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离子通道与帕金森病纹状体神经元兴奋性相关性研究进展

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[摘要]帕金森病是一种由中脑黑质多巴胺能神经元逐渐丧失而引起的神经退行性疾病,其发病机制尚不明确,研究认为纹状体神经元兴奋性异常与帕金森病发病存在相关性,其中离子通道在维持细胞静息膜电位、调节神经元的兴奋性中起重要作用,不过离子通道对神经元兴奋性的调控机制还不完全清楚。本文对离子通道及其调控机制与帕金森病纹状体神经元兴奋相关性,以及离子通道在帕金森病发病中的作用的研究进展进行了综述,期望发现新的治疗靶点,通过改变离子通道功能治疗帕金森病。

[关键词]帕金森病;非选择性钠离子通道;电压门控钾离子通道;电压门控钙离子通道;神经元兴奋性
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Research progress on the correlation between ion channel and excitability of striatum neurons in Parkinson´s disease

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] Parkinson's disease (PD) is a neurodegenerative disorder due to gradual loss of dopaminergic neurons in the substantia nigra in the midbrain, however, the pathogenesis is unclear. There is a correlation between the excitability of striatal neurons and PD. Ion channels are important to maintain membrane potential and regulate excitability of neurons, but ionic mechanisms for modulation of neurons excitability are not fully understood. This article reviews the relationship between ion channels and excitability of striatal neurons in PD and ion channel changes in the pathogenesis of PD, in order to find new targets to treatment PD by intervening ion channels.

[KEYWORDS] Parkinson's disease; Sodium leak channel non-selective protein; Voltage-dependent K^+ channel; Voltage-gated calcium channel; Neuronal excitability

帕金森病(Parkinson's disease, PD)是影响全球约600万人的第二常见神经退行性疾病,其病理特征是黑质致密部多巴胺能神经元丢失,导致纹状体多巴胺缺失[1]。研究发现神经元释放的多巴胺可持续增强直接通路纹状体神经元的内在兴奋性[2],多巴胺能神经元缺失可引起脑内多巴胺减少,引起纹状体投射神经元兴奋性改变,从而导致直接和间接引起通路平衡紊乱,导致患者出现帕金森病运动及非运动症状。离子通道在调节纹状体神经元兴奋性中起着重要作用[3]。现有研究发现非选择性钠

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离子通道(sodium leak channel non-selective protein, NALCN)、电压门控钾离子通道(voltage-dependent K^+ channel,Kv7,又称KCNQ)、电压门控钙离子通道(voltage-gated calcium channel, CaV)均参与维持神经元静息膜电位(resting membrane potential, RMP),对神经元兴奋性的调节起重要作用[4-6],离子通道的功能改变可能与疾病发生发展相关[7],但具体的离子通道及其调控机制尚不清楚。本文对NALCN、Kv7、CaV在调节纹状体神经元兴奋性中的作用进行综述,分析离子通道与纹状体神经元兴奋性的相关性。研究表明离子通道调控机制改变与帕金森病发病相关,干预离子通道能改善帕金森病的症状,是治疗帕金森病新的思路。

1 帕金森病中纹状体神经元兴奋改变

现有的研究表明中枢神经系统中的多巴胺能信号在调节运动行为、动机、学习和记忆等方面起重要作用[8],多巴胺能神经元的丢失是帕金森病发病的重要病理改变。多巴胺通过增加直接投射到基底节输出层的棘状投射神经元(spinous projection neurons, SPN)的兴奋性差异调节纹状体投射神经元的兴奋性,这种兴奋性差异是由于纹状体神经元多巴胺受体在投射神经元上的差异表达所致:(1)直接投射的SPN表达多巴胺1受体(dopamine 1 receptors,D1R),直接投射到黑质网状部;(2)间接投射的SPN表达多巴胺2受体(dopamine 2 receptors,D2R),投射到苍白球的外部[8]。纹状体神经元兴奋性改变在控制目标导向运动和习惯方面起着关键作用,直接通路SPN可促进情景中适当的行为活动和习惯,而间接通路SPN抑制不恰当的行为和习惯[9]。研究认为帕金森病的症状是由于纹状体直接和间接通路活动水平改变所致[10]。在帕金森病中,多巴胺能信号失去适当的时间和尺度,使纹状体多巴胺信号传递偏向增加间接通路SPN的活性[11]。其中,D1受体激活增加纹状体投射神经元兴奋性[2],D2受体激活可降低纹状体投射神经元兴奋性[12]。激活的D2受体抑制大脑运动皮层的活动,引起患者出现运动僵硬和缓慢[13]。现有的研究表明在帕金森病状态下多巴胺能神经元减少,导致纹状体神经元去多巴胺化,在低剂量的多巴胺的刺激下纹状体神经元偏向激活D2受体,导致纹状体神经元兴奋性发生改变,引起大脑皮质运动区的活动减少,进而引发帕金森病症状,但是导致纹状体神经元兴奋性的改变的具体调控机制尚未知。若找到引起纹状体神经元兴奋性改变的信号通路,可通过调控该信号通路改变帕金森病症状来治疗帕金森病。

