抑郁症研究和治疗的新靶标: JNK 信号通路的作用

张军涛^{1,2}, 林文娟^{1,2*}

1. 中国科学院心理研究所心理健康重点实验室, 北京 100101;

2. 中国科学院大学心理学系, 北京 100049

* 联系人, E-mail: linwj@psych.ac.cn

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摘要 c-Jun氨基端激酶(c-Jun N-terminal kinase, JNK)属于丝裂原激活的蛋白激酶(mitogen-activated protein kinase, MAPK)家族中受应激激活的一类激酶。众多研究表明, 在神经萎缩、炎症反应、氧化应激、心理应激事件中均显著涉及JNK的激活, 而这些事件均与抑郁症紧密相联。近年来运用基因敲除和JNK抑制剂等手段证明JNK的确参与抑郁症状的调控; 同时不少抗抑郁药的疗效涉及对JNK活性的调节, 这些已初步确立JNK与抑郁症之间的关联。本文综述了近年来报道有关JNK与抑郁症关联的研究结果, 并全面地考察了其可能的作用机制, 涵盖神经萎缩、神经发生、神经突触可塑性、神经炎症、氧化应激、神经兴奋性毒性和糖皮质激素抵抗7个方面, 提出确立JNK为靶标进行研究抑郁症的新途径。此外, 结合目前围绕JNK进行药物研发和干预JNK途径带来的抗抑郁效果的研究进展, 我们认为以JNK为靶标治疗抑郁症具有可观的应用前景。

关键词 抑郁症, c-Jun 氨基端激酶, 神经萎缩, 神经发生, 突触可塑性, 神经炎症, 兴奋性毒性, 糖皮质激素抵抗

抑郁症是全球发病率最高的一类精神疾病, 它会导致患者行动能力受损并丧失照顾自身生活的能力甚至导致自杀。根据WHO的数据, 全世界约有3.22亿人口在受抑郁症困扰, 并且每年大约有85万人死于抑郁症疾病^[1]。然而目前关于抑郁症的发病机制尚未被彻底阐明, 并且临床上许多抗抑郁药相比安慰剂疗效并不显著^[2]。现今的抗抑郁药主要基于抑郁症的单胺类递质缺陷假说以及谷氨酸能假说等研发的, 包括单胺氧化酶抑制剂、三环类抗抑郁药、选择性5羟色胺重吸收抑制剂、5羟色胺和去甲肾上腺素重吸收抑制剂、NMDA受体拮抗剂等, 但普遍存在起效较慢、治愈率低、复发率高或副作用大等问题, 这与人们对抑郁症的病理机制缺乏清晰的了解有关^[3]。探索新的研究和治疗途径迫在眉睫。

JNK 激酶(c-Jun N-terminal kinase)属于 MAPK

(mitogen-activated protein kinase)家族的重要成员, 由于它可调控细胞内外不同的应激反应, 因此也被称为应激激活蛋白激酶。研究发现JNK的诸多调控功能与抑郁症的病理机制有高度相关性。抑郁症的许多病理因素如神经炎症、神经兴奋性毒性、氧化应激、大脑缺血、心理应激等均能促使JNK活性升高。近年来, 人们发现一些有关JNK信号通路的基因畸变与精神类疾病相关联^[4-6]。尤其值得注意的是, 敲除*Jnk*基因后能直接对抑郁或焦虑样行为产生影响。例如基因敲除*Jnk1*能够促进成年期海马神经发生从而缓解了小鼠焦虑和抑郁样行为^[7]。不少抗抑郁药的药效机理也涉及对JNK的活性调节。已有学者提出将JNK及其下游通路作为抑郁症治疗靶点的假设^[8], 但这一假设还依赖于针对JNK的药物研发进展以及有待临床检验。

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本文将从4个方面对JNK的研究进展及与抑郁症的关系进行阐述: (1) JNK激酶及其信号调控通路; (2) JNK与抑郁症; (3) JNK可能参与抑郁症发生的调控机制; (4) JNK作为抑郁症治疗新靶点的前景. 借此为抑郁症的研究提供新思路 and 为抑郁症的治疗提供新靶点.

