Advances in Clinical Medicine 临床医学进展, 2023, 13(12), 19265-19270
Published Online December 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13122712

Hans汉斯

脑肿瘤相关癫痫发病机制的研究进展

焦　菲[1]，祝增金[2]，王兰桂[3*]

[1]青海大学研究生院，青海　西宁
[2]海东市第二人民医院，青海　海东
[3]青海大学附属医院神经内科，青海　西宁

收稿日期：2023年11月18日；录用日期：2023年12月12日；发布日期：2023年12月18日

摘　要

痫性发作是脑肿瘤患者最常见的症状。脑肿瘤和癫痫之间有着共同的遗传、分子和细胞学机制。脑肿瘤相关癫痫的发病机制可能与神经元兴奋性传递增强、抑制性传递受损、丝氨酸/苏氨酸激酶(B-Raf proto-oncogene, serine/threonine kinase, BRAF)、异柠檬酸脱氢酶(Isocitrate Dehydrogenase, IDH)和磷脂酰肌醇3-激酶(Phosphatidylinositol 3-kinase, PIK3CA)的遗传突变、炎症、血液动力学损伤和星形胶质细胞功能障碍有关。本文旨在阐述脑肿瘤相关癫痫的发病机制以期发现新的靶点研究新的抗癫痫药。

关键词

脑肿瘤，癫痫，发病机制

Research Progress on the Pathogenesis of Brain Tumor Related Epilepsy

Fei Jiao[1], Zengjin Zhu[2], Langui Wang[3*]

[1]Graduate School of Qinghai University, Xining Qinghai
[2]Haidong Second People's Hospital, Haidong Qinghai
[3]Department of Neurology, Affiliated Hospital of Qinghai University, Xining Qinghai

Received: Nov. 18th, 2023; accepted: Dec. 12th, 2023; published: Dec. 18th, 2023

Abstract

Epileptic seizures are the most common symptom in patients with brain tumors. There is a common genetic, molecular, and cellular mechanism between brain tumors and epilepsy. The pathogenesis of brain tumor related epilepsy may be related to increased neuronal excitatory transmis-

*通讯作者。

文章引用: 焦菲, 祝增金, 王兰桂. 脑肿瘤相关癫痫发病机制的研究进展[J]. 临床医学进展, 2023, 13(12): 19265-19270.
DOI: 10.12677/acm.2023.13122712

sion, impaired inhibitory transmission, genetic mutations in serine/threonine kinase and phosphatidylinositol 3-kinase, inflammation, hemodynamic damage, and astrocyte dysfunction. This article aims to elucidate the pathogenesis of brain tumor related epilepsy, with the aim of discovering new targets and researching new anti epileptic drugs.

Keywords

Brain Tumor, Epilepsy, Pathogenesis

1. 引言

癫痫是大脑神经元异常放电，导致短暂性的大脑神经功能障碍的一种慢性疾病。年发病率为28.8/100,000，人群总体患病率为7/1000，我国现约有900万左右癫痫患者，因此癫痫已经成为神经科仅次于头痛的第二大常见病[1]。自19世纪以来脑肿瘤和癫痫之间的关系就被发现[2]。癫痫发作是脑肿瘤患者最常见的症状。无论病变的解剖部位和肿瘤的组织学类型如何，癫痫患者的脑肿瘤发生率在4%~10%之间，脑肿瘤中癫痫的发生率在35%~70%之间。脑肿瘤相关癫痫(Brain tumor related epilepsy, BTRE)占继发性癫痫的12%，占所有癫痫病例的4%~10% [3] [4]。导致肿瘤发生和癫痫发生的潜在机制尚不能完全阐明。研究[5]表明肿瘤发生和癫痫发生之间的共同遗传、分子和细胞机制就像一枚硬币的正反面，其中包括神经元兴奋性传递增强、抑制性传递受损、BRAF、IDH和PIK3CA基因的遗传突变、炎症、血液动力学损伤和星形胶质细胞功能障碍[6] [7]。抗癫痫药物和肿瘤药物之间也存在这相互的影响，参与脑肿瘤相关癫痫发病机制[6] [8] [9]。下面就以上机制做一综述。

