水分子和离子来调节二次转运[11]。

2.2. 离子性水肿

离子性水肿发生在细胞毒性水肿之后，可在内皮功能障碍的早期发生。由于细胞毒性水肿形成的离子浓度梯度，Na^+、Cl^-和水首先通过管腔膜转运到内皮细胞内，然后再通过脑毛细血管内皮细胞的管腔膜转运到管腔外[9]。Na^+是离子水肿的主要驱动因素，它可以推动氯离子和水的流入，进而平衡电梯度和渗透梯度。

水通过质膜运输有三种可能的方式。首先，水可以通过简单的扩散穿过内皮细胞膜[10]。其次，水和离子的一些共同运输通道，以及一些内皮转运蛋白，如 NKCC1、KCC、MCT1 和 GAT-1，可以调节水的二次运输[11]。第三，脑内皮细胞表达一些可以调节被动水转运的膜蛋白[9]。

2.3. 血管源性脑水肿

血管源性水肿发生在离子性水肿之后，其特征是血脑屏障被破坏[12]。随着水肿的进展，形成跨内皮通透性孔道，因此水和一些血浆蛋白可通过这些孔道外渗到脑间质[13]。蛋白质和水分通过胞饮作用进入间质液。胞饮作用是血液溶质被内皮细胞的质膜折叠包裹以吸收和运输物质的生物学过程。研究表明血管源性水肿也可以通过内皮细胞的细胞旁转运发生，炎症和脑缺血可触发内皮细胞转运，增加内皮细胞的通透性[14]。有证据表明，内皮细胞收缩引起的血脑屏障破坏不足以替代紧密连接破坏[15]。内皮细胞收缩可能有助于促进血管源性水肿的形成，而不是引发血管源性水肿。VEGF 信号传导可产生细胞旁通透性孔。当其表达由脑损伤触发时，紧密连接蛋白表达降低，血管通透性增加，水肿形成增强[16]。先前的研究表明，实验性大鼠脑卒中后早期给予重组 VEGF 药物，将会增加水肿的形成[17]。造成这一结果的原因是 VEGF 信号传导可产生细胞旁通透性孔道。当其表达由脑损伤触发时，紧密连接蛋白表达降低，血管通透性增加，从而水肿形成增强。

3. 脑水肿形成相关的因素

脑水肿的机制是基于 Starling 在 19 世纪末提出的原理[18]。Starling [18]建立了经毛细血管的基本模型促进水肿形成的驱动力，并提出脑水肿形成过程中需要两个要素：驱动力以及渗透性孔隙[19]。影响这一过程的因素很多，它们之间往往存在复杂的相互作用。因此脑水肿的机制非常复杂。下面，简要地总结在这一背景下作为研究重点的因素。

3.1. AQP4 与脑水肿

水通道蛋白(AQP)是一种膜蛋白，允许水分子在磷脂双脂膜上双向运动。其中，AQP1、AQP4、AQP9 和 AQP11 是在中枢神经系统(CNS)中表达的主要成员[20]。AQP4 由星形胶质细胞表达，并在水分运输中发挥双向作用，参与脑水肿的形成和消退[21]。AQP4 主要表达在四个大脑区域：血管旁星形胶质细胞的端足、胶质外膜下的星形胶质细胞突起、室管膜基底外质膜下的星形胶质细胞突起和室管膜外胶质下的星形胶质细胞突起[7]。

星形胶质细胞和 AQP4 在脑水肿的清除和调节中起着至关重要的作用[9]。AQP4 还可以促进淋巴系统的流动，消除脑内有毒物质沉积，调节脑水肿的形成[22]。缺血性脑卒中后 AQP4 的显著高表达可能促进脑水肿的形成[23]。当 AQP4 被敲除或抑制时，缺血性脑卒中后脑水肿的形成减少。有研究表明，甲状腺激素治疗可通过抑制 AQP4 来减弱脑水肿，可能对脑卒中后患者具有神经保护作用[24]。相关研究表明，吸入硫化氢可减轻大鼠脑水肿，其机制主要是抑制了 AQP4 蛋白表达[25]。在永久性大脑中动脉闭塞

