·专题讲座·

癫痫持续状态病理学研究进展

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【摘要】 癫痫持续状态为病死率和病残率较高的中枢神经系统常见急危重症，其引起的脑损伤严重程度是影响患者预后的重要因素。从癫痫持续状态诱发的脑组织病理改变角度结合分子水平加以研究，有望揭示其脑损伤机制，为探索癫痫持续状态新的预测与治疗方法提供理论依据。

【关键词】 癫痫持续状态； 病理学； 综述

Research progress on pathological changes of brain caused by status epilepticus

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【Abstract】 Status epilepticus (SE) is a common neurological emergency with high disability and mortality rates. The degree of brain injury after SE is a key factor related to the prognosis of patients. The specific mechanism of brain injury after SE could be studied by combining pathological changes and molecular level changes. This paper summarizes the research progress of SE pathology and the underlying mechanism to provide a theoretical basis to explore new therapies and diagnostic methods of SE.

【Key words】 Status epilepticus; Pathology; Review

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2001年，国际抗癫痫联盟（ILAE）建议将癫痫持续状态（SE）定义为：发作持续时间超过该类型大多数患者的发作时间或反复发作，且发作间期中枢神经系统功能未恢复至基线水平[1]。此前，Lowenstein等[2]提出定义：单次惊厥发作持续时间超过5分钟或2次以上发作，发作间期意识未完全恢复，该定义似乎更适合临床操作。凡经足量一线抗癫痫药物（AEDs）治疗无效，通过添加另一种药物后仍无法终止发作和改善脑电活动者，称为难治性癫痫持续状态（RSE）[3]。癫痫持续状态分为惊厥性和非惊厥性，以惊厥性癫痫持续状态常见，占45%～74%。患者可伴随出现智力障碍、神经功能不可逆性损害，且使癫痫猝死（SUDEP）风险增加，严重影响患者生活质量和身心健康；其病理改变主要发生在大脑皮质和皮质下结构、小脑、脑干和边缘系统，在海马组织中可表现为颗粒细胞和中间神经元缺失、新生神经元增殖、神经胶质细胞活化、突触环路重建、血-脑屏障破坏，以及微血管重塑等。本文仅对癫痫持续状态病理改变及其分子病理学机制研究进展进行概述。

一、病理改变

1. 神经元缺失和扩散 早在1997年，Buckmaster等[4]首次应用免疫组织化学染色检测到海人酸（KA）诱导的癫痫持续状态小鼠海马齿状回门区神经元数目减少，与正常对照组相比，癫痫持续状态组小鼠海马门区神经元数目减少52%。我们科研小组的同类研究也发现，匹罗卡品致痫小鼠海马CA1和CA3区锥体细胞层神经元数目明显减少、排列紊乱，细胞呈扩散改变[5-6]。2013年，Scholl等[7]对氯化锂-匹罗卡品致痫大鼠的研究发现，丘脑、杏仁核、下丘脑腹侧核和边缘系统皮质存在神经元死亡，且非惊厥性癫痫持续状态（NCSE）可以导致神经元损害和死亡。既往研究认为，癫痫持续状态引起的细胞死亡方式主要为坏死[8]，因兴奋性神经递质

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谷氨酸释放增加所致。其机制为突触前膜释放过量谷氨酸，激活突触后膜N-甲基-D-天冬氨酸受体（NMDAR），导致神经元异常增多的钙离子内流和细胞器内钙离子释放，从而激活胞质蛋白酶（如能够水解细胞骨架及其他蛋白质的钙蛋白酶Ⅰ）[8]和神经元型一氧化氮合酶（nNOS），后者使一氧化氮、过氧亚硝酸基产生增加，DNA结构受损[9]，进一步激活DNA修复聚ADP-核糖聚合酶（PARP），从而使细胞内ATP减少，诱发细胞坏死。有研究显示，癫痫持续状态尚可引起细胞凋亡[10]。细胞凋亡系由基因决定的细胞自动结束生命的过程，其特点是单细胞发生胞核浓缩、碎裂，胞核碎块被胞膜包裹形成特异性“凋亡小体”。尽管凋亡机制有异于坏死，但二者之间存在重叠。癫痫持续状态期间海马组织呈现缺氧缺血、水肿，诱发兴奋性氨基酸释放、钠离子和钙离子内流，启动凋亡蛋白caspases活化和级联反应，产生包括自由基、神经元型一氧化氮合酶和介导凋亡的核心执行蛋白caspase-3等一系列凋亡通路相关分子，导致胞质、胞核，以及细胞骨架蛋白降解失活，进而诱发大量神经元凋亡[11]。Sun等[12]认为，微小RNA（miRNA）中miR-365-5p和miR-99b-3p与癫痫持续状态后的神经元凋亡密切相关。近年来，癫痫持续状态后神经元凋亡研究颇受关注，病理改变结合基因组学为靶向治疗可行性提供了基础。

