Advances in Clinical Medicine 临床医学进展, 2024, 14(8), 844-852
Published Online August 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.1482292

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多不饱和脂肪酸跨血脑屏障转运机制及其对抑郁症潜在影响的研究进展

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收稿日期：2024年7月19日；录用日期：2024年8月11日；发布日期：2024年8月21日

摘　要

多不饱和脂肪酸(Polyunsaturated Fatty Acid, PUFA)在大脑发育和功能中发挥着不可或缺的作用。近年来，PUFA与神经系统疾病之间的关系备受关注，尤其是其对血脑屏障(Blood-Brain Barrier, BBB)功能的影响。研究发现，PUFA状态的异常与多种神经精神疾病如重度抑郁症、双相情感障碍、精神分裂症、阿尔茨海默病和注意缺陷多动障碍等密切相关。本文综述了当前关于PUFA通过BBB进入中枢神经系统(Central Nervous System, CNS)的转运机制的研究进展，并探讨了n-3 PUFA与抑郁症之间的潜在关系。

关键词

多不饱和脂肪酸，血脑屏障，n-3多不饱和脂肪酸，抑郁症，研究进展

Research Progress on the Transport Mechanism of Polyunsaturated Fatty Acids across the Blood-Brain Barrier and Their Potential Impact on Depression

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文章引用: 张玲, 张恒, 陈琦, 徐嘉林. 多不饱和脂肪酸跨血脑屏障转运机制及其对抑郁症潜在影响的研究进展[J]. 临床医学进展, 2024, 14(8): 844-852. DOI: 10.12677/acm.2024.1482292

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Received: Jul. 19th, 2024; accepted: Aug. 11th, 2024; published: Aug. 21st, 2024

Abstract

Polyunsaturated Fatty Acids (PUFAs) play an indispensable role in brain development and function. In recent years, the relationship between PUFAs and neurological disorders has garnered significant attention, particularly their influence on Blood-Brain Barrier (BBB) function. Research has revealed that aberrant PUFA status is closely associated with various neuropsychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia, Alzheimer's disease, and attention-deficit/hyperactivity disorder. This review summarizes the current advancements in the study of PUFA transport mechanisms through the BBB into the Central Nervous System (CNS) and explores the potential relationship between n-3 PUFAs and depression.

Keywords

Polyunsaturated Fatty Acids, Blood-Brain Barrier, n-3 Polyunsaturated Fatty Acids, Depression, Research Progress

1. 引言

随着对神经系统疾病机制的深入研究，外周血与脑组织之间的 BBB 以及血液与脑脊液之间的血－脑脊液屏障(Blood-Cerebrospinal Fluid Barrier, BCSFB)在维护大脑稳态、抵御有害物质侵袭方面的作用愈发显著。这些屏障不仅是神经系统的天然防御机制，更在调控营养物质进入大脑方面扮演着关键角色[1]。近年来，PUFA，特别是 n-3 PUFA，在神经系统健康中的潜在价值受到了学术界的广泛关注。为了更全面地理解 PUFAs 如何在神经系统中发挥作用，探究其通过 BBB 的转运过程及其随后的生理效应显得尤为重要。因此，本综述旨在系统回顾 PUFA 跨血脑屏障的转运机制，并探讨这些机制与抑郁症潜在关联的研究进展，以期为相关领域的深入研究提供参考和启示。

2. PUFA 的分类

人的大脑富含脂质，尤其是磷脂和胆固醇，分别占据了大脑脂质的 24%和 22% [2]。这些脂质是构成细胞膜的重要组分，在中枢神经系统(Central Nervous System, CNS)中的浓度异常高，几乎占据了大脑干重的一半。值得注意的是，脑脂质中有高达 35%的比例是由 PUFA 所构成[3]。这类脂肪酸(Fatty Acid, FA)虽然人体无法直接通过 2-碳片段来合成，但却是人体营养所不可或缺的[4]。从化学结构上来看，PUFA 的特点是其分子中含有两个或更多的顺式双键。它们可以根据从碳链甲基(ω)端开始计数的第一个双键所在的碳原子位置，被进一步细分为 n-3、n-6 和 n-9 三个主要类别[5]。其中，n-3 家族的 PUFA 主要包括 α-亚麻酸(ALA, 18:3n-3)、二十碳五烯酸(EPA, 20:5n-3)和二十二碳六烯酸(DHA, 22:6n-3)，而 n-6 家族的 PUFA 则主要包含了亚油酸(LA, 18:2n-6)和花生四烯酸(AA, 20:4n-6)。重要的是，这两大系列的 FA 在人体内并不能相互转化，且它们各自具有独特的生物学作用[6]。ALA 和 LA，分别作为 n-3 和 n-6 PUFA 的