2. 神经元兴奋性传递增强

神经元兴奋性的增强在胶质母细胞瘤的增殖和进展中起着重要作用，因为突触和神经回路的电兴奋整合促进了胶质瘤的进展。神经胶质瘤和神经元之间的通信可以通过神经胶质瘤突触进行，该突触可以诱导由氨甲基磷酸亚型谷氨酸受体介导的突触后电位[10] [11]。此外，氨甲基磷酸的拮抗剂可以延缓肿瘤生长和侵袭[10] [12]。胶质瘤释放的谷氨酸会诱导肿瘤周围网络的超兴奋性。这种机制是由钠依赖性谷氨酸摄取不足、神经胶质谷氨酸转运蛋白减少以及胱氨酸/谷氨酸转运体系统(cystine/glutamate transporter, Xc-系统)介导的。Xc-系统是氨基酸转运体家族中的重要亚型。Xc-系统由轻链溶质载体家族成员7A11和重链溶质载体家族成员3A2两种蛋白质组成[13]。研究表明，轻链溶质载体家族成员7A11可作为转录激活因子4的靶标，在人胶质母细胞瘤细胞U87和U251中，过表达转录激活因子4通过增加溶质载体家族成员7A11的表达，抑制肿瘤细胞发生铁死亡，促进血管生成，促进胶质母细胞瘤的增殖[14] [15]。另有研究证实，通过敲低胶质母细胞瘤细胞的溶质载体家族成员7A11表达，或采用Nutlin-3活性对应体释放出p53负性调节溶质载体家族成员7A11，细胞中脂氧合酶的活性增加，促进胶质母细胞瘤铁死亡，抑制小鼠原位肿瘤的生长和迁移[16]。该系统还可将细胞外胱氨酸交换为细胞内谷氨酸。Xc-系统的阻断剂可减少自发和诱发的神经电活动，因此显示出潜在的抗肿瘤和抗癫痫作用[17] [18]。神经元活动还引起非突触活动依赖性钾电流，通过间隙连接介导的肿瘤级联放大，形成电耦合网络。神经元电活动包括癫痫

发作，在神经胶质瘤网络中产生同步的钙瞬变。生长因子的活性调节释放也促进神经胶质瘤的生长[10] [11]。

3. 抑制性传递受损

除了增强兴奋性传递外，神经抑制受损也可能导致神经网络过度兴奋。神经元抑制性传递受损可导致 γ-氨基丁酸去极化，而不是超极化，这种活性是由神经元氯离子协同转运蛋白 2 和 Na-K-2Cl 协同转运蛋白 1 的表达变化引起的氯化物稳态紊乱所致[19]。最近提出的另一种机制是，由于肿瘤释放的蛋白水解酶降解神经网络，导致肿瘤周围抑制性中间神经元的活性降低或丧失[20]。

4. BRAF、IDH 和 PIK3CA 基因的遗传突变

4.1. BRAF

BRAF 是一种人类基因，编码 B-Raf 蛋白。B-Raf 蛋白参与细胞内部发送信号，从而指导细胞生长。B-Raf 是一种 766 个氨基酸的调节信号转导丝氨酸/苏氨酸特异性蛋白激酶。BRAF 基因已被证明具有肿瘤和癫痫诱导特征。在小鼠模型中，大脑早期发育过程中神经干胞中出现的 BRAFV600E 体细胞突变导致神经元细胞具有致痫特性，神经胶质细胞具有致瘤特性。BRAFV600E 刺激 RE1 沉默转录因子的表达，已知该因子通过抑制编码离子通道、受体的基因和其他基因亚群来促进癫痫发生[21]。另一项研究证实，BRAFV600E 在神经祖细胞中的表达导致高度兴奋的神经元表型和炎症免疫反应增加[22]。