2. 新生神经元增殖　正常成熟脑组织存在两个主要的新生神经元增殖部位：一个位于侧脑室下层，产生的神经元从嘴侧迁移流迁移至嗅球，逐渐分化为中间神经元；另一个位于海马齿状回颗粒细胞下层，产生新生颗粒细胞。对电点燃或化学点燃颞叶癫痫模型的研究发现，癫痫持续状态可诱导海马齿状回颗粒细胞下层新生神经元异常增殖，增殖数目与癫痫发作程度呈正相关[13]。癫痫持续状态时增殖的神经元主要来源于成熟时程较晚的神经元前体细胞（NPCs），即表达双皮质素（DCX）的Ⅲ型神经前体细胞[14-15]。双皮质素标记的神经前体细胞更易因癫痫发作的刺激而加速增殖和迁移并分化为成熟神经元[16]（图1）。经膜片钳法研究显示，匹罗卡品致痫大鼠模型海马新生神经元兴奋性增高，具有自发性暴发放电的能力[17]。癫痫持续状态尚可诱导新生神经元异常迁移至门区和内分子层，成为异位新生神经元并生成巨大的基底状树突，与周围神经元形成异常突触联系，构成反复放电的兴奋性神经环路的结构基础。然而，也有学者认为，神经元增殖具有降低癫痫易感性的作用[18]。动物实验表明，经Na^+-K^+-$2Cl^-$共转运体抑制剂布美他尼（bumetanide）治疗后，癫痫小鼠海马齿状回双皮质素阳性细胞数目和基底状树突增加，但癫痫发作频率减少[14-15]；而以低剂量辐射小鼠海马或全脑后，在癫痫持续状态早期虽可抑制神经元增生，但癫痫发作程度更为严重，潜伏期缩短、发作频率增加[19-20]。

3. 苔藓纤维出芽　苔藓纤维（MF）为海马齿状回颗粒细胞之轴突。正常情况下，苔藓纤维穿过多形细胞层终止于CA3区和门区中间神经元，并与门区中间神经元和CA3区锥体细胞树突建立神经联系；癫痫发作时CA3区锥体细胞和门区神经元受损，内分子层神经信号传导缺失，苔藓纤维与靶细胞离断，从而触发苔藓纤维异常出芽返回内分子层，并与该层颗粒细胞和中间神经元树突形成新的突触联系[21]，是海马齿状回内部回返性兴奋性神经环路形成和强化的重要组成部分，亦是导致痫样放电易化和扩散的机制之一。苔藓纤维出芽（MFS）是颞叶癫痫的典型病理改变，亦可见于癫痫持续状态。Timm染色是评价苔藓纤维出芽常用的组织形态学方法（图2），随着影像学检查技术的不断进步，锰离子增强MRI（MEMRI）可对化学药品诱导癫痫小鼠模型进行活体扫描，研究发现，小鼠齿状回和CA3区苔藓纤维出芽信号强度明显增强，表明MEMRI可以作为一种检测苔藓纤维出芽的非侵入性方法[22-23]。目前有关苔藓纤维出芽对癫痫病情的影响仍存争议：部分学者认为，苔藓纤维出芽可在齿状回形成新的突触，并在齿状回树突-颗粒细胞突触间传递兴奋性输出，产生或增强兴奋性神经通路[24]；另一部分学者则认为，苔藓纤维出芽可以产生抑制性作用，因为部分异常的苔藓纤维出芽可作用于颗粒细胞层γ-氨基丁酸（GABA）抑制性中间神经元[25]。Sloviter等[26]以海人酸致癫痫持续状态模型小鼠为研究对象，检测突触重建过程中不同阶段颗粒细胞的兴奋性，其结果显示，以癫痫持续状态结束瞬间颗粒细胞兴奋性最高，30天后兴奋性逐渐降低；而反复自发性癫痫发作可抑制颗粒细胞兴奋性，颗粒细胞兴奋性降低可能阻碍神经元放电，减少癫痫发作。该项研究对以往关于苔藓纤维出芽可加重癫痫持续状态的理论提出挑战，有可能为癫痫持续状态的治疗提供新的研究方向。

