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性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 Idoleamine 2,3-Dioxyenase 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 activitions 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 RudolphMoos 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得抑郁症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 TNFα。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 %的人有重性抑郁症的发生[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的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[26,31]和其他急性期蛋白质,如 C - 反应蛋白 (CRP)[25] 结合珠蛋白[30]和一些嘌呤[32]。重性抑郁症患者存在明显的免疫激活和细胞因子增高的现象。重性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 metal 分析中显示:CRP,IL-1,IL-6 与抑郁的发病具相关性[25],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[45]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 - kB 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 origina）[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 在炎性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[78]。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[79]。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[80]。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[72]。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[73,74]，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[81]。

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 I 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 KYNNMDA 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 中犬尿喹啉酸酸也上升时 KYN/ 犬尿喹啉酸的比值却未改变[56]。

3.6 可能的新药研究方向

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-alpha 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化酶 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（celecoxil）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-methlytryptophar）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[101-105]。

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。

参考文献(References)

[1] Ustun TB, Ayuso-Mateos JL, Chatterji S, et al. Global burden of depressive disorders in the year 2000[J]. Br J Psychiatry, 2004,184:386-392

[2] Linda Brannon, Jess Feist. Health Psychology: an introduction to behavior and health[M]. Pacific Grove, California: Brooks / Cole Publishing Company, 1996, 72-85

[3] Yirmiya R, Weidenfeld J, Pollak Y, et al. Cytokines, "depression due to a general medical condition," and antidepressant drugs[J]. Advances in Experimental Medicine and Bioligy, 1999, 461:283-316

[4] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report[J]. Am J Psychiatry, 2006, 163(11):1905-1917

[5] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis [J]. Psychosom Med, 2009, 71(12):171-186

[6] Kim YK, Na KS, Shin KH, et al. Cytokine imbalance in the pathophysiology of major depressive disorder[J]. Prog VVeuropsychopharmacol Biol Psychiatry, 2007, 31(5):1044-1053

[7] Maes M, Bosmans E, Meltzer HY. Immunoendocrine aspects of major depression. Relationships between plasma interleukin-6 and soluble interleukin-2 receptor, prolactin and cortisol[J]. Eur Arch Psychiatry Clin Neurosci,1995, 245(3):172-178

[8] Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood [J]. Brain Behav Immun, 2010, 24(4):558-563

[9] Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans [J]. Arch Gen Psychiatry, 2001, 585(5):445-452

[10] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression[J]. Trends Immunol, 2006, 27:24-31

[11] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression[J]. Biol Psychiatry, 2009, 65:732-741

[12] Aubert A, Vega C, Dantzer R, et al. Pyrogens specifically disrupt the acquisition of a tak involving cognitive processing in the rat[J]. Brain, Behavior, and Immunity, 1995, 9(2): 129-148

[13] Capuron L, Gumnick JF, Musselman DL, et al. Neuropsychopharmacology, 2002, 26:643-652

[14] Musselman DL, Lawson DH, Gumnick JF, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression:results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine[J]. Mol Psychiatry, 2001,11:680-684

[15] Capuron L, Ravaud A, Miller AH, & Dantzer R. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy[J]. Am J Psychiatry, 2004, 160:1342-1345

[16] Raison CL, Borisov AS, Broadwell, et al. Brain-immune communication pathways[J]. Brain Behav Immun, 2005, 21: 828-835

[17] Zorrilla EP, Luborsky L, McKay JR, et al. Molecular mechanisms of microglial activation[J]. Adv Neuroimmunol, 2001, 6:191-222

[18] Howren MB, Lamkin DMand Suls J. Regulatory T cells increased while IL-1beta decreased during antidepressant therapy[J]. J Psychiatr Res, 2009, 44:1052-1058

[19] Miller AH, Maletic V andRaison CL. Mechanisms of cytokine-induced behavioral changes: psycho-neuroimmunology at the translational interface[J]. Brain Behav Immun, 2009, 23:149-158

[20] Dowlati Y, Herrmann N, Swardfager, et al. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation[J]. J Neurosci,2010,29: 2089-2102

[21] Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm[J]. Brain Behav Immun,2003, 17(Suppl 1):S119-124

[22] Capuron L, Gumnick JF, Musselman DL, et al. Neuropsychopharmacology, 2002, 26:643-652