必需营养前体。在人体内，ALA 通过一系列代谢步骤，在微粒体酶系统的作用下形成 EPA 和 DHA。LA 也可以经过一系列生化反应转化为 AA [7]。值得一提的是，ALA 和 LA 都是人体不可或缺的 FA，但由于人体无法自行合成，因此必须通过食物来获取。同样地，当人体自身无法合成足够的 EPA、DHA 和 AA 时，这些重要的 FA 也必须通过饮食来补充[8]。在脑部的 PUFA 中，AA 和 DHA 占据了主导地位，分别约占 50%和 40% [9]。其中，DHA 作为最丰富的 n-3 PUFA，在大脑和视网膜中的含量特别高，远超 EPA 数百倍[10]。而 EPA 在大脑中的浓度则相对较低，因为它会迅速通过 β 氧化作用进行分解[11]。

n-3 与 n-6 多 PUFA 家族在精神病学研究中占据重要地位。研究显示，在神经退行性或炎症性疾病患者中，n-6 PUFA 与 n-3 PUFA 的比值呈现上升态势，而 n-3 PUFA 的浓度则显著降低[12]。这种体内 FA 比例的变化可能与这些疾病的病理机制密切相关。更深入的研究表明，n-3 PUFA 摄入量减少或血液浓度降低与抑郁症及帕金森病发病风险的增加有直接联系[13]。值得注意的是，EPA 不仅能有效减轻炎症反应，还能上调神经营养因子的表达，从而在抑郁症和精神分裂症的治疗中表现出显著疗效。然而，DHA 并未展现出类似的治疗效果[14]。另外，Song C 等[15]研究发现，富含 AA 的饮食可刺激小鼠的糖皮质激素分泌，并在高架十字迷宫测试中引发小鼠的焦虑样行为。综上所述，这些 PUFA 在大脑的发育、结构维护以及功能发挥中扮演着至关重要的角色。

3. BBB 的结构和功能

众多前瞻性研究已证实，富含 n-3 PUFA 的饮食对于改善正常衰老进程中的认知功能以及预防神经认知疾病的发展具有显著效果[16] [17]。然而，目前科研界尚未明确阐述 PUFA 如何从血液传递至大脑[18]。在探讨这一问题时，我们必须考虑大脑的三个主要血脑界面，即 BBB、BCSFB 以及血蛛网膜屏障(Blood-Arachnoid Barrier, BAB)。其中，物质进出 CNS 主要依赖于 BBB 和 BCSFB 的调控[19]。值得注意的是，BAB 在脂质运输与代谢中的具体作用目前仍不明确，相关研究也较为缺乏[20]。BBB 作为脑组织与血液之间的关键细胞屏障，在维持 CNS 内环境稳定方面发挥着至关重要的作用。完全分化的 BBB 是由一个复杂的系统组成，包括高分化的内皮细胞及其下方的基底膜(其中嵌入了大量的周细胞)、血管周围的抗原呈递细胞，以及星形胶质细胞的终足及其相关的脑实质基底膜的包绕层[21]。该系统配备如葡萄糖转运体、有机阳离子转运体、P-糖蛋白及多药耐药相关蛋白等多种转运体，是 BBB 通透性低的关键因素，限制大分子如蛋白质和药物进入 CNS，但允许水、电解质、葡萄糖等小分子自由通过[22]。这些细胞通过复杂的相互作用，动态地调控着 BBB 的功能，严格控制着物质在脑组织与血液之间的运输，确保其能够有效地保护大脑免受有害物质的侵害，同时允许必要的营养物质进入大脑[23]。