2 离子通道与纹状体神经元兴奋性

最新的研究表明纹状体神经元兴奋性的改变主要是由于离子通道功能发生改变,在帕金森病的动物模型中发现了离子通道改变[14]。研究发现离子浓度改变与帕金森病相关[15],且离子通道参与静息膜电位、神经元的兴奋性调节。

2.1 钠离子通道及其调控机制

在神经元的静息电位起主要作用的钠离子通道NALCN,在大多数神经元静息状态下NALCN主要介导一种基础钠漏电流,其电位很小,在培养的小鼠海马神经元电压为70 mV时,电流约10～20 pA[16]。NALCN与UNC80、UNC79形成钠离子通道复合体共同发挥离子通道功能[17]。NALCN是电压非依赖性的离子通道,是一种保守的阳离子通道,传导永久性的钠漏电流,并进行永久性钠泄漏[18]。研究发现阻断脊髓的投射神经元的NALCN可显著降低静息膜电位超极化的幅度,抑制NALCN活性可显著减弱神经元的兴奋性[19]。在NALCN敲除的神经元中其静息膜电位比野生型神经元的静息膜电位高约10 mV,并且对钠离子变化不太敏感,而NALCN的过度表达导致RMP产生20 mV去极化,揭示NALCN是决定细胞外钠离子对神经元兴奋性的主要因素[20],亦表明NALCN可促进钠离子在细胞内的运动,是维持兴奋性细胞静息膜电位、调节神经元兴奋性的重要因素[21]。

人类NALCN基因缺陷导致NALCN相关脑病。杂合子表现为四肢和面部先天性挛缩、肌肉张力减退和全身发育迟缓[22],双等位基因NALCN变异导致婴儿张力减退、精神运动迟缓[23]。NALCN基因突变导致严重的婴儿非癫痫性脑病,引起运动功能障碍[24]。研究表明多巴胺与D2受体结合通过Gi/o蛋白偶联通路抑制NALCN介导的钠漏电流,降低多巴胺能神经元的放电频率,减弱神经元的兴奋性[25]。NALCN介导的钠漏电流可驱动多巴胺能神经元的起搏,在NALCN基因敲除的小鼠中多巴胺能神经元不存在自主产生的自发放电[26]。以上研究表明NALCN功能障碍可抑制多巴胺能神经元的放电,导致多巴胺释放减少。我们推测当中脑的多巴胺释放减少时,在纹状体投射神经元神经元内低剂量的多巴胺易与D2受体结合,而激活的D2受体可抑制NALCN功能导致纹状体神经元的兴奋性下降,进而抑制皮层的运动功能,导致患者出现帕金森病症状。干预NALCN可能改善帕金森病的运动症状,可成为未来治疗帕金森病新的思路。

2.2 钾离子通道及其调控机制

在脑内广泛表达的钾离子通道Kv7是由四个Kv7亚基的不同组合组成的电压依赖性钾通道，其对神经元兴奋性调节依赖于Kv7通道复合体。通道复合体包括：PIP2是一种阴离子磷脂，可改变通道功能。PIP2与Kv7的交互作用对于通道功能是必需的[27]。C末端的钙调素结合位点重叠，钙调素在Kv7通道向质膜的传输中起作用，充当Ca^{2+}传感器，并促进Kv7通道与PIP2的相互作用，钙调素结合位点是电流抑制的关键靶点[28]；N末端的蛋白激酶A磷酸化的共同位点，可增加Kv7电流[29,30]。Kv7通道是一种外向钾电流，缺乏失活性，是电压门控非失活钾电流（又称M电流）的基础[31]，并在静息膜电位附近被激活。研究发现Kv7参与调节静息膜电位，参与动作电位复极和抑制膜去极化，通道开放时可超极化神经元，减少神经元的放电，防止神经元过度兴奋，可调节神经元过度兴奋引起的症状[32,33]。

