· 综述 ·

蛋白激酶C在抑郁症神经免疫炎症机制中的研究进展

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【摘要】 近年来, "炎症假说" 颇受关注, 该假说认为炎症反应参与抑郁症的发病。小神经胶质细胞作为中枢神经系统的免疫细胞, 激活时会增加炎症细胞因子的释放, 引发机体的炎症状态, 进而参与抑郁症的发生发展。蛋白激酶在调节小胶质细胞的激活中发挥重要作用, 其中蛋白激酶C(PKC)可能是此过程中最重要的一种激酶。此外, PKC的表达水平和活动变化可能均与抑郁症的发病机制密切相关。文章对PKC进行简要概述, 并通过总结动物及临床研究证据来明确PKC与抑郁症之间的关系, 进一步对可能参与抑郁症发病机制的PKC相关信号通路进行重点阐述, 以期为抑郁症免疫炎症假说提供研究思路, 为寻找抗抑郁治疗新靶点提供科学依据。

【关键词】 抑郁症; 蛋白激酶C; 小神经胶质细胞; 神经免疫炎症; 信号通路; 综述
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Research progress of protein kinase C in the neuroimmune-inflammatory mechanism of depression

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【**Abstract**】 Much attention has been paid to the "inflammatory hypothesis" in recent years, which suggests that inflammation is involved in the pathogenesis of depression. Activation of microglia, the immune cells of the central nervous system, increases the release of inflammatory cytokines and triggers an inflammatory state in the body, which in turn is involved in the development of depression. Protein kinases have been found to play an important role in regulating microglia activation, and protein kinase C (PKC) is probably the most important kinase in this process. In addition, it was found that changes in both PKC expression levels and activity may be closely related to the pathogenesis of depression. Therefore, we will first provide a brief overview of PKC, and then clarify the relationship between PKC and depression by summarizing evidence from animal and clinical studies. Finally, we will focus on PKC-related signaling pathways involved in the pathogenesis of depression to provide research ideas for the immuno inflammatory hypothesis of depression and provide scientific basis for finding new targets for antidepressant therapy.

【**Key words**】 Depressive disorder; Protein kinase C; Microglia; Neuroimmune inflammation; Signaling pathway; Review
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抑郁症是一种高致残、高疾病负担的临床常见精神障碍，是以显著而持久的心境低落为主要临床特征[1]。荟萃分析显示，2020年全球有2.46亿人口患有抑郁症，较预期增加了28%[2]。我国2019年精神卫生流行病学调查结果表明，国人的抑郁症终身患病率为3.4%，12个月患病率为2.1%，其流行率仅次于焦虑障碍而位列精神障碍疾病第二[3]。然而，抑郁症的病因仍然未知，诊断尚不明确。目前基于神经递质/受体学说研发的抗抑郁药物仅对50%左右的患者有效，且起效缓慢，而在接受治疗的抑郁症患者中，有高达27%的患者病情无法缓解并继续发展成慢性抑郁症[4]。这说明神经递质/受体并非缓解抑郁症状的直接靶点或唯一途径。

近年来，“炎症假说”颇受关注，该假说认为炎症反应参与抑郁症的发病[5]。有荟萃分析显示，抑郁症患者体内存在多种中枢及外周炎症细胞因子升高，如IL-6、TNF-α；同时，抗感染治疗能够产生明显的抗抑郁效果，特别是以炎症因子增加为特征的抑郁症患者[6-7]。然而，相关的免疫炎症过程及机制至今尚未明确。众所周知，小胶质细胞作为中枢神经系统的巨噬细胞，是中枢神经免疫炎症相关疾病的主要媒介。当小胶质细胞激活时会释放多种细胞因子，引发机体的炎症状态[8]。有研究人员进一步发现，蛋白激酶C(protein kinase C，PKC)可能在调节小胶质细胞激活中发挥重要作用。如全氟辛烷磺酸可通过刺激PKC相关信号通路来激活小胶质细胞，参与神经免疫炎症过程[9-10]。同时有研究发现，PKC与抑郁症的发病密切相关。研究人员通过对抑郁患者死后大脑进行分析发现，抑郁患者PKC的表达显著低于健康对照者[11]。然而，目前对于PKC及小胶质细胞可能参与抑郁症的病理机制研究仍然较少。

