Kv7/KCNQ钾离子通道开放剂研究进展

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摘要 电压门控型Kv7/KCNQ钾离子通道广泛存在于神经系统, 在调节神经兴奋性中发挥着重要的作用。Kv7/KCNQ通道开放剂成为临床治疗神经过度兴奋相关疾病癫痫和疼痛的一种新的策略。目前, 已报道的Kv7/KCNQ通道开放剂有近30种。该文将对开放剂作用特点、作用位点及其临床应用前景进行总结。

关键词 Kv7通道; KCNQ通道; 开放剂; 癫痫; 疼痛

Advance in Kv7/KCNQ Potassium Channel Openers

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Abstract The voltage-gated Kv7/KCNQ potassium channels are found to be expressed wildly in the central nervous system and play a pivotal role in controlling neuronal excitability. Kv7/KCNQ channel opener become a new tool for clinical intervention of membrane excitability related disorders, such as seizure and pain. Currently nearly thirty kinds of kv7/KCNQ channel openers have been reported. In this paper, we summarized the activation characteristics, activation sites and clinical application of Kv7/KCNQ channel openers.

Keywords Kv7 channel; KCNQ channel; opener; seizure; pain

电压门控型钾离子通道Kv7家族由*KCNQ*基因编码。Kv7/KCNQ电压门控钾通道在控制细胞兴奋性中发挥着重要作用[1]。针对Kv7钾通道调节剂的研究, 为治疗神经过度兴奋相关疾病(如癫痫、疼痛)的新药研发提供了广阔的空间。此外, 开放剂作用机制及结合位点的研究对离子通道功能特点的认识也具有十分重要的意义[2]。本文将对目前已发现的Kv7/KCNQ钾离子通道开放剂作用特点、开放剂作用位点及其临床应用前景进行总结和讨论。

1 Kv7/KCNQ通道生理病理意义

Kv7通道家族已克隆出Kv7.1、Kv7.2、Kv7.3、Kv7.4、Kv7.5五个亚型[3]。Kv7.1通道主要表达于心肌组织上, 并与KCNE通道共同编码组成延迟整流钾离子通道(slowly activated delayed rectifier potassium current, IKs)。IKs通道电流在心肌动作电位去极化过程中发挥着重要作用[4]。Kv7.1通道功能缺失型突变体被证实可引起遗传性1型QT间期延长综合征(long QT syndrome1, LQT1), 另有突变体引起Jervell Lange-Nielsen综合征(JLNS), 即伴有神经性耳聋的先天性长QT间期综合征[5]。

大量研究表明, Kv7.2、Kv7.3和Kv7.5通道蛋白以四聚体形式共表达, 所产生的电流是M电流的分子基础[6]。Kv7.2及Kv7.3通道主要分布在脑部, 包括

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与癫痫发作密切相关的部位, 如皮层、海马、丘脑区以及疼痛传导通路中的脊髓背根神经节感觉神经元、脊髓背角神经细胞和三叉神经元等[7-8]。*Kv7.2*和*Kv7.3*通道基因突变或M通道功能失调, 则可引发良性家族性新生儿惊厥症(benign familial neonatal seizures, BFNS)[9]。*Kv7.2*基因敲除的小鼠表现为普遍的癫痫和学习记忆障碍等。此外, Kv7/M通道在许多疼痛模型中发挥重要作用, 如慢性神经性疼痛、炎性疼痛和癌骨转移疼痛等[10]。*Kv7.2*基因突变还可引发外周神经超兴奋性疾病(peripheral nerve hyperexcitability, PNH), 即肌纤维抽搐和神经性肌强直, 临床特点表现为自发和持续的肌肉组织过度兴奋、肌束震颤、痛性痉挛等[11]。还有研究发现, 在杏仁核兴奋引发焦虑的大鼠模型中, Kv7通道功能上调可以降低神经元过度兴奋, 有效地缓解焦虑症状[12]。