4. PUFA 通过血脑屏障的运输

关于 PUFA 穿越血脑屏障的机制，目前已知的主要有三种方式，分别是被动扩散、通过跨膜蛋白的运输以及胞吞作用[24]。具体而言，PUFA 既可以被动地通过内皮膜扩散，也可以通过跨膜蛋白运输进入内皮细胞内。一旦进入 BBB 的内皮细胞，PUFA 通过与脂肪酸结合蛋白(Fatty Acid Binding Protein, FABP)相结合，在细胞质中被运输，并最终被送达大脑[25]。另外，PUFA 也可以通过脂肪酸转运蛋白(Fatty Acid Transport Proteins, FATPs)介导的胞吞作用直接运输到大脑，这一过程中涉及到初级内吞小泡或网格蛋白包被的囊泡[26]。

血浆中的 PUFA 以酯化和非酯化(游离)两种形式存在，以各自独特的方式穿越血脑屏障。其中，血液中的非酯化 PUFA 通常与白蛋白结合形成复合物，以此方式穿越血脑屏障。为了能通过内皮细胞膜进行被动扩散，非酯化 PUFA 需要从白蛋白中解离出来。该过程包括吸附、跨膜运动和解吸三个步骤，且均不涉及与蛋白质或受体的结合[27]。Melissa Ouellet 等[28]研究显示，放射性标记的 DHA 直接注入脑颈

动脉后，仅有不到10%停留在脑血管内皮细胞，表明大部分DHA可穿越BBB。但DHA与白蛋白的结合可能阻碍其通过BBB，降低穿越效率。Strosznajder J等[29]研究发现，BBB对PUFA的通透性主要受三个关键因素影响：(1) PUFA对血液中循环的白蛋白的相对亲和力；(2) PUFA和白蛋白之间的分离率；(3)内皮细胞和神经细胞对PUFA的代谢与利用。另外，关于非酯化PUFA的被动扩散机制，目前存在几种理论，包括翻转扩散(flip-flop)、FATPs的促进作用，或是这两种机制的结合。这些机制共同揭示了非酯化PUFA如何在生物体内实现有效的跨膜转运[30]。

酯化的PUFA主要以三酰基甘油、胆固醇酯和磷脂的形式存在，与载脂蛋白共同构成血浆脂蛋白。Lacombe RJS等[27]的研究发现，当DHA被酯化为溶血磷脂胆碱-DHA (Lysophosphatidylcholine-DHA, LPC-DHA)时，其穿越BBB的效率显著提高。这一发现为PUFA通过酯化改性以增强其透过BBB的能力提供了有力证据。除了上述机制，Edmond还提出了PUFA的特异性转运模型。在该模型中，位于内皮细胞管腔膜上的脂蛋白受体，虽不与脑实质直接接触，却能让脂蛋白进入内皮细胞。内皮细胞随后处理这些脂蛋白，释放出PUFA，并将其转移至特定转运体。管腔膜外侧则存在多种转运体，如单羧酸转运体和FATPs [31]。因PUFA结构多样，故存在不同的FATPs进行选择性跨膜转运[32]。例如，FATP1是对胰岛素敏感的长链脂肪酸(Long-Chain Fatty Acids, LCFAs)转运体，FATP2主要存在于肝脏和肾脏皮质，而FATP4则定位于小肠上皮细胞顶端，负责吸收膳食脂质。研究显示，FATP4对摄取LCFAs和极长链脂肪酸至关重要，同时，FATP1也是大脑中的主要FATPs [33]-[36]。另外，LCFAs可通过FATP复合物直接穿越质膜，或与CD36结合后再由FATPs转运。低FA与白蛋白比值时，CD36的转运效率更高[37]。被内皮细胞摄入后，LCFAs迅速被长链脂酰辅酶A合成酶激活以防外排。同时，LCFAs和酰基辅酶A (Acyl Coenzyme A，Acyl-CoA)与FABP及Acyl-CoA结合蛋白的结合，有助于转运体和合成酶的卸载过程，并作为细胞内脂肪酸的缓冲[38]。要深入了解FATP介导的转运机制和蛋白在能量稳态中的作用，还需更多研究。

