P2X7受体在精神疾病中的研究进展

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摘要 P2X7受体属于ATP激活的非选择性阳离子通道型受体。P2X7受体在免疫细胞和神经系统中的胶质细胞中高表达, 其通道开放可能与炎症反应、免疫应答和细胞调亡相关。研究发现, P2X7受体参与了多种精神疾病的发病机制, 其机制涉及神经炎症发生、神经可塑性改变、细胞凋亡和神经递质释放异常等, 提示该受体有望成为治疗精神疾病的新靶点, 该文主要综述P2X7受体在抑郁症、双相情感障碍、精神分裂症和焦虑症这几类常见精神疾病中的研究进展。

关键词 P2X7受体; 抑郁症; 双相情感障碍; 精神分裂症; 焦虑症

The Progress of P2X7 Receptor in Psychiatric Disorders

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Abstract The P2X7 receptor is a trimeric adenosine triphosphate (ATP)-gated non-selective cation channel and is expressed predominantly in immune cells and glial cells in the nervous systems. Activation of P2X7 channel is correlated with the inflammatory reactions, immune responses and cell apoptosis. Recently, it has been reported that the P2X7 receptor contributes to the pathogenesis of various psychiatric disorders. The mechanisms may involve genesis of neuroinflammation, alteration of neural plasticity, cell apoptosis and abnormal releases of neurotransmitters in the nervous system. The studies indicate that the P2X7 receptor could be a potential target of novel interventions of psychiatric disorders. This review summarizes recent progress of the P2X7 receptor in several prevalent mental disorders, such as depression, bipolar disorder, schizophrenia and anxiety.

Keywords P2X7 receptor; depression; bipolar disorder; schizophrenia; anxiety disorder

P2X7受体是以ATP为配体的离子通道P2X受体的亚型之一。P2X7受体参与调控多种生理现象, 如细胞增殖和凋亡、感觉传导通路、免疫应答、内脏感觉和运动等[1]。P2X7受体在神经系统分布广泛, 其表达水平和功能变化与多种精神疾病均有关联, 提示该受体与精神疾病的病理过程密切相关, 可能成

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为未来治疗精神疾病的潜在靶点。本文就P2X7受体在常见精神疾病中作用的最新研究进展作一综述。

1 P2X7受体的结构特征和分布

1.1 P2X7受体基因和蛋白结构特点

编码人类*P2RX7*的序列位于12号染色体长臂(12q24.31)上[1]。人类*P2RX7*具有高度多态性, 目前已鉴定出超过150种单核苷酸多态性(SNPs), 其中部分SNPs与重度抑郁症和双相情感障碍有关[2]。P2X7受体亚基由1个胞内氨基末端(26个氨基酸)、1个胞外结构域(282个氨基酸)、2个跨膜螺旋(每个约24个氨基酸)和1个胞内羧基末端(239个氨基酸)组成。P2X7受体的胞内末端可与多种蛋白质和脂质结合[1], 提示该受体可能是多种信号通路的共同调控节点。

1.2 P2X7受体在中枢神经系统的表达分布

在非神经系统中, P2X7受体广泛表达于免疫细胞(单核细胞、淋巴细胞和巨噬细胞等)和血源性细胞。在神经系统中, P2X7受体集中表达于小胶质细胞和星形胶质细胞[1]。有研究发现, P2X7受体在神经元中也有表达[3]。Metzger等[4]通过构建人源化P2X7受体小鼠分析P2X7受体在全脑中的表达分布, 结果显示, P2X7受体在小脑、皮质、海马脑区的神经元中表达, 其中在海马CA3区谷氨酸(glutamic acid, Glu)能锥体神经元胞体的表达最为丰富, 提示P2X7受体可能参与中枢(如海马)谷氨酸能神经系统的部分生理活动。解剖学和组织学证据进一步显示, 神经元P2X7受体可能集中表达于中枢神经系统的突触前神经末梢[5-6]。

尽管有证据支持神经元表达P2X7受体, 但在功能水平上, 该受体在神经元中是否发挥主要功能仍然存在争议。鉴于神经元–胶质细胞之间存在双向对话[3], 有部分研究人员认为神经胶质细胞可能是P2X7受体发挥生理功能的主要场所。胶质细胞的P2X7受体激活后, 通过神经元–胶质细胞的双向对话, 间接改变神经元活动。