1 JNK激酶及其信号调控通路

JNK与MAPK家族其他成员一样, 其磷酸化底物分子的丝氨酸/苏氨酸位点. JNK家族存在JNK1, JNK2和JNK3三种亚型, 它们在组织表达分布、活性调节和功能上具有差异. JNK1和JNK2在全身各处包括脑组织都广泛表达, 但JNK3却主要在脑组织中表达^[9].

在成年小鼠脑中JNK处于组成型活化状态, 但在外周器官中如肺脏、心脏、肝脏、肌肉、脾脏、肾脏等中则无组成型活化, 提示JNK信号在成年脑中可能存在重要作用^[10].

JNK激酶涉及的信号转导通路如图1所示, 众多抑郁症中涉及的病理因素, 例如炎症因子(TNF- α 、IL-1 β 、IL-6等)、氧化应激、神经兴奋性毒性、糖皮质激素, 心理应激事件都能调节JNK的活性, JNK很可能是这些上游信号调控抑郁行为的重要效应分子.

JNK激酶与其他MAPK激酶一样, 受三级激酶级联信号调控, MKK4和MKK7是其直接上游激活蛋白, 涉及的MAPK激酶激酶则包括MEKK1, MEKK4,

图1 (网络版彩色) JNK的信号调控通路, 包括能调控JNK活性的细胞内外第一信使、细胞内能调节JNK活性的上游信号分子和JNK的下游调控底物或调控表达的信号分子. 炎症反应、氧化应激、兴奋性毒性、糖皮质激素水平上升、心理应激等这些与抑郁症病因密切相关的信号事件均能调节JNK的活性. 本图展示了能被JNK磷酸化的底物, 包括介导线粒体凋亡途径的Bcl-2, Bcl-xL, Bad和Bim-EM; 转录因子p53, c-JUN, c-Fos, c-Myc, ATF-2以及GR; 参与突触可塑性调节的AMPA和PSD95; 参与树突形态构建、轴突生长和寻路等调节的MAP-2和MAP-1b. 此外, JNK促进TNF- α , IL-1 β , iNOS和COX-2这些促炎症反应信号分子或酶的表达. MKK, MAPK激酶; MAP3Ks, MAPK激酶激酶; MKP/DUSP, 有丝分裂原激活蛋白激酶磷酸酶, 又称双特异性磷酸酶; JIP, JNK相互作用蛋白, 与JNK结合调节JNK的活性; iNOS, 可诱导性一氧化氮合酶; COX-2, 环氧合酶-2; GR, 糖皮质激素受体; AMPAR, AMPA型谷氨酸受体; PSD95, 突触后致密蛋白95; MAP, 微管结合蛋白

Figure 1 (Color online) Schematic diagram of the JNK signaling pathway, including extracellular first messengers, intracellular upstream modulators of JNK signaling, and downstream substrates of JNK kinase. Many signaling events closely involved in depression pathophysiology have been showed to modulate the activity of JNK, including inflammation, oxidative stress, excitotoxicity, elevation of glucocorticoid, psychological stress and so on. This figure shows the substrates which could be phosphorylated by JNK, including signaling molecules involved in mitochondrial apoptotic pathway such as Bcl-2, Bcl-xL, Bad and Bim-EM; transcription factors such as p53, c-JUN, c-Fos, c-Myc, ATF-2 and GR; AMPAR and PSD95, which are involved in modulation of synaptic plasticity; MAP-2 and MAP-1b, which are involved in dendritic architecture, axonal growth and pathfinding. In addition, JNK could promote the expression of the inflammation-associated protein including TNF- α , IL-1 β , IL-6, iNOS and COX-2. MKK, MAPK kinase; MAP3Ks, MAPK kinase kinase; MKP/DUSP, dual-specificity MAP kinase phosphatases; JIP, JNK-interacting protein; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; GR, glucocorticoid receptor; AMPAR, AMPA glutamate receptor; PSD95, postsynaptic density protein 95; MAP, microtubule-associated protein

MLK1, MLK3, ASK1, TAOK2等, 已知它们在神经系统中均含有重要的功能^[9].

在JNK激酶的下游, 能够被JNK磷酸化而调控活性的底物分子众多, 它们与抑郁症的各种病理机制均有着千丝万缕的关联, 包括调控细胞凋亡的Bcl-2家族的成员^[11]和转录因子p53^[12]; 参与应激和炎症反应的转录因子AP-1^[13]; 与HPA轴功能亢进和糖皮质激素抵抗相关的糖皮质激素受体GR^[14,15]; 涉及神经突触可塑性的AMPA^[16,17]和PSD95^[18]; 涉及细胞骨架失调和树突萎缩的微管结合蛋白MAP1B和MAP2^[19]等.

