

炎症诱发抑郁症 吲哚胺 2,3 双加氧酶的激活是关键环节之一 *

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摘要: 本文通过回顾临床前期及临床期两阶段的文献,着重介绍炎症激活及抑郁症之间的相关联系并进一步探讨其机制。目前,抑郁症的机制研究热点之一是炎症反应又称为细胞因子假说,其中色氨酸--犬尿氨酸通路(KP)在该假说中的作用得到了越来越多的证实。该假说认为,色氨酸--犬尿氨酸途径是聚焦于抑郁症相关代谢产物改变的综合性通路。炎症性抑郁症的产生是由于在免疫功能及神经递质改变下产生的炎症细胞因子激活了吲哚胺 2,3-双加氧酶,从而进一步引发抑郁。吲哚胺 2,3-双加氧酶的活性增加,不仅会导致色氨酸的衰竭同时还引起通过犬尿氨酸途径代谢的神经毒性产物的增加,而这两种改变都被认为与抑郁症的发病密切相关。在此基础上,我们主要聚焦于慢性病患者接受细胞因子治疗的相关研究,来探讨免疫激活病人中抑郁症发病的高风险性从而证明这一假说。这项工作的目的是希望通过对色氨酸--犬尿氨酸通路的研究,从吲哚胺 2,3-双加氧酶的抑制,激活它的细胞因子的调节及寻找在犬尿氨酸途径中其它的靶点等方面来抗抑郁,从而为新型的抗抑郁药的发展提供新的方法途径。

关键词: 抑郁症;炎症;吲哚胺 2,3 双加氧酶;犬尿氨酸;色氨酸

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The Important Role of Indoleamine 2,3-Dioxygenase in the Depression Induced by Inflammation*

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ABSTRACT: This paper reviews the preclinical and clinical two-stage literature, We Mainly focused on chronic patients receiving cytokine therapy research. To explore and study the pathophysiological basis of the immune activation and depression both in the patients. We using IDO to be a strating point for both, then to prove depression induced by inflammation is due to that in immune activations neurotransmitter changes and cytokines produced. The same time, that induced IDO increased cause tryptophan depletion and kynurenine metabolism of neurotoxicproducts increased eventually leading to the generation of depression. We want to provide a new target for study the new antidepressants drugs.

Key words: Depression; Inflammation; IDO; Kynurenine; Tryptophan

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前言

抑郁症是一种常见的可导致精神残疾和自杀死亡的精神疾病,其主要表现为情绪持久低落,思维迟钝,意志行为减少,严重者还伴有自杀倾向。据有关文献报道其发病率约 10%,而 50%-70% 的自杀都与抑郁有关。在世界范围内,抑郁的发病率呈现出不断上升的趋势,并伴随着低龄化的发展。据世界卫生组织推测,在 2020 年,抑郁将从全球所有重大非致命性疾病中带来巨大负担的第 4 大疾病,跃升为第 2 大疾病^[1]。医学研究表明,抑郁并非一般的情绪或性格问题,而是一种有明确生物学基础的疾病,因此又可以将抑郁看作是一种心理神经免疫紊乱性疾病。1964 年 George Solomon 和 Rudolph Moos 第一次使用了心理神经免疫学这一术语^[2]。他们认为免疫系统可以影响神经系统的功能,从而改变行为和心理过程,这样一种认识也促进

了心理神经免疫学研究领域的建立和迅速发展。Smith 等在 1991 年最早报道了抑郁症与细胞因子异常相关的研究结果,发现白细胞介素(IL-1)可引起与抑郁症相关的某些激素的活动异常,此后有学者提出了抑郁症是由免疫细胞活化后所分泌的细胞因子导致的理论,即“抑郁症的细胞因子学说”^[3],为抑郁症的研究和治疗带来了新的方向。然而,从抑郁症的治疗效果来看,目前抑郁的治疗普遍存在治疗用时较长且疗效甚微的情况。单从症状缓解这一方面来看,初步治疗后病人的症状大约有 35% 得到缓解,获得约 70% 的好转则需要至少连续四个疗程的治疗^[4]。因此,我们有必要明确抑郁症的病理生理机制从而使抑郁的治疗产生更好的疗效。