2 P2X7受体激活与下游信号通路

2.1 P2X7受体的生理病理功能

P2X7受体与ATP的亲和力较低, 激活P2X7受体需较高浓度的ATP。P2X7受体激活之后, 不仅开放离子通道, 并且可在细胞膜上形成非选择性的大分子孔道, 允许分子量小于900 kDa的大分子和离子从该膜孔道自由通过[7], 使细胞内渗透压迅速改变, 并发生胞内外代谢物质交换。P2X7受体激活涉及活性氧产生、溶酶体酶释放、细胞膜金属蛋白酶脱落、细胞内病原体杀伤、多核巨细胞的形成以及参与T细胞核因子活化等。其中, 单纯的离子通道开放就可以完成吞噬作用和转录因子的激活, 而细胞内病原体的杀伤和多核巨细胞的形成过程则依赖于大分子孔道[1](图1)。然而, P2X7受体是如何完成通道–孔道之间的状态转化目前尚不清楚。鉴于P2X7受体两种不同状态存在功能上的差异, 提示在研究P2X7受体功能和作用机制时, 需要甄别离子通道和孔道的不同作用。

此外, P2X7受体广泛参与先天性和适应性免疫应答。P2X7受体激活对炎症因子的表达和分泌发挥了重要作用, 其中对白介素-1β(interleukin-1β, IL-1β)和白介素-6(interleukin-6, IL-6)的分泌起到了关键调节作用[8-9]。最近, Barbera-Cremades等[10]的研究发现, P2X7受体诱导TNF-α转化酶活化从而介导TNF-α产生, 这提示P2X7受体可能影响炎症因子生成和释放的多个阶段。除了控制炎症因子释放以外, P2X7受体还可调节多种神经递质的释放。敲除小鼠*P2rx7*基因可上调杏仁核中单胺能神经递质(如5-HT)的水平[11]。由于神经元重摄取GABA和谷氨酸依赖胞外Na^+浓度, P2X7受体激活使胞外Na^+浓度降低, 从而降低大鼠皮层神经末梢GABA和Glu的摄取, 且Glu的下调幅度大于GABA。因为突触间隙中Glu累积可诱发长时程增强(LTP), 提示P2X7受体可能通过调节Glu重摄取, 进而影响皮层突触可塑性[12]。

在大多数生理条件下, 由于胞外ATP浓度较低, P2X7受体处于关闭状态。在机体炎症、组织损伤和缺血缺氧等病理状态下, 活化的免疫细胞、巨噬细胞或小胶质细胞等可释放高浓度ATP, 激活P2X7受体。P2X7受体激活后可通过大分子孔道进一步释放ATP, 形成P2X7受体激活和ATP释放之间的正反馈, 放大下游信号, 并启动危险相关分子模式(damage associated molecular patterns, DAMP)激活周围的免疫细胞。同时, P2X7受体募集NLRP3炎症小体(nucleotide-binding and oligomerization domain-like receptor 3 inflammasome), 控制炎症因子, 如IL-1β的成熟和释放[13]。以上实验证据揭示, P2X7受体可参与免疫细胞和胶质细胞活化、炎症