2 JNK与抑郁症

JNK的激活常见于各种神经退化性疾病当中, 尤其在阿尔茨海默病中已被确定为重要的致病分子^[20]. 抑郁症也同样属于神经系统结构和功能减退的疾病, 其病理机制与阿尔茨海默病在神经萎缩、炎症反应和氧化应激等方面具有相似之处^[21]. 近10年来的研究成果已逐渐凸显JNK在抑郁行为调控中的重要作用.

一项对不可预期慢性温和应激抑郁型和母婴隔离应激抑郁型小鼠的海马进行全基因组表达谱筛查研究发现, *Jnk1*(又名*Mapk8*)在两种类型的抑郁型小鼠中相对于对照组均呈现差异表达, 因此表明JNK1激酶可能属于抑郁症病理中关键的或共同的信号分子^[22]. 同时多项研究报道JNK活性缺失的小鼠在焦虑水平和抑郁样行为方面发生改变. Mohammad等人^[7]报道*Jnk1*敲除或JNK活性抑制的小鼠表现出成年期海马细胞增殖、存活和细胞成熟增加, 相应地在行为测试中焦虑样行为减少; 而该抗焦虑样效应可以被神经发生抑制剂所阻断, 这表明JNK1通过调控神经发生从而调控焦虑样行为. Kirstin等人^[23]发现*Jnk1*敲除的小鼠在旷场测试、新异物体识别测试和水迷宫测试中均表现出更加活跃的探索行为, 表明焦虑水平降低, 但*Jnk2*和*Jnk3*敲除的小鼠的行为则表现出焦虑或抑郁样的趋势. Nicoletta等人^[24]报道经过悬尾测试和强迫游泳应激的小鼠海马和前额叶JNK的活性上升, 而用JNK的抑制剂II侧脑室注射的小鼠则在悬尾测试和强迫游泳应激中的表现出抗抑郁样的行为.

JNK也参与到与炎症反应相关的抑郁症状中, 这与JNK属于与炎症反应紧密关联的分子有关. 例

如, 中枢注射TNF- α 诱发的小鼠社交探索行为减少和不动时间增多的病态反应能够被JNK的抑制剂DJNKI-1提前侧脑室注射所消除^[25]. 在脂多糖LPS诱发的小鼠抑郁行为的机制中涉及JNK的活性, 首先一种潜在的抗炎药和抗抑郁药匹格列酮能够下调JNK的活性, 减少神经细胞凋亡, 并且逆转LPS诱发的抑郁样行为; 其次用JNK的激动剂茴香霉素处理则消除了匹格列酮的抗抑郁效应^[26]. 同时抗抑郁药曲唑酮也能够通过抑制JNK的活性而保护人类的神经元样细胞免受LPS和TNF- α 处理诱发的炎症损伤, 从而提高细胞活力^[27]. 这些都提示JNK可能是炎症抑郁症的重要病理分子.

各种应激反应能够显著调控JNK的活性并与抑郁样行为相关联. 急性应激能够快速提高中枢中的JNK活性, 并能导致短暂的抑郁样行为^[28,29]; 慢性应激则可导致结构和分子层面(例如MAPK家族激酶)病理性的改变从而导致抑郁症^[30-33]. 有研究报道, 强迫游泳应激和束缚应激都能够激活众多脑区比如杏仁核、海马、下丘脑、蓝斑等中的JNK激酶^[34-36]. 这快速的活化可能由升高的糖皮质激素介导^[37], 也有可能去甲肾上腺素有关^[38]. 急性应激导致的海马CA1和CA3区的JNK活化削弱了认知功能, 导致联想学习能力降低. 用JNK的抑制剂能缓解而用JNK激动剂又能模拟急性应激对情景性恐惧中记忆能力的削弱^[39]. 慢性或长期应激也能显著影响JNK的活性. 例如, 慢性不可预期温和应激导致小鼠海马中JNK磷酸化水平上升^[40,41]. 长期心理压力还会导致血管内皮细胞炎症反应增加和JNK活性上升^[42]. 而长期的JNK活化往往标识着细胞处于脆弱、生长受阻和易于凋亡的状态^[43], 因此慢性应激导致的JNK活性的升高可能是应激对机体产生损伤效应并致抑郁的机制之一. 然而也有研究报道, 在慢性产前应激导致子代雄鼠抑郁的模型中, 海马中JNK的活性是下降的^[44]. 慢性应激对JNK活性调节的结果不一样, 可能与动物种属、性别、应激的方式、饲养方式等有关.