因此，现简要概述PKC，然后通过总结来自动物及临床研究的证据探讨PKC与抑郁症发病之间的关系。最后，对PKC可能参与抑郁症的发病机制进行重点阐述。

一、PKC概述

PKC是一种丝氨酸/苏氨酸的蛋白激酶，由Nishizuka[12]于1977年在小鼠脑胞质中首次发现。PKC为一酶家族，在分子结构和酶特性的基础上，目前已知的13个PKC家族成员主要被分为3类：(1)经典PKC(α，β1，β2，γ)：被钙和二酰基甘油(diacyl glycerol，DAG)激活；(2)新型PKC(δ，ε，η，θ)：被DAG以钙独立的方式激活；(3)非典型PKC(ζ，λ/ι)：既不需要钙也不需要DAG激活，但它们对磷脂敏感[13-14]。所有的PKC同工酶都有两个功能域，即C端催化域和N端调控域。催化域包含一个保守的ATP和镁的结合位点以及一个底物蛋白质中磷受体序列的结合位点；调控域则是由保守的C1和C2两个结构域组成。在非活性状态下，调控域与催化域结合抑制着酶的活性；而这种分子内的相互抑制作用的解离引起酶的激活。值得注意的是，催化域和调控域都可以产生调节PKC活性的药物(引起PKC的抑制或激活)，但这些结构域也对实现药物的选择性和安全性提出了巨大的挑战[15]。

随着研究进展，研究人员发现PKC在全身多种组织中均有表达，如脑、心、肺、皮肤、肌肉、血小板、造血细胞和内皮细胞等[16-17]。研究人员还发现PKC在脑组织多种成分中也均有表达，如神经元、神经胶质细胞、平滑肌细胞、内皮细胞及其他脑组织细胞[18-19]。其中在脑组织中，PKC亚基主要包括PKCα，β，δ，ε，γ和ζ等类型[20]。而且大部分PKC同工酶在神经元和神经胶质中参与情绪调节的大脑区域(如海马、额叶皮质)中高度表达，这可能是多种情绪障碍疾病发生的基础[21-23]。

PKC是信号转导途径的主要介质，介导多种信号通路，如丝裂原活化蛋白激酶和应激活化蛋白激酶级联反应、核因子-κB(nuclear factor，NF-κB)信号转导、糖原合成酶激酶信号转导、蛋白激酶B信号转导以及信号转换器和转录激活因子调控的基因表达等[24-25]。在生理条件下，PKC的激活是通过细胞外激动剂，如生长因子、激素、细胞因子或抗原，与它们的同源G蛋白偶联受体或受体酪氨酸激酶相互作用而实现的。此外，研究人员还发现PKC也是细胞增殖、分化、凋亡、转换等生理过程的关键调节因子[26-28]。这提示PKC可能在多种疾病病理生理机制中发挥重要作用。

二、PKC与抑郁症

陆续有研究发现机体的许多疾病均与PKC相关，如心脑血管疾病[16]、糖尿病[29]、肿瘤相关性疾病[17]等，而近年来更受到关注的是其在神经系统疾病以及精神疾病中的作用，尤其是抑郁症[30-31]。现从动物实验和临床研究两个方面来探讨PKC与抑郁症之间的相关性。

1.动物实验：Han等[32]将实验大鼠分为健康对照组、抑郁模型组和帕罗西汀治疗组进行研究发现，抑郁模型组大鼠的PKC含量较健康对照组明显降低；而且与抑郁模型组比较，帕罗西汀治疗组PKC

表达水平明显升高。而且，与健康对照组相比，抑郁模型组大鼠的空间学习和记忆功能明显下降(如逃逸潜伏期延长，目标象限时间百分比和穿越平台次数减少)。经过帕罗西汀治疗后，抑郁症模型大鼠受损的空间学习和记忆功能得到明显改善，几乎可达到与正常对照动物相当的水平。以上表明，帕罗西汀可能通过PKC信号通路来改善大鼠抑郁模型的空间学习记忆功能，从而发挥抗抑郁作用。Ramos-Hryb等[33]发现通过给予抑郁症小鼠模型三菊酯(PKC抑制剂)可改善由熊果酸引起的悬尾试验静止时间的减少；首次描述了抑郁症小鼠模型中熊果酸的抗抑郁作用可能依赖于PKC的激活。强迫游泳试验小鼠模型常用于抑郁症的行为学测试[34]。Ito等[35]通过构建小鼠游泳应激模型发现，与非游泳应激小鼠相比，应激小鼠前额叶皮层磷酸化PKCβI和血清素转运体水平显著降低。他们还发现通过给予PKC激活剂可显著减弱应激小鼠增强的不动性和减少社交互动时间，并增加血清素周转；而使用PKC抑制剂可加剧暴露在轻度应激下小鼠的活动能力和社交能力的下降。