4. 血-脑屏障破坏　血-脑屏障破坏是癫痫持续状态特征性的早期病理改变之一，其在癫痫持续状

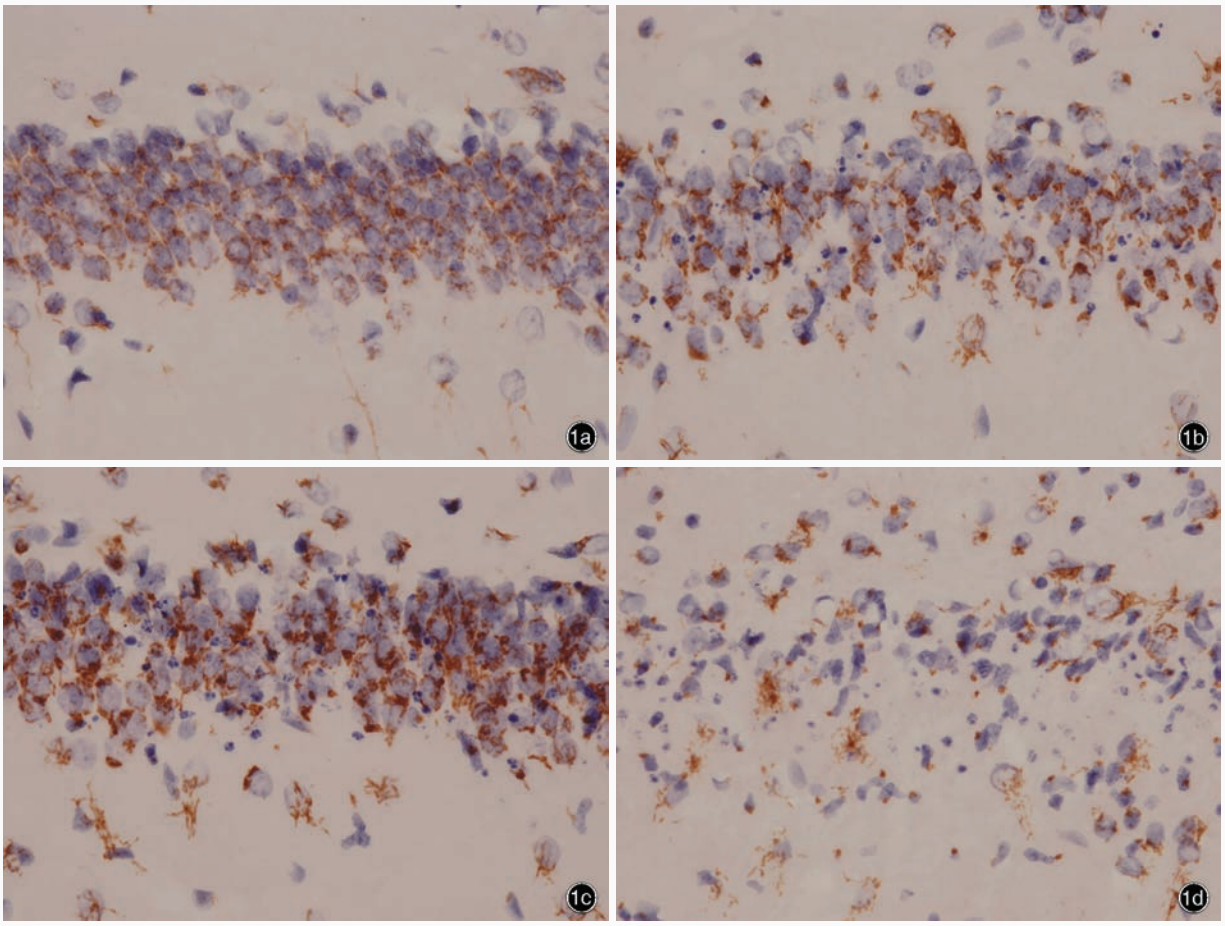

图1 小鼠海马组织光学显微镜观察所见 免疫组织化学染色(ABC三步法) ×400 1a 正常对照组小鼠DCX蛋白主要表达于胞质树突和轴突 1b 癫痫持续状态模型组小鼠发作第1周时,颗粒细胞层DCX阳性神经元数目增加 1c 癫痫持续状态模型组小鼠发作第4周时,颗粒细胞层DCX阳性神经元数目达峰值水平 1d 癫痫持续状态模型组小鼠发作第8周时,DCX阳性神经元数目呈下降趋势