在人类抑郁症患者的研究中, 也发现JNK信号与抑郁症具有较高关联度. 在人类重度抑郁症患者的外周血淋巴细胞的基因表达谱分析中, CD4+T细胞的TCR信号通路中的JNK信号相对于对照组更加活跃^[45]. 通过对97对虽为同卵双胞胎但却一个为抑郁患者一个为非抑郁患者的白血细胞进行表观遗传研究, 发现*Jnk*基因和受JNK调控的转录因子基因*API*

和NF- κ B的表现遗传修饰具有显著差异^[46]。

以上数据表明, JNK的活性与抑郁症有密切的关系, 然而对这方面的研究方兴未艾, 后续仍需大量研究来论证和阐明JNK在抑郁症中的作用和机制。

3 JNK参与抑郁症调控可能的机制

虽然目前对于JNK参与抑郁症调控的机制研究仍相对甚少, 但根据JNK的信号调控功能和抑郁症的病理机制相互关联的分析, 发现JNK与众多抑郁症发病机制的调控因子有关。正如抑郁症本身是一种多病因的疾病一样, JNK介入抑郁症的机制可能也是多途径、多方面的。下面就七个方面可能的机制进行阐述:

3.1 神经退化

神经退化是在抑郁症病人脑中发现的普遍现象, 神经细胞凋亡, 树突萎缩, 胶质细胞数量减少和神经发生减少是导致神经退化的重要原因。在抑郁症病人脑中发现明显的海马体积减小, 神经细胞数量减少和树突萎缩^[47]。尸检结果显示在抑郁症病人的前额叶皮层和眶额皮层的小胶质细胞的数量减少和神经细胞胞体减小^[48,49]。

JNK在神经细胞凋亡信号调控中处于关键位置。例如, 即使在高毒性条件下, *Jnk2/3*基因的双突变使得整个大脑黑质中的多巴胺神经元群都避免了凋亡^[50]。在*Nbn*基因缺陷小鼠中皮层的萎缩和小脑细胞的凋亡与高水平的JNK活性有关^[51]。JNK能通过下调抗凋亡蛋白Bcl-2和Bcl-XL和上调促凋亡蛋白Bax的活性发挥促细胞凋亡的作用^[52]。在大鼠重复不可预期应激导致的抑郁模型中, 大脑皮层和海马等脑区的抗凋亡蛋白Bcl-2或Bcl-xl的mRNA表达水平下调^[53]; 而在另外的研究报道中, 运用同样的抑郁模型对海马进行蛋白组学分析发现JNK活性水平升高^[41]。

此外, JNK可以在各种应激条件下抑制控制蛋白质合成的mTORC1的活性, 这也可导致神经细胞萎缩^[54]。JNK在生理条件下组成性地与mTORC1结合并且在激活后可以磷酸化mTORC1, 从而导致mTORC1失活^[55]。抗抑郁剂噻萘普汀能够在大鼠原代海马神经细胞受到毒性应激条件下, 通过提高被JNK抑制的mTORC1活性, 增加脑源性神经生长因子(brain derived neurotrophic factor, BDNF)和突触蛋白的合

成, 促进树突的生长和提高树突棘的密度, 这可能是噻萘普汀的抗抑郁机制之一^[56]。

3.2 神经发生

根据抑郁症的神经发生理论, 减少的神经发生导致神经可塑性降低, 这是促进抑郁症的机制之一^[57-59]。JNK能够破坏胚胎神经干细胞的干细胞特性, 减慢干细胞神经发生的节奏^[60], 促进胚胎期神经干细胞退出细胞周期^[61], 抑制小脑颗粒细胞前体增殖和促进其分化^[62]。有直接证据表明, 对*Jnk1*基因敲除模型小鼠、用JNK抑制剂侧脑室注射或用反转录病毒定向抑制海马DG区JNK活性后, 均发现小鼠中海马区神经元的增殖、存活和成熟增多, 并且在行为层面上表现出焦虑和抑郁样行为减少^[7]。