2.临床研究：Pandey等[11]通过对正常对照者、抑郁自杀(depressed suicide)者和抑郁非自杀(depressed nonsuicide，DNS)者前额叶皮质区的多种PKC同工酶蛋白和mRNA表达进行测定发现，抑郁自杀者和DNS者前额叶皮质区多种PKC同工酶(如PKCα、PKCβ i、PKCβ ii和PKCδ)的蛋白和多种PKC同工酶(如PKCα、PKCβ i、PKCδ和PKCε)的mRNA表达降低。该研究提供了PKC同工酶在抑郁症患者大脑中失调的证据，清楚地显示了PKC在抑郁症患者大脑中的异常。双相情感障碍是一种情感障碍性疾病，其特征是躁狂或轻躁狂和抑郁症的交替发作，美国精神病学协会分类学中也增加了抑郁症的混合特征指标，承认了抑郁症和双相情感障碍存在混合症状的可能性，这代表了双相情感障碍和抑郁症之间的结构桥梁[36-37]。Hayashi等[38]利用双相情感障碍患者和健康对照组的脂肪细胞进行突触后信号分析发现，与对照组相比，双相情感障碍组PKC通路的基础活性没有显著提高(P=0.10～0.12)。然而，在使用艾司西酞普兰(P=0.000 52)或锂(P=0.004)刺激后，双相情感障碍组PKC通路活性发生了明显变化，艾司西酞普兰被证明能激活突触后PKC信号通路的激活，而锂治疗可降低双相躁狂患者血小板PKC和G蛋白偶联受体的活化。这支持了PKC信号通路在双相情感障碍疾病中增加的观点。还有研究发现，他莫西芬是一种能够通过血脑屏障的相对特异性PKC抑制剂[39]。一项目的是评价他莫西芬对躁狂情绪发作疗效的荟萃分析显示，不论他莫昔芬作为单一疗法还是情绪稳定剂的附加疗法对治疗急性躁狂都是有效的[31]。

以上动物实验及临床研究结果均提示抑郁症患者体内存在PKC表达或者功能异常，PKC的表达水平和活动变化与抑郁症的发病机制密切相关。

三、PKC在抑郁症发病机制中的作用

既往多项研究表明，PKC可能通过小胶质细胞介导的神经免疫炎症过程参与抑郁症的发生发展。此外，经进一步研究发现，PKC可能通过NF-κB相关的信号通路调控神经免疫炎症过程。

1. PKC通过神经免疫炎症反应参与抑郁症的发生：Mukhara等[40]发现，AD患者的大脑中存在小胶质细胞的激活以及炎症细胞因子的增高，如IL-6、TNF-α。Sarajärvi等[41]通过AD动物模型发现，PKC可通过降低动物模型小胶质细胞中TNF-α的产生发挥神经保护作用。此外，有研究人员发现AD患者大脑中存在多种PKC的水平和活性下降，而且PKC的激活不足与神经炎症异常密切相关[42-43]。某些PKC激活剂，如DAG-内酯和苔藓虫素已被证明可以显著减轻AD的病理生理特征，如认知功能障碍[44]。还有报道显示，小鼠骨髓细胞上表达的T激活受体-1可通过PKC信号通路来抑制脑出血后的小胶质细胞极化而减轻神经炎症反应[45]。以上证据表明，PKC与小胶质细胞介导的神经免疫炎症过程密切相关。

进一步研究发现，Wang等[46]通过利用慢性轻度应激(chronic mild stress，CMS)建立的抑郁动物模型发现，12周的CMS可诱发小鼠显著的抑郁和焦虑样行为，同时也引起了小胶质细胞激活和炎症细胞因子的增加，如白细胞介素-1β(interleukin-1β，IL-1β)、IL-6等。二甲胺四环素可被用作小胶质细胞激活抑制剂，他们发现通过给予小鼠慢性二甲胺四环素治疗可逆转由CMS引起的抑郁样行为，并显著抑制了小胶质细胞的激活，同时发现动物模型体内IL-1β、IL-6等炎症细胞因子的mRNA水平的降低。此外，有研究发现，在健康的志愿者中，激活剂量的脂多糖(lipopolysaccharide，LPS)可导致抑郁症状的发生[47]。Arioz等[48]通过LPS诱导建立抑郁动物模型发现，抑郁小鼠模型体内存在小胶质细胞的