4.2. 异柠檬酸脱氢酶

异柠檬酸脱氢酶 1 (Isocitrate dehydrogenase 1, IDH1)和异柠檬酸脱氢酶 2 (Isocitrate dehydrogenase, IDH2)基因的突变通常在星形细胞瘤、少突胶质瘤和胶质母细胞瘤中更显著[23]。在 IDH 突变型胶质瘤中，PI3K/AKT/mTOR 信号转导与较短的无进展生存期(PFS)有关[24]。IDH 突变与更高的术前癫痫发作发生率和更严重的术后癫痫发生率相关[25]。导致这种结果的原因可能是这些突变导致肿瘤的中间体 D-2-羟基戊二酸(D-2-hydroxyglutaric acid, D2-HG)增加[26]。D2-HG 在结构上类似于谷氨酸，并且已知通过激活谷氨酸受体，特别是 N-甲基-d-天冬氨酸受体来模拟其活性。D2-HG 可破坏细胞内钙稳态，抑制线粒体呼吸链，引发活性氧的产生，并增加神经元的放电速率，导致兴奋性细胞损伤和神经退行性变[26]。最近的数据表明，D2-HG 对 mTOR 通路的过度激活是 IDH 突变神经胶质瘤患者癫痫发生的潜在机制，在不同条件下，这种信号通路可以触发神经元死亡和癫痫发生的相反作用(即神经保护和抗癫痫与致痫) [27] [28]。

4.3. PIK3CA

PIK3CA 突变在胶质细胞瘤中也很常见。由磷脂酰肌醇 3-激酶突变导致的肿瘤具有不同的分子特性，导致癫痫发生的两个主要原因是选择性使神经元超极化和突触重塑。这些变化可能是 PIK3CA 阳性肿瘤中选择性表达的糖蛋白(GPC)家族分泌成员所致。特别是在 GPC 家族中，已发现 GPC3 可驱动胶质瘤形成和引起细胞超级化[29]。

5. 炎症、血流动力学损伤

5.1. 炎症

炎症也在脑肿瘤相关癫痫的病理生理学中发挥作用。神经胶质瘤中先天免疫系统和适应性免疫系统都有显著的激活[30]。星形胶质细胞和小胶质细胞介导的炎症可以促进癫痫发生和癫痫复发，随后的癫痫

发作会使神经炎症持续存在，尤其是当内源性抗炎机制失败时[31]。促炎细胞因子如白介素-1 和趋化因子具有神经调节特性；在过量生产时，它们可以诱导肿瘤周围网络的超极化兴奋，通过改变电压门控(Na^+, K^+, Ca^{2+})和受体偶联离子通道(NMDA、AMPA 和 GABA 受体)的功能来降低癫痫发作阈值[32] [33] [34]。

5.2. 血流动力学

神经胶质瘤还会损伤正常的血流动力学。在胶质瘤浸润的皮质区域，神经－血管耦合逐渐被破坏。虽然癫痫发作在未浸润的皮层表现出正的神经血管耦合，但神经胶质瘤浸润区域表现出血流动力学反应紊乱，导致癫痫发作引起缺氧[35]。

6. 星形胶质细胞功能障碍

尽管星形胶质细胞的研究不如神经元，但它可以成为恶性细胞并导致癫痫。在抑制性神经元中星形胶质细胞的功能受损时可导致钾稳态丧失，水通道蛋白、缝隙连接的功能发生改变。星形胶质细胞受损时对谷氨酸的摄取减少，神经递质供应中断[32]。这些变化还可引起神经细胞过度兴奋，导致癫痫的发生[36]。在星形细胞性脑肿瘤中，腺苷激酶在肿瘤周围浸润组织中高表达。腺苷激酶的过度表达降低了细胞外腺苷，从而导致癫痫发作。肿瘤伴癫痫患者周围浸润组织中腺苷激酶的表达明显高于非癫痫患者。星形胶质细胞功能障碍导致癫痫发生的另一原因可能与星形胶质细胞周围活性氧和铁水平的增加有关。活性氧和铁水平的增加会促使星形胶质细胞产生促炎因子。这种促炎因子可能有助于上述促癫痫的炎症过程[37]。