Kv7.4主要表达于内耳的耳蜗和前庭器官以及中枢听觉传导通路。已证实*Kv7.4*基因突变可引发遗传性耳聋症(deafness nonsyndromic autosomal dominant 2, DFNA2)[13]。近期有研究发现, Kv7.4在骨骼肌、内脏和血管平滑肌中均有表达[14]; Kv7.5除了表达于脑部, 在血管平滑肌中也有分布[15]。激活Kv7.4和Kv7.5通道可降低血管张力, Kv7通道已成为抗高血压药物新的潜在作用靶点[16]。

2　Kv7通道开放剂

目前已发现的Kv7/M通道开放剂有近30种(表1), 对神经元Kv7通道的作用主要包括使通道激活的电压依赖性向超极化方向改变、减慢通道激活和去活时间常数以及增大电流幅度。其中, 第一个被发现同时研究最深入的一个Kv7通道开放剂是瑞替加滨(retigabine; D-23129)。Retigabine能够激活Kv7.2-Kv7.5通道, 对Kv7.1通道具有微弱的抑制作用。Retigabine对Kv7通道家族选择性强弱顺序为Kv7.3>Kv7.2/Kv7.3>Kv7.2>Kv7.4[17]。

灭酸酯类(fenamate)是一大类重要的Kv7通道激活剂, 代表化合物包括甲氯灭酸(meclofenamic acid)、双氯芬酸(diclofenac)[18]以及在两者基础上结构改造合成的芬那酯类衍生物NH6和NH29等一系列化合物。甲氯灭酸选择性增大Kv7.2通道电流作用强于Kv7.3通道。双氯芬酸选择性增大Kv7.2-Kv7.4通道电流, 反而抑制Kv7.5电流[19]。化合物NH6相对甲氯灭酸和双氯芬酸选择性较强, 对Kv7.1和Kv7.1/KCNE1通道没有作用[20]。化合物NH29选择性更强, 对Kv7.1、Kv7.1/KCNE1和Kv7.3通道没有作用, 对Kv7.4通道作用极微弱。有趣的是, NH29对TPRV1通道具有抑制作用, 有利于疼痛等相关疾病的治疗[21]。

丙烯酰胺类化合物(acrylamides), 如Acrylamides (S)-1和Acrylamides(S)-2, 也被报道能激活Kv7通道。(S)-1开放Kv7.2-Kv7.5通道, 同时抑制Kv7.1通道。与其他开放剂不同, (S)-1对Kv7.2和Kv7.2/Kv7.3通道的作用具有电压依赖性, 在高电压情况下抑制通道的活性而在低电压情况下增强通道的活性。(S)-1对Kv7.4和Kv7.5的作用则是在所有电压情况下都具有增强通道活性的作用[22]。(S)-2的EC_{50}为0.06 μmol/L, 效价比(S)-1强约55倍[23]。

BMS204352是早期发现的Kv7通道激动剂, 2-羟基吲哚(oxindole)类似物。该化合物同时也是BK通道激动剂, 对GABA通道有微弱的抑制作用[24]。BMS204352同样开放Kv7.2-Kv7.5通道, 选择性增大Kv7.5通道电流6倍, 但其强烈抑制Kv7.1通道, 抑制率为96%[25]。有趣的是, BMS204352的右旋异构体对Kv7家族通道具有抑制作用, 抑制率约为95%[12]。

吡硫锌(ZnPy)是Kv7通道的强效开放剂, 该化合物具有分子结构简单的特点。ZnPy能够激活Kv7.2-Kv7.5通道, 但对Kv7.3通道无作用[26]。虽然ZnPy能增大Kv7.1通道电流, 但对Kv7.1和KCNE1亚基形成的IKs电流无作用[27]。

ZTZ系列共报道了10个化合物, 构效关系的研究提示氯和溴取代基为该系列化合物的必需取代基, 如果氯和溴取代基缺失将降低其开放Kv7通道活性[28]。以先导化合物ZTZ240为例, 最显著的特点为增大Kv7.2通道的去活时间常数可达数百倍[28]。ZTZ233又名ICA27243, 化合物ICA27243是美国Icagen公司研发的Kv7通道开放剂, 具有高选择性和效价较高的特点。ICA27243对Kv7.2/Kv7.3通道选择性作用高于Kv7.4和Kv7.3/Kv7.5通道[29]。