因子生成以及神经递质释放和重摄取, 从而调节神经系统功能。

2.2 P2X7受体的下游信号通路

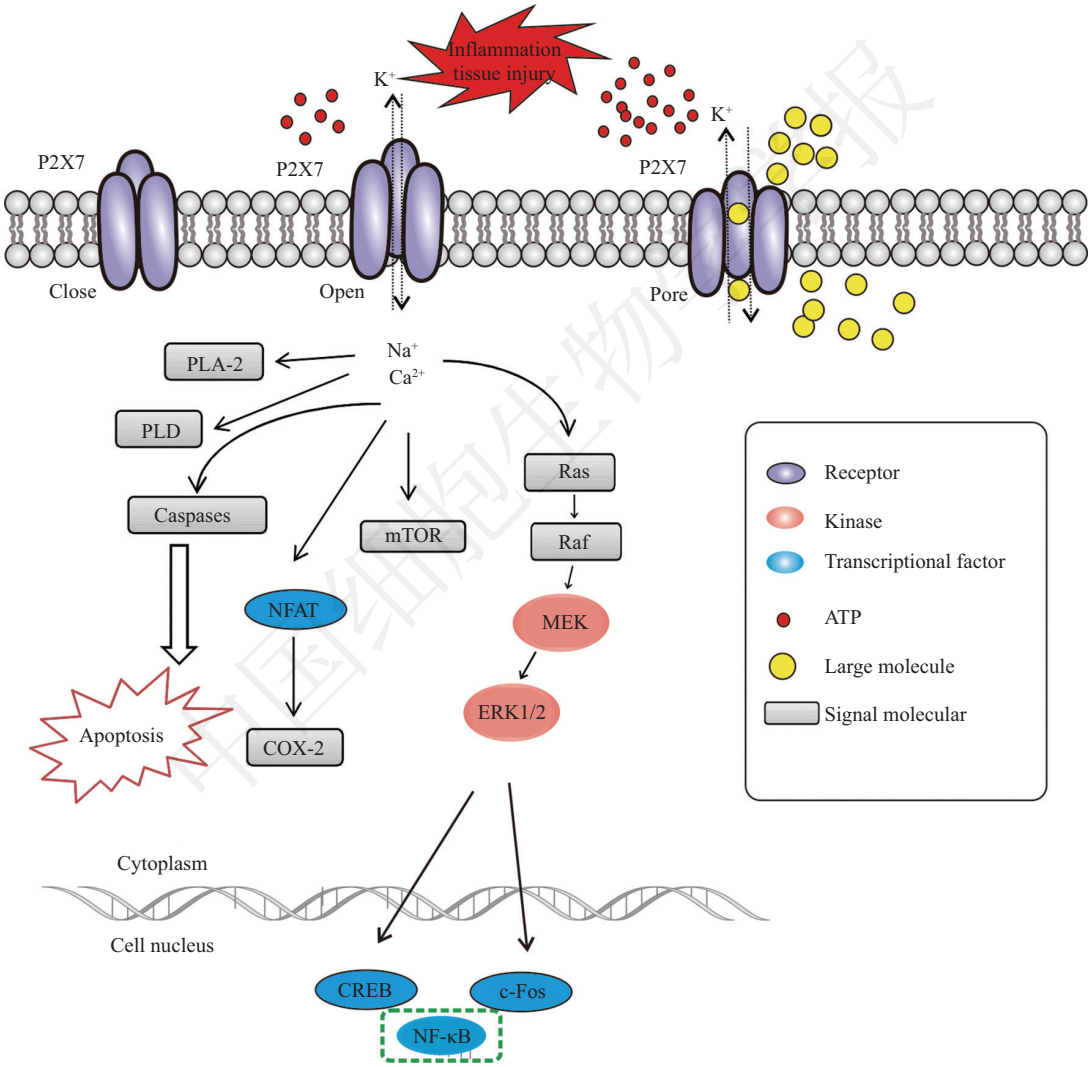
有文献报道, P2X7受体参与细胞内多种下游信号通路的激活。例如: 磷脂酶A2(PLA-2)、磷脂酶D(PLD)、半胱天冬酶(caspases)、活化T淋巴细胞核因子(NFAT)、哺乳动物靶蛋白(mTOR)、Ras-Raf-MEK-ERK1/2信号通路、环氧核酶-2(COX-2)、环磷腺苷效应元件结合蛋白(CREB)、c-Fos、核因子(NF-κB)等[14](图1)。

3 P2X7受体与精神疾病

3.1 P2X7受体在抑郁症中的作用

抑郁症是一种以情绪低落、思维迟钝和语言动作减少为主要特征, 并伴有食欲减退、睡眠障碍和自杀倾向的精神疾病[15]。

有临床研究指出, *P2RX7*的单核苷酸多态性rs2230912(Gln460Arg)与抑郁症有很强的关联[2]。在表达rs2230912(*hP2RX7*-Gln460Arg)的HEK293细胞系的培养基中加入P2X7受体激动剂, 发现Gln460Arg杂合细胞的钙离子内流减少, 提示P2X7



在不同浓度的ATP刺激下, 细胞膜上P2X7受体由关闭转为开放和大分子孔道两种不同的功能状态。在高浓度的ATP刺激下P2X7受体通道开放, 导致磷脂酶A2(PLA-2)、磷脂酶D(PLD)、半胱天冬酶(caspases)、活化T淋巴细胞核因子 (NFAT)、哺乳动物靶蛋白(mTOR)、Ras-Raf-MEK-ERK1/2信号通路、环氧核酶-2(COX-2)的激活, 通过磷酸化或脱磷酸化等方式活化c-fos、CREB及NF-κB等转录因子。

The P2X7 receptor on the cell membrane changed from closed to open and macromolecular pores in different concentrations of ATP. High level of ATP activates the P2X7 receptor, and triggers multiple intracellular downstream signals, e.g. PLA-2 (phospholipase A-2), PLD (phospholipase D), caspase, NFAT (nuclear factor of activated T cells), mTOR (mammalian target of rapamycin), Ras-Raf-MEK-ERK 1/2 signal pathway. These proteins are translocated into the nucleus, and then activate transcription factors (e.g. c-fos, CREB and NF-κB) through phosphorylation or dephosphorylation.