[23] 迟松，林文娟. 抑郁症神经内分泌免疫学的研究进展及心理治疗的作用[J].中国临床心理学杂志, 2003, 11(1):77-80
Chi Song, Ling Wen-juan. Depression, neuroendocrine immunology research and the role of psychotherapy [J]. Chinese Journal of Nervous and Mental Diseases, 2003,11(1):77-80

[24] 王东林，林文娟.细胞因子与抑郁症发病机制研究进展[J].中国神经精神疾病杂志, 2007, 33(9):572-574
Wang Dong-ling, Lin Wen-juan. Cytokine and depression pathogenesis research [J]. Chinese Journal of Nervous and Mental Diseases, 2007, 33(9):572-574

[25] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis [J]. Psychosom Med, 2009,71(12):171-186

[26] Kim YK, Na KS, Shin KH, et al. Cytokine imbalance in the pathophysiology of major depressive disorder[J]. Prog VVeuropsychopharmacol Biol Psychiatry, 2007, 31(5):1044-1053

[27] Owen BM, Eccleston D, Ferrier IN, Young AH. Raised levels of plasma interleukin-1beta in major and postviral depression[J]. Acta Psychiatr Scand, 2001, 103(3):226-228

[28] Levine J, Barak Y, Chengappa KN, et al. Cerebrospinal cytokine levels in patients with acute depression[J]. Neuropsychobiology,1999, 40(4):171-176

[29] Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression [J]. J Affect Disord, 1995, 34

(4):301-309

[30] Zorrilla EP, Luborsky L, McKay JR, et al. The relationship of depression and stressors to immunological assays: a meta-analytic review [J]. Brain Behav Immun, 2001, 15(3):199-226

[31] Hestad KA, Tonseth S, Stoen CD, et al. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy[J] . JECT, 2003, 19(4):183-188

[32] Maes M, Scharpe S, Meltzer HY, et al. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response[J]. Psychiatry Res, 1994, 54(2):143-160

[33] Levine J, Barak Y, Chengappa K N, et al. Cerebrospinal cytokine levels in patients with acute depression[J]. Neuropsychobiology, 1999,40 (4):171-176

[34] Brambilla F, Maggioni M. Blood levels of cytokines in elderly patients with major depressive disorder [J]. Acta Psychiatr Scand, 1998,97(4):309-313

[35] Carpenter LL, Heninger GR, Malison RT, et al. Cere-brospinal fluid interleukin (IL)-6 in unipolar major depression[J]. J Affect Disord, 2004, 79(1-3):285-289

[36] Mossner R, Mikova O, Koutsilieri E, et al. Consensus paper of the WFSBP Task Force on Biological Markers: biological markers in depression[J]. World J Biol Psychiatry, 2007, 8(3):141-174

[37] Maes M, Yirmyia R, Noraberg J, et al. The inflammatory and neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression [J]. Metab Brain Dis, 2009, 24(1):27-53

[38] Lin A, Song C, Kenis G, et al. The in vitro immunosuppressive effects of moclobemide in healthy volunteers[J]. J Affect Disord, 2000, 58 (1):69-74

[39] Maes M, Song C, Lin AH, et al. Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion[J]. Neuropsychopharmacology, 1999, 20(4): 370-379

[40] Kubera M, Lin AH, Kenis G, et al. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio[J]. J Clin Psychopharmacol, 2001,21(2):199-206

[41] Sluzewska A, Rybakowski JK, Laciak M, et al. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine [J]. Ann N Y Acad Sci,1995,762:474-176

[42] Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood [J]. Brain Behav Immun, 2010,24(4):558-563

[43] Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans[J]. Arch Gen Psychiatry, 2001, 585(5):445-452

[44] Spath Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men[J]. J Clin Endocrinol Metab, 1998,83 (5):1573-1579

[45] Brydon L, Harrison NA, Walker C, Steptoe A, et al. Critchley HD Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in [J]. Biol Psychiatry, 2008, 63 (11):1022-1029

[46] Eisenberger NI, Inagaki TK, Rameson LT, et al. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences[J]. Neuroimage, 2009, 47(3):881-890

[47] Frenois F, Moreau M, O'Connor J, et al. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior[J]. Psychoneuroendocrinology, 2007, 32(5):516-531

[48] O'Connor JC, Lawson MA, Andre C, et al. Induction of IDO by bacille Calmette-Guerin is responsible for development of murine depressive-like behavior[J]. J Immunol, 2009, 182(5):3202-3212

[49] O'Connor JC, Andre C, Wang Y, et al. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin [J]. J Neurosci, 2009, 29(13): 4200-4209

