

多胺代谢在精神分裂症中的研究进展

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摘要: 多胺代谢在中枢神经系统和其他器官的多种细胞功能中发挥重要作用。越来越多研究表明多胺代谢与精神分裂症 (schizophrenia, SCZ) 的病理变化密切相关。在 SCZ 患者和该疾病的动物模型中, 已经证实了多胺及其前体、衍生物、代谢酶和相关基因表达的变化。该文就多胺代谢在 SCZ 中的研究进展进行综述, 以期靶向多胺代谢的 SCZ 治疗提供新的思路。

关键词: 多胺代谢; 精神分裂症

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Progress of polyamine metabolism in pathogenesis of schizophrenia

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Abstract: Polyamine metabolism plays an important role in a variety of cellular functions in the central nervous system and other organs. More and more studies have shown that polyamine metabolism is closely related to the pathological changes of schizophrenia. In patients with schizophrenia and in animal models of the disease, it has been confirmed that there are changes in the polyamines, their precursors, derivatives, metabolic enzymes and expression of related genes. This article reviews the research progress of polyamine metabolism in schizophrenia, in order to provide a new idea for schizophrenia treatment targeting polyamine metabolism.

Key words: polyamine metabolism; schizophrenia

精神分裂症 (schizophrenia, SCZ) 是一种复杂的精神障碍, 其主要症状包括幻觉、妄想、思维紊乱和认知缺陷^[1]。虽然 SCZ 的发病率相对较低, 但对患者及其家人造成严重的负担。尽管目前已有许多抗精神病类药物在治疗 SCZ 上取得了重大进展, 但这些药物仍存在一定比例的耐药性及副作用等。目前对于 SCZ 的病因仍然知之甚少, 研究重点在递质多巴胺和谷氨酸上, 包括纹状体多巴胺的过度传递、多巴胺 D2 受体增加、NMDA 谷氨酸功能的破坏等。但已有研究证实多种神经递质和神经调节剂, 包括 γ -氨基丁酸 (GABA)、甘氨酸、D-丝氨酸、5-羟色胺 (5-HT)、乙酰胆碱、多胺

及其衍生物和相关合成酶等, 也都与其病理生理学有关^[2-6]。因此, 本文对多胺代谢在 SCZ 中可能的调节机制进行阐述, 以期临床治疗 SCZ 提供新的思路。

1 中枢神经系统中的多胺代谢

多胺是普遍存在于动植物所有组织和细胞类型中的脂族聚阳离子, 包括腐胺 (putrescine, PUT)、亚精胺 (spermidine, SPD)、精胺 (spermine, SPM) 等。多胺代谢能通过多胺的合成、分解和转运, 以及单个多胺间的相互转化进行高度调节, 从而在机体中发挥重要作用^[7]。而在中枢神经系统中, 多胺具有独特的生物化

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学性质,且主要在神经元中合成。同时,在多胺囊泡转运蛋白的作用下,多胺能实现在神经元和神经胶质细胞中的双向转运,从而参与神经系统处理、传递和存储信息^[8-9]。值得注意的是,神经胶质细胞在多胺转运过程中,主要参与的是多胺的摄取和释放,而不是合成^[10]。然而,研究发现在新生儿中,星形胶质细胞也可以通过鸟氨酸脱羧酶(ornithine decarboxylase, ODC)合成足量的多胺^[11]。

有研究表明,天然多胺、SPM和SPD及其前体PUT均以较高的浓度存在,同时也表现出许多神经生理学和代谢方面的作用,包括控制核酸和蛋白质的合成、调节离子通道和钙依赖性递质释放等^[12]。但由于它们在血脑屏障中的转运受限,导致其在中枢神经系统中的存在主要是由脑源性局部合成^[6]。此外,有研究发现神经元能通过ODC,使鸟氨酸转化为PUT^[13]。还有研究在神经元中发现了参与多胺代谢相关的酶和酶调节剂,如抗ODC、抗酶抑制剂(AZINs)、SPD/SPM N1-乙酰转移酶(SAT1)、SPD合成酶(SRM)、SPM氧化酶(SMOX)、精氨酸酶(ARG)和精氨酸脱羧酶(ADC)等^[6, 10, 14-17]。还有研究证明,神经调节剂胍丁胺及其前体精氨酸可穿过血脑屏障,且胍丁胺在大脑中的浓度和定位由外周胍丁胺和精氨酸水平以及ADC的内源合成来决定,并能对各种神经递质和信号通路的调节起到重要作用^[18]。此外,胍丁胺降解酶胍胺酶(AGMAT)也存在于神经元中,可将胍丁胺降解转化为PUT。另外,胍丁胺代谢酶,又称为胍胺酶样蛋白,除了被发现存在于脑神经元中,还发现其也存在于星形胶质细胞中^[6]。