吡唑并咪唑嗪类化合物是本实验室合成及报道的一系列具有开放Kv7通道作用的化合物。采用Rb^+流出高通量筛选, 这一系列化合物构效关系为: 母环上R取代基以三氟甲基为必需取代基, R1以苯环及萘环为最佳取代基, R2以含多个强吸电子集团为最佳取代基。QO-58为先导化合物, 选择性作

用于Kv7.2和Kv7.4通道, 对Kv7.3通道作用影响较微弱。另外, QO-58作用类似ZTZ240能够显著延长Kv7.2通道去活常数近10倍[30]。本实验室还发现, 非甾体抗炎药塞来昔布(celecoxib)也具有激活Kv7.2-Kv7.5通道的作用。不同的是, 塞来昔布对Kv7.1通道具有抑制作用, 最大抑制率为60%[31]。

3 Kv7通道开放剂作用位点

Kv7通道开放剂增加通道电流的机制主要包括降低通道激活阈值、增加通道开放频率及稳定通道的开放构象等。开放剂与通道结合时引发多种效应, 促进一系列构象改变以打开通道。当离子通道某些氨基酸残基发生改变时, 这些开放剂的活性消失或者下降, 这些氨基酸残基位点被我们称为作用位点。影响开放剂作用的通道残基可能是改变了开放剂与通道作用的亲和力或阻碍了开放剂诱导的构象改变。这些小分子化合物作用机制的研究对于我们了解Kv7通道功能特点具有重要意义。

Retigabine激活Kv7通道的作用与Kv7.2-Kv7.5通道第五次跨膜(S5)上的一个保守的色氨酸残基有关, 在相应的Kv7.1通道上其对应位置是亮氨酸(leucine)残基。研究发现, 当Trp-236位点突变为亮氨酸残基时, Kv7.2-Kv7.5通道就不再被retigabine所增强。相反, 当Kv7.1通道相应的亮氨酸残基突变为色氨酸残基时, 突变的Kv7.1通道变为对retigabine敏感。可见, 保守的色氨酸明显是retigabine介导的强化作用所必需的[32]。有趣的是, Trp-236位点也是很多其他Kv7通道开放剂的作用位点, 如BMS-204352、Acrylamides(S)-1、Acrylamides(S)-2、ZTZ240和塞来昔布[22,31,33-34]。这表明, 这几类化合物可能以相似的方式作用于Kv7通道并需要相同的分子基础。

基于对Kv7.2通道的单定点突变研究, ZnPy的分子作用位点也已有报道, 分别是S5区的亮氨酸残基(Leu249)、位于S5区和孔区之间连接肽段上的亮氨酸残基(Leu275)和S6片段上的丙氨酸残基(Ala306)。对亮氨酸残基Leu249和Leu275进行双突变, 虽然ZnPy并不引起IV曲线改变, 但仍能导致通道总电导的提高。相反地, 对S6片段上的Ala306进行突变, 只引起很小的ZnPy诱导的通道总电导提高, 但仍可导致IV曲线超极化方向变化。因此, 这三个位点代表了ZnPy作用的两种不同的关键调控位点[35]。

