油脂营养

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高脂饮食造成认知功能损伤的机制探索

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摘要:长期的高脂饮食(HFD)会造成大脑能量代谢紊乱,引发认知障碍,影响大脑功能。旨在为膳食营养或临床手段改善 HFD 介导的认知功能障碍提供理论基础,系统梳理了 HFD 造成认知功能损伤的机制。HFD 通过神经炎症、氧化应激、线粒体功能障碍、胰岛素抵抗、血脑屏障受损、表观遗传紊乱和破坏突触可塑性等途径的单一或复合作用,造成大脑认知功能受损或下降。未来研究应进一步探索大脑代谢性损伤的确切机制,并通过研究提供预防或治疗 HFD 造成的认知功能障碍的有效手段。

关键词:高脂饮食;认知障碍;机制探索

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Mechanism exploration of cognitive impairment caused by high fat diet

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Abstract: Long－term high fat diet (HFD) causes energy metabolism disorders in the brain, triggering cognitive impairment and affecting brain function. Aiming to provide a theoretical basis for improving HFD－mediated cognitive dysfunction through dietary nutrition or clinical interventions, the mechanisms causing cognitive impairment by HFD were systematically reviewed. HFD causes impaired or decreased cognitive function in the brain through single or compounded effects of neuroinflammation, oxidative stress, mitochondrial dysfunction, insulin resistance, impaired blood－brain barrier, epigenetic disorders, and disrupting synaptic plasticity. Future research should further explore the precise mechanisms of metabolic brain injuries and provide effective means for preventing or treating cognitive dysfunction caused by HFD through research.

Key words: high fat diet; cognitive impairment; mechanism exploration

高脂饮食(High fat diet,HFD)通常是指膳食脂肪供能占总能量 30% 以上的饮食,长期摄入 HFD 会破坏机体的正常能量代谢,导致代谢紊乱,造成肝脏、肠道等器官损伤,诱发肥胖、糖尿病、高血压等代谢性疾病,并增加心血管疾病的发病风险[1－4]。HFD 对全身代谢和外周组织器官的伤害已经广为人知,而其对大脑的伤害一直未得到详细论述。大脑对能量摄入与消耗高度敏感,研究发现,HFD 会影响大脑认知功能,并对心理健康、情绪管理和神经发育造成不良影响,进而增加心理疾病、精神疾病和神经系统疾病的发病风险[5]。本文总结了现有研究中 HFD 造成认知功能损伤的机制,以期为膳食营养或临床手段改善 HFD 介导的认知功能障碍提供理论基础。

1　高脂饮食对认知功能的影响

大脑是人体神经系统中最大且最复杂的结构,也是神经系统最高级的部分,是控制运动、产生感觉及实现高级脑功能(如语言、思维、记忆、情感、想象等)的高级神经中枢,主导机体的一切活动过程,对机体具有重要意义。大脑虽只占体质量的 2%,但却需要消耗机体 20% 的葡萄糖和氧气来维持其正

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常运作,这些物质主要通过血脑屏障(Blood brain barrier,BBB)输送至大脑。HFD 带来的营养过剩和过多脂肪摄入已被证实会对大脑的形态、结构和功能造成一定程度的损伤,并影响相关行为的发生。

动物实验表明,HFD 喂养 1 d 就会使小鼠在情景记忆任务中的表现迅速下降,并在恢复正常饮食后出现记忆缺陷的逆转[6];而从青年期到中年期的慢性 HFD 喂养会对小鼠的行为和海马神经可塑性产生负面影响,诱导产生焦虑、抑郁和记忆障碍[7]。富含饱和脂肪酸(SFA)的饮食会使大鼠在行为学实验中表现不佳,出现学习记忆能力下降,体现了 HFD 对认知功能的损伤[8];同样地,在豚鼠模型中,喂养高 SFA 的 HFD 会使豚鼠在青春期的社会对抗中表现较差,并对大脑信号传导过程产生负面影响[9-10]。此外,HFD 对认知功能的损伤还存在遗传效应,母代摄入 HFD 会增加成年后代个体与年龄相关的认知功能障碍风险,影响后代的学习记忆能力,与后代的行为障碍密切相关[11-12]。