3.3 神经突触可塑性

抑郁症往往伴随着神经元树突棘减少, 突触数量减少, 兴奋性突触体积变小, 突触蛋白表达减少, 兴奋性突触电流减弱等^[63,64], 这些改变也关联着突触可塑性的改变。突触可塑性可以包括单个突触增强或减弱对神经递质信号反应的能力、突触发生和清除的能力等^[65], 长时程增强(LTP)和长时程抑制(LTD)是两种重要的突触可塑性形式, 例如LTP可导致树突棘体积增大, 对谷氨酸的敏感性提高, 促进新树突棘的形成等, 而LTD则相反^[65,66]。已有报道运用经颅磁刺激方法进行测量, 发现重度抑郁症患者皮层类似LTP样的突触可塑性相对于健康人显著减弱^[67]。

已知JNK是参与到突触可塑性调节中的重要信号分子。例如在炎性条件下(如LPS, IL-1 β 和TNF- α 刺激)通过激活JNK导致了LTP的削弱^[68-70]和LTD的增强^[71]。在*Jnk1*基因敲除小鼠中和在用JNK抑制剂处理的大鼠中不再能诱导LTD的出现^[72]。用JNK抑制剂DJNKI-1处理能阻止阿尔茨海默病中突触致密区突触后蛋白和谷氨酸受体的减少, 兴奋性突触体积的减小和逆转LTD的增强^[20]。具体的分子机制可能包括多种途径, 比如NMDAR能够激活JNK^[73], 而反过来JNK和其支架蛋白JIP1又是NMDAR功能所必需的^[74]。JNK还能磷酸化PSD95蛋白和谷氨酸受体AMPA亚基GluR2L, 促使前者其在膜上聚集和促使后者插入细胞膜表面, 这都直接调节了突触可塑性^[75,76]。另有证据表明, 在应激条件下海马的JNK在

调节条件性恐惧学习中对突触可塑性和记忆的调节发挥着重要的作用,可能海马中JNK2和JNK3持久的激活参与到最初的应激反应中,最终导致了LTP和记忆的削弱^[39].

上述数据皆提示JNK可能在抑郁症的突触可塑性的改变中发挥着重要的作用.

3.4 神经炎症

越来越多的证据表明重度抑郁症与体内炎症反应增多密切相关^[77~80],并且炎症几乎影响到抑郁症发生的方方面面,包括改变神经递质的表达、神经内分泌的功能、神经突触可塑性、神经发生,生长存活以及与情绪调节相关的神经环路等等^[80,81].

JNK在炎症反应调控中发挥着关键性的作用,例如TNF- α , IL-1 β , TGF- β , B淋巴受体, T淋巴受体介导的炎症反应能激活JNK^[52];而激活的JNK又进一步促进炎症因子的表达,包括TNF- α , IL-1 β , IL-6, 促炎性酶环氧酶COX-2和诱导性一氧化氮合酶iNOS的表达^[82,83].小胶质细胞是中枢神经系统中主要炎症反应细胞,抑郁症与小胶质细胞免疫状态失衡有密切关系^[84].体外培养的小胶质细胞在受到炎症因子刺激时,可以通过激活JNK/c-JUN信号途径促进TNF- α , IL-6, IL-1 β , IDO等的表达^[85,86];用JNK抑制剂SP600125处理则能抑制小胶质细胞的以上炎症因子和酶类的产生^[86,87].在LPS外周注射的动物模型中,海马和皮层中小胶质细胞的激活和炎症细胞因子表达的上升均与JNK的激活相关^[88].而TNF- α , IL-6, IL-1 β , 以及IDO和COX-2的表达上升均与抑郁症的发生有密切关联^[80,89,90].在TNF- α 诱导的抑郁症中,JNK活性发挥着重要的作用^[25,91].