综上，本文主要介绍了脑肿瘤相关癫痫的发病机制，主要为神经元兴奋性传递增强、抑制性传递受损、BRAF、IDH 和 PIK3CA 基因的遗传突变、炎症、血液动力学损伤和星形胶质细胞功能障碍等，分别从分子、遗传和神经电生理方面做了解释。目前抗癫痫药物主要是一些离子通道的阻断剂，对于上述作用机制的研究尚不足，了解癫痫的发病机制不仅能对癫痫治疗的整体方向提供全新思路，还能为新药的研发提供思路，为癫痫患者带来福音。

参考文献

[1] Falco-Walter, J. (2020) Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. *Seminars in Neurology*, **40**, 617-623. https://doi.org/10.1055/s-0040-1718719

[2] Van Gijn, J. (2011) Localised Convulsions from Tumour of the Brain by 1882-1886. *Brain*: *A Journal of Neurology*, **10**, 2795-2797. https://doi.org/10.1093/brain/awr241

[3] Seidel, S., Wehner, T., Miller, D., *et al*. (2022) Brain Tumor Related Epilepsy: Pathophysiological Approaches and Rational Management of Antiseizure Medication. *Neurological Research and Practice*, **4**, Article No. 45. https://doi.org/10.1186/s42466-022-00205-9

[4] Van Breemen, M.S., Wilms, E.B. and Vecht, C.J. (2007) Epilepsy in Patients with Brain Tumours: Epidemiology, Mechanisms, and Management. *The Lancet Neurology*, **6**, 421-430. https://doi.org/10.1016/S1474-4422(07)70103-5

[5] Aronica, E., Ciusani, E., Coppola, A., *et al*. (2023) Epilepsy and Brain Tumors: Two Sides of the Same Coin. *Journal of the Neurological Sciences*, **446**, Article ID: 120584. https://doi.org/10.1016/j.jns.2023.120584

[6] Slegers, R.J. and Blumcke, I. (2020) Low-Grade Developmental and Epilepsy Associated Brain Tumors: A Critical Update 2020. *Acta Neuropathologica Communications*, **8**, Article No. 27. https://doi.org/10.1186/s40478-020-00904-x

[7] De Groot, M., Reijneveld, J.C., Aronica, E., *et al*. (2012) Epilepsy in Patients with a Brain Tumour: Focal Epilepsy Requires Focused Treatment. *Brain*: *A Journal of Neurology*, **135**, 1002-1016. https://doi.org/10.1093/brain/awr310

[8] Siegelin, M.D., Schneider, E., Westhoff, M.A., *et al*. (2021) Current State and Future Perspective of Drug Repurposing in Malignant Glioma. *Seminars in Cancer Biology*, **68**, 92-104. https://doi.org/10.1016/j.semcancer.2019.10.018

[9] Stritzelberger, J., Lang, J.D., Mueller, T.M., *et al*. (2021) Anti-Seizure Medication Is Not Associated with an Increased Risk to Develop Cancer in Epilepsy Patients. *Journal of Neurology*, **268**, 2185-2191. https://doi.org/10.1007/s00415-020-10379-4

[10] Venkataramani, V., Tanev, D.I., Strahle, C., *et al*. (2019) Glutamatergic Synaptic Input to Glioma Cells Drives Brain Tumour Progression. *Nature*, **573**, 532-538. https://doi.org/10.1038/s41586-019-1564-x

[11] Venkatesh, H.S., Morishita, W., Geraghty, A.C., *et al*. (2019) Electrical and Synaptic Integration of Glioma into Neural Circuits. *Nature*, **573**, 539-545. https://doi.org/10.1038/s41586-019-1563-y

[12] Lange, F., Weßlau, K., Porath, K., *et al*. (2019) AMPA Receptor Antagonist Perampanel Affects Glioblastoma Cell Growth and Glutamate Release *in Vitro*. *PLOS ONE*, **14**, e0211644. https://doi.org/10.1371/journal.pone.0211644

[13] Lin, W., Wang, C., Liu, G., *et al*. (2020) SLC7A11/xCT in Cancer: Biological Functions and Therapeutic Implications. *American Journal of Cancer Research*, **10**, 3106-3126.

