抗抑郁药的研究进展

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抑郁症已经成为一种高发病率和高死亡率的疾病,预计在 2020 年将会成为影响人类健康的第二类疾病[1]。抑郁症是遗传和环境因素共同引起的,机制可能是诱发中枢 5-羟色胺(5-HT)或去甲肾上腺素(NE)、多巴胺(DA)和神经肽等神经递质含量降低及其受体功能下降有关,近年来还有发现可能与下丘脑-垂体-肾上腺轴负反馈失调[2]、谷氨酸传导障碍[3]、神经免疫异常[4]等因素有关。目前对抗抑郁药物研究主要集中在阐明生物学改变机制方面,这些研究成果也很大程度地促进了新药的研发。

1 选择性五羟色胺再摄取抑制药(Selective Serotonin Reuptake Inhibitor,SSRIs)

SSRIs 类抗抑郁药药理机制主要是抑制神经突触再吸收五羟色胺(5-HT)以提高细胞外神经后突触与五羟色胺结合水平从而发挥药效。目前常用的 SSRIs 类药物主要是氟西汀、帕罗西汀、舍曲林等。这类药物是临床常用到的一类抗抑郁药[5-6]。5-HT 为重要的神经递质,参与多种生理功能及病理状态的调节,如睡眠、摄食、体温、精神情感调节。研究发现抑郁症患者 5-HT 水平的降低能影响情感水平[7],SSRIs 主要是通过提升 5-HT 水平来达到抗抑郁效果的。SSRIs 在临床上发挥药效往往需要几周的时间,而 5-HT 水平在运用这类药物的时候就会出现提高,这种延迟作用暗示这类抗抑郁药可引起复杂下游调控机制改变[8],如基因调控改变[1,9]、神经回路改变[10],信号通路改变[11-12]。

2 三环类抗抑郁药(tricyclic antidepressants,TCAs)

三环类抗抑郁药理机制与 SSRIs 类相似,主要也是通过阻断胺泵、减少突触前膜对生物胺的回收,特别是减少去甲肾上腺素(NE)和 5-HT 的再吸收,使突触后受体部位有效神经递质的浓度增高,起到抗抑郁作用。常用药物有丙咪嗪、阿米替林、氯丙咪嗪等。有研究证明 SSRIs 类和 TCAs 类抗在临床药效抗抑郁的机制都很相似,但 SSRIs 类抗抑郁药服药的依从性较好。近期也研究证明 TCAs 类抗抑郁药也能通过激活兴奋性突触改变神经细胞的可塑性从而达到抗抑郁的作用[13]。

3 单胺氧化酶抑制剂(monoamine oxidase inhibitor,MAOI)

有实验证实 MAOI 可逆转利血平引起的淡漠,脑单胺含量却升高,推测其中枢兴奋和抗抑郁作用

[34] Law CK, Yip PSF, Chan WSC, et al. Evaluating the effectiveness of barrier installation for preventing railway suicides in Hong Kong[J]. J Affect Disord, 2009, 114(1-3): 254-262.
[35] You J, Lin MP, Leung F. A Longitudinal Moderated Mediation Model of Nonsuicidal Self-injury among Adolescents[J]. J Abnorm Child Psychol, 2014.
[36] Tang J, Ma Y, Guo Y, et al. Association of aggression and non-suicidal self injury: a school-based sample of adolescents[J]. PLoS one, 2013, 8(10): e78149.
[37] Saraff PD, Pepper CM. Functions, lifetime frequency, and variety of methods of non-suicidal self-injury Among college students[J]. Psychiatry Res, 2014, 219(2): 298-304.
[38] Chartrand H, Sareen J, Toews M, et al. Suicide attempts versus nonsuicidal self-injury among individuals with anxiety disorders in a nationally representative sample[J]. Depress Anxiety, 2012, 29(3): 172-179.
[39] Shingleton RM, Eddy KT, Keshaviah A, et al. Binge/purge thoughts in nonsuicidal self-injurious adolescents: An ecological momentary analysis[J]. Int J Eat Disord, 2013, 46(7): 684-689.
[40] Victor SE, Klonsky ED. Correlates of suicide attempts among self-injurers: A meta-analysis[J]. Clin Psychol Rev, 2014, 34(4): 282-297.