(MCAO)动物模型中，AQP 抑制剂和脑溶血素联合治疗可减轻脑水肿[26]。经 AQP4 抑制剂 TGN-020 治疗后，缺血后 MCAO 模型大鼠脑水肿在第 3 天和第 7 天减轻[27]。而 AQP4 在脑卒中后脑水肿的过程中起着复杂的双重作用，在早期加重脑水肿形成，在后期减轻水肿[28]。然而，这种功能的机制尚不清楚。缺血性脑卒中后 AQP4 抑制剂的应用已成为研究热点。由于细胞毒性水肿、离子性水肿和血管源性水肿形成的时限尚不清楚，因此 APQ4 抑制剂治疗的开始和终止时间仍然是一个亟待解决的问题。

3.2. SUR1-TRPM4 与脑水肿

磺酰脲受体 1 (SUR1)属于由 ABCC8 编码的腺苷 50-三磷酸(ATP)结合超家族成员，是瞬时受体电位 TRPM4 通道介导中枢神经系统细胞肿胀的关键介质[29]。SUR1-TRPM4 在中枢神经系统无异常时不表达，仅在中枢神经系统损伤后表达[30]。在所有中枢神经元中，中枢神经系统损伤触发缺氧诱导因子 1 转录因子的激活，从而诱导 SUR1 与 TRPM 4 结合，增加其 Ca^{2+}敏感性，并使该通道对 ATP 耗尽敏感[31]。SUR1-TRPM4 通道通过调节 Na^{+}在管腔膜上的流入和 Na^{+}在管腔膜上的流出，参与离子水肿的形成。在中枢神经系统严重损伤和 ATP 耗竭的情况下，通过 SUR1-TRPM4 通道的过量 Na^{+}流入会导致适应不良的细胞肿胀和细胞毒性水肿[9]。由于 SUR1 的调控机制依赖于基因转录和 ATP，因此在脑缺血再灌注中发挥重要作用[9]。SUR1-TRPM4 和 AQP4 可以形成一种新的异聚水/离子通道复合物，协同调节星形胶质细胞膨胀[32]大量研究表明，SUR1-TRPM4 在缺血性脑卒中中表达上调。在大鼠模型中，脑卒中再灌注 2 小时后，脑内皮细胞中的 TRPM4 上调，siRNA 治疗抑制 TRPM4 可减少梗死体积和脑水肿[33]。此外，给予 TRPM4 特异性抗体可以通过抑制通道电流来防止缺氧细胞肿胀[34]。鉴于 SUR1-TRPM4 通道在细胞毒性和离子水肿中的特殊驱动作用，SUR1-TRPM4 的药理学研究已成为脑卒中治疗研究的热点。动物实验研究表明，SUR1-TRPM4 通道抑制剂格列美脲可减少小鼠脑卒中，在减少野生型小鼠脑水肿方面与格列本脲一样有效[35]。目前，SUR1-TRPM4 通道抑制剂是唯一进入临床试验治疗缺血性脑卒中后脑水肿的药物[3]。临床试验结果表明，静脉注射格列本脲可减少脑水肿和中线移位[36]。探索性研究表明，格列本脲可以缓解水分积聚，提高存活率，减少中线偏移动，以及减弱基质金属蛋白酶 9 (MMP-9)的表达[37]。一项评估口服格列本脲治疗缺血性脑卒中后脑水肿疗效的临床研究中表明，格列本脲不会增加早期死亡及低血糖的发生，并且可以预防脑水肿[38]。这些发现促进了大规模脑梗死 III 期临床试验的开展。

3.3. MMP-9 和脑水肿

基质金属蛋白酶(Matrix Metalloproteinases, MMPs)是一组锌内肽酶，可以降解几乎所有类型的细胞外膜蛋白[39]。人体中有超过 23 种不同类型的 MMP。根据它们的底物特异性，它们分为胶原酶、明胶酶、基质金属弹性蛋白酶、牙釉质蛋白酶等[40]。MMP 可以介导基底膜蛋白的破坏，导致血脑屏障通透性增加，渗出白细胞、脑水肿和出血性转化。正常情况下 MMP 的表达水平很低，而 MMP-2 和 MMP-9 的表达水平在脑缺血后数小时内显著升高[41]。