[50] O'Connor JC, Lawson MA, Andre C, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice[J]. MolPsychiatry, 2009, 14(5):511-522

[51] Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C[J]. Psychosomatics, 2003, 44(2):104-112

[52] Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study [J]. Gen Hosp Psychiatry, 2003, 25(1):34-38

[53] Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C[J]. Mol Psychiatry, 2002, 7(9): 942-947

[54] Kraus MR, Schafer A, Faller H, et al. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy [J]. J Clin Psychiatry, 2003, 64(6):708-714

[55] Bonaccorso S, Puzella A, Marino V, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms[J]. Psychiatry Res, 2001, 105(1-2): 45-55

[56] Wichers MC, Kenis G, Koek GH, et al. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol[J]. J Psychosom Res, 2007, 62(2):207-214

[57] Fujigaki H, Saito K, Fujigaki S, et al. The signal transducer and activator of transcription 1alpha and interferon regulatory factor 1 are not essential for the induction of indoleamine 2,3-dioxygenase by lipopolysaccharide: involvement of p38 mitogen-activated protein kinase and nuclear factor-kappaB pathways, and synergistic effect of several proinflammatory cytokines[J]. J Biochem, 2006, 139: 655-662

[58] Schwarcz R, & Pellicciari R . Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities[J]. J Pharmacol Exp Ther, 2002, 303: 1-10

[59] Bender DA. Biochemistry of tryptophan in health and disease[J]. Mol Aspects Med, 1983, 6(2):101-197

[60] Schafer A, Wittchen HU, Seufert J, Kraus MR. Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C - a critical review [J]. Int J Methods Psychiatr Res,2007,16(4):186-201

[61] Bonaccorso S, Puzella A, Marino V, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms [J]. Psychiatry Res, 2001,105(1-2): 45-55

[62] Wichers MC, Kenis G, Koek GH, et al. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol[J]. J Psychosom Res, 2007, 62(2):207-214

[63] Delgado PL, Price LH, Miller HL, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus[J]. Endocrinology, 1994, 146: 4192-4199

[64] Bonaccorso S, Marino V, Puzella A, et al. Shifting the imbalance from Th1/Th2 to Th18/treg: the changing rheumatoid arthritis paradigm[J]. Joint Bone Spine, 2002, 75: 383-385

[65] Capuron L, Ravaud A, Neveu PJ, Miller AH. Baseline mood and psychosocial characteristics ofpatients developing depressive symptoms during interleukin-2 and/ or interferon-alpha cancer therapy[J]. Brain Behav Immun, 2002, 18:205-213

[66] Capuron L, Neurauter G, Musselman DL, et al. Vitamin E status and quality of life in the elderly: influence of inflammatory processes[J]. Br JNutr, 2003, 102: 1390-1394

[67] O'Connor JC, Lawson MA, Andre C, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma [J]. Proc Natl Acad Sci USA, 2009, 100:14293-14296

[68] O'Connor JC, Lawson M A, et al. Induction of IDO by bacille Calmette-Guerin is responsible for development of murinedepressive-like behavior[J]. J Immunol, 2009, 182:3202-3212

[69] Schrocksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation[J]. Clin Chim Acta, 2006, 364(1-2):82-90

[70] Schaechter JD, Wurtman RJ. Serotonin release varies with brain tryptophan levels[J]. Brain Res, 1990, 532(1-2):203-210

[71] Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines [J]. J Psychopharmacol, 2008, 22(4):343-396

[72] Hood SD, Bell CJ, Nutt DJ. Acute tryptophan depletion. Part I: rationale and methodology [J]. Aust N Z J Psychiatry, 2005, 39(7): 558-564

[73] Reimold M, Batra A, Knobel A, et al. Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study [J]. Mol Psychiatry, 2008, 13(6):606-613, 557

[74] Joensuu M, Tolmunen T, Saarinen PI, et al. Reduced midbrain serotonin transporter availability in drug-naive patients with depression measured by SERT-specific [(123)I] nor-beta-CIT SPECT imaging [J]. Psychiatry Res, 2007, 154(2):125-131

[75] Sargent PA, Kjaer KH, Bench CJ, et al. Brain serotonin1 A receptor binding measured by positron emission tomography with [11C] WAY-100635: effects of depression and antidepressant treatment[J]. Arch Gen Psychiatry, 2000, 57(2):174-180