2 精神分裂症中的多胺代谢

既往认为SCZ是由于大脑某些部位多巴胺相关机制的缺陷而导致的。1983年, Richardson-Andrews^[19]提出包括SCZ在内的中枢神经系统病变所涉及的病理机制调控点是多胺而非多巴胺。

2.1 多胺调控

有研究发现,SCZ患者血液中的所有多胺水平都会显著增高,并且会受到抗精神病类药物的影响^[20-22]。但在使用氯氮平治疗耐药性SCZ患者中,却并未发现多胺水平的改变,说明上述效应可能还与治疗反应有关^[23]。此外,还有研究发现,在SCZ患者的成纤维细胞中也伴随有SPM和总多胺的水平升高^[13]。为了更清晰了解SCZ患者大脑中多胺的变化,又有研究对SCZ患者死后脑组织中的SPM、SPD和PUT等多胺进行检测,

发现SPM、SPD和PUT水平均高于正常大脑组织^[24-25]。另外,在早发性SCZ患者的血中发现PUT的前体胍丁胺浓度降低^[26],而在首次发病和慢性SCZ患者的血浆和死后大脑中则发现胍丁胺的浓度显著增加,但经过药物治疗后,血液中胍丁胺的浓度会有所下降^[6]。

2.2 多胺代谢相关基因的表达调控

早在2002年,就已有研究使用cDNA微阵列对SCZ患者所有主要代谢途径进行基因表达谱分析,发现鸟氨酸-多胺代谢调节途径中的ODC抗酶抑制剂(OAZIN)和鸟氨酸转氨酶(OAT)的基因表达一致下降,且OAZIN和OAT还参与了多胺生成的调节。有趣的是,研究还发现鸟氨酸-多胺代谢还能影响谷氨酸和天冬氨酸的代谢,并且多胺还可以直接作为强效的NMDA受体拮抗剂。因此,提示谷氨酸和天冬氨酸水平的降低,伴随ODC活性和多胺生成的减少,可能是SCZ患者大脑代谢状态的特征。值得注意的是,这种减少并不是患者长期接受抗精神病药物治疗的结果,因为在接受氟哌啶醇治疗的猴子中,仅OAZIN的表达略有减少^[27]。后来有研究发现SAT1及其编码基因是调节多胺分解代谢的主要因子,并进一步研究SAT-1-1415T/C单核苷酸多态性(single nucleotide polymorphism, SNP)与SCZ的相关性,结果显示SAT-1-1415T/C SNP与SCZ之间有没有显著关联,但在女性患者中发现等位基因C与精神病理之间有轻度关联^[28]。此外,还有研究通过对SCZ的聚合功能基因组学(convergent functional genomics, CFG)进行分析,发现编码AZIN1的基因AZIN1型的CFG评分有3.0,说明AZIN1型是与SCZ相关的候选基因^[29]。而Maycox等^[30]对两个大型SCZ队列的基因表达进行分析,却并没有发现任何与多胺代谢相关的差异表达基因。

2.3 多胺代谢酶调控

目前已有研究证实了SCZ患者的脑组织或血液有涉及多胺代谢酶的改变,说明SCZ在发生发展中受到多胺代谢酶的调控。早在1980年,就已有研究发现急性SCZ患者的血浆多胺氧化酶(PAO)活性会显著降低,但其活性降低与SCZ的亚型、发病年龄或药物治疗无关^[31]。有趣的是,Dahel等^[32]却在SCZ患者的血清中发现PAO活性显著增高,还发现经电休克治疗后,患者的PAO可恢复到正常水平。另外,在对SCZ患者的研究中发现,额叶皮层、海马体或内嗅皮层的ODC水平均正常^[24]。然而,SCZ新生大鼠模型的皮质神经元中却观察到ODC活性增加^[33]。还有研究发现与正常人相比,SCZ患者血清中的SMOX活性会显著

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