最新的研究结果表明:A)临床中抑郁的产生主要与炎症激活的增加相关^[5-7] B)健康人急性炎症反应的发生也可能会导致抑郁样行为和症状的出现^[8-9]。在这篇文章中,我们想通过回

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顾相关文献来证明,通过改变吲哚胺 2,3-双加氧酶(IDO)的活性可以增加炎症反应从而影响情绪及行为改变,并最终导致抑郁,并希望借此机会进一步阐明炎症和抑郁之间的相互关系。

1 免疫功能,细胞因子,抑郁

越来越多的研究表明,持续的天然免疫系统的激活将导致抑郁症相关症状的发展^[10,11],其基础是神经免疫和脑内促炎细胞因子的产生。细胞因子是由免疫活性细胞分泌的具有调节免疫应答生物活性的信号分子。它包括白介素(IL)、干扰素(IFN)和肿瘤坏死因子(TNF)等几类。其中炎性细胞因子直接和间接参与炎症反应过程,它包括 IL-1, IL-6, IFN- γ 和 TNF α 。IL-1, IL-6 和趋化性细胞因子又被称为促炎性细胞因子,是启动炎症反应的关键细胞因子。而另一些通过抵抗细胞激活和调节炎性细胞因子的产生来抵抗免疫应答,如 IL-4, IL-10, IL-13 等称为抗炎细胞因子。第一篇关于细胞因子诱导病态行为的报告是由 Aubert 等人于 1995 年在 Brain, Behavior, and Immunity 杂志上发表的^[12]。Yirmiya 是第一个将病态行为与抑郁进行类比的生理心理学家,他用实验证明了那些被细胞因子作用过的大鼠,对糖水的奖励不再感兴趣,而其中一些可以通过慢性给予抗抑郁药进行治疗^[3]。

临床发现,在肥胖、老龄化及风湿性关节炎、动脉粥样硬化、充血性心力衰竭等非感染性慢性免疫激活疾病中普遍伴随着抑郁症的增加^[13]。如,用 IFN- α 治疗癌症和病毒感染(如慢性丙型肝炎)的患者中有高达 45% 的人有重度抑郁症的发生^[14,15,16]。此外,还有大量的文献表明,在医疗患者和严重抑郁症病人的血液和脑脊液中炎症标志物的浓度升高,包括促炎性细胞因子、急性期反应物、趋化因子和粘附分子等^[17,18,19,20]。特别是,细胞因子治疗的某些类型的癌症和病毒感染对抑郁症状的发展的诱导,这一部分的人数占近期研究人数中相当大一部分比例^[21,22]。

2 抑郁症中的细胞因子变化

早年的研究发现抑郁症患者的细胞免疫功能和免疫细胞数目出现改变,主要包括有丝分裂原刺激的淋巴细胞增生反应降低、白细胞数目增加、自然杀伤细胞的数目和活性以及淋巴细胞亚群数目的改变^[23]。而近年来的研究则强调了抑郁症患者的免疫激活,即免疫激活产生的细胞因子能影响中枢神经系统的多个方面,包括神经递质代谢、神经内分泌功能、神经可塑性以及与抑郁性行为改变有关的信息过程^[24]。事实上,在抑郁症患者体内能频繁地观察到促炎细胞因子的水平循环升高。如,抑郁症患者血中 IL-1^[25,27] (在脑脊液(CSF)中同样呈现出增加趋势^[28])、IL-6^[25,26,28-30]、TNF α ^[26,31] 和其他急性期蛋白质,如 C-反应蛋白(CRP)^[29]、结合珠蛋白^[30] 和一些嘌呤^[32]。重度抑郁症患者存在明显的免疫激活和细胞因子增高的现象。重度抑郁症病人脑脊液中 IL-1beta 的增加与抑郁严重程度相关^[33]。同时也存在一些相反的结果^[34,35],但总的说来在抑郁相关性的 meta 分析中显示,CRP、IL-1、IL-6 与抑郁的发病具相关性^[29],同时也暗示血浆 IL-6 和可溶性 IL-2 受体可以作为抑郁症的生物学检测标志物^[36]。

此外,文献结果显示运用抗抑郁药治疗抑郁症可以逆转精神障碍患者炎性标志物的表达^[37]。丙咪嗪、氯丙咪嗪、文拉法

辛、氟西汀、舍曲林和曲唑酮已被证明可以减少在体外培养的人的血液样本 IFN- γ /IL-10 的比率(比率=促炎细胞因子/抗炎细胞因子),从而起到抗炎的作用^[38-40]。用氟西汀治疗抑郁症还可使患者血清 IL-6 降低^[41]。