图1 P2X7受体的功能状态及下游信号通路

Fig.1 Functional states of the P2X7 receptor and its downstream signaling pathways

受体功能受损; 与此同时, 利用人源化P2X7小鼠(*hP2RX7*)模型敲入人类*hP2RX7*-Gln460Arg, 发现杂合小鼠在社交挫败实验中表现出焦虑增加和快感缺失, 提示rs2230912与P2X7受体功能和情绪障碍相关[16]。此外, 杂合小鼠的睡眠结构发生改变, 具体表现为小鼠进入快速动眼睡眠(REMS)潜伏期延长、慢波活动(SWA)和深度非动眼睡眠(NREMS)时间减少, 这与人类杂合子携带者的睡眠表现一致[17], 对啮齿类动物和人类进行睡眠剥夺后, 脑内P2X7受体表达上调[17], 这提示了SNP-rs2230912可能通过改变睡眠结构参与抑郁症发病。

已有多项基础研究证实, *P2rx7*$^{-/-}$小鼠表现出抗抑郁表型[18-21]。另有研究显示, P2X7受体参与了CUMS或脂多糖(LPS)诱发的抑郁样行为, 提前给予P2X7受体拮抗剂干预, 可以反转CUMS或全身给予LPS诱发的抑郁样行为[22], 提示了P2X7受体与抑郁症发病的相关性。

有研究表明, 慢性炎症和炎症因子与精神疾病的发生和发展相关[23]。炎症因子不仅在抑郁症患者的血浆、脑脊液和死后脑组织中的含量较高[24], 而且高水平的炎症因子与老年抑郁症和产后抑郁症有关[25-26]。有研究表明, 在CUMS刺激下, P2X7受体转录和表达水平上调, 并可通过激活P2X7R-NLRP3-IL-1β通路参与了IL-1β的成熟[27-28], 提示P2X7受体通过促炎反应参与抑郁症的病理过程。在中枢神经系统内, P2X受体激活使小胶质细胞活化, 并引起IL-1β等炎症因子释放, 导致抑郁样行为; 相反, 使用P2X7受体拮抗剂可以抑制小胶质细胞释放IL-1β, 减轻抑郁样行为[29]。以上研究提示, P2X7受体可能通过促进炎症反应参与抑郁症的发病。

P2X7受体参与抑郁症发病的另一可能机制为, P2X7受体激活损伤了海马突触可塑性。临床研究证实, 抑郁症患者海马体积较小[30], 海马树突棘密度显著降低[31]。而习得性无助模型的建立可使正常小鼠海马齿状回(dentate gyrus, DG)中树突棘数量减少, 而*P2X7*基因敲除鼠没有出现类似的现象[32]。Hajszan等[33]也发现, 随着习得性无助模型的建立, *P2rx7*$^{-/-}$小鼠的海马CA1和DG区域中突触密度显著减少, 而CA3区域仅显示轻微降低, 证明敲除*P2X7*基因对抑郁小鼠海马区CA3中突触丢失的保护效应更为显著, 提示下调P2X7受体导致的抗抑郁效果可能涉及改善海马CA3的突触可塑性。此外, 脑源性神经营养因子(brain derived neurotrophic factor, BDNF)可促进神经元存活和再生, 并增强海马突触可塑性, 如上调海马长时程增强, 促进海马DG区神经元再生[34]。研究表明, BDNF的表达水平下调与抑郁症发病有很强的关联, BDNF下调可能是抑郁行为发生的关键机制之一[35]。在抑郁症患者脑内海马中检测到BDNF mRNA和蛋白表达减少[36], 抑郁症患者血清BDNF水平降低[37], 在小鼠脑内注射外源性BDNF可以改善小鼠的抑郁样行为[36]。P2X7受体活化抑制神经元对Glu的再摄取, 促进突触间隙中Glu的堆积, 过度活化突触外NR2B受体, 进而下调海马BDNF的表达。野生型小鼠接受腹腔注射LPS后, 海马BDNF水平显著低于*P2rx7*$^{-/-}$小鼠, 提示P2X7受体与抑郁诱发的海马BDNF减少相关。