3.5 氧化应激

研究发现在重度抑郁症患者体内氧化应激水平也高于普通人^[92],一项研究通过元分析发现重度抑郁症病人体内氧化应激标志物——8-羟基-2-脱氧鸟苷酸和F2-异前列腺素浓度升高最为显著^[93].JNK激酶活性与氧化应激关联密切,首先JNK能够在氧化应激条件下被激活,从而介导氧化应激带来各种病理损伤效应^[94,95];其次JNK也能促进ROS的产生^[96].此外,JNK还能促进与氧化应激也密切相关的COX-2和iNOS的表达^[97,98],前者在催化生成前列腺素的同时能促进氧自由基ROS的产生,后者催化NO的产

生,而NO容易与超氧阴离子O²⁻形成过氧自由基ONOO⁻^[82,99,100].

3.6 神经兴奋性毒性

重度抑郁症还伴随有神经系统兴奋性毒性,表现在兴奋性递质谷氨酸释放量增多,而过多的兴奋性转导会导致BDNF释放量减少,并对神经元和胶质细胞产生兴奋性损伤^[80],从而可能导致神经元和胶质细胞的数量和体积减少^[101].JNK激酶活性被广泛报道参与介导NMDA型谷氨酸受体激动剂NMDA和KA型谷氨酸受体激动剂红藻氨酸引发的兴奋性毒性^[102,103].基因敲除*Jnk3*或者抑制JNK的活性都显著增强神经细胞对兴奋性毒性的抵抗性,减少神经细胞的凋亡^[103,104].在兴奋性毒剂刺激下,JNK的调控不仅涉及到细胞凋亡通路,还涉及到对AMPA受体从高尔基体到细胞质膜表面穿梭的调节,可以起到降低表面GluR1的数量从而形成对神经细胞过度兴奋的适应性调节^[105].

3.7 糖皮质激素受体功能受损

抑郁症与糖皮质激素受体的功能受损有关.在正常情况下由下丘脑-垂体-肾上腺轴(the hypothalamic-pituitary-adrenal axis, HPA轴)调节产生的糖皮质激素能与糖皮质激素受体(glucocorticoid receptor, GR)结合,通过负反馈调节机制,使过度亢进的HPA轴活动恢复正常;但当糖皮质激素受体发生功能障碍,则导致HPA轴负反馈机制失效,从而导致糖皮质激素抵抗^[106].研究发现,重度抑郁症患者体内糖皮质激素受体的功能受损是一种普遍的现象^[14],同时抑制GR的功能能够加重炎症导致的抑郁症状^[107].JNK能磷酸化人类的GRSer226位点(在大鼠中对应的是GRSer246位点),使得GR转录活性受到抑制,从而导致糖皮质激素抵抗效应^[8,108].在克罗恩炎性肠病人体内发现肠表皮细胞中JNK的活性升高与糖皮质激素抵抗特点呈正相关关系^[109].用抑制剂SP600125抑制JNK的活性后导致小鼠海马HT22细胞GR的转录活性增强,同时增加GR对地塞米松(人工合成的糖皮质激素类激素)的反应敏感性^[110].细胞因子诱导的糖皮质激素抵抗能够被JNK的抑制剂VIII部分逆转^[111].

4 以JNK为靶点治疗抑郁症的前景

2015年塞尔维亚的学者Jovicic^[8]最早提出以调

节JNK激酶信号为治疗抑郁症新途径的医学假设,该假说基于此前的研究发现即JNK能够磷酸化GRSer226位点从而促进糖皮质激素受体抵抗而提出。从现有证据来看,以JNK为靶标治疗抑郁症展现出可观的前景。

4.1 现有抗抑郁药对JNK活性的调节

不少抗抑郁药都能调节到JNK的活性,从而可能由JNK途径介导抗抑郁的效应。其中一些抗抑郁药被报道通过抑制JNK的活性起到抗抑郁的作用。比如,前面提到的五羟色胺受体拮抗剂和重吸收抑制剂曲唑酮能够阻止炎症因子对在体外培养的人类神经样细胞中JNK的活化,这可能是曲唑酮发挥神经保护作用 and 抗抑郁的机制^[27];具有抗抑郁效果的药物红景天甙具有缓解疲劳和压力的作用,口服七天红景天甙的兔子在急性不动应激后血液中JNK磷酸化水平低于服用安慰剂的兔子^[112];抗焦虑性的中草药逍遥散能够通过下调海马中JNK的活性从而改善了慢性不动应激导致的大鼠焦虑样行为^[113];具有抗抑郁疗效的中药柴胡疏肝散能够显著下调慢性不可预期应激造成的大鼠海马中的JNK的表达水平,这可能是柴胡疏肝散抗抑郁效果的分子机制^[114]。因此,调节JNK的活性或许可以成为抗抑郁药治疗效果的一项指标,以JNK靶点特异性地治疗抑郁症具有潜在的可能性。

