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高脂饮食与焦虑症的关联及其作用机制的研究进展

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摘　要

焦虑症(Anxiety)，又称为焦虑性神经症，是神经症这一大类疾病中最常见的一种，以焦虑情绪体验为主要特征，其高患病率、高复发率以及较高的自杀和致残率给社会带来了巨大的负担。近年来的研究表明，饮食习惯与焦虑症之间存在密切的联系。自改革开放以来，中国人的饮食模式发生了显著变化，其中高脂饮食(high-fat diet, HFD)在饮食结构中的比例不断增加，HFD是指吃大量富含脂肪的食物，会影响机体代谢、伤害肝脏、诱发肥胖及其并发症等多种疾病。已有大量研究证实，HFD可导致动物表现出焦虑和抑郁的情绪，但其对焦虑症的具体影响机制尚不完全明确。本文通过综合分析现有文献资料，探讨了HFD与焦虑症之间的关联性，并分析了HFD诱导焦虑症的潜在发病机制。

关键词

高脂饮食，焦虑症，发病机制

Research Progress on the Association between High-Fat Diet and Anxiety Disorders and Its Mechanism of Action

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Abstract

Anxiety, also known as anxiety neurosis, is the most common type of neurosis, characterized

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primarily by the experience of anxiety. Its high prevalence, high recurrence rate, and relatively high rates of suicide and disability place a significant burden on society. Recent studies have indicated a close relationship between dietary habits and anxiety disorders. Since the reform and opening up, there have been significant changes in the dietary patterns of Chinese people, with an increasing proportion of high-fat diet (HFD) in their dietary structure. HFD refers to the consumption of large amounts of foods rich in fat, which can affect metabolism, damage the liver, and induce obesity and its complications among various diseases. Numerous studies have confirmed that HFD can lead to anxiety and depressive behaviors in animals, but the specific mechanisms by which it affects anxiety disorders are not yet fully understood. This paper explores the association between HFD and anxiety disorders and analyzes the potential pathogenic mechanisms of HFD-induced anxiety disorders through a comprehensive analysis of existing literature.

Keywords

High-Fat Diet, Anxiety Disorder, Pathogenesis

1. 引言

焦虑症(Anxiety)，亦称焦虑性神经症，是一种以持续、过度的焦虑、担忧、紧张和恐惧为特征的精神障碍[1]。近年来，焦虑症的患病率急剧上升，已成为一个日益严重的公共卫生问题[2]。据 2019 年统计，全球约有 3.01 亿人患有焦虑症，目前估计全球人口中约有 4%的人受此疾病影响[3]。由于其高患病率、慢性病程和常见的合并症，世界卫生组织(WHO)已将焦虑症列为第九大健康相关残疾原因[4]。焦虑症不仅对患者的生活质量产生严重影响，还对社会经济造成重大负担，占全球疾病负担的 3.3%，在 30 个欧洲国家造成的经济损失约为 740 亿欧元[5]。

目前，关于焦虑症的发病机制，主流观点认为主要与神经递质传递失衡有关[6]。基于这一机制开发的传统抗焦虑药物虽然在一定程度上有效，但存在副作用较大、成瘾性较强等问题[7]，因此，深入研究焦虑症的发病机制对于开发更有效的治疗方法具有重要意义。

近年来，饮食因素在情绪相关疾病中的作用逐渐受到关注。高脂饮食(high-fat diet, HFD)被认为是焦虑症发病的潜在危险因素[8]。然而，HFD 对焦虑症的具体影响机制尚未完全明确。现有研究表明，其可能机制涉及脂类代谢紊乱、炎症反应加剧、下丘脑－垂体－肾上腺(Hypothalamic-Pituitary-Adrenal, HPA)轴功能失调、色氨酸代谢异常、肠道微生物－肠－脑轴(Gut-Brain Axis, GBA)的改变以及氧化应激调节失衡等多个方面[9] [10]。本文将对近年来关于 HFD 诱发焦虑症的可能机制进行系统综述，旨在为焦虑症患者的饮食干预提供科学依据。