5-HT能神经递质在抑郁症的发病机制中起重要作用, 5-HT受体和递质转运也是临床上抗抑郁药的主要靶点之一。临床研究中观察到, 抑郁症患者淋巴细胞5-HT表达的减少, 并且这种减少可以通过抗抑郁药物部分逆转[38]。Csolle等[11]发现, 在LPS诱发的抑郁模型中, *P2rx7*$^{-/-}$小鼠海马5-HT释放水平高于野生型小鼠, 提示P2X7受体激活与海马5-HT释放有关; 有意思的是, P2X7受体对中缝核神经元投射至海马的轴突末梢释放的5-HT有相反的调节作用。Goloncser等[38]选择性激活*P2rx7*$^{-/-}$小鼠的中缝核中部的5-HT神经元末梢和中缝核投射至海马的部分5-HT能神经元之后, *P2rx7*$^{-/-}$小鼠的5-HT释放比野生型小鼠少; 使用P2X7受体拮抗剂JNJ-47965567也可以得到类似的结果。这提示P2X7受体可以调节中缝核及中缝核投射至海马的部分神经元的5-HT释放。说明P2X7受体对5-HT的调节作用在不同脑区和神经环路有所差异, P2X7受体对五羟色胺能神经元功能和5-HT的释放有更为复杂的调节作用。

在动物模型和抑郁症患者的研究中均发现, P2X7受体表达水平与抑郁症的病程呈正相关, 但P2X7受体参与抑郁症发病的细胞分子机制和特异性的神经环路仍不清楚, P2X7受体可能同时在不同脑区发挥作用并激活了多条细胞内下游信号通路。因此, 改变P2X7受体的表达和功能, 能够干预抑郁症的病理过程, 应用P2X7受体的拮抗剂可能成为治疗抑郁症的新方法(表1)。

3.2 P2X7受体在双相情感障碍中的作用

双相障碍属于一种心境障碍, 指躁狂和抑郁交

表1 P2X7受体参与抑郁症的总结

Table 1 Summary of the involvement of the P2X7 receptor in depression

类型 Types	主要发现 Main results	种属 Species	模型/患者 Models/patients	研究阶段 Research stages	参考文献 References
Genetic change related	The P2RX7 gene polymorphism rs2230912 is associated with depression	Human	Depression patients	Clinical research	[2]
	Hp2rx7 mice sleep architecture was significantly disturbed	Human	Depression patients	Clinical research	[17]
Phenotypic change related	The function of P2X7 receptor was impaired in heterozygous mice, heterozygous mice shows higher levels of anxiety and anhedonia accompanied in chronic social defeat test	Humanized mice	*Hp2rx7*	Fundamental research	[16]
	Knockout of P2X7 reduces the depression-like behavior induced by LPS	Mice	*P2rx7*$^{-/-}$+LPS	Fundamental research	[18-21]
	P2rx7$^{-/-}$ mice have resilience c-fos expression in the dental gyrus of the hippocampus and the basolateral amygdala in the repeated forced swim test	Mice	*P2rx7*$^{-/-}$+FST	Fundamental research	[18]
	P2X7 antagonists reverse the depression-like behavior induced by CUMS	Mice/rats	CUMS+BBG/A438079	Fundamental research	[22]
Inflammatory reaction related	The releases of IL-1β and TNF-α and the activation of NLRP3 are blocked by the P2X7 antagonists	Mice/rats	CUMS+BBG/A438079	Fundamental research	[22]
	P2X7R is related to proliferation and activation of microglial cells. Depression patients have higher levels of IL-1β in the plasma, the cerebrospinal fluid and the brain	Human	Depression patients	Fundamental research	[24-25,27]
	The level of IL-1β is decreased in *P2rx7*$^{-/-}$ mice after LPS injection	Mice	*P2rx7*$^{-/-}$+LPS	Fundamental research	[27]
	P2X7R is involved in the maturity of IL-1β. The release of IL-1β in the microglial cell is blocked by the P2X7 antagonist	Mice	*P2rx7*$^{-/-}$+CUMS	Fundamental research	[27,29]
	Activation of the P2X7-NLRP3-IL-1β pathway in hippocampal glial cells mediates chronic stress-induced depressive-like behaviors	Mice/rats	*P2rx7*$^{-/-}$+CUMS	Fundamental research	[22]
Synaptic plasticity related	Knockout of P2X7 suppresses spine synapse plasticity in the learned helplessness model of depression	Mice	*P2rx7*$^{-/-}$+learned helplessness	Fundamental research	[13]
	P2rx7$^{-/-}$ mouse has a decrease of synaptic density in the hippocampal CA1 and DG, but not in CA3, in the learned helplessness model	Mice	*P2rx7*$^{-/-}$+learned helplessness	Fundamental research	[32-33]
Neurotransmitter release related	GABA and glutamate releases in the hippocampal slices of *P2rx7*$^{-/-}$ mice decrease after application of electrical stimuli or ATP incubation	Mice	*P2rx7*$^{-/-}$+electrical stimulation/ATP	Fundamental research	[38]
	Activation of the endogenous P2X7R modulates 5-HT release in the hippocampus	Mice	*P2rx7*$^{-/-}$+JNJ-47965567	Fundamental research	[38]