值得注意的是，Nguyen LN等[39]发现了主要促进剂超家族域包含蛋白2A (Major facilitator super-family domain containing 2A, Mfsd2a)，它是DHA进入大脑的主要转运体。这一发现改变了我们对PUFA如何通过血脑屏障运输的理解。Mfsd2a在大脑内皮细胞中表达，并能以溶血磷脂酰胆碱(Lysophosphatidylcholine, LPC)或磷脂酰胆碱的形式运输DHA。Mfsd2a的缺失对血脑屏障的发育和正常功能产生了重大影响[40]。在mfsd2a基因敲除的小鼠中，脑膜中的DHA水平显著降低，同时伴随着海马体和小脑神经元的丢失，以及小头畸形、认知缺陷和严重的焦虑[41]。此外，Mfsd2a还参与了脑内皮细胞脂质组成的调节，特别是维持DHA水平[42]。

PUFA穿越BBB的另一途径是胞吞，具体包括网格蛋白依赖性和小泡介导的两种内吞方式。网格蛋白依赖性内吞依赖于网格蛋白外壳形成的囊泡，通过适配器蛋白识别并内化跨膜蛋白，将低密度脂蛋白(Low-Density Lipoprotein, LDL)送至溶酶体降解，释放胆固醇和PUFA，同时受体被回收至质膜。另一方面，小泡的形成依赖于胆固醇，并且这些小泡内含有特定的小泡蛋白，该类蛋白具有结合胆固醇的能力[43]。在BBB内皮细胞层面，已观测到这些结构中存在着LDL受体。这些受体能够通过质膜转移LDL，从而有效防止其发生降解[44]。

5. PUFA对抑郁症的作用

抑郁症作为一种常见且易反复发作的衰弱性疾患，归属于情感或情绪失调类的精神和行为障碍。近十年来，PUFA在抑郁症中的作用逐渐成为研究焦点，特别是n-3 PUFA，被认为对抑郁症具有潜在的预防和治疗功效[45]。多项研究表明，膳食中n-3 PUFA的缺乏可能与情绪障碍的发病有关，抑郁症患者有较低的DHA和EPA水平。因此，合理补充n-3 PUFA可能为情绪障碍的治疗开辟新的途径[46] [47]。Lin

PY 等[48]研究发现，含有更高比例 EPA 的补充剂比富含 DHA 的补充剂对抑郁症的治疗更有效，尽管其具体机制仍有待阐明。Martins JG 等[49]的研究揭示，在非大脑环境中，EPA 和 DHA 的功能存在差异。EPA 与其 20-碳 n-6 同源物 AA 在与 cPLA2α 和 COX-1 的结合上存在竞争关系，且 EPA 是比 DHA 更强的 PPARα 激活剂。相反，DHA 对脂质筏结构的影响更为显著。另外，n-6 与 n-3 PUFAs 的比值，已成为评估个体 PUFA 状态的关键指标。在抑郁症患者中，n-6 与 n-3 PUFA 的比值常呈现显著上升的趋势。Rizzo AM 等[50]研究发现，高 DHA 水平、高总 n-3 PUFA 含量以及低 n-6 与 n-3 PUFA 的比值与抑郁症的风险显著降低相关。n-6 与 n-3 PUFA 比值能够影响单胺能神经传递，进而对主要情绪障碍产生影响，包括影响精神障碍的改善以及认知功能的变化。此外，相对于 n-6 PUFA 的水平，较低的 n-3 PUFA 水平也与自杀企图和自杀风险的增加相关联。值得注意的是，相对于 n-6 PUFA 的水平，n-3 PUFA 的较低含量与自杀企图及自杀风险的增加存在关联[51]。另外，Appleton KM 等[52]研究发现，n-3 PUFA 对于仅表现出轻度抑郁症状或尚未被确诊为抑郁症的个体而言，其效用并不显著。不过，也有研究表明，在患有严重抑郁症状或被明确诊断为抑郁症的个体中，n-3 PUFA 展现出了一定的治疗益处[53]。然而，Bloch MH 等[54]的研究揭示，相较于安慰剂，n-3 PUFA 展现出轻微至中度的正面效应，但此种效应的强度对于患有重度抑郁症(Major Depressive Disorder, MDD)的患者而言，可能并不具备显著的临床意义。此外，先前的研究也表明，n-3 PUFA 对于 MDD 的改善作用较为微弱且不显著[55]。

