·专题综述·

大脑皮质下结构与癫痫

张琼 冯莉

【摘要】 随着神经电生理学、神经影像学等技术的快速发展，已有大量证据显示癫痫的发生发展与皮质-皮质下神经网络密切相关。本文拟就丘脑、下丘脑、小脑、基底节、脑干等皮质下结构参与癫痫发生发展的相关研究，以及目前神经调控治疗耐药性癫痫所针对的重要皮质下神经核团靶点进行综述，以为发掘癫痫治疗新靶点提供帮助。

【关键词】 癫痫； 大脑皮质； 神经网； 电刺激疗法； 综述

Subcortical structures and epilepsy

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【**Abstract**】 With the rapid development of neuroelectrophysiology, neuroimaging and other technologies, a large amount of evidence has shown the occurrence and development of epilepsy was closely related to cortico-subcortical neural network. This paper aims to review the relevant studies on the involvement of subcortical structures such as thalamus, hypothalamus, cerebellum, basal ganglia and brainstem in the occurrence and development of epilepsy, as well as some important targets of subcortical nucleus for the treatment of drug-resistant epilepsy (DRE) by neuroregulation, in order to provide help for the exploration of new intervention targets for epilepsy treatment.

【**Key words**】 Epilepsy; Cerebral cortex; Nerve net; Electric stimulation therapy; Review

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19世纪末，英国神经病学家Hughlings Jackson教授提出，大脑皮质神经元异常放电是导致癫痫发作的主要原因[1]。此后很长一段时间，癫痫起源于大脑皮质的观点被广泛接受。直至20世纪50年代，加拿大Penfield和Jasper教授在其有关中枢脑理论的研究中提出丘脑和脑干也可能是癫痫发作起源时，方引起对大脑皮质下结构的关注[2]。随后部分动物实验进一步验证了皮质下结构对皮质神经元电活动及痫样放电的影响[2]，由于缺乏基于癫痫患者的直接临床证据，皮质下结构致痫的观点目前仍存争议。近年来，越来越多的研究表明，癫痫是一种脑网络疾病，大脑皮质及皮质下结构均参与其发生发展[3-7]。为更好地理解皮质下结构在癫痫发病机制中的作用，本文将重点阐述丘脑、下丘脑、小脑、基底节、脑干等皮质下结构与癫痫的关系，为探究癫痫治疗的新靶点提供研究方向。

一、丘脑

丘脑是间脑中最大的卵圆形灰质核团，接受来自基底节、小脑、边缘系统等的神经纤维传入，信息整合后再广泛传递至大脑皮质，因此丘脑在控制新皮质信息交流方面作用显著。丘脑前核和中央核通过非特异性丘脑-皮质回路维持皮质兴奋性[8]。同时，该回路还有助于维持不同脑区之间皮质连接的稳定性[9-11]。最新研究认为，丘脑可能参与不同

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丘脑-皮质网络的组成并司职不同功能。一项基于立体定向脑电图(SEEG)的研究发现,丘脑结构异常可能与约86%的局灶性痫样放电的扩散和泛化有关,痫样放电扩散至丘脑可能是局灶性癫痫网络扩展和癫痫外科手术预后不良的电生理学指标[12-13]。He等[14]认为,颞叶致痫灶切除手术预后欠佳者的丘脑功能连接更强,提示耐药性癫痫若合并丘脑结构与功能异常则预后不良。基于SPECT对癫痫发作期-发作间期成像的分析显示,颞叶癫痫发作时,脑深部核团以内侧丘脑最先受累,即该部位最先出现异常放电[1]。针对儿童局灶性癫痫网络的影像学研究显示,颞叶癫痫患儿致痫灶同侧的丘脑前核和丘脑外侧背核之间功能连接增强[15]。一项关于结构MRI的研究表明,颞叶癫痫患者致痫灶对侧海马及双侧丘脑体积缩小,且同侧丘脑萎缩程度与海马硬化程度呈正相关($r=0.680$,$P<0.001$)[16]。提示丘脑在局灶性发作过程中发挥重要作用,亦为研究海马与丘脑的相互关联机制提供新的思路。而对于部分额叶癫痫患者而言,虽然丘脑在病程中受累较晚,滞后于皮质,但其可能参与对痫样放电的调控并维持癫痫后期的电活动[17-18]。

丘脑-皮质回路在全面性发作中的作用也是不可或缺的[19]。特发性全面性癫痫(IGE)是以失神发作、肌阵挛发作和全面性强直-阵挛发作(GTCS)等为主要表现,可单独或以不同组合形式出现的全面性癫痫综合征。特发性全面性癫痫的动物实验及临床数据均提示丘脑可能参与癫痫起源。大鼠失神癫痫模型证实,丘脑-皮质回路受累是产生失神癫痫特征性棘慢复合波的原因[20]。针对特发性全面性癫痫的fMRI研究发现,丘脑-皮质回路存在广泛性激活和功能连接增强[20]。进一步的MRS分析证实,特发性全面性癫痫患者丘脑神经元存在代谢障碍,主要表现为丘脑N-乙酰天冬氨酸(NAA)/肌酸(Cr)比值下降,谷氨酸和谷氨酰胺水平升高[21-23]。针对青少年肌阵挛癫痫(JME)的头皮脑电图和体感诱发电位(SEP)监测研究表明,丘脑和皮质神经元兴奋性均明显增高[24-25]。上述研究结果提示,特发性全面性癫痫患者存在明确的丘脑-皮质回路异常,而这即可能是神经元痫样放电并快速泛化的结构与功能基础。