临床研究表明,摄入 HFD(约 75% 的脂肪)5 d 就能够引起抑郁样行为,并损害恢复速度和注意力[13];摄入 HFD 7 d 会降低注意力并延长简单反应时间,诱发神经炎症[14]。人类流行病学证据表明,过多地摄入 SFA 会损害前瞻性记忆,影响记忆速度和灵活性,导致神经系统疾病,与较差的认知表现、高阿尔茨海默病(AD)发病率有关[15-17]。HFD 所导致的身体质量指数(BMI)上升、内脏脂肪积累、肥胖、2 型糖尿病都与认知功能下降有关,是脑损伤和认知障碍的危险因素。

2 高脂饮食造成认知功能损伤的机制

目前对 HFD 造成认知功能损伤的潜在机制研究主要集中在神经炎症、氧化应激、线粒体功能障碍、胰岛素抵抗、BBB 受损、表观遗传紊乱和突触可塑性破坏[18-20]等。

2.1 高脂饮食与神经炎症

炎症是 HFD 摄入后机体的常见反应,其中与认知功能障碍相关的效应主要体现在下丘脑、海马等脑区,具体表现为炎症因子水平上升、小胶质细胞和星形胶质细胞的激活[21-22],其中白细胞介素 6(IL-6)、肿瘤坏死因子 α(TNF-α)等炎症因子已被证实会对神经发育、大脑功能造成损害[23-27]。

下丘脑是控制能量稳态和调节内分泌活动的高级神经中枢,在控制体质量和食欲方面发挥重要作用,但其功能易受 HFD 影响。同时,下丘脑-垂体-肾上腺反应轴(HPA)是重要的神经内分泌应激调节系统,负责调节机体的应激反应,HFD 通过对下丘脑的负面作用刺激 HPA 反应,这也是亲代 HFD 影响后代健康的关键因素[28-29]。总之,HFD 诱导的下丘脑炎症会破坏正常的能量调节稳态,导致饱腹感信号传导障碍,进而引起食欲亢进,使得暴饮暴食持续并进一步造成体质量上升和引发肥胖,导致对认知产生负面影响[30]。

海马是参与认知过程的主要脑区,负责记忆和定向功能。Lam 等[31]发现 12 周的 HFD 喂养会在小鼠海马体腹侧引起显著的星形胶质细胞激活;Kang 等[32]在 HFD 喂养的小鼠中发现了海马 Toll 样受体 4(TLR4)、还原型辅酶(NADPH)等炎症指数的显著上升;Yu 等[33]在 HFD 诱导的认知障碍大鼠模型中也观察到了海马炎症反应的增强,包括 TLR4 的激活,白细胞介素 1β(IL-1β)、TNF-α 和 IL-6 的产生,以及小胶质细胞和星形胶质细胞的激活。

2.2 高脂饮食与氧化应激

由于较高的脂质含量、对氧气和能量的高需求,大脑极易受到氧化应激而损伤。Azmi 等[34]发现 HFD 喂养会改变大鼠额叶皮层和海马体中超氧化物歧化酶(SOD)、过氧化氢酶(CAT)和谷胱甘肽过氧化物酶(GPX)的 mRNA 水平;Li 等[35]发现 HFD 喂养会增加小鼠脑部丙二醛(MDA)的含量,降低 SOD 和 CAT 的活性和表达水平,造成小鼠脑部氧化应激损伤。

目前多项研究均同步观察到了氧化应激水平增加和认知功能下降现象,揭示了氧化应激与认知障碍的潜在联系。Mei 等[36]使用阿魏酸治疗 HFD 诱导的认知障碍小鼠时发现,在小鼠学习记忆能力改善的同时,观察到了氧化应激损伤的逆转;Head[37]观察到了大脑氧化损伤和老年人认知障碍的关联,同时揭示了抗氧化成分的摄入与抗氧化剂的使用对健康认知和 AD 风险下降之间的联系。流行病学证据表明[38],饮食中抗氧化成分的摄入量与老年人的行为表现和认知功能有关。在认知功能下降普遍出现的衰老过程和帕金森、AD 等神经退行性疾病中,氧化应激损伤被认为是主要致病因素,且在老年人和患者的大脑中都观察到了氧化应激水平的上升[39]。总之,氧化应激损伤与认知功能下降在 HFD 喂养、衰老和神经退行性病变中同步出现,存在密切的联系。