BBG: 亮蓝G; CUMS: 慢性应激; LPS: 脂多糖; A438079: P2X7受体拮抗剂; JNJ-47965567: P2X7受体拮抗剂; *P2rx7*$^{-/-}$: *P2rx7*基因敲除; *Hp2rx7*: 人源化P2X7R动物。

BBG: brilliant blue G; CUMS, chronic unpredictable mild stress; LPS: lipopolysaccharide; A438079: P2X7 receptor antagonist; JNJ-47965567: P2X7 receptor antagonist; *P2rx7*$^{-/-}$: *P2rx7* gene knockout; *Hp2rx7*: humanized P2X7R animals.

替发作的一类疾病, 又称双相情感障碍。已有遗传学研究证明, P2X7受体与双相情感障碍发病机制相关, 如人类*P2RX7*的SNP(*rs2230912_A*)与双相情感障碍相关[2]。一项临床研究表明, *P2RX7*与1型双相情感障碍的快速循环相关[17]。快速循环(rapid circulation, RC)是双相情感障碍的一种严重形式, 其特征是疾病的频繁发作, 而RC患者的双相症状更易受到睡眠障碍和昼夜紊乱的影响[39], 该实验显示, 睡眠剥夺的RC患者外周血单核细胞的*P2RX7* mRNA表达水平升高[17], 其机制可能是P2X7受体通过间接调节Glu水平, 进而改变昼夜节律[40]。此外, *rs2230912_A*在RC患者中比非RC患者更常见。

神经炎症也是双相情感障碍发病的风险因素之一, P2X7受体可能通过促进炎症反应参与双相情感障碍发病。临床研究结果表明, 双相障碍患者的P2X7受体活化水平和炎症因子水平较正常人群高[41]。与

正常受试者相比, 双相情感障碍患者的血清和血浆中IL-6、IL-8、TNF-α等炎症因子水平升高[42]。Söderlund等[43]研究发现, 双相情感障碍患者脑脊液的IL-1β水平也显著升高。动物研究进一步表明, 选择性P2X7受体拮抗剂或*P2rx7*$^{-/-}$小鼠可减轻苯丙胺(amphetamine, AMPH)诱导的大鼠兴奋躁动现象, 并可以降低IL-1β和TNF-α等促炎因子的水平[44]。

综上所述, 双相情感障碍与P2X7受体的活化相关联, P2X7受体可能通过介导炎症因子的释放参与双相情感障碍的发病, 提示P2X7受体可能是双相情感障碍的潜在治疗靶点(表2)。

3.3 P2X7受体在精神分裂症中的作用

精神分裂症是一种以阳性症状、阴性症状和认知功能障碍为主要临床表现的精神疾病。Kovanyi等[45]首次研究了P2X7受体在精神分裂症动物模型的作用, 在五氯苯酚(pentachlorophenol, PCP)的诱导下, 野生型小鼠出现运动过强、刻板印象行为、共济失调和社交退缩等行为学表现, 而敲除*P2RX7*或给予P2X7受体拮抗剂JNJ-42253432可以反转这一现象。该研究还发现, P2X7受体参与精神分裂症的机制还涉及NMDA受体通路; 在细胞分子水平, 用PCP处理的成年野生型小鼠, 其背外侧前额叶皮层中NR2A亚基mRNA表达水平增高, 而在*P2rx7*$^{-/-}$小鼠的dlPFC中NR2A和NR2B亚基mRNA表达水平并无显著变化, 这一实验结果提示PCP对NMDA受体亚基表达的影响受内源性P2X7受体调节。