基于丘脑在局灶性和全面性癫痫发生发展中的作用,近年来,研究者开始尝试将丘脑作为神经调控治疗耐药性癫痫的潜在靶点[26-30]。迷走神经刺激术(VNS)通过增强双侧丘脑与双侧中央前回之间的功能连接,改善丘脑-皮质回路功能继而抑制癫痫发作及其扩散[31]。静息态fMRI(rs-fMRI)研究显示,迷走神经刺激术治疗有效的耐药性癫痫患者其丘脑与前扣带回、岛叶皮质之间的功能连接更强[32]。对癫痫模型大鼠进行的迷走神经刺激实验证实,电刺激可以显著增加大鼠丘脑、下丘脑、海马以及杏仁核等脑区血流量[31]。此外,丘脑也是癫痫患者脑深部电刺激术(DBS)和经颅磁刺激(TMS)的重要靶点[31,33-36],目前已有较多的证据证实,丘脑前核深部电刺激术可有效减少局灶性发作频率及发作强度,而电刺激丘脑正中核则是更适用于全面性癫痫的神经调控治疗[26-27,37]。

二、下丘脑

下丘脑位于丘脑沟以下,构成第三脑室下部的侧壁和底部,主要包括乳头体、结节部和视上部,是边缘系统、网状结构的重要联络点。目前,下丘脑参与癫痫发作过程的证据主要见于下丘脑错构瘤(HH)致癫痫,其中痴笑性发作是最具特征性的癫痫发作类型[2],患者通常表现为发作性发笑,持续数秒或数十秒后突然停止,发作时无神志丧失,每天可发作数十次,主要于婴幼儿期发病[2]。随着年龄的增长,痴笑性发作可能更加频繁,也可继发双侧强直-阵挛发作,甚至可伴认知功能障碍或性早熟。下丘脑错构瘤致癫痫是皮质下结构参与癫痫的最直接证据[1],脑电图提示大多数患者痫样放电来源于额颞叶,但是切除致痫灶后却并未取得预期疗效,仍时有发作,提示痫样放电可能来源于更深部的脑组织[2]。通过立体定向脑电图记录下丘脑错构瘤患者痴笑性发作之过程,可见在发作起始时肿瘤内组织即出现低波幅快波活动[38],即脑深部下丘脑错构瘤可诱发痫性脑电波,成为痫样放电的起源,证明脑深部皮质下结构发生病理改变后也可致痫。对下丘脑错构瘤致癫痫患者进行的SPECT显像表明,发作期患者肿瘤区域呈持续性高灌注[39],进一步证明下丘脑错构瘤参与此类癫痫发作过程。电刺激下丘脑错构瘤可诱发痴笑性发作,手术切除肿瘤或立体定向射频毁损术可以减少发作甚至实现无发作[26]。进一步验证下丘脑错构瘤本身即可能为痫样放电的起源,直接参与癫痫发作过程。但下丘脑错构瘤的体积与癫痫发作严重程度是否存在相关性目前仍未确定,尚待进一步探索。

目前,已有研究通过立体定向脑电图电极在下

丘脑错构瘤患者的乳头体-丘脑束层面记录到痫样放电，提示下丘脑后部也可能是脑深部电刺激术治疗下丘脑错构瘤致癫痫的潜在干预靶点[40]。也有研究尝试将乳头体-丘脑束作为刺激靶点用于治疗下丘脑痴笑性癫痫的案例，术后癫痫发作频率和严重程度均得到不同程度改善[41]，但尚待积累更多临床病例以证实其有效性和安全性。

三、小脑

早在20世纪30年代，即有学者认为小脑与癫痫的发生发展无直接关联性，但经过一个世纪的研究与探索，越来越多的证据提示小脑在癫痫的发生发展过程中扮演重要角色。研究发现，局灶性和全面性癫痫患者常伴小脑萎缩和小脑局部神经功能改变[42-45]。基于颞叶癫痫的SPECT研究显示，癫痫发作时小脑灌注明显增加，小脑神经元呈同步异常放电，且与海马神经元放电呈锁时关系，提示小脑是颞叶癫痫痫样放电扩散、泛化和功能受累的重要皮质下结构[1-2]。根据一项个案报道，颅内深部电极在1例左侧小脑胶质瘤合并癫痫患儿的肿瘤组织内监测到发作间期典型局灶性放电，手术切除肿瘤后随访4个月，未再出现癫痫发作[1]，提示小脑也可能是痫样放电的起源脑区。

