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The Effect of $GABA_A$ Receptor and Its Treatment of Neonatal Epilepsy

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Abstract

The drug phenobarbital which acts as $GABA_A$ receptor modulator is recently found to have a poor clinical outcome and even a long-term injury to brain. The reason may lie on the excitatory effect of $GABA_A$ receptor in developing brain rather than the inhibitory effect in developed brain. Transporter NKCC1 and KCC2 along with L-type Ca^{2+} channel take part in the generation of the excitatory effect, which indicates a new way of target therapy of neonatal epilepsy.

Keywords

Neonatal Epilepsy, $GABA_A$ Receptor, Treatment, NKCC1

$GABA_A$受体效应与新生儿癫痫治疗

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摘　要

近年来的研究显示苯巴比妥类等针对性作用于$GABA_A$受体的药物在新生儿癫痫治疗中的临床疗效不佳，且可能导致进一步的远期脑损害，原因在于新生脑中$GABA_A$受体表现为兴奋性效应，随着神经系统发育而逐渐转化为成熟脑中的重要抑制性受体。位于神经元细胞膜上的转运蛋白NKCC1、KCC2及L型Ca^{2+}通道共同参与了新生期$GABA_A$受体激活后兴奋性效应的形成。

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关键词

新生儿癫痫，$GABA_A$受体，治疗，NKCC1

1. 背景

癫痫(epilepsy)是一种临床常见的以神经元细胞异常放电导致惊厥(seizures)反复发作为特征的神经系统疾病，是由于脑内兴奋性/抑制性递质失衡、神经网络异常激活所致[1]。文献报道癫痫的发病机制与神经系统的成熟度有关，新生儿期癫痫发病率高于其他各年龄组[2] [3] [4]。然而，新生儿期癫痫反复发作将进一步导致皮层神经网络结构和功能的损害，增加抽搐易感性、影响远期认知发育，并导致远期行为及学习功能异常[5] [6] [7] [8]。此外，新生儿期癫痫同时亦是儿童期难治性癫痫的重要危险因素[9]，故其治疗在临床工作中长期受到重视。

2. $GABA_A$ 能药物在新生儿癫痫治疗中的疗效及远期作用存疑

γ-氨基丁酸(gamma-aminobutyric acid, GABA)是中枢神经系统内主要的抑制性递质之一，通过结合其离子通道型受体$GABA_A$及代谢型受体$GABA_B$在全脑各个区域广泛影响着各种神经生理及病理过程[10]。多年以来，提高 GABA 能的抑制作用是癫痫临床治疗的重要思路，而以 GABA 受体为标靶的临床药物则广泛应用于癫痫的治疗。这其中最重要的莫过于以经典抗癫痫药物苯巴比妥类及苯二氮卓类、神经类固醇类等作用于 $GABA_A$ 受体复合物的药物[10] [11]。特别是苯巴比妥及苯妥英，长期被 WHO 推荐为成人、儿童及新生儿抗癫痫的一线用药[12]。

但近年的报道显示，由于新生儿神经系统发育不完善的特殊性，苯巴比妥类等作用于 $GABA_A$ 受体复合物的的经典抗癫痫药物在新生儿癫痫治疗中的疗效远不及年长儿及成人[13]，甚至可能导致进一步的远期脑损害[14] [15]。如 Ikonomidou 等的研究团队验证了苯巴比妥对新生大鼠中枢神经系统的影响，结果提示新生期应用苯巴比妥可能会影响神经系统发育，继而诱导神经元细胞凋亡[16]。

3. $GABA_A$ 能药物对新生儿癫痫疗效不佳的可能与其兴奋性效应有关

$GABA_A$ 能药物在新生儿癫痫治疗中的不良表现可能与 $GABA_A$ 受体在未成熟中枢神经系统中表现为兴奋性效应有关。近年来已有多项体内及体外研究显示，未成熟脑中 $GABA_A$ 受体活性表现为兴奋性，并随着脑发育的成熟，其对神经元细胞的作用逐渐从兴奋性转向抑制性[17]。而经典的抗癫痫药物如苯巴比妥类、苯二氮卓类及神经类固醇类等通过增强 $GABA_A$ 受体效应，在成熟脑中稳定神经元细胞膜电位达到抑制惊厥发作的作用，但在新生脑中效应则可能相反。故苯巴比妥类等 GABA 能药物对新生儿癫痫疗效不佳。此现象在数项体内及体外实验中均得到证实[17] [18] [19]。