2. 高脂饮食与焦虑症显著相关

HFD 是指饮食中脂肪含量摄入过高的饮食方式[11]。改革开放以来，中国人的膳食模式发生了巨大的变化，从基于谷物消费的传统饮食向基于富含高脂肪、高糖和高蛋白质的多样化饮食转变[12]。在一项前瞻性人群研究中发现，饮食模式可能与焦虑症风险增加密切相关，以高摄入黄油、牛奶甜点和低摄入酒精、面包为特征的饮食模式与焦虑症状的风险升高相关[13]。大量动物实验已证明 HFD 与小鼠焦虑样行为密切相关[14] [15]。HFD 是肥胖/超重、糖尿病以及高脂血症等代谢性疾病的危险因素，Meta 分析结

果表明，与正常体质量者相比，肥胖和超重人群更易产生焦虑症[16]。HFD 在焦虑症中起到的潜在作用将成为未来科学研究的热点。研究 HFD 对焦虑症具体影响机理，能够对焦虑症患者在饮食上给予指导和帮助，同时，为开发抗焦虑食品提供理论依据。

3. 高脂饮食诱导焦虑症发病的可能相关机制

3.1. 脂类代谢

脂质组学在精神疾病的诊断、治疗以及预后具有极其重要的意义。在一项队列研究中表明，高水平的甘油三酯(Triglyceride, TG)和低水平的高密度脂蛋白胆固醇(High density lipoprotein cholesterol, HDL-C)与焦虑和压力相关疾病的风险增加有关[17]。一项涉及超过 12,000 名参与者的横断面研究表明，血清多不饱和脂肪酸(Polyunsaturated fatty acid, PUFA)比率与焦虑症状的严重程度呈负相关[18]。在一项针对人类参与者的研究中，发现焦虑症状与磷脂酰胆碱和鞘磷脂的血清浓度呈负相关，此外，焦虑症状与血清神经酰胺水平呈正相关[19]。动物实验也提供了相关证件，给予小鼠 8 周以上 HFD，小鼠在开放场、社会互动测试和认知功能测试中表现出焦虑样行为，究其原因脂质成分改变可能是 HFD 诱导的焦虑样行为的主要原因，其可能与不饱和脂肪酸结合的外周磷脂水平降低和前额叶皮层中谷氨酸系统的改变有关[20]。这些研究结果表明，脂质代谢的异常与精神疾病的发病机制密切相关，脂质组学的研究有助于开发新的诊断标志物和治疗靶点。

3.2. 炎症反应

动物研究表明，长期 HFD 喂养后，炎症可能会影响参与情绪调节和焦虑的下丘脑外区域(即前额叶皮层、杏仁核、海马体) [21]。4 个月的 HFD 喂养导致先天免疫系统的激活，包括炎性细胞因子(即 IL-6, IL-1β, TNFα)的升高[22]。邓祖跃等人以 HFD 喂养小鼠发现，高脂血症通过活化炎症小体途径增加 IL-1β 的释放[23]。同时，在首发广泛性焦虑障碍组 IL-1α、IL-6、IL-12 水平显著高于正常对照组，并且状态焦虑与炎症因子均呈显著正相关[24]。综上所述，推测出 HFD 通过炎症因子诱导焦虑症的发生。

HFD 除了引起肥胖等代谢表型外，还会导致肠道屏障完整性破坏[25]。在此条件下通过肠道屏障进入循环的脂多糖(Lipopolysaccharide, LPS)等会引发长期低水平的炎症。首先 LPS 能诱导小鼠的焦虑样行为[26]，其次这类低水平炎症增加循环中游离脂肪酸和细胞因子的含量，对外周和中枢都造成影响，从而导致神经性炎症[27]，神经炎症通过刺激 IL-33/NF-κB 轴和减少杏仁核中脑源性神经营养因子(Brain-derived neurotrophites, BDNF)的表达来增强焦虑回路中的活动[26]。