2.3 高脂饮食与线粒体功能障碍

大脑由于自身储能有限以及高能量需求而高度依赖线粒体功能,在衰老、认知损伤和神经退行性疾病等相关疾病中都发现了线粒体相关的功能障

碍[40-42]。线粒体功能障碍对认知功能的损伤不是单一作用的,而是与氧化应激、炎症反应等途径协同作用于中枢神经系统(CNS)导致的结果。氧化应激会影响线粒体膜通透性和 Ca^{2+} 稳态,扰乱线粒体呼吸链,造成线粒体功能障碍,加剧神经元损伤,最终造成认知损伤和神经退行性疾病[43-44]。此外,线粒体功能障碍、线粒体动力学改变还与脑部炎症、小胶质细胞活化和突触可塑性障碍等密切相关[45-47],可知线粒体功能障碍导致的认知损伤是多途径介导的。

HFD 会使机体产生大量的游离脂肪酸(FFA),FFA 的降解主要通过线粒体 β-氧化实现,FFA 过量会影响线粒体呼吸链,导致线粒体损伤和相关功能障碍。Zuliani 等[48]研究发现,HFD 降低了线粒体呼吸链功能,改变大脑代谢,降低了认知能力;Yang 等[49]研究发现,HFD 喂养导致小鼠海马体出现线粒体功能异常,并表现出抑郁行为;Mancini 等[50]的研究也揭示了 HFD 喂养下线粒体功能障碍与 AD 发病风险之间的联系。总之,HFD 带来的营养过剩通过影响线粒体呼吸链造成线粒体功能障碍,通过氧化应激损伤、炎症反应和突触可塑性障碍等途径共同作用于大脑,造成神经元损伤,导致认知功能下降。

2.4　高脂饮食与胰岛素抵抗

大脑是一个对胰岛素敏感的器官,在下丘脑、海马和大脑皮层等区域广泛分布着选择性表达的胰岛素受体。胰岛素已被证实在大脑中具有多重作用,包括调节葡萄糖代谢和影响突触可塑性,并参与认知过程[51],而胰岛素抵抗(IR)与认知功能障碍的密切联系也被广泛提及[52-53]。Sherzai 等[54]发现 IR 与 60 岁以上老年人较低的认知表现显著相关;一项针对芬兰老年人的纵向研究显示[55],血清胰岛素含量与 IR 可能是无 AD 老人 7 年后认知评价的独立预测因子;Gabay 等[56]在青年女性中同样发现了 IR 对大脑结构和功能的潜在负面影响;Akhtar 等[57]在 AD 动物模型中也观察到了 IR、氧化应激和线粒体功能障碍引起的 Tau 蛋白病理学变化和神经退行性变。

海马是大脑中主要负责学习与记忆功能的脑区,能通过存储和调节与膳食相关的记忆来控制饮食的摄入,同时海马还对饥饿和饱腹信号敏感,能够协同记忆一起调节进食行为[58-59];进食行为能直接通过营养物质代谢介导内分泌系统,从而调节胰岛素的分泌和传递,同时机体的胰岛素信号也能刺激大脑对进食行为进行调控,这意味着进食行为、IR 和海马功能之间存在密切联系。Soto 等[60]通过对海马体中胰岛素受体的定向灭活实验发现,小鼠的空间学习和记忆能力下降,并表现出代谢异常、焦虑样行为增加和认知功能损伤。葡萄糖转运蛋白 4(GluT4)是一种胰岛素依赖性跨膜载体蛋白,可促进葡萄糖跨细胞膜移动。研究表明,GluT4 可能在海马记忆过程中起着核心作用[61],这有可能是 IR 导致认知障碍的基础。综上所述,HFD 会损害正常的食欲调节和摄食行为,影响进食相关的大脑信号传导,导致代谢紊乱并加剧 IR,作用于海马等大脑区域,影响大脑正常功能,进而损害认知功能。