[76] Drevets WC, Thase ME, Moses Kolko EL, et al. Serotonin-1 A receptor imaging in recurrent depression: replication and literature review [J]. Nucl Med Biol, 2007, 34(7):865-877

[77] Yatham LN, Liddle PF, Shiah IS, et al. Brain serotonin2 receptors in major depression: a positron emission tomography study [J] . Arch Gen Psychiatry, 2000,57(9):850-858

[78] Fernstrom JD. Diet-induced changes in plasma amino acid pattern: effects on the brain uptake of large neutral amino acids, and on brain serotonin synthesis[J]. J Neural Transm Suppl, 1979,(15): 55-67

[79] Raison CL, Dantzer R, Kelley KW, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression [J]. Mol Psychiatry, 2010, 15(4):393-403

[80] Raison CL, Borisov AS, Majer M, et al. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression[J]. Biol Psychiatry, 2009, 65(4):296-303

[81] MacKenzie CR, Heseler K, Mü ller A, Däubener W. Role of indoleamine 2,3-dioxygenase in antimicrobial defence and immuno-regulation:tryptophan depletion versus production of toxic kynurenines[J]. Curr Drug Metab, 2007, 8(3):237-244

[82] Wichers M C, Koek, et al. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol [J]. JPsychosom Res, 2005,62: 207-214

[83] Schwarcz R, & Pellicciari R. Lymphocyte function in major depressive disorder[J]. Arch Gen Psychiatry, 2002, 41:484-486

[84] Knox WE, Mehler AH. The conversion of tryptophan to kynurenine in liver. I. The coupled tryptophan peroxidase-oxidase system forming formylkynurenine[J]. J Biol Chem, 1950, 187(1):419-430

[85] Silva NM, Rodrigues CV, Santoro MM, et al. Expression of indoleamine 2,3-dioxygenase, trypto-phan degradation, and kynurenine formation during in vivo infection with Toxoplasma gondii: induction by endogenous gamma interferon and requirement of interferon regulatory factor 1[J]. Infect Immun, 2002,70(2):859-868

[86] Okuda S, Nishiyama N, Saito H, Katsuki H. 3-Hydroxykynurenine, an endogenous oxidative stress generator, causes neuronal cell death with apoptotic features and region selectivity[J]. J Neurochem, 1998, 70(1):299-307

[87] Stone TW. Endogenous neurotoxins from tryptophan [J]. Toxicon, 2001,39(1):61-73

[88] Santamaria A, Galvan-Arzate S, Lisy V, et al. Quinolinic acid induces oxidative stress in rat brain synaptosomes [J]. Neuroreport, 2001, 12 (4):871-874

[89] Behan WM, McDonald M, Darlington LG, Stone TW. Oxidative stress as a mechanism for quinolinic acid-induced hippocampal damage: protection by melatonin and deprenyl [J]. Br J Pharmacol,1999,128 (8):1754-1760

(下转第 2762 页)

Fever of Unknown Origin[J]. Clinica1 Medica1 Journal of China, 2004, 11:488-489

[10] Jason JB, David S. Fever of Unknown Origin Caused by Tuberculosis [J]. Infectious Disease Clinics of North America, 2007, 21:947-962

[11] **林冰. 发热待查住院** 452 **例临床资料对比分析** [J]. **疑难病杂志**, 2006,5:424-426
Lin Bing. Analysis on clinical data of 452 hospitalized patients with fever of unknown origin[J]. Chin J Diffic and Compl Cas, 2006, 5:424-426

[12] Stamatis PE, Angelos VP, Aphrodite GT, et a1. Fever of unknown origin: Discrimination between infectious and non-infectious causes [J]. European Journal of Internal Medicine, 2010, 21: 137-143

[13] **王甜,牟建军,时晔.高龄患者发热待查的临床诊治体会**[J].**基层医学论坛,** 2009, 13:875-876
Wang Tian, Mou Jian-jun, Shi Ye. Experience of the diagnosis and treatment for fever in the senior patients[J]. Medical Forum, 2009,13: 875-876

[14] Salih SB, Saeed AB, Alzahrani M, et al. Primary CNS lymphoma presenting as fever of unknown origin[J]. J Neurooncol, 2009, 93:401-404

[15] **秦北宁,孙永利,马丽.以发热待查为表现的亚急性甲状腺炎** 13 **例分析**[J]. **现代中西医结合杂志**, 2006, 15:938
Qin Bei-ning, Sun Yong-li, Ma li, et al. Analysis of 13 cases of subacute thyroiditis with fever of unknown origin[J]. Modern Journal of Integrated Traditional Chinese and Western Medicine, 2006, 15:938