针对小脑潜在致痫能力的探索起始于20世纪70年代，尝试以小脑作为刺激靶点的脑深部电刺激术[41]，结果显示，超过50%的癫痫患者经小脑深部电刺激术治疗后发作频率可减少50%以上[46]。此外，最近在颞叶癫痫模型小鼠实验中证实，采用闭环光遗传技术对小脑深部特异性神经回路进行干预可有效缩短电刺激诱导的海马痫样放电持续时间，并可减少癫痫发作频率[47]。基于上述研究结果，预测以小脑作为神经调控干预靶点可能在不久的将来成为癫痫外科手术的新选择。

四、基底节

基底节位于脑白质深部，主要由尾状核、豆状核（壳核和苍白球）、屏状核，以及杏仁核、红核、黑质和丘脑底核等神经核团组成，接收来自大脑新皮质、丘脑、海马等神经纤维的传入，同时也传出神经纤维投射至丘脑、脑干等，在运动控制和认知功能维持中发挥重要作用[48]。传统观点认为，基底节病变不会导致癫痫，但越来越多的研究发现基底节可能在癫痫的发生、痫样放电的扩散和泛化中起重要作用。

基于立体定向脑电图研究显示，局灶性发作时皮质-纹状体的脑电同步可能是癫痫发作终止的电生理学机制[12]。颞叶癫痫发作过程中出现的发作性姿势异常、旋转性发作和发作性肌张力障碍可能是致痫灶同侧痫样放电扩散、泛化至基底节所致[2]。SPECT研究显示，颞叶癫痫发作期患者致痫灶同侧壳核灌注增加时可伴对侧肢体肌张力障碍[1]。Pizzo等[12]应用视觉分析和信号定量方法[致痫性指数（EI）]对局灶性癫痫患者发作期立体定向脑电图数据进行分析，其根据基底节尾状核和壳核记录到的高致痫性指数推测尾状核和壳核可能参与局灶性痫样放电的扩散与泛化。基于神经药理学、神经电生理学和功能神经影像学的研究证据，基底节亦是局灶性耐药性癫痫的易受累脑区[49]。对癫痫患儿的MRI研究显示，内侧颞叶癫痫（mTLE）可合并杏仁核体积增大[50]；而在特发性全面性癫痫患者的结构成像中也观察到左侧丘脑、壳核及双侧苍白球萎缩现象[12]。这些研究均为基底节参与癫痫的发生和扩散提供证据。

已有研究显示，低频（4～8 Hz）电刺激尾状核可有效抑制来源于双侧海马和杏仁核的痫样放电，但高频（30～100 Hz）电刺激则产生促进癫痫网络扩散和泛化的作用[41]。Chkhenkeli等[51]尝试应用低频（4～8 Hz）电刺激纹状体治疗30例耐药性颞叶癫痫患者，其中21例（70%）达到完全无发作。由此可见，基底节在耐药性癫痫的神经调控治疗中具有潜在的应用前景，但目前以基底节作为刺激靶点的脑深部电刺激术的相关研究较少，因此暂未成为耐药性癫痫常用神经调控靶点[43,48]。

五、脑干

各种皮质下结构与癫痫的相关研究中，脑干是关注相对较少的脑区，脑干在癫痫中的作用及其所扮演的角色尚未得到充分认识[2,52]。SPECT研究显示，局灶性癫痫患者脑干被盖上部灌注明显增加[1]；PET研究发现，纳入的44例婴儿痉挛症（IS）患儿中21例（47.73%）存在脑干代谢增加[53]；对10例婴儿痉挛症患儿的MRI研究表明，6例（6/10）存在脑干听觉诱发电位（BAEP）异常如V波振幅降低、V波峰潜伏期延长等，且存在脑干萎缩[1]。一项基于尸检的婴儿痉挛症免疫组化研究显示，患儿痉挛发作越少，其脑干儿茶酚胺神经元数目也相应减少[2]。以上研究提示，脑干参与局灶性或全面性癫痫的发生与发展。对全面性癫痫患者同步脑电和脑干听觉诱发电位的监测发现，脑干腹侧听觉诱发电位的

wave-Ⅲ波在头皮多棘慢复合波出现前即已呈现双相波动，提示脑干腹侧可能通过网状上行激活系统影响皮质兴奋性，进而介导癫痫发生[54]。针对癫痫猝死(SUDEP)患者的结构成像研究发现，此类患者在皮质广泛变薄的同时还常合并脑干或小脑萎缩，提示脑干可能参与癫痫猝死的发生，进一步证实脑干对癫痫的发生发展存在重要影响[55-56]。

综上所述，随着神经影像学、神经电生理学等新型诊断技术的发展和应用，对大脑皮质下结构参与癫痫病因学机制的认知不断深入；皮质-皮质下神经网络紊乱是癫痫产生、扩散、泛化主要原因的观点被广泛了解并接受。针对广泛皮质下神经核团进行脑深部电刺激术可能是耐药性癫痫神经调控治疗颇具前景的治疗手段，期待未来能结合多模态神经影像学和大脑深部电生理学等技术更好地了解大脑皮质下结构和功能在癫痫发生发展中的作用，不断发掘癫痫治疗新靶点。

利益冲突 无

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