2.5　高脂饮食与血脑屏障(BBB)受损

BBB 是维持神经系统稳态的严格通透性屏障,其主要功能是防止大多数物质通过血液进入脑组织,从而保护大脑免受外部有害物质的侵害,维持脑组织内部环境的基本稳定。BBB 的完整性对大脑乃至整个 CNS 功能具有重要的生物学意义。研究发现,HFD 会增加 BBB 的通透性[62],诱导其损伤。炎症反应可能是 HFD 介导 BBB 损伤的关键途径之一,如 De Paula 等[63]在喂养 HFD 3 d 的小鼠中同时观察到炎症因子 IL-6、TNF-α 的增加,海马体 BBB 通透性的增加,以及记忆功能的受损。在机体发育过程中,肠道微生物的组成变化有助于 BBB 的功能与通透性。营养研究已公认,长期 HFD 会引起肠道菌群失调,并通过肠脑轴作用引起大脑相关功能受损以及神经行为的恶化。Wu 等[64]在 HFD 诱导的肠道菌群紊乱小鼠中观察到了焦虑样、抑郁样行为的增加以及学习记忆功能的下降,同时在 HFD 喂养小鼠的海马体和前额叶皮层中检测到了与 BBB 完整性和稳定性相关因子的表达水平下降。胆固醇能为神经细胞提供营养,维持大脑内正常的胆固醇含量对保护大脑功能至关重要,而 HFD 会降低机体低密度脂蛋白受体(LDLr)的含量,使血液 LDL 水平升高并伴随 IR 增强,造成体内胆固醇稳态出现异常,导致脑胆固醇代谢失衡,进而造成 BBB 损伤,引起认知缺陷[65]。

2.6　高脂饮食与表观遗传紊乱

HFD 对机体健康的伤害被证实是可以遗传的。妊娠期和产后的 HFD 被认为与后代晚年肥胖的发生有关。Pang 等[66]研究发现,在妊娠期接受 HFD 喂养的母体,其后代成年个体的肝脏中检测到了核受体 DNA 的高甲基化水平以及过氧化物酶增殖激活受体 α(Pparα)mRNA 水平的降低,Pparα 的主要功能是参与肝脂肪代谢以及脂肪细胞的分化,妊娠期的 HFD 通过 Pparα 的 DNA 去甲基化导致其后代

在成年后出现 Pparα mRNA 水平降低,进而引发脂质代谢紊乱与肥胖,从而对后代健康产生长期影响。Sheth 等[67]研究发现,对父母双方进行 HFD 喂养,其诱导产生的糖尿病前期相关的表观遗传印记可传递给后代,增加后代代谢紊乱的风险。Natale 等[68]研究发现,亲代 HFD 会通过表观遗传紊乱影响后代海马神经的发生,且这种影响还可能传递至多代。Lin 等[69]发现 HFD 依赖性的大脑重塑会遗传给下一代,而来自母系亲代的 HFD 喂养会造成第三代成年大鼠的海马依赖性学习和记忆功能受损。由此可见,HFD 介导的表观遗传紊乱不仅损害个体健康,诱导疾病发生,还会通过表观遗传印记对后代健康产生影响,诱导 HFD 相关负面结果在后代个体中的发生。

2.7 高脂饮食与突触可塑性

突触可塑性是指神经元之间连接(突触)的强度和结构在学习和记忆过程中发生改变的能力。HFD 会破坏这种可塑性,进而影响认知功能。Hao 等[70]研究发现,HFD 会破坏神经元之间的突触连接和海马区脑细胞,导致学习和记忆能力下降。Boitard 等[71]在一项从断奶到成年期的长期 HFD 喂养实验中发现,HFD 会导致海马依赖性记忆和可塑性受损。Pan 等[16]发现 HFD 喂养会使小鼠在物体定位和新物体识别等行为测试中表现出认知能力下降,并观察到海马 RNA 转录谱中与认知功能和突触可塑性相关基因的改变。Lin 等[69]研究发现,HFD 喂养大鼠会影响其海马突触可塑性和认知能力。吉晓静等[72]研究表明,HFD 喂养的大鼠海马 CA3 – CA1 区通路的突触传递效率显著降低,表现为长时程增强(LTP)减弱,这种变化与记忆功能受损密切相关,尤其是在老年个体中更为明显。此外,海马组织中的胰岛素信号传导、IR 和小胶质细胞表型的变化都可能参与了 HFD 对海马神经可塑性的负面影响[7,73],进一步造成认知功能的损伤。

3 总结与展望

大脑是机体一切生理活动的指挥中心,其精密的功能对膳食能量摄入敏感,短期或长期的 HFD 均会给机体带来过量的 FFA,通过神经炎症、氧化应激、线粒体功能障碍、BBB 障碍、IR、表观遗传紊乱以及破坏突触可塑性等途径单一或复合作用,造成大脑认知功能受损或下降,并与 AD、神经退行性疾病的发生存在潜在联系。现有营养研究中,多关注 HFD 外周代谢性损伤的预防或治疗,在已明确 HFD 对大脑功能损伤的作用下,应进一步探索大脑代谢性损伤的确切机制,并通过深入研究提供预防或治疗 HFD 造成的认知功能障碍的有效手段。

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