[14] Polewski, M.D., Reveron-Thornton, R.F., Cherryholmes, G.A., *et al*. (2017) SLC7A11 Overexpression in Glioblastoma Is Associated with Increased Cancer Stem Cell-Like Properties. *Stem Cells and Development*, **26**, 1236-1246. https://doi.org/10.1089/scd.2017.0123

[15] Polewski, M.D., Reveron-Thornton, R.F., Cherryholmes, G.A., *et al*. (2016) Increased Expression of System xc- in Glioblastoma Confers an Altered Metabolic State and Temozolomide Resistance. *Molecular Cancer Research*: *MCR*, **14**, 1229-1242. https://doi.org/10.1158/1541-7786.MCR-16-0028

[16] Yang, X., Liu, J., Wang, C., *et al*. (2021) miR-18a Promotes Glioblastoma Development by Down-Regulating ALOXE3-Mediated Ferroptotic and Anti-Migration Activities. *Oncogenesis*, **10**, Article No. 15. https://doi.org/10.1038/s41389-021-00304-3

[17] Buckingham, S.C., Campbell, S.L., Haas, B.R., *et al*. (2011) Glutamate Release by Primary Brain Tumors Induces Epileptic Activity. *Nature Medicine*, **17**, 1269-1274. https://doi.org/10.1038/nm.2453

[18] Campbell, S.L., Buckingham, S.C. and Sontheimer, H. (2012) Human Glioma Cells Induce Hyperexcitability in Cortical Networks. *Epilepsia*, **53**, 1360-1370. https://doi.org/10.1111/j.1528-1167.2012.03557.x

[19] Pallud, J., Le Van Quyen, M., Bielle, F., *et al*. (2014) Cortical GABAergic Excitation Contributes to Epileptic Activities around Human Glioma. *Science Translational Medicine*, **6**, 244ra89. https://doi.org/10.1126/scitranslmed.3008065

[20] Tewari, B.P., Chaunsali, L., Campbell, S.L., *et al*. (2018) Perineuronal Nets Decrease Membrane Capacitance of Peritumoral Fast Spiking Interneurons in a Model of Epilepsy. *Nature Communications*, **9**, Article No. 4724. https://doi.org/10.1038/s41467-018-07113-0

[21] Koh, H.Y., Kim, S.H., Jang, J., *et al*. (2018) BRAF Somatic Mutation Contributes to Intrinsic Epileptogenicity in Pediatric Brain Tumors. *Nature Medicine*, **24**, 1662-1668. https://doi.org/10.1038/s41591-018-0172-x

[22] Goz, R.U., Akgül, G. and Loturco, J.J. (2020) BRAFV600E Expression in Neural Progenitors Results in a Hyperexcitable Phenotype in Neocortical Pyramidal Neurons. *Journal of Neurophysiology*, **123**, 2449-2464. https://doi.org/10.1152/jn.00523.2019

[23] Yan, H., Parsons, D.W., Jin, G., *et al*. (2009) IDH1 and IDH2 Mutations in Gliomas. *The New England Journal of Medicine*, **360**, 765-773. https://doi.org/10.1056/NEJMoa0808710

[24] Mohamed, E., Kumar, A., Zhang, Y., *et al*. (2022) PI3K/AKT/mTOR Signaling Pathway Activity in IDH-Mutant Diffuse Glioma and Clinical Implications. *Neuro-Oncology*, **24**, 1471-1481. https://doi.org/10.1093/neuonc/noac064