Figure 1 Optical microscopy findings. Immumohistochemical staining (ABC) × 400 In mice hippocampus of normal control group, DCX protein was mainly expressed in dendrites and axons of the cell body (Panel 1a). On the 1st week after SE, DCX positive cells of granular cell layer in hippocampus of SE model group increased gradually (Panel 1b). On the 4th week after SE, the number of DCX positive cells of granular cell layer reached the peak (Panel 1c). On the 8th week after SE, the number of DCX positive cells of granular cell layer showed a decreasing trend (Panel 1d).

态病情进展过程中具有重要作用。伊文蓝(EB)染色或血清球蛋白对癫痫持续状态小鼠血-脑屏障的病理改变研究显示,在化学药物诱导癫痫持续状态后的最初数日内,小鼠血-脑屏障即可发生血清球蛋白渗漏,但以潜伏期渗透性改变最为严重,至自发性癫痫发作期血清球蛋白渗漏程度逐渐下降[27];癫痫持续状态3个月时,常规实验室技术已不能进一步检测血-脑屏障的病理改变,仅能通过共聚焦显微镜检测神经元和神经胶质细胞对血清球蛋白的摄取率,并能在边缘系统检测到少量球蛋白渗漏[28]。血-脑屏障受损可通过钾离子内流导致神经元去极化或血清球蛋白渗漏引起神经胶质细胞激活、钾离子缓冲受损、炎症反应和突触重塑等一系列病理改变,使癫痫病情进展[29-30]。

5. 血管重建 目前认为,血管出芽、延长、内皮前体细胞整合,以及最终形成血管管腔的一系列病理过程是血管重建的关键步骤。动物实验结果显示,癫痫持续状态后数小时,匹罗卡品致痫小鼠海马微血管密度即明显增加,由昆布氨酸(laminine)和绿色荧光蛋白(GFP)联合标记的新生血管数目以发病后7天最多[31]。我们科研小组的前期研究结果发现,癫痫持续状态第7天小鼠海马门区微血管密度低于正常对照组,随后逐渐升高,至第28天达峰值水平、至第56天略有下降(图3),提示癫痫持续状态