一项 Meta 分析显示，MMP-9 水平在卒中合并严重脑水肿和出血性转化的患者中较高[42]。缺血后，MMP-9 的表达增加，这与细胞外基质破坏和随后的血管通透性增加密切相关[43]。MMP-9 在脑缺血缺氧后迅速增加，通过降解紧密连接和细胞外基质破坏血管壁的完整性，增加血脑屏障的通透性，进而导致神经元死亡、脑水肿和出血性转化[44]。有研究发现，MMP-9 参与维持 AQP-4 水通道的结构完整性，参与脑水肿的调控[45]。体外研究表明，MMP-9 沉默下调星形胶质细胞中 AQP-4 的表达[46]。另外有研究表明，MMP-9 与缺血性卒中引起的炎症有关，并参与血脑屏障的破坏[47]。MMP 抑制剂可以通过部分阻止紧密连接蛋白的降解来减少脑缺血相关的脑水肿[45]。另一项研究表明，在小鼠大脑中动脉闭塞－再灌注模型中，MMP-9 的下调可减轻血脑屏障的破坏和脑水肿的程度[48]。研究报道，MMP-9 可能是评估缺

血性卒中血脑屏障通透性和预测出血转化最有前景的生物标志物之一[49]。因此，这方面还需要进一步的探索研究。

3.4. MicroRNAs 与脑水肿

MicroRNAs (miRNAs)是一类长度约为 22 个核苷酸的非编码单链 RNA 分子，由内源性基因编码，可在转录水平调控基因表达，已成为新的疾病治疗靶点[50]。MiR-1 的表达与缺血性损伤和细胞凋亡有关[51]。

抗 MiR-1 治疗后脑梗死体积可减小[52]。应用 MiR-1 拮抗剂可显著减少脑水肿和血脑屏障损伤[53]。值得注意的是，研究表明，其他 miRNA，如 miRNA-132 和 miRNA-1906，是治疗脑水肿的潜在靶点[54]。然而，其机制尚不清楚，需要进一步研究。

3.5. 脑静脉和脑水肿

颅内静脉系统是颅内循环血容量的主要组成部分，占 70%~80%。近年来，对颅内静脉的研究越来越受到关注。越来越多的研究表明，在急性缺血性卒中期间，脑静脉的功能性反流可能与动脉血流同样重要，并且脑静脉反流的状态可能提供关于患者的更多信息，例如预测预后。

一项临床研究发现，横窦发育不全或闭塞与颅内循环时间延长和脑自主调节受损有关，与大脑中动脉大面积梗死后严重脑水肿呈正相关[55]。另一项临床研究表明，在急性缺血性卒中治疗后，无论 CT 血管造影(CTA)上的侧支血管状态如何，静脉流出与脑水肿的形成有关。良好的静脉流出与神经功能恢复有关[56]。该研究团队还发现，治疗前良好的静脉流出与接受血管内治疗的急性缺血性卒中患者的成功再灌注、良好的侧支循环和良好的预后相关[57]。

3.6. 炎症反应和脑水肿

最近的研究认识到，炎症反应在缺血性脑卒中的血脑屏障破坏中起着重要作用。脑缺血导致死亡或坏死神经细胞和神经胶质细胞释放的炎症抑制信号减少，这可能会激活静止的脑免疫细胞[58]。脑免疫细胞的活化进一步上调促炎因子和趋化因子的表达，激活 MMPs 破坏血脑屏障的完整性，从而吸引外周免疫细胞进入受损部位，促进不可逆的梗死核心区域的发展，导致继发性血脑屏障损伤[59]。免疫细胞，包括脑免疫细胞(CIC)和外周免疫细胞(PIC)，在这一过程中起着至关重要的作用。

缺血性脑卒中后，包括中性粒细胞、单核细胞和 T 淋巴细胞在内的外周免疫细胞导致微血管疾病和炎症分子的分泌，从而增加血脑屏障的通透性。在缺血性中风的晚期，这些细胞有助于血脑屏障的修复和血管生成[60]。

研究发现，在小鼠 MCAO 模型中，特异性阻断中性粒细胞与小静脉内皮细胞的粘附，可以显著减少脑梗死和神经功能缺损的体积，并改善短期和长期的功能预后[61]。其他研究表明，中性粒细胞可能表达抗炎表型，中性粒细胞的 N2 极化有助于小胶质细胞和巨噬细胞对中性粒细胞的吞噬作用，从而减少脑水肿和梗死体积[62]。因此，中性粒细胞可能在缺血性脑卒中的演变中可能发挥着双重作用。