[25] Neal, A., Kwan, P., O'brien, T.J., *et al*. (2018) IDH1 and IDH2 Mutations in Postoperative Diffuse Glioma-Associated Epilepsy. *Epilepsy & Behavior*: *E&B*, **78**, 30-36. https://doi.org/10.1016/j.yebeh.2017.10.027

[26] Li, X., Strasser, B., Jafari-Khouzani, K., *et al*. (2020) Super-Resolution Whole-Brain 3D MR Spectroscopic Imaging for Mapping D-2-Hydroxyglutarate and Tumor Metabolism in Isocitrate Dehydrogenase 1-Mutated Human Gliomas. *Radiology*, **294**, 589-597. https://doi.org/10.1148/radiol.2020191529

[27] Mortazavi, A., Fayed, I., Bachani, M., *et al*. (2022) IDH-Mutated Gliomas Promote Epileptogenesis through d-2-Hydroxyglutarate-Dependent mTOR Hyperactivation. *Neuro-Oncology*, **24**, 1423-1435. https://doi.org/10.1093/neuonc/noac003

[28] Zeng, L.H., Mcdaniel, S., Rensing, N.R., *et al*. (2010) Regulation of Cell Death and Epileptogenesis by the Mammalian Target of Rapamycin (mTOR): A Double-Edged Sword? *Cell Cycle* (*Georgetown*, *Tex*), **9**, 2281-2285. https://doi.org/10.4161/cc.9.12.11866

[29] Yu, K., Lin, C.J., Hatcher, A., *et al*. (2020) PIK3CA Variants Selectively Initiate Brain Hyperactivity during Gliomagenesis. *Nature*, **578**, 166-171. https://doi.org/10.1038/s41586-020-1952-2

[30] Prabowo, A.S., Iyer, A.M., Anink, J.J., *et al*. (2013) Differential Expression of Major Histocompatibility Complex Class I in Developmental Glioneuronal Lesions. *Journal of Neuroinflammation*, **10**, Article No. 778. https://doi.org/10.1186/1742-2094-10-12

[31] Vezzani, A., Ravizza, T., Bedner, P., *et al*. (2022) Astrocytes in the Initiation and Progression of Epilepsy. *Nature Reviews Neurology*, **18**, 707-722. https://doi.org/10.1038/s41582-022-00727-5

[32] Aronica, E., Ravizza, T., Zurolo, E., *et al*. (2012) Astrocyte Immune Responses in Epilepsy. *Glia*, **60**, 1258-1268. https://doi.org/10.1002/glia.22312

[33] Devinsky, O., Vezzani, A., Najjar, S., *et al*. (2013) Glia and Epilepsy: Excitability and Inflammation. *Trends in Neurosciences*, **36**, 174-184. https://doi.org/10.1016/j.tins.2012.11.008

[34] Vezzani, A., Auvin, S., Ravizza, T., *et al*. (2012) Glia-Neuronal Interactions in Ictogenesis and Epileptogenesis: Role of Inflammatory Mediators. In: Noebels, J.L., Avoli, M., Rogawski, M.A., *et al*., Eds., *Jasper's Basic Mechanisms of the Epilepsies*, National Center for Biotechnology Information (US), Bethesda.

[35] Montgomery, M.K., Kim, S.H., Dovas, A., *et al*. (2020) Glioma-Induced Alterations in Neuronal Activity and Neurovascular Coupling during Disease Progression. *Cell Reports*, **31**, Article ID: 107500. https://doi.org/10.1016/j.celrep.2020.03.064

[36] Coulter, D.A. and Steinhäuser, C. (2015) Role of Astrocytes in Epilepsy. *Cold Spring Harbor Perspectives in Medicine*, **5**, a022434. https://doi.org/10.1101/cshperspect.a022434

[37] De Groot, M., Iyer, A., Zurolo, E., *et al*. (2012) Overexpression of ADK in Human Astrocytic Tumors and Peritumoral Tissue Is Related to Tumor-Associated Epilepsy. *Epilepsia*, **53**, 58-66. https://doi.org/10.1111/j.1528-1167.2011.03306.x