已有研究表明, 精神分裂症的核心特征之一为背外侧前额叶皮层(dorsolateral prefrontal cortex, dlPFC)中微环路的状态和功能改变[46]。用PCP诱导的精神分裂症动物模型中, dlPFC中P2X7受体的功能增强; *P2rx7*$^{-/-}$小鼠或注射了P2X7受体拮抗剂JNJ-47965567的小鼠, 其dlPFC锥体神经元的NMDA受体电流幅度比野生型或对照小鼠低[45]。研究人员还分析了精神分裂症相关基因, 在注射PCP后, 小鼠dlPFC的神经调节蛋白1(*neuregulin1*, *NRG1*)表达水平升高。而*NRG1*是精神分裂症的主要易感基因之一[47], 其主要通过酪氨酸激酶受体4(receptor tyrosine-protein kinase 4, ErbB4)和NR2亚基的磷酸化来改变NMDA受体水平及其功能。在*P2rx7*$^{-/-}$小鼠的dlPFC中未发现PCP诱导*NRG1* mRNA的上调, 这表明P2X7受体-NRG1信号传导之间的特异性相互作用, 可能与谷氨酸能突触传递有关。

综上, P2X7受体可能通过调节前额叶的谷氨酸受体通路和神经兴奋性参与精神分裂症的发生发展, 但是针对其他脑区和其他可能通路的研究仍相对缺乏(表3)。

3.4 P2X7受体在焦虑症中的作用

焦虑症是一种以阵发性或持续性的焦虑情绪为主要临床症状的精神疾病, 并伴有植物神经功能紊乱及运动不安。编码*P2RX7*的基因位于染色体12q24.31上, 该区域是抑郁和焦虑障碍的重要遗传区域, 提示其可能与焦虑等情感障碍有关[48]。Xie等[49]发现, 同时存在焦虑和抑郁症状的原发性干燥综合征(primary Sjogren's syndrome, pSS)患者的$CD14^{-}$外周血单核细胞(peripheral blood mononuclear cell, PBMC)膜上的P2X7受体表达显著高于无焦虑

表2 P2X7受体参与双相情感障碍的总结

Table 2 Summary of the involvement of the P2X7 receptor in the bipolar disorder

类型 Types	主要发现 Main results	种属 Species	模型/患者 Models/patients	研究阶段 Research stages	参考文献 References
Genetic change related	The *P2RX7* gene polymorphism is associated with the biopolar disorder	Human	Biopolar disorder patients	Clinical research	[2]
Phenotypic change related	P2X7R expression is related with sleep deprivation and affects the rapid cycling in the bipolar disorder	Human	Bipolar disorder patients	Clinical research	[17]
Inflammatory reaction related	The activation of P2X7R and the levels of pro-inflammatory cytokines are increased in the bipolar disorder patients	Human	Bipolar disorder patients	Clinical research	[42-43]
Phenotypic change related	Knockout of P2X7 or application of P2X7 antagonists alleviates responsiveness and locomotor activity caused by AMPH and reduces the levels of inflammatory factors	Mice	AMPH+BBG/ *P2rx7*$^{-/-}$	Fundamental research	[44]

AMPH: 苯丙胺; BBG: 亮蓝G; *P2rx7*$^{-/-}$: *P2rx7*基因敲除。

AMPH: amphetamine; BBG: brilliant blue G; *P2rx7*$^{-/-}$: *P2rx7* gene knockout.

表3 P2X7受体参与精神分裂症的总结

Table 3 Summary of the involvement of the P2X7 receptor in schizophrenia

类型 Types	主要发现 Main results	种属 Species	模型/患者 Models/patients	研究阶段 Research stages	参考文献 References
Phenotypic change related	Knockout of P2X7 or application of P2X7R antagonists reverses schizophrenia-like behavioral induced by PCP	Mice	PCP+JNJ-42253432/ *P2rx7*$^{-/-}$	Fundamental research	[45]
	Knockout of P2X7 or application of P2X7 antagonists reverses PCP-evoked upregulation of the P2X7R function in the prefrontal cortex	Mice	PCP+JNJ-42253432/ *P2rx7*$^{-/-}$	Fundamental research	[45]
Synaptic transmission related	PCP increased the transcription NR2A and NRG1 mRNA in wild type mice, but not in *P2rx7*$^{-/-}$ mice. *P2rx7*$^{-/-}$ mice has lower amplitude of NMDA-mediated current in cotext neurons	Mice	PCP+*P2rx7*$^{-/-}$	Fundamental research	[45]

PCP: 五氯苯酚; JNJ-47965567: P2X7受体拮抗剂; *P2rx7*$^{-/-}$: *P2rx7*基因敲除。

PCP: pentachlorophenol; JNJ-47965567: P2X7 receptor antagonist; *P2rx7*$^{-/-}$: *P2rx7* gene knockout.