4.2 以JNK为靶点的候选药物

目前已经开发了一些JNK为靶点的抑制剂和药物,包括JNK的ATP竞争性抑制剂SP600125, JNK激酶上游混合谱系激酶抑制剂MLKi, 多肽类抑制剂如DJNKI-1和TAT-TIJIP, 自然界类抑制物如 ω -脂肪酸和姜黄素^[115]等。

这些药物在实验室和临床前研究使用,帮助探索以JNK为靶点治疗神经退化性疾病如阿尔茨海默病和帕金森等精神类疾病的效果,并且已经取得了许多的进展。从治疗疾病的效果上我们或许可以得到以JNK为靶点治疗抑郁症的启示。例如,在阿尔海默兹疾病APPswe/PS1dE9双转基因小鼠模型中,3个月的SP600125静脉注射能够显著提升认知缺陷,降低炎症和减少皮层和海马区的突触损失,并且长期使用SP600125对小鼠并无大的副作用^[6];在AD转基因模型TGCRND8小鼠中,JNK的抑制剂DJNKI-1能

改善突触前蛋白和谷氨酸受体的流失;阻止兴奋性突触体积的减小,最后能逆转认知功能的削弱^[20];长期受糖皮质激素应激被认为是抑郁症或阿尔茨海默病的致病因素,对小鼠皮下注射DJNKI-1逆转慢性糖皮质激素摄入对海马中GSK-3 β 活性的降低,对caspase-3活性的增加和对认知能力的削弱^[116]。基于阿尔茨海默病中的病理症状与抑郁症有许多相似之处,JNK可能是治疗抑郁症的新靶标。

对于抑郁症的治疗,在动物实验上已有证据表明用JNK的抑制剂DJNKI-1通过侧脑室注射能促进海马神经发生从而减少了动物焦虑样行为^[7];用SP600125通过侧脑室注射能抑制慢性不动应激导致的动物焦虑样行为^[113]。研究表明不饱和脂肪酸omega-3具有抗抑郁的功效^[117],而且omega-3的作用机制涉及对JNK活性的抑制^[118,119]。

5 结语

JNK作为MAPK家族的重要成员,其信号通路在抑郁症调控中的重要位置已经得到越来越多的认可。众多抑郁症的病理因素如炎症应激、氧化应激、心理应激、兴奋性毒性等都能影响JNK的活性;而JNK的下游能调控有关神经萎缩、神经发生、神经突触可塑性、神经炎症、糖皮质激素受体抵抗等有关的信号通路,这些均可能是JNK调控抑郁症的作用机制。以JNK为靶点的候选药物也正在开发,并取得了一定的成绩。因此,确立JNK为靶标不仅为抑郁症研究提供新思路,而且为抑郁症治疗提供了新的药物靶点,对抑郁症病理机制的揭示和抑郁症的临床治疗具有一定的意义。然而以JNK为靶点治疗抑郁症仍存在诸多待解决的问题,主要包括:

(1) 目前对于JNK与抑郁症存在相关性的文献较多,但关于是否存在因果关系的证据并不多。近几年才出现专门以JNK为靶标研究并明确了其在抑郁症中作用的科研论文,但主要采用JNK基因敲除的小鼠为研究对象,这与常见抑郁模型的基因背景不同,对JNK基因敲除小鼠的研究结果对普通抑郁模型的借鉴意义有限。因此还需要从常见抑郁模型入手,比如先天遗传抑郁型、应激抑郁型、炎症抑郁型等,全面考察JNK在抑郁症中的作用。