表1 Kv7通道开放剂

Table 1 Summary of Kv7 channel activators

化合物名称 Compound name	靶基因 Target genes	半数有效浓度(μmol/L) EC50 (μmol/L)	作用位点 Acting sites
Acrylamides (S)-1[22]	Activate Kv7.2, Kv7.3, Kv7.4, Kv7.5 and Kv7.2/Kv7.3; Inhibit Kv7.1	3.28	Trp236
Acrylamides (S)-2[23,34]	Activate Kv7.2	0.06	Trp236
BMS-204352[24]	Activate Kv7.5>Kv7.4>Kv7.2, K7.3, Kv7.2/Kv7.3; Inhibit Kv7.1	–	Trp236
Celecoxib[31]	Activate Kv7.2, Kv7.3, Kv7.4, Kv7.5 and Kv7.2/Kv7.3; Slightly inhibit Kv7.1	4.9	Trp236
Diclofenac[18-19]	Activate Kv7.2, Kv7.3, Kv7.4 and Kv7.2/Kv7.3; Inhibit Kv7.5	2.6	–
Meclofenamic acid[18]	Activate Kv7.2, Kv7.3 and Kv7.2/Kv7.3	11.7	–
NH6[20]	Activate Kv7.2/Kv7.3	18	–
NH29[21]	Activate Kv7.2; Inhibit TPRV1	14	Arg198 and Arg207 in the voltage sensing domain (VSD)
Retigabine[17,32]	Activate Kv7.3>Kv7.2/Kv7.3>Kv7.2>Kv7.4, slightly inhibit Kv7.1	0.34	Trp236
QO-58[30]	Activate Kv7.1, Kv7.2, Kv7.4 and Kv7.2/Kv7.3	2.3	Ala306, Leu275 and Val224Val225Tyr226
ZTZ240[28]	Activate Kv7.2, Kv7.4 and Kv7.5	9.8	Trp236 and Ala309
ICA27243[29]	Activate Kv7.2/Kv7.3>Kv7.4>Kv7.3/Kv7.5	0.4	–
Zinc pyrithione[26-27]	Kv7.1, Kv7.2, Kv7.4, Kv7.5 and Kv7.2/Kv7.3	1.7	Leu249, Leu275 and Ala306

–: 无相关文献。

–: no related paper.

ZTZ240作用位点包括S5上的色氨酸残基(W236)和S6上的丙氨酸残基(A309)。ZTZ240引起Kv7.2W236L突变体通道IV曲线左移程度降低。将A309丙氨酸残基突变为半胱氨酸、结氨酸和甘氨酸, ZTZ240对通道饱和电压下激活电流增大作用几乎消失, 并且突变体通道去活时间常数延长程度降低[33]。

本实验室建立了QO-58和Kv7.2通道S5-S6区域相互作用计算机嵌合模拟模型, 模拟结果提示, 氨基酸残基Aal306和Leu275参与QO-58与Kv7.2通道的相互作用。电生理结果证实, 突变体Kv7.2(A306T)和Kv7.2(L275A)降低了QO-58开放Kv7.2通道的作用效能。氨基酸链$Val^{224}Val^{225}Tyr^{226}$在除了Kv7.3通道以外的所有Kv7家族成员中为保守序列。构建的突变体通道Kv7.2(VVY224, 225, 226AIC)不再被QO-58激活, 但仍能被retigabine激活。这些结果提示, Kv7.2通道氨基酸链$Val^{224}Val^{225}Tyr^{226}$也在QO-58激活Kv7.2通道过程中起重要作用[30]。

化合物NH29被报道嵌合于S1、S2和S4链接头处形成的外表面沟壑里, 位于稳定开放状态下Kv7通道的2个保守带电荷基团之间。独具特点的是, NH29作用位点位于S4位电压感受器(VSD)上, NH29不再影响突变体R198A和R207W电流电压激活曲线[21]。

4　Kv7通道调节剂临床应用

Kv7通道开放剂具有巨大的潜在临床应用价值。Retigabine具有体内体外广谱和强抗惊厥特性, 在绝大多数临床前癫痫动物模型中都有效[36]。随后, 已经完成的临床III期实验表明, retigabine对传统治疗惊厥和癫痫的药物无效的顽固性癫痫患者的癫痫部分发作的治疗也是有效的[37]。2011年, retigabine(Potiga; ezogabine)经美国FDA批准作为辅助药物联合已有药物用于治疗癫痫部分性发作[38-39]。此外, retigabine在很多疼痛模型中也是有效的, 并有望用于其他神经疾病, 包括偏头痛和神经性疼痛等[8]。

化合物flupirtine是retigabine的结构类似物, 该化合物已经在欧洲等国家上市近20年, 用于治疗各种类型的疼痛[40]。此外, flupirtine处于治疗肌纤维痛临床II期研究中, 目标为改善肉骨骼痛和所有肌纤维痛的症状, 如情绪、疲劳、认知症状、睡眠紊乱等。Flupirtine同时还处于神经性疼痛临床II期研究中, 用于辅助阿片类药物的治疗[41]。

综上所述, Kv7通道开放剂对神经过度兴奋相关疾病的治疗具有广阔的应用范围和不可低估的应用价值。

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