3 情感,行为改变

健康人身上模拟急性炎症反应,如,注射内毒素^[42,43]、IL-6^[44] 或 IFN- β ^[45],也能诱导出类似抑郁的症状(如疲劳、缺乏动力、厌食、睡眠不足)。虽然这些症状仅短暂存在,但产生这种症状的微妙的认知与抑郁中存在的很相似,包括社会孤立感^[42,46] 和精神运动迟滞^[47]等。与抑郁症不同的是,这些症状在不长时间内可以迅速解决。

3.1 动物模型中 IDO 的激活及动物状态:

在动物实验水平,急性和慢性的免疫系统的激活确实能诱导小鼠抑郁样行为的产生。已经有关于急性炎症反应诱导抑郁的抑郁症动物模型的报导,并且在最初的病态行为之后使用了悬尾实验和蔗糖消耗实验进行模型鉴定^[47]。

动物模型支持炎症诱导的抑郁样行为的产生可能是由于 IDO 的激活这一假说。在动物病态行为模型中,IDO 的激活可能是由于 IDO 的 mRNA 高表达也可能是由于血浆中犬尿氨酸通路(KP)中的代谢产物的增多造成的^[48]。这些导致激活的来源,一部分可能是通过 IFN- γ 和 TNF 诱导的。例如,在一些 IFN- γ 基因敲除(KO)小鼠和用 TNF 受体拮抗剂(依那西普)治疗的动物中都能观察到 IDO 的激活和抑郁样行为(强迫游泳和糖水消耗实验中的)减少^[49]。此外,在这些动物模型中,IDO 的拮抗剂都能够阻止抑郁样行为的产生^[48,50] 并且在这些例子中所给予的犬尿氨酸与抑郁样行为之间存在着剂量依赖的关系^[50]。

3.2 临床慢性炎症反应中 IDO 的激活与抑郁

如上所述,急性炎症反应可以在健康人身上重现疾病行为和抑郁性认知。但在慢性炎症反应下是否也存在相似的通路或机制的研究。

在临床慢性炎症反应中,由于丙型肝炎患者必须要接受 6 至 12 个月的 IFN- α 治疗的基础方案,因而用 IFN- α 治疗的慢性丙型肝炎(HCV)患者可以作为一个研究炎症与抑郁症相关性的理想的研究群体。经评估,这些患者在接受治疗期间抑郁的发生率可高达约 25%^[51,52] 到 33%^[53,54]。

与抑郁症患者中观察到的结果相似^[4],在 HCV 患者中,IFN- α 可以使免疫激活增加,其中促炎细胞因子(如 IL-1, IL-6, IL-8 和 TNF- α ^[55,56])明显升高。虽然 IFN- α 是通过外周给药,但在给药组的 CSF 中也观察到 IFN- α , IL-6 和单核细胞趋化蛋白-1 的增加,证明其对中枢也具有免疫调节的能力。促炎性细胞因子和犬尿氨酸(KYN)-色氨酸(TRP)的比率(反映 IDO 的活性增加)的增加在血液和脑脊液中则都能观察到。

3.3 炎症反应中的 IDO

IDO 是一种能由 IFN- α , IFN- γ 和 TNF- α 中的一种或几种结合的细胞因子通过激活若干炎症信号通路激活的酶,同时它也是 TRP-KYN 通路中的第一限速酶。当细胞因子主要通过信号转导和转录 1A(STAT1a),干扰调节因子(IRF)-1, NF- κ B 和 p38 促分裂原活化蛋白激酶(P38 MAPK)^[57] 等激活炎症信号