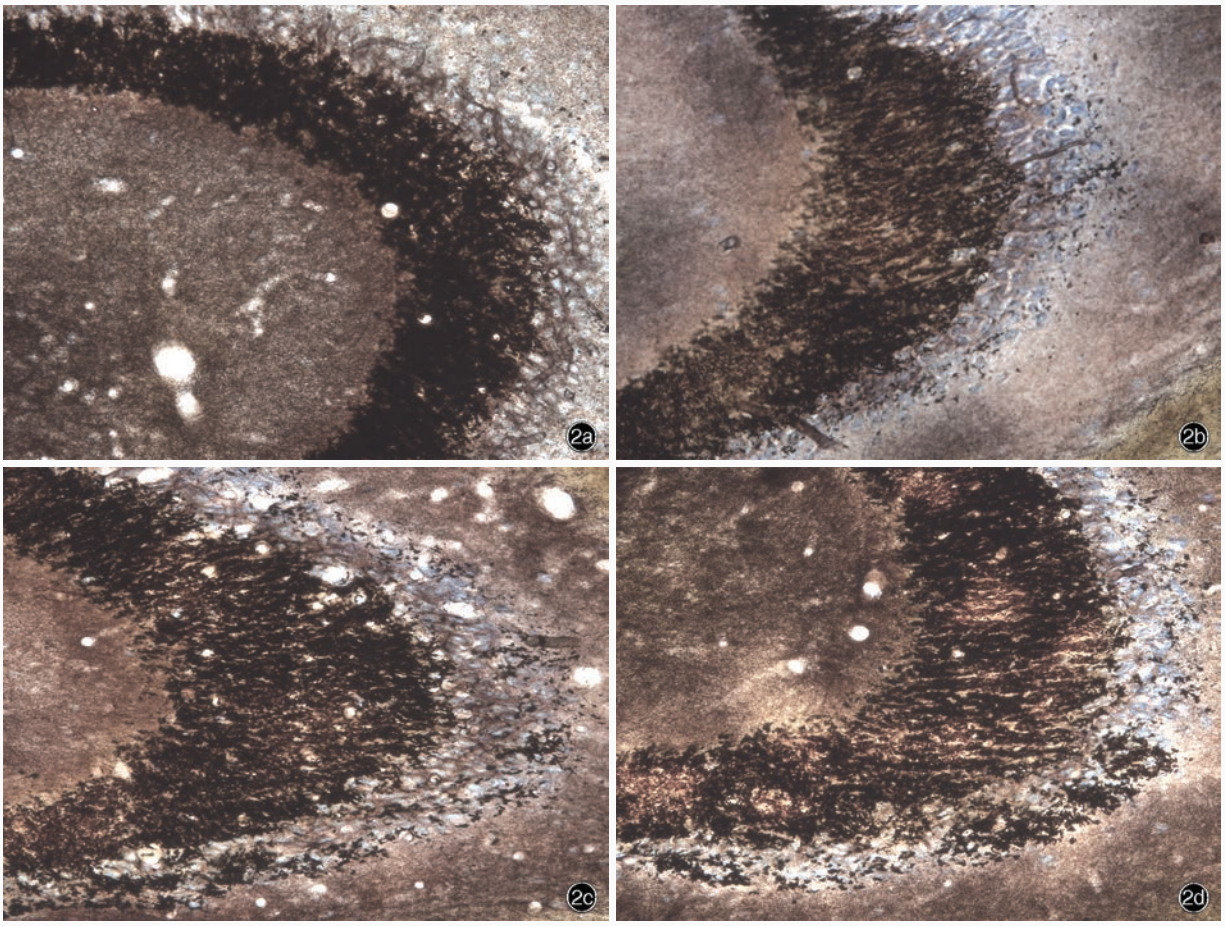

图2 戊四氮点燃模型大鼠海马CA3区光学显微镜观察所见 Timm染色 ×200 2a 正常对照组海马CA3区起始层、锥体层未见Timm颗粒 2b 癫痫发作3天组即可在海马CA3区起始层观察到Timm颗粒 2c 癫痫发作2周组海马CA3区起始层Timm颗粒明显增多 2d 癫痫发作4周组海马CA3区起始层Timm颗粒达峰值水平，可见浓密的层状带Timm颗粒沿CA3区连续分布

Figure 2 Optical microscopy findings of hippocampal CA3 region in pentylenetetrazole kindling rat model of epilepsy. Timm staining ×200 Timm granules were not seen in the start layer and pyramid layer of CA3 region in nomal control group (Panel 2a). Timm granules were found in the start layer of CA3 region 3 d after epileptic seizure (Panel 2b). Timm granules were obviously increased in the start layer of CA3 region 2 weeks after epileptic seizure (Panel 2c). Timm granules reached the peak in the start layer of CA3 region 4 weeks after epileptic seizure. Densely stratiform Timm granules were continuously distributed along the CA3 region (Panel 2d).

后小鼠海马门区微血管密度改变持续至自发性癫痫发作期。癫痫持续状态致血-脑屏障破坏是血管重建的重要诱发因素之一，血管内皮生长因子(VEGF)/血管内皮生长因子受体-2(VEGFR-2)信号转导通路在其中发挥关键作用：缺氧和炎症反应激活蛋白-1、缺氧诱导因子-1α(HIF-1α)、特异蛋白-1及信号转导因子和转录激活因子3(STAT3)等为VEGF激活因子，可通过VEGFR-2调节内皮细胞生长、血管通透性，并调控基底膜降解[32]，有研究表明，于海人酸诱导的原代癫痫大鼠海马组织中加入抗VEGF抗体，可以减轻血管重建并诱导紧密连接发生降解[33]。然而，研究显示，经胶原蛋白Ⅳ标记的颞叶癫痫患者海马组织，尤其是硬化的CA1区血管多呈萎缩性改变，表面可见棘样突起；电子显微镜观察突起主要源于基底膜，为血管异常出芽，且缩小的血管管腔内存在活化的星形胶质细胞[34]。上述病理改变认为是单纯的正常血管崩解所致[34]，并无确切证据提示这种血管变化具有普遍性，尚待提供更多实验室证据。