同样，脑免疫细胞，包括小胶质细胞、星形胶质细胞和血脑屏障周细胞，对缺血性卒中起着重要的免疫调节作用。在脑缺血后的几分钟内，小胶质细胞和星形胶质细胞被激活并释放一些促炎因子，如 TNF-α、NF-κB、IL-1β 和 IL-6 [63]。它们促进炎症反应，破坏血脑屏障结构，增加血脑屏障通透性，以及不受控制的 MBE 和脑出血[64]。在大鼠永久性 MCAO 模型中，使用 TNF-α 受体抑制剂预处理可以保护神经损伤、脑梗塞和水肿[65]。NF-κB 通常被认为是体内炎症的“中心环节”，在缺血再灌注损伤过程中起着重要的介导作用。抑制 NF-κB 表达可以减少炎症级联，保护血脑屏障的结构和功能[66]。脑缺血后，周细胞表达炎症表型(CD11b 阳性)，上调促炎细胞因子表达，促进血脑屏障通透性增加[67]。周细胞

的吞噬作用可能有助于缺血性卒中炎症的消退和血脑屏障的修复[60]。因此，周细胞在缺血性脑卒中可能发挥着双向作用，有待进一步研究证实。

脑免疫细胞与外周免疫细胞在一个微妙而复杂的网络中相互作用。此外，免疫细胞参与的炎症反应表型在脑缺血的起始、进展和消退阶段是不同的。单纯针对某一种免疫细胞的治疗可能会影响到其他免疫细胞，甚至导致缺血性卒中的不良结果。

4. 脑水肿的治疗

目前，临床上用于减轻脑水肿的主要药物是渗透性利尿剂，特别是甘露醇和高渗盐水。主要机制是通过建立血管内渗透梯度，使水从细胞间隙流向血管内空间。这种干预的主要功能是降低颅内压增高和减轻占位效应，但可能会引发严重的并发症，如肾损伤和水电解质紊乱[68]。对于脑水肿的治疗，去骨瓣减压术是一种有效的方法，可以降低死亡率并改善预后，但大多数幸存患者会有严重残疾[69]。此外，这些干预措施只能在破坏性水肿完全发展后应用，并且是高风险和低疗效的方法。与消除水肿的治疗相比，预防中枢神经系统水肿的形成可能更有价值[5]。

从脑水肿的潜在分子机制出发，选择靶点、研究新药物来预防和治疗脑水肿是目前的研究热点。已经进行了大量的研究来调查这些目标。这些研究包括使用 SUR1-TRPM4 通道抑制剂治疗[35]，AQP-4 阻滞剂[26]，MMP-9 抑制剂[70]，离子通道阻滞剂，如 NKCC1 和 NHE [71]，VEGF 相关药物[72]，miRNAs [73]，以及其他一些保护剂，如骨化三醇和 3-氨基苯甲酰胺[74]。然而，这些研究大多涉及动物实验，很少涉及临床试验。格列本脲是一种有效的 SUR1-TRPM4 通道抑制剂，已知已进入脑卒中后脑水肿治疗的临床试验。一项探索性试验表明，格列本脲与水扩散率和 MMP-9 水平降低有关，表明血管源性水肿减少[75]。一项研究表明，使用静脉注射格列本脲与安慰剂相比，静脉注射格列本脲可降低有 MBE 风险的大面积前半球梗死患者的中线偏移、NWU 和 MMP-9 表达[76]。

5. 结论

缺血性脑水肿具有较高的发病率、死亡率和致残率，越来越受到学者们的关注。正在进行的研究已经发现一些新靶点，从而为进一步研究影像标记物、多模态监测数据分析和潜在治疗方法提供了可能性。目前脑水肿的治疗仍以临床经验为主，主要针对脑水肿发展后的对症治疗。这种治疗不能从根本上遏制恶性脑水肿的发生和进展。因此，进一步明确脑水肿的发生机制，寻找有效的治疗靶点，从而确定更有效的诊疗方式具有重要意义。

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