(2) 对于JNK存在的3种亚型,除了JNK1与抑郁症的关系从现有证据看比较明确外,JNK2和JNK3则不甚明了。弄清这些亚型对抑郁症影响的差异,有利

于区分亚型进行干预,或许有利于提高治疗的精准性和减少副作用。

(3) 对于JNK调控抑郁症的系统机制有待全面揭示。除了已报道的JNK通过神经炎症机制和海马神经发生机制来调控抑郁行为外,其他可能的机制如神经退化、氧化应激、神经兴奋性毒性、神经突触可塑性、糖皮质激素抵抗等均有待考察。因为抑郁症是全身系统性的症状,包括中枢神经系统、免疫系统、内分泌系统等各个方面的反应以及交互作用,而JNK的调控功能也非常广泛,多角度地考察能避免认识上的片面性。

(4) 以JNK为靶点治疗抑郁症可能的副作用有待

评估。因为在正常生理条件下,JNK的活性仍是机体所必需的,比如在神经系统发育、微管系统的维持,创伤的修复以及免疫防御等。因此针对JNK的治疗需要在药物的选择、剂量、疗程等方面进行实践摸索,以最大限度降低治疗的副作用。

未来的研究可以围绕以上问题展开,期望越来越多的人开始关注并探索JNK与抑郁症的关系。随着JNK调控抑郁症机制研究的深入开展,抑郁症的分子病理本质将越来越清晰明了。总之,确立JNK为靶标不仅为抑郁症研究提供新思路,而且可能为治疗抑郁症带来新的策略和新的药物靶点。

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Summary for “抑郁症研究和治疗的新靶标: JNK 信号通路的作用”

The JNK signaling pathway as a potential new target for depression

Juntao Zhang^{1,2} & Wenjuan Lin^{1,2*}

¹ Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China;

² Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China

* Corresponding author, E-mail: linwj@psych.ac.cn

Depression is a widespread chronic medical illness that can affect thoughts, mood, and physical health. It is characterized by low mood, lack of energy, sadness, insomnia, and an inability to enjoy life. So far, however, clinical studies have shown that patients with depression do not have a satisfactory therapeutic outcome. The pathogenesis of depressive disorder is still not well understood. In recent years, c-Jun N-terminal kinase (JNK) has received more and more recognition for its signaling pathway in the regulation of depression. In this article, we review new research progress in the contribution of JNK signaling to depression and summarize the possible underlying mechanisms. JNK is an important member of the mitogen-activated protein kinases (MAPK) family, and it is also known as stress activated protein kinase because it regulates various responses to environment stresses outside and inside cells. The JNK family has three subtypes of JNK1, JNK2 and JNK3, which are different in tissue expression distribution, activity regulation and function. The pathological factors of depression such as inflammatory stress, oxidative stress and psychological stress can affect the activity of JNK and JNK downstream can regulate the neurodegeneration, neurogenesis, synaptic plasticity, neuroinflammation, glucocorticoid receptor resistance and other related signaling pathways, which are involved in the pathophysiology of depression. Examination of *Jnk* knockout mice has revealed JNK imposes neurogenesis-dependent control of anxiety behavior. In inflammation-induced models of depression, JNK plays important roles in depressive-like behavior through promoting the expression of proinflammatory cytokines and inflammation-related enzymes. Depressive-like behavior induced by various stress often involves alteration of JNK signaling. For example, the hippocampus in wild-type mice exposed to chronic unpredictable mild stress had higher p-JNK protein expression. Human studies also show dysregulated expression of *Jnk* gene in blood white cells of depressed patients. All these data indicate that there is a close relationship between JNK and depression. Furthermore, candidate drugs targeting JNK have been developed and showed certain antidepressant effects. However, there are still many problems to be solved in the understanding the regulation mechanisms of JNK in depression. These mainly include: (1) Although there are many literatures on the correlation between JNK and depression, there is not much evidence on whether there is a causal relationship. (2) Although the relationship between JNK1 and depression is relatively clear, JNK2 and JNK3 remain ambiguous. (3) The systemic mechanism of JNK regulating depression needs to be fully revealed on all aspects of the reaction and interaction, including the central nervous system, immune system, endocrine system and so on. (4) The possible side effects of treating depression with JNK as a target need to be evaluated. Future research could be carried out on the above issues. With the development of research based on JNK mechanism, the molecular pathologic nature of depression could be more elucidated. Focusing on JNK as a target may provide new ideas for depression research and bring new strategies and new drug targets for prevention and treatment of depression.

depression, c-Jun N-terminal kinase, neurodegeneration, neurogenesis, synaptic plasticity, neuroinflammation, excitotoxicity, glucocorticoid resistance

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