二、分子病理学机制

自单次癫痫发作诱导癫痫持续状态的最初数秒开始，脑组织即出现神经递质释放、离子通道开放/关闭，以及多种蛋白磷酸化改变[35]；此后数秒至数分钟，神经受体运输和功能随之发生障碍，表现为突触前膜抑制性神经递质γ-氨基丁酸A型受体($GABA_AR$)β2/β3亚基和γ2亚基减少并从胞膜迁移

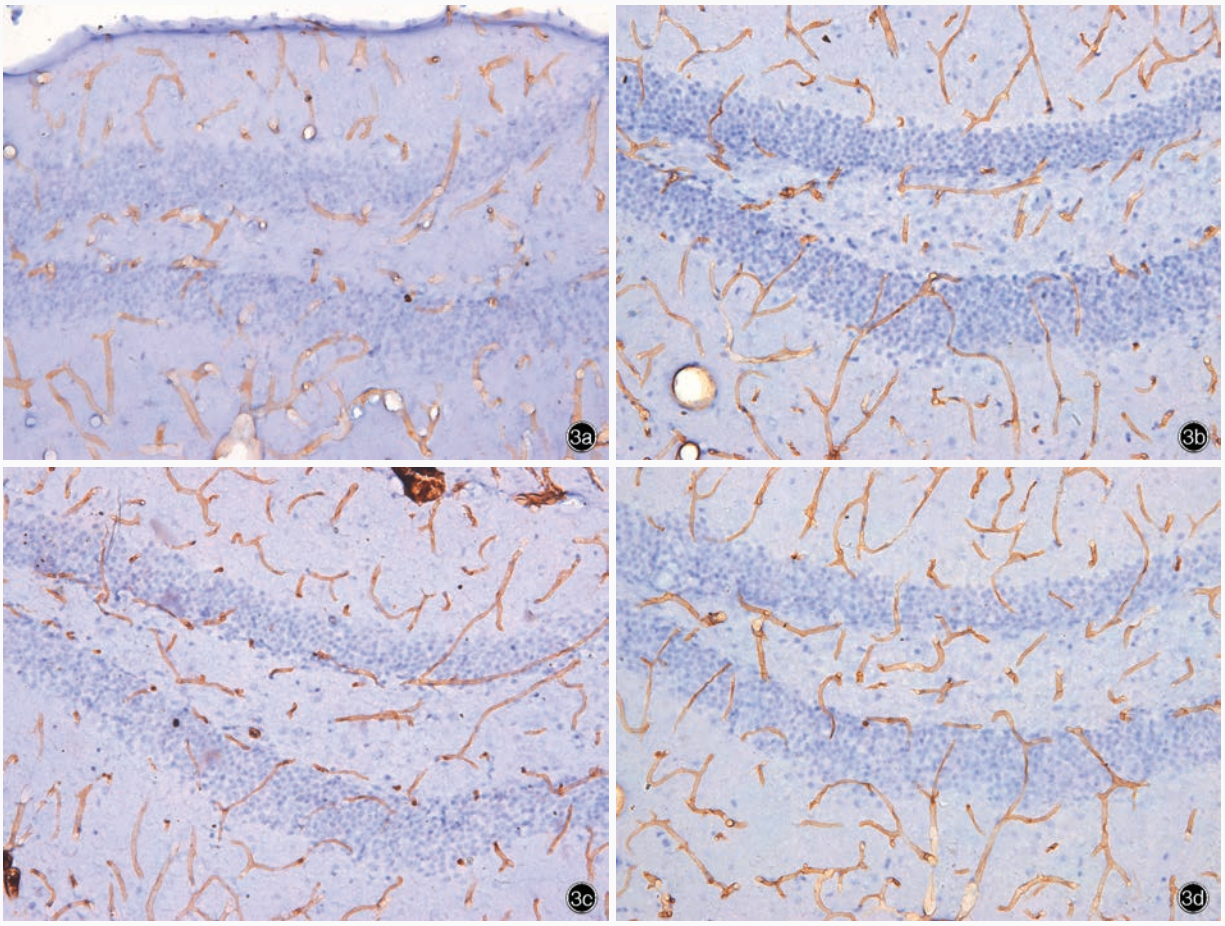

图3 小鼠海马组织光学显微镜观察所见 免疫组织化学染色(ABC三步法) ×200 3a 正常对照组小鼠海马门区微血管走行整齐,且多与海马长轴平行 3b 癫痫持续状态第7天时,小鼠海马门区微血管排列稍显紊乱、少量微血管横穿颗粒细胞层 3c 癫痫持续状态第14天时,小鼠海马门区微血管排列明显紊乱、分支增多,且横穿颗粒细胞层的微血管增多 3d 癫痫持续状态第28天时,小鼠海马门区微血管多呈碎片状,微血管与颗粒细胞下层排列松散