n-3 PUFA 与抑郁症之间的潜在联系，可能归因于这些必需 FA 的低摄入与遗传因素导致的磷脂代谢异常之间的复杂交互作用。具体而言，这种交互可能导致细胞对 n-3 PUFA 的摄取能力下降[56]。进一步的研究表明，细胞对 n-3 PUFA 摄取的减少与脂肪酸辅酶 A 脂肪酶 4 以及/或者 IV 型磷脂酶 A2 的活性减弱有显著关联。值得注意的是，这些酶编码基因的功能性低变异均与 MDD 的发病风险增加密切相关[57]。另外，有研究认为，抑郁症状的严重程度与炎性因子相关。抑郁症患者的血浆中抗炎细胞因子白细胞介素-4、白细胞介素-10 和 TGF1 水平降低，而大脑小胶质细胞产生的促炎细胞因子则改变 5-羟色胺代谢，并降低海马神经突触可塑性[58]。n-3 PUFA 通过多方面机制对炎性因子产生显著影响。它能够置换细胞膜上的 AA，抑制炎性介质的产生，并通过改变细胞膜流动性来调控信号传导[59]。此外，n-3 PUFA 还能影响基因表达，抑制前炎症因子的产生，并发挥神经保护与抗炎作用。更重要的是，n-3 PUFA 能降低特定炎性因子如 TNF-α 和白细胞介素-6 的水平，从而可能改善抑郁症患者的症状[60]。另外，n-3 PUFA 还通过增强 g 蛋白介导的信号转导、膜结合酶(Na+/K+-ATPase)和蛋白激酶 C 来调节信号转导[61]。

总之，PUFA 在精神疾病预防方面的潜在效用还有待深入探究。从现有的研究来看，PUFA 的作用可能是多方面的：它不仅可能通过维护和增强大脑结构、与磷脂代谢相互作用以保持大脑功能，进而调节信号传导；同时，它还可能预防或减少抑郁状态下的炎症反应[62]。现有大量证据显示，长链 n-3 FA (Long-Chain n-3 Polyunsaturated Fatty Acids, LCn-3)的缺乏与不同精神疾病的病理生理进展机制有关，这种缺乏可能增加包括自杀和心血管疾病在内的过早死亡风险[63] [64]。新研究显示，LCn-3 脂肪酸能增强抗抑郁药和情绪稳定剂的治疗效果。n-3 PUFA 可能通过改善血脑屏障功能等途径，在抑郁症治疗中发挥积极作用，展现出良好的应用潜力。因此，由于 n-3 PUFA 脂肪酸具有长期安全使用的记录，且总体成本效益比高，这为将其纳入精神疾病治疗方案提供了有力支持[65] [66]。然而，目前临床研究结果并不统一，仍需要大规模的临床研究来进一步验证。同时，关于 PUFA 的最佳剂量、不同类型 PUFA 的理想比例以及给药时间等问题，也有待深入探究。

6. 小结

PUFA 对神经系统健康的影响已成为当代研究的焦点。随着对 PUFA 与神经系统疾病关系的深入探索，我们逐渐认识到 PUFA 在维持 BBB 功能及 CNS 稳态中的关键作用。PUFA 可通过改善 BBB 功能等

机制，对抑郁症的治疗产生积极作用，具有良好的应用前景。本文系统综述了 PUFA 跨 BBB 转运的最新研究进展，揭示了其通过被动扩散、跨膜蛋白运输及胞吞作用等多种方式进入 CNS 的复杂机制。这些发现不仅增进了我们对 PUFA 在神经系统中作用的理解，而且为开发针对神经精神疾病的创新疗法提供了理论基础。鉴于神经系统疾病的普遍性和当前治疗方法的局限性，未来对 PUFA 在神经保护和疾病治疗中的潜力的深入研究显得尤为紧迫和重要。

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