3.3. 下丘脑－垂体－肾上腺(Hypothalamic-Pituitary-Adrenal, HPA)轴

给予小鼠 HFD 14 周，小鼠出现明显的焦虑样行为，其可能的机制是 HFD 造成小鼠 HPA 轴亢进，血浆皮质酮和血浆瘦素水平增加，脑氧化应激升高，显示出焦虑行为改变[28]。HFD 能引起 HPA 轴亢进[29]，HPA 轴功能亢进是焦虑样行为的发病机制之一，其可能是在应激下，HPA 轴出现高反应性，下丘脑释放大量促肾上腺皮质激素(Adrenocorticotrophic hormone, ACTH)释放激素，诱导垂体合成并释放大量 ACTH，刺激肾上腺皮质分泌，增加血液中皮质酮[30]，人群研究证明皮质醇与焦虑是有关联的[31]；另一种可能是与 HPA 轴相关蛋白的表达下降有关[32]。同时，在围产期暴露 HFD 改变了成年后代大脑中皮质类固醇受体和炎症基因的表达，可能导致成年期内分泌对压力的反应增强和焦虑行为增加[33]。

3.4. 色氨酸代谢

色氨酸(Trp)是一种必需氨基酸，仅通过饮食来源获得，它在蛋白质生物合成中起着至关重要的作用，并作为合成多种重要生物活性化合物的前体，影响多种病理生理过程，包括神经元功能、新陈代谢、炎症

反应、氧化应激、免疫反应和肠道稳态[34]。HFD 会导致 Trp 代谢失调[35]。Trp 代谢物与焦虑和抑郁的发病机制密切相关[36]。HFD 诱导焦虑症可能与色氨酸三个代谢途径有关，一是通过犬尿氨酸通路的 Trp 代谢，研究人员在对小鼠给予 4 周慢性约束压力测试后发现，降低 5-羟色胺(5-hydroxytryptamine, 5-HT)水平，破坏犬尿喹啉酸/喹啉酸平衡，诱导了焦虑抑郁样行为[37]；二是通过 5-HT 通路的 Trp 代谢，具体表现为给予小鼠 HFD 后，表现出代谢异常及焦虑样症状，其可能机制是 HFD 通过损伤小鼠海马中 5-HT 介导的神经传递途径，进而诱导小鼠焦虑抑郁样行为[38]，同样地，在无菌小鼠中发现过量的色氨酸羟化酶(Tryptophan hydroxylase, TPH)与焦虑样行为有关[39]；三是 Trp 通过微生物－吲哚代谢途径，HFD 能够刺激吲哚胺类物质的产生诱导 Try 分解代谢，从而产生其他色氨酸分解代谢物，诱导肥胖症中神经精神症状的发作[40]。

3.5. 肠－脑轴

肠道微生物(gut microbes)是人体第二大脑，与宿主共同构建的复杂生态系统，数万亿微生物定植于胃肠道，维持着宿主代谢稳态[41]。研究发现，短期的食用 HFD 就能影响机体肠道微生物的多样性和组成[42]，可能通过影响肠道微生物－肠－脑轴信号传导，增加脑干中 5-HT 相关基因的表达，从而引发焦虑样行为[43]。而肠道微生物及其代谢物也能调节焦虑样行为[44] [45]。在西方社会广泛采纳的西式饮食(即高脂肪和/或高糖，低纤维)可以减少产生短链脂肪酸(Short-chain fatty acid, SCFA)细菌[46]，而产生丁酸类的菌群的丰度降低可能导致焦虑症状的增加[47]。此外，在一项益生菌改善焦虑样行为的实验中发现，这种行为的改善是通过肠－脑轴的调节促进了大脑中乙酸盐以及促炎细胞因子水平的降低，对海马体和前额叶皮层中神经元增殖和存活的信号通路产生了积极影响[48]。

3.6. 氧化应激调节

HFD 下，机体摄入过多的脂质，线粒体脂肪酸氧化代谢加快，会产生大量活性氧(Reactive oxygen species, ROS)。同时，高脂状态还会抑制抗氧化酶的活性，打破氧化与还原的生理平衡，造成氧化应激[49]。大脑神经细胞富含不饱和脂肪酸，对氧化应激极为敏感。过量的 ROS 攻击神经元细胞膜、线粒体膜、内质网等细胞结构，损伤神经元，影响神经可塑性，导致焦虑情绪产生[50]。研究人员给予小鼠 12 周 HFD，发现 HFD 显著增加了血清丙二醛水平，并降低了总谷胱甘肽水平，诱发小鼠焦虑样行为[51]。HFD 不但可以通过氮氧化物增加 ROS，也可通过破坏氧化还原平衡，诱发脑损伤和相关情绪功能障碍[52]。