Figure 3 Optical microscopy findings. Immumohistochemical staining (ABC) ×200 Capillaries of hippocampal hilus in normal control group ran regularly and were mainly parallel to the long axis of hippocampus (Panel 3a). On the 7th day of SE, the distribution of capillaries of hippocampal hilus was mildly irregular, and a few capillaries traversed the granular cell layer (Panel 3b). On the 14th day of SE, the distribution of capillaries of hippocampal hilus was obviously irregular with increased branches, and more capillaries traversed the granular cell layer (Panel 3c). On the 28th day of SE, capillaries of hippocampal hilus were fractional, the arrangement of capillaries and lower granular cell layer was loose (Panel 3d).

至细胞内导致神经受体功能失活[36-37];齿状回-颗粒细胞突触后$GABA_AR$微抑制性突触后电流(mIPSCs)波幅下降[37],而兴奋性谷氨酸受体[包括NMDAR和α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体(AMPAR)]在突触膜表面数目增加,同时亦伴随NMDA微兴奋性突触后电流(mEPSCs)和NMDA相关紧张性电流增加[38]。抑制性/兴奋性神经递质及其受体网络失衡是癫痫持续状态发生机制之一,其中$GABA_A$与苯二氮䓬类药物疗效有关,$GABA_AR$功能受到抑制可以导致苯二氮䓬类药物结合GABA的能力或抗癫痫作用降低,癫痫持续状态时间越长,$GABA_A$相关性苯二氮䓬类药物抵抗作用越强[36]。癫痫持续状态发作数分钟或数小时,脑组织病生理改变主要表现为神经肽表达异常,包括兴奋性神经递质中的P物质、神经激肽B和速激肽(tachykinins)表达水平升高,抑制性神经肽Y、生长激素抑制素(somatostatin)、甘丙肽(galanin)和强啡肽(dynorphin)表达水平下降[39],大脑处于高兴奋性状态。癫痫持续状态发生数日或数周时,则可引起脑内多种基因突变和表观遗传学改变。虽然大量动物实验研究显示癫痫持续状态与细胞存活、突触可塑性、神经递质释放等多种基因突变有关,然而遗憾的是,至今尚未明确导致成人癫痫持续状态首发的基因[40]。目前的分子病理学机制研究更关注表

观遗传学在癫痫持续状态中的作用。Miller-Delaney等[41]采用全基因组DNA甲基化方法对模型小鼠进行分子学研究，其结果显示，癫痫持续状态小鼠海马组织有321个基因发生甲基化，约90%基因启动子呈现低甲基化。我们科研小组的前期研究也发现，氯化锂-匹罗卡品致痫大鼠于癫痫持续状态24小时海马组织有19种微小RNA表达水平升高、7种降低，通过生物信息学方法对表达下调的微小RNA参与有丝分裂原激活蛋白激酶（MAPK）通路和长时程通路调节，以及神经细胞死亡和炎症反应过程的变化进行检测，结果显示，miR-34a与癫痫持续状态致神经元坏死和凋亡相关[42-43]。目前，在癫痫持续状态过程中与炎症反应、发育和神经元死亡等相关的多种微小RNA被确定，表明微小RNA在癫痫持续状态过程中可能起关键性调节作用。根据微小RNA具有生物学稳定性良好、携带信息量大和存在于体液中等生物学特性，推测将来可以作为预测癫痫持续状态的生物学标志物[44]。

三、结语

近年来，随着对多种癫痫持续状态动物模型的研究，发现癫痫持续状态引起的多种病理改变均与脑损伤密切相关。然而，迄今对于单次癫痫发作如何进展为癫痫持续状态、如何转化为难治性癫痫持续状态的病理改变及其具体机制和相关表观遗传学改变仍未阐明，动物模型研究成果亦未通过临床试验的验证。因此，对癫痫持续状态今后的研究方向和关注热点，仍以病理学及分子病理学机制研究作为重点，争取早日指导临床治疗。

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