通路时,IDO被激活,导致生成五羟色胺(5-HT)的主要氨基酸TRP的衰竭,转为合成犬尿氨酸原(kynurenine original)^[58]。

事实上,膳食中只有约1%的TRP是通过5-HT途径代谢,最终在大脑中合成5-HT^[59],而绝大多数的TRP是通过KP通路在IDO及色氨酸2,3-双加氧酶(TDO)作用下代谢的。在正常情况下,TDO是TRP-KYN通路中的关键性酶,当免疫激活时,炎症诱导性的IDO激活成关键性酶。这时,IDO的增加和TDO的作用相结合使得KP途径的代谢能力大大提升,加大TRP通过此途径的代谢量。此时血清TRP浓度可降低25%-50%,仅留比例较少的TRP转化为5-HT^[60-62]。事实上,在抑郁易感人群中已经发现抑郁症状的促成与膳食TRP的急性衰竭有关^[63]。在给予IFN- α 治疗的患者中,抑郁的发展和外周血中色氨酸的减少及犬尿氨酸的增加与IDO的激活一致,表明了IDO在炎症诱导抑郁症中的作用^[64-66]。此外,在用细菌脂多糖(LPS)或结核菌素(BCG)治疗的小鼠中,阻断IDO确实能抑制抑郁样行为的产生^[67,68]。

与许多酶一样,体内IDO活性通过产物的比例判断(KYN/TRP的比例)。比值越大,反映酶的活性越大,值小意味着活性越小^[69]。

目前,关于炎症激活能促使IDO激活最终导致抑郁的机制有两种假说:TRP的衰竭和KYN的毒性作用。

3.4 色氨酸耗竭与抑郁

脑内5-HT的含量与抑郁的发病密切相关。5-HT是由色氨酸在限速酶色氨酸羟化酶作用下通过5-羟色氨酸(5-HTP)产生的。在正常情况下,限速酶色氨酸羟化酶,只有50%左右饱和。因此5-HT的合成主要看有效的TRP的量^[70]。许多有效的抗抑郁药(如SSRIs类药物)的主要功能是增加5-HT在突触间隙的可用性^[71]。TRP/大量中性氨基酸(LNAA)的比值是一个较为准确的测量脑内色氨酸可用性的方法^[72]。在用干扰素治疗丙型肝炎的患者脑脊液中,色氨酸水平没有发生改变^[73]。5-HT的代谢产物5-羟酸(5HIAA)减少,这种减少与抑郁的症状具有相关性^[69]。因此,即使出现TRP水平未改变,在总体上减少脑5-HT转化可能仍然与抑郁症有关。使用急性色氨酸耗竭(ATD)技术,通过降低TRP其前身在脑的可用性,使5-HT迅速减少可以起到抗抑郁的作用^[74]。另外,在脑成像研究报告中,抑郁症中枢5-HT系统的改变包括5-HT转运体减少^[75,76]、5-HT-1a受体减少^[75,76]及5-HT-2a受体减少^[77]。TRP衰竭可能造成免疫激活,代谢性毒物等的累积从而进一步影响免疫调节^[80]。

3.5 犬尿氨酸过剩与抑郁

值得注意的是,除了TRP的衰竭,KYN对神经递质的功能和行为也具有重要影响^[82]。例如,在小鼠体内单独注射KYN能诱导出抑郁样行为^[67]。此外,基于相关代谢酶的表达差异,在星形胶质细胞KYN优先转换犬尿喹啉酸(KA),在小胶质细胞则转化为喹啉酸(QUIN)^[83]。

在正常情况下,TRP通过肝脏酶TDO代谢生成KYN^[84]。免疫激活的情况下,IDO的活性增加,造成可检测的KYN增加,TRP减少^[60,61,85]。KYN主要羟基(犬尿氨酸羟化酶)是3-羟基犬尿氨酸(3-HK)。犬尿氨酸酶作用于3-HK和KYN;3-HK形成3-羟基氨基苯甲酸(3-HAA);KYN形成邻氨基苯甲酸。3-HAA在3-羟基氨基苯甲酸加氧酶的作用下被转换成

QUIN;KYN也可以在犬尿氨酸氨基转移酶的作用下被转换成犬尿喹啉酸,并且3-HK在犬尿氨酸转氨酶II的作用下可以转换为黄尿酸。虽然KYN被假定具有神经保护作用^[90],但在KYN代谢产物中一些通过调节神经传递产生神经损伤而另一些可能直接具有神经毒性。QUIN是一种NMDA受体激动剂和KYN/NMDA受体拮抗剂,由于可以增加氧化应激而被认为具有神经毒性^[88,89]。而3-HK由于增加参与神经元编程性细胞死亡细胞活性氧化物种类的形成被认为具有神经毒性^[86,87]。临床前实验表明,在免疫激活的情况下犬尿氨酸转氨酶活性是不变的,然而IDO、3-HK、KYN、犬尿氨酸酶和3-HAA加氧酶的活性增加^[48,91]。因此,KYN代谢远离KP途径转向3-HK/QUIN途径,这一结果将导致神经毒性的产生加强而具有神经保护作用的代谢产物减少引起神经进一步损伤。在体内,我们可以通过犬KYN/犬尿喹啉酸的比值间接评估犬KYN代谢产物中神经毒性和神经保护性通路的相对平衡关系^[55,92]。