表4 P2X7受体参与焦虑症的总结

Table 4 Summary of the involvement of the P2X7 receptor in anxiety

类型 Types	主要发现 Main results	种属 Species	模型或患者 Models/patients	研究阶段 Research stages	参考文献 References
Genetic changes related	The P2RX7 polymorphism rs2230912 is associated with anxiety	Human	Anxiety disorder patients	Clinical research	[2]
Phenotypic changes related	Over-expression of P2X7R on the surface of PBMC in pSS patients.	Human	pSS patients	Clinical research	[49]
Phenotypic changes related	Knockout of P2X7 relieves anxiety-like behavior induced by LPS	Mice/rats	*P2rx7*$^{-/-}$+LPS	Fundamental research	[21-22]
Inflammatory reaction related	The P2X7R antagonist reverses anxiety-like behavior induced by CUMS via P2X7/NLRP3/IL-1β pathway	Mice/rats	CUMS+BBG	Fundamental research	[22,28,50]

PBMC: 外周血单核细胞; pSS: 原发性干燥综合征; BBG: 亮蓝G; CUMS: 慢性应激; LPS: 脂多糖; *P2rx7*$^{-/-}$: *P2rx7*基因敲除。

PBMC: peripheral blood mononuclear cell; pSS: primary Sjogren's syndrome; BBG: brilliant blue G; CUMS: chronic unpredictable mild stress; LPS: lipopolysaccharide; *P2rx7*$^{-/-}$: *P2rx7* gene knockout.

和抑郁症状的pSS患者。ATP刺激后, 外周血CD14^{-} PBMC膜上的P2X7受体表达与焦虑、抑郁评分呈显著正相关。P2X7受体可能通过调节促炎症因子、基因多态性等参与pSS患者及其合并焦虑抑郁状态的发病。这一结论提示, 可将P2RX7作为研究位点, 分析pSS患者的基因多态性, 进而研究pSS与合并焦虑、抑郁等心理障碍的相关性。

最近研究发现, CUMS和P2X7受体激动剂均可诱发小鼠的焦虑行为, 而小鼠海马内微量注射P2X7受体拮抗剂BBG和A438079均可改善CUMS导致的焦虑样行为[22,50], 在*P2rx7*$^{-/-}$小鼠也观察到焦虑样行为的改善[21-22]。其机制可能为, CUMS导致胞外ATP积聚并持续激活P2X7/NLRP3轴, 从而促进IL-1β合成和释放, 提示CUMS可能通过激活P2X7/NLRP3诱发炎症反应, 并引起焦虑样行为(表4)。

4 结论与展望

综上, P2X7受体参与精神疾病的机制涉及激活小胶质细胞、释放多种炎症因子(如IL-1β、IL-6和TNF-α等)、调控5-HT的释放、激活胞内NLRP3信号通路、抑制突触后膜对Glu和GABA的再摄取、抑制BDNF释放和调节NMDA受体功能等。其中的共同关键机制可能是P2X7受体上调炎症水平, 影响多种神经递质的释放和传递, 进而直接或间接改变关键脑区(如海马和前额叶)神经元的突触可塑性, 影响疾病的发生发展过程。

P2X7受体在精神疾病中的作用机制研究尚处于初始阶段, 未来可以从以下几个方面进行深入探索。(1)P2X7受体在中枢神经系统中的表达和分布仍存在争议, 它在疾病发生发展过程中的功能变化和涉及的疾病相关特异性神经环路特征尚不清楚。

(2)以往针对P2X7受体对神经递质调控的研究多集中于Glu释放, 对于其他神经递质如GABA、5-TH研究甚少, 且有文献指出, P2X7受体对5-HT的调节作用在不同脑区和神经环路有所差异[11,38], 其具体机制目前仍不清楚。(3)研究指出P2X7受体在海马CA3锥体神经元表达最为丰富[4], 该脑区的表达P2X7受体神经元是否有特殊的生理功能？ (4)P2X7受体存在离子通道和非选择性大分子孔道两种状态, 在未来的研究中需要甄别其在疾病中发挥的不同作用。(5)目前, 对P2X7受体参与精神疾病的研究多集中于P2X7/NLRP3/IL-1β通路, 该受体是否通过其他免疫相关通路参与精神疾病。将来, 利用光遗传学、高分辨显微技术、CRISPR基因编辑工具和神经环路示踪等技术对这些问题展开研究, 有助于更好阐明P2X7受体的生理和病理功能。

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