最新研究发现中脑的多巴胺能神经元释放多巴胺通过Kv7调节纹状体神经元的兴奋性，主要是通过多巴胺与D2受体结合通过Gi/o蛋白和氧化还原依赖性细胞途径增强M电流，D2受体激活可介导的自身抑制，减少神经元的放电和递质释放[34]。Kv7通道开放剂瑞替加滨（retigabine）对Kv7通道功能的刺激导致进纹状体兴奋性显著降低，在帕金森病状态下参与调节纹状体神经元的兴奋性[35]。Kv7是纹状体神经元兴奋性调节的重要靶点，是一个很有前途的新的药物靶点的钾通道[36]。以上的研究表明Kv7参与调节纹状体神经元的兴奋性，其通道可作为新的药物靶点来治疗纹状体神经元兴奋性异常引起的疾病，如帕金森病和药物成瘾。

2.3 钙离子通道及其调控机制

电压门控钙离子通道是α、β、γ、δ亚单位组成的复合体，是膜电位变化到细胞内钙离子瞬变的关键传感器，具有快速控制电压依赖性钙离子进入的功能[6]。钙离子通道的亚单位与ankyrin B蛋白结合，当ankyrin B蛋白缺失或者功能障碍时可显著降低表达系统中的T型全细胞电流密度[37]。T型电压门控钙通道又称CaV3，具有特异性的低阈值激活和慢失活特性，是许多神经元起搏的基础，在控制神经元兴奋性方面起着重要作用，其功能障碍与中枢神经系统疾病相关[38-40]。在大鼠的神经元中存在超极化诱导的反弹爆发放电，抑制CaV3通道功能可使神经元的反跳爆发被显著抑制[41]，提示神经元的超极化诱导的反弹爆发放电与CaV3相关。

在帕金森病患者中CaV对多巴胺的门控作用在纹状体神经元中存在差异，当纹状体神经元的胞外Ca^{2+}减少，导致静息膜电位去极化和动作电位持续放电，引起神经元兴奋性的增加[42]，通过特异性阻断CaV3使细胞膜过度极化，并消除爆裂和不规则放电，并减轻神经元过度兴奋[43,44]。研究发现多巴胺可通过CaV3调节多巴胺能神经元功能[45]，主要是通过特异性抑制$G_{\beta2}$亚单位途径抑制T型钙电流，可减少小鼠纹状体多巴胺的释放[46]。现有研究发现CaV3通道的功能异常与多种神经发育、神经和精神疾病有关[47]，钙通道阻滞剂可诱导药物相关的帕金森病综合征[48]。明确CaV3功能及其调控机制，有利于新型通道调节剂的开发和新的药物靶点的发现[49]，为未来治疗疾病提供了可能。

3 总结与展望

研究发现在帕金森病状态下多巴胺与纹状体投射神经元受体结合存在偏向性，易与表达D2受体的间接通路的投射神经元结合，导致纹状体投射神经元兴奋性异常。纹状体投射神经元的兴奋性主要是通过离子通道调节的，现已发现NALCN、Kv7、CaV3均参与调节纹状体神经元兴奋性。在帕金森病时，NALCN、Kv7、CaV3离子通道功能均发生改变。当中脑的D2受体激活导致NALCN离子通道被抑制，减低神经元的兴奋性。D2受体激活后亦可导致Kv7离子通道开放，导致纹状体兴奋性显著降低，介导D2受体的自身抑制，减少神经元的放电和递质释放。多巴胺可阻断CaV3离子通道，使细胞超极化导致纹状体神经元兴奋性下降。可从离子通路与神经元兴奋性调节角度分析离子通道在帕金森病中的作用及其可能存在的治疗靶点。文献综述提示纹状体神经元兴奋性与离子通道的调节相关，但离子通道调控机制在帕金森病发病中尚不清楚，因此，进一步研究帕金森病中离子通道与纹状体神经元兴奋性的相关性，有助于深入了解帕金森病的发病机制，为未来治疗帕金森病提供新的治疗的靶点。

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