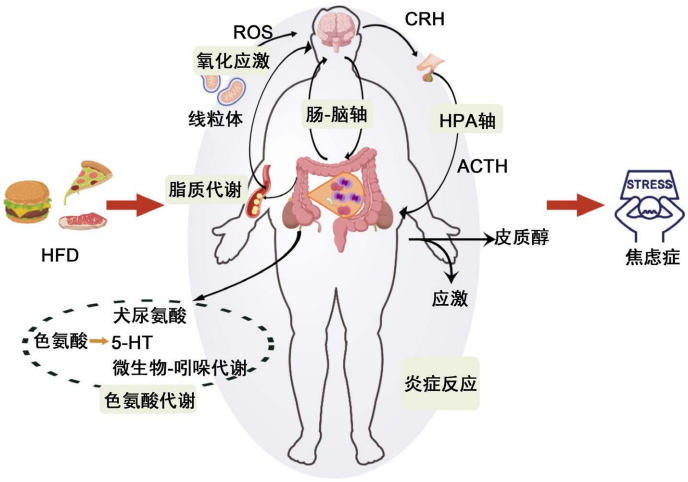
3.7. 其他

随着相关研究的不断深入，HFD 诱发焦虑症的可能相关机制不断得到揭示。研究报道，给予小鼠 8 周 HFD 喂养后，小鼠出现相应的焦虑样行为，其可能的机制为 HFD 通过抑制 AMP 活化蛋白激酶磷酸化和促进 mTOR 向磷酸化转变以抑制自噬，从而导致小鼠出现焦虑样行为[53]。此外，越来越多的研究发现，表观遗传学在焦虑情绪产生中起到重要作用[54]。

HFD 诱导焦虑症的机制较为复杂，涉及多个相互关联的因素。一方面，肠道微生物能调节机体抗氧化剂代谢，维持肠道稳态[55]。但 HFD 易致肠道微生物失衡，使肠道屏障功能受损，有害物质及微生物趁机侵入血液循环，引发全身性炎症反应，其中 IL-1β、IL-6 和 TNF-α 等细胞因子过度释放，进而激活 HPA 轴[56]。另一方面，色氨酸作为肠道微生物与宿主相互影响的关键代谢物[57]，其代谢过程可影响神经元功能、炎症反应、氧化应激和肠道稳态等，而炎症因子又会强烈刺激 HPA 轴[58]，如此形成一个相互作用、相互影响的复杂机制网络，共同促使焦虑症的发生。具体见图 1。

4. 展望

综上所述，HFD 是肥胖、糖尿病以及代谢综合征等多种代谢性疾病的危险因素之一，HFD 不仅对



注：HFD：高脂饮食；ROS：活性氧；5-HT：5-羟色胺；HPA 轴：下丘脑－垂体－肾上腺轴；CRH：促肾上腺皮质激素释放激素；ACTH：促肾上腺皮质激素。

Figure 1. Possible mechanisms of HFD-induced anxiety disorders
图 1. HFD 诱发焦虑症的可能机制

身体健康产生负面影响，还可能引发焦虑样行为。其发病机制涉及多种复杂因素的相互作用，包括脂质代谢紊乱、炎症反应、肠道菌群－脑轴的改变、色氨酸代谢失调等。

从目前的研究来看，健康的饮食习惯对于预防和控制焦虑症的发生和发展具有重要意义。饮食指导可以作为一种有效的干预措施，帮助改善心理健康状况。然而，人们对 HFD 导致焦虑症的具体机制认识仍然有限，目前尚不清楚其详细的病理生理过程。因此，未来的研究需要进一步探索 HFD 诱导焦虑样行为的具体机制，以便更好地理解其病理过程，并为临床干预提供更为科学的依据。

此外，研究还应关注不同人群对 HFD 的反应差异，以及如何通过饮食调整来有效缓解由 HFD 引起的焦虑症状。通过深入研究，我们可以更好地制定个性化的饮食干预方案，帮助人们在面对 HFD 的挑战时，保持良好的心理健康状态。

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