有数据表明,在IFN- α 治疗的患者中,外周血中KYN显著增加,而在CSF中QUIN和碱性磷酸酶也显著增加^[93],CSF中KYN和QUIN的增加与抑郁症状的增加具有相关性。然而,CSF中犬尿喹啉酸也上升时KYN/犬尿喹啉酸的比值却未改变^[95]。

3.6 可能的研究新方向

一些初步的研究已经报道了抗炎药对抑郁症的治疗作用。在生物学治疗方面,在美国和欧洲,IL-1和TNF- α 的拮抗剂已经被允许广泛用于自身免疫障碍和炎症性疾病的研究中,而药物的靶点主要是有限的几个如环氧酶1,2(COX-1, COX-2)等立刻能用或正在研究中的炎症信号转导通路。一个随机双盲临床试验报告中显示,瑞波西汀(reboxetine)和COX-2抑制剂塞来昔布(celecoxib)联合用药的效果优于瑞波西汀和安慰剂的效果^[94]。然而,在这一方面也存在着更深层的问题,当五羟色胺再摄取抑制剂(SSRIs)类药和非甾体抗炎药联合使用时会增大胃肠道出血的风险性^[95],COX-2抑制剂单独使用会增加心血管疾病和各种原因的死亡率,其发生率甚至高于其它抗炎类药物^[96,97]。纵然如此,上述研究结果表明细胞因子或其信号通路对于IDO的激活及抗抑郁症方面的作用可以作为一个研究未来新的抗抑郁药物的新的靶点。第一个方向:是拮抗或减少IDO的激活。药物1-MT(1-methyltryptophan)可以抑制IDO,并已在炎症诱导的动物模型中成功地减少动物的抑郁样行为^[49]。临床试验中1-MT开始作为一个假定抗癌药在人类中使用(试验标号NCT00567931, <http://clinicaltrials.gov>)。然而,也有人对此存在一些怀疑,如它是否能在人体内抑制IDO。此外,IDO可能自身具有免疫抑制剂的作用,突出了免疫功能的复杂性^[98]。在埃默里大学,利用英夫利昔单抗(infliximab)治疗难治性抑郁症的疗效评估的临床试验已即将完成(试行标识符NCT00463580, <http://clinicaltrials.gov>),这为阻断促炎性细胞因子诱导IDO引发抑郁症的治疗提供了另一条途径。第三种方法是,阻断过剩的KYN代谢产物的下游行动。从NMDA受体的激动剂与拮抗剂的比值中能看出NMDA受体激动剂可以引起向抑郁症的转移,NMDA受体拮抗剂可能具有抗抑郁作用。然而,人类直接使用NMDA受体拮抗剂会产生严重的副作用,如出现镇静状态,记忆障碍和精神病^[99,100]。因此,设计

NMDA 受体操纵的化合物, 成为一个新的研究靶点。尽管这样, 一些小的研究使用氯胺酮(NMDA 受体拮抗剂)治疗难治性抑郁症已经显示出可喜的结果^[101-109]。

4 小结

总之, 已有许多证据表明抑郁症涉及免疫的多方面的变化, 尤其是伴随着一些促炎性细胞因子的增加。在增加的炎症反应标志物中, 无论是外周还是中枢都有 IDO 的激活。与此相应地, 在动物和人类中诱导炎症激活增加将导致病态行为, 在同期高风险的 HCV 患者人群中炎症激活的增加伴随着重型抑郁症的发生。虽然以上的数据不足以证明炎症、IDO 和抑郁及情绪间的因果关系, 但其多样性和一致性都有力的支持和证明了, 炎症诱导 IDO 激活引发抑郁这条途径可以作为未来的抗抑郁药物研究的新的靶点。

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