活化、炎症小体的激活以及炎症细胞因子水平的增高；此外他们发现褪黑素治疗可改善由LPS诱导的抑郁样行为，同时还可观察到模型小鼠体内小胶质细胞活化和炎症小体激活的显著抑制以及炎症细胞因子的降低。此外，Li等[49]在未经治疗的抑郁患者体内发现了转运蛋白或外周苯二氮受体(translocator protein or peripheral benzodiazepine receptor，TSPO)水平的升高，在给予患者认知行为治疗后，观察到患者抑郁症状的减轻，同时还检测到患者体内TSPO水平的降低。既往有研究发现TSPO不仅介导炎症和损伤，其配体还参与调控小胶质细胞活化和相关的炎症反应[50]。由此可见，小胶质细胞活化参与抑郁症的发生。

2. PKC参与神经免疫炎症反应的信号通路：Fu等[51]在小鼠小胶质细胞中发现LPS可通过PKC途径介导小胶质细胞中炎症因子的表达增加，如IL-1β和TNF-α。Zeng等[52]发现，LPS可通过激活PKC/NF-κB信号通路，从而产生炎症细胞因子。NF-κB是一种转录因子，在免疫细胞的炎症激活和细胞因子分泌中发挥核心作用[53-54]。NF-κB活化可使小鼠小胶质细胞在病理条件下产生促炎因子，如TNF-α、IL-1β[55]。Kappa B激酶抑制剂(inhibitor of kappa B kinase，IKK)是NF-κB激活的中枢调节因子，NF-κB的抑制分子(inhibitor of NF-κB，IκB)在细胞质中与NF-κB结合，是NF-κB信号转导的主要制动器，而IKK可被各种刺激激活，使IκB磷酸化，继而激活NF-κB[56-57]。Zeng等[52]还发现，PKC抑制剂可显著抑制IKK、IκB和NF-κB的磷酸化，证实了PKC是IKK/IκB/NF-κB信号通路的上游调控因子。有研究也发现，PKC可通过激活IKK，引起IκB磷酸化，从而引起NF-κB的活化[58]。这表明PKC在IKK/IκB/NF-κB信号转导中发挥关键作用。

还有研究发现，PKC可以通过调控c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)和NF-κB的活化来介导炎症反应[59-60]。JNK又被称为应激活化蛋白激酶，是哺乳类细胞中丝裂原活化蛋白激酶信号通路的另一亚类[61]。Zhou等[62]通过动物实验发现，NF-κB的激活及下游炎症反应的启动需要JNK的激活，JNK可通过抑制NF-κB的激活减少炎症反应。Zeng等[52]也发现，JNK的活化在调节小胶质细胞内的炎症信号级联中起着关键作用。JNK抑制剂可降低PKC、IκB和NF-κB的磷酸化水平，但对IKK无抑制作用，提示JNK可能通过靶向PKC和IκB/NF-κB复合体从而影响PKC/NF-κB信号通路。

四、总结及展望

综上所述，各种证据均表明PKC参与抑郁症的发病机制。PKC可能通过介导小胶质细胞活化，增加炎症细胞因子释放，引发机体的炎症状态，进而参与抑郁症的发生发展。

未来可在已有证据的基础上深入探索以PKC、小胶质细胞活化及神经免疫炎症为核心的抑郁症发病机制，进一步研究它们之间及其上下游可能存在的病理生理机制。此外，PKC不仅可能通过参与免疫炎症过程，还可能通过许多其他生理过程如神经发育、神经递质传递、突触可塑性等在抑郁症的发生发展中发挥重要作用[63]。因此，进一步研究和开发PKC及其相关信号通路靶向的新型抗抑郁药物是治疗抑郁症的一种有前景的治疗策略。未来可推进有关针对PKC信号系统的治疗方法的研究，为寻找抗抑郁治疗的新靶点及提高抗抑郁治疗的有效性提供科学根据。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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