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是因为大脑单胺氧化酶受抑制单胺降解减少及突解间隙单胺类受体含量升高的缘故。这类药物包括异丙肼、异卡波肼、苯乙肼、反苯环丙胺，目前对此类药物研究很少见，主要原因其严重的不良反应，所以逐渐停用。但有研究报道 MAOI 如经皮肤吸收不会引起很大副作用，小剂量运用不会引起厌食[14]。此类新开发药物，如 TV327，在抑郁模型上已证明能够降低强迫游泳实验的不动时间[15]。

4 去甲肾上腺素再摄取抑制剂(NRI)

抑郁症患者体内存在去甲肾上腺合成不足和释放减少，从而导致 NE 缺乏，去甲肾上腺素再摄取抑制剂主要是增加突触前膜对去甲肾上腺素的再吸收，增加中枢神经系统对去甲肾上腺素再吸收的功能从而发挥抗抑郁作用，这类药物包括去甲丙咪嗪、马普替林和去甲替林，由于其存在抗胆碱能的作用，临床运用较局限，故此类药物的研究主要集中在选择性比较高的药物，如瑞博西宁(reboxetine)，瑞博西宁能有效降低抑郁症的发病率，也能明显降低 NRI 类药物引起的并发症[16]。

5 新型抗抑郁药

虽然目前抗抑郁药的研究主要集中在 SSRIs 和 TCAs 类抗抑郁药，但也不乏出现了新型抗抑郁药的研究，如纤维生长因子(Fibroblast Growth Factor-2，FGF-2)，FGF-2 能够降低慢性不可预知性应激(Chonic unpredictable stress，CUS)模型的在强迫游泳中的不动时间，而这可能是通过增加前额去星形胶质细胞来实现的[17-18]。同时也有研究发现，硫化氢也能改善抑郁及焦虑症状，而其可能的机制也在继续探究中[19]。

随着社会压力的增大，由于抑郁症引起的自杀人数是增长趋势的，医药系统对抑郁症治疗投入的资金越来越多，但是收效甚微，主要原因是对抑郁症的发病机制及生物学改变未完全阐明，抗抑郁药的作用也是不尽人意，所以如果能对抑郁症引起机体的潜在改变能做更深入的研究，将会促进抗抑郁药开发，从而降低抑郁症的高发病率和高死亡率。

参 考 文 献

[1] Kang HJ, Voleti B, Hajszan T, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder[J]. Nat Med, 2012, 18(9): 1413-1417.

[2] Gupta D, Radhakrishnan M, Bhatt S, et al. Role of Hypothalamic-pituitary-adrenal-axis in Affective Disorders: Anti-depressant and Anxiolytic Activity of Partial 5-HT1A Agonist in Adrenalectomised Rats[J]. Indian J Psychol Med, 2013, 35(3): 290-298.

[3] Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets[J]. Science, 2012, 338(6103): 68-72.

[4] Antonioli M, Rybka J, Carvalho LA. Neuroimmune endocrine effects of antidepressants[J]. Neuropsychiatr Dis Treat, 2012, 8: 65-83.

[5] Gordon M, Melvin G. Selective serotonin re-uptake inhibitors--a review of the side effects in adolescents[J]. Aust Fam Physician, 2013, 42(9): 620-623.

[6] Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review[J]. Prog Neuropsychopharmacol Biol Psychiatry, 2003, 27(1): 85-102.

[7] Heninger GR, Delgado PL, Charney DS. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans[J]. Pharmacopsychiatry, 1996, 29(1): 2-11.

[8] Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature[J], 2008, 455(7215): 894-902.

[9] Campbell S, Macqueen G. The role of the hippocampus in the pathophysiology of major depression[J]. J Psychiatry Neurosci, 2004, 29(6): 417-426.

[10] Ihara N, Ueda S, Kawata M, et al. Immunohistochemical demonstration of serotonin-containing nerve fibers in the mammalian hippocampal formation[J]. Acta Anat (Basel), 1988, 132(4): 335-346.

[11] Remondes M, Schuman EM. Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory[J]. Nature, 2004, 431(7009): 699-703.

[12] Cai X, Kallarackal AJ, Kvarta MD, et al. Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression[J]. Nat Neurosci, 2013, 16(4): 464-472.

[13] von Wolff A, Holzel LP, Westphal A, et al. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis[J]. J Affect Disord, 2013, 144(1-2): 7-15.

[14] Culpepper L, Kovalick LJ. A review of the literature on the selegiline transdermal system: an effective and well-tolerated monoamine oxidase inhibitor for the treatment of depression[J]. Prim Care Companion J Clin Psychiatry, 2008, 10(1): 25-30.

[15] Asnis GM, Henderson MA. EMSAM (deprenyl patch): how a promising antidepressant was underutilized[J]. Neuropsychiatr Dis Treat, 2014, 10: 1911-1923.

[16] Versiani M, Mehilane L, Gaszner P, et al. Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder[J]. J Clin Psychiatry, 1999, 60(6): 400-406.

[17] Elsayed M, Banasr M, Duric V, et al. Antidepressant effects of fibroblast growth factor-2 in behavioral and cellular models of depression[J]. Biol Psychiatry, 2012, 72(4): 258-265.

[18] Kajitani N, Hisaoka-Nakashima K, Morioka N, et al. Antidepressant acts on astrocytes leading to an increase in the expression of neurotrophic/growth factors: differential regulation of FGF-2 by noradrenaline[J]. PLoS One, 2012, 7(12): e51197.

[19] Chen WL, Xie B, Zhang C, et al. Antidepressant-like and anxiolytic-like effects of hydrogen sulfide in behavioral models of depression and anxiety[J]. Behav Pharmacol, 2013.

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