GABA 能效应的转化由 Na^+, $K^+/2Cl^-$协同转运蛋白(Na^+-K^+-$2Cl^-$ cotransporter 1, NKCC1)和 K^+/Cl^-协同转运蛋白(KCC2)的在新生脑内的差异性表达决定[17]。在未成熟神经元细胞中，介导 Cl^-向神经元细胞内摄取的 NKCC1 高表达，同时介导 Cl^-向细胞外转运的 KCC2 低表达，使细胞内 Cl^-浓度增高。当 $GABA_A$ 受体开放，Cl^-外流，细胞膜去极化，则神经元细胞兴奋性增高。而在神经元细胞逐渐成熟后，NKCC1

和 KCC2 的表达此消彼长，细胞内 Cl^-浓度较细胞外高，$GABA_A$ 受体开放则导致 Cl^-内流，细胞膜超极化，神经元细胞兴奋性降低。同时，未成熟神经元细胞中的 $GABA_A$ 受体的激活引起瞬时 Ca^{2+}流入神经元细胞内，继而进一步促进了细胞膜去极化[20]，使神经元细胞兴奋性增高。

研究显示，$GABA_A$ 受体介导的膜去极化兴奋性作用是未成熟脑相比成熟脑更易出现惊厥发作的重要原因之一[21]，此效应同时与神经发育过程中突触可塑性及兴奋性的调节密切相关[22]。在哺乳动物的发育过程中，脑内 GABA 能系统对神经元细胞兴奋性到抑制性作用的转换对大脑功能的最终完善非常重要。与此同时，未成熟脑内其他未成熟的电压和递质门控通道(如 N-甲基-D-天冬氨酸受体，即 NMDA 受体等)、突触结构、神经网络和各类支持性神经胶质细胞等，和 GABA 的兴奋性效应共同导致未成熟脑的兴奋性增高，增加了抽搐的发生几率[6]。

4. GABA 在新生脑内的兴奋性效应提示了新的药物研究方向

NKCC1 及 KCC2 在新生脑内的差异性表达共同导致了 GABA 的去极化兴奋性效应，提示作用于此二类转运蛋白的药物也许将成为特异性针对新生儿癫痫的新药物靶点[23]。

Yamada 等曾报道新生新皮层神经元细胞内 Cl^-的浓度与 NKCC1 mRNA 的表达正相关，而与 KCC2 的表达负相关。应用 NKCC1 特异性抑制剂布美他尼可抑制 NKCC1 对 Cl−向细胞内转运，降低神经元细胞内 Cl^-的浓度[24]。Succol 和 Tyzio 等研究者也相继验证过类似结论[25] [26]。NKCC1 对 GABA 受体效应的调节作用亦在 NKCC1 敲除的小鼠谱系[27]和在体 NKCC1 RNA 干扰抑制实验[28]中得到验证。Kahle 等曾报道过一例单用布美他尼治疗新生儿抽搐的病例，结果显示单用布美他尼可缩短抽搐持续时间，降低抽搐频率，同时亦未引起明确副作用[29]。此外亦有研究报道 NKCC1 特异性抑制剂布美他尼能提高新生期抽搐治疗中 $GABA_A$ 受体正调质(如经典抗癫痫药物苯巴比妥)的疗效[30]。有关布美他尼对新生脑的远期细胞形态、功能及神经行为学的影响仍需进一步研究[31] [32] [33]。

相比 NKCC1，对 KCC2 的研究则不够充分。有研究显示对新生大鼠应用 KCC2 拮抗剂或抑制 KCC2 在神经元细胞膜上的表达可维持 $GABA_A$ 受体介导的去极化效应、推迟 $GABA_A$ 效应从兴奋性向抑制性的转化[34] [35]，但由于至今未找到特异性 KCC2 激动剂，KCC2 激动剂能否逆转新生脑内 $GABA_A$ 兴奋性效应则至今尚无确切研究结论[36]。

此外，未成熟皮质神经元细胞中的 $GABA_A$ 受体的激活引起的 Ca^{2+}瞬时内流应可被 L 型 Ca^{2+}通道阻滞剂尼莫地平(nimodipine)和硝苯地平(nifedipine)阻滞[37]。这提示 L 型 Ca^{2+}通道阻滞剂或许能通过抑制神经元细胞膜去极化，甚至促进细胞膜超极化，从而降低细胞膜兴奋性，针对性治疗新生儿癫痫。

5. 总结

综上所述，$GABA_A$ 受体在未成熟脑内表现为兴奋性效应，而非传统观念认为的抑制性效应。作为 $GABA_A$ 受体正调质的经典抗癫痫药物如苯巴比妥类及苯二氮卓类在新生儿中疗效不佳，甚至可能进一步诱导兴奋性脑损伤及远期行为学改变，故针对新生儿癫痫的治疗方案亟需更新。特异性作用于脑内 NKCC1 及 KCC2 蛋白及 L 型 Ca^{2+}通道阻滞剂的药物可望成为新一代抗新生儿癫痫的重要药物。

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