[16] **于连玲,张锦.发热待查** 254 **例临床分析**[J].**宁夏医学杂志**,2008,30: 799-800
Yu Lian-ling, Zhang Jin. Clinical analysis of 254 cases with fever of unknown origin[J]. Ningxia Med J, 2008, 30:799-800

[17] **徐薇.发热待查的诊断思路**[J]. **现代实用医学**, 2006, 18:775-779
Xu Wei. Diagnostic measure of fever of unknown origin [J]. Modern Practical Medicine, 2006, 18:775-779

[18] **范学工,全俊.发热待查的诊断思路和处理原则**[J].**中国感染控制杂志**, 2009, 8:228-231
Fan Xue-gong, Quan Jun. Diagnostic measure and treatment principle of fever of unknown origin[J]. Chin J Infect Control, 2009, 8:228-231

[19] Abidi K, Khoudri I, Belayachi J, et al. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units[J]. Crit Care, 2008, 12:69

[20] Sanders S, Barnett A, Correa-Velez I, et al. Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever[J]. J Pediatr, 2008, 153:570-754

[21] Cunha BA. Fever of unknown origin (FUO): diagnostic importance of serum ferritin levels[J]. Scand J Infect Dis, 2007, 39:651-652

[22] **李静波,张静萍,陈佰义**.541 **例不明原因发热病因回顾性分析**[J]. **中华医院感染学杂志,**2011, 21:1587-1589
Li Jing-bo, Zhang Jing-ping, Chen Bai-yi. Etiological factors for 541 patients with fever of unknown origin: a retrospective analysis[J]. Chin J Nosocomiol, 2011, 21:1587-1589

(上接第 2756 页)

[90] Stone TW, Addae JI. The pharmacological manipulation of glutamate receptors and neuroprotection [J]. Eur J Pharmacol, 2002, 447(2-3): 285-296

[91] Saito K, Crowley JS, Markey SP, Heyes MP. A mechanism for increased quinolinic acid formation following acute systemic immune stimulation[J]. J Biol Chem, 1993, 268(21):15496-15503

[92] Wu HQ, Guidetti P, Goodman JH, et al. Kynurenergic manipulations influence excitatory synaptic function and excitotoxic vulnerability in the rat hippocampus in vivo[J]. Neuroscience, 2000, 97(2):243-251

[93] Raison C L, Dantzer R, Kelley, et al. Cytokines sing the blues: inflammation and the pathogenesis of depression[J]. Trends Immunol, 2010, 27:24-31

[94] Muller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine[J]. Mol Psychiatry, 2006, 11(7):680-684

[95] Mendlewicz J, Kriwin P, Oswald P, et al. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study[J]. Int Clin Psychopharmacol, 2006, 21(4):227-231

[96] Kerr SJ, Sayer GP, Whicker SD, et al. All-cause mortality of elderly Australian veterans using COX-2 selective or non-selective NSAIDs: a longitudinal study[J]. Br J Clin Pharmacol, 2011, 71(6):936-942

[97] Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident[J]. Aliment Pharmacol Ther, 2007, 25(8):913-924

[98] Lob S, Konigsrainer A, Rammensee HG, Opelz G, Terness P. Inhibitors of indoleamine-2,3-dioxygenase for cancer therapy: can we see the wood for the trees[J]. Nat Rev Cancer, 2009,9(6):445-452

[99] Bergink V, van Megen HJ, Westenberg HG. Glutamate and anxiety [J]. Eur Neuropsychopharmacol, 2004, 14(3):175-183

[100] Swanson CJ, Bures M, Johnson MP, et al. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders [J]. Nat Rev Drug Discov, 2005, 4(2):131-144

[101] Aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression[J]. Biol Psychiatry, 2010, 67(2):139-145

[102] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ket-amine in depressed patients [J]. Biol Psychiatry, 2000, 47(4): 351-354

[103] Mathew SJ, Murrough JW, Rot M, et al. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placeb-controlled continuation trial[J]. Int J Neuropsychopharmacol, 2010, 13(1):71-82

[104] Machado Vieira R, Yuan P, Brutsche N, et al. Brain-derived neu-rotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist[J]. J Clin Psychiatry, 2009,70(12):1662-1666

[105] Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression[J]. Arch Gen Psychiatry, 2006,63(8):856-864