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肥胖成因的新视角：代谢性炎症诱导食物奖赏异常*

代玉玺[1)] 何玉秀[1,2)**] 陈 巍[1,2)]
([1)] 河北师范大学体育学院，石家庄 050024；[2)] 河北省人体运动生物信息测评重点实验室，石家庄 050024）

摘要 近年来，肥胖已成为全球亟待解决的重要公共卫生问题。越来越多的研究发现，食物奖赏在肥胖的形成与发展过程中发挥重要作用。最近的研究表明，由于能量过剩引发的代谢性炎症可能通过多种生理途径干扰正常的奖赏信号传递，从而促进肥胖的发展。基于这一观点，推测产生肥胖的原因可能与代谢性炎症诱导食物奖赏异常有关。因此，深入探讨肥胖、食物奖赏和代谢性炎症之间的关系，总结代谢性炎症诱导食物奖赏异常的可能机制，可为预防和治疗肥胖提供新的思路和理论支持。

关键词 肥胖，食物奖赏，代谢性炎症
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肥胖的防治一直是公共卫生领域和学术界备受瞩目的热点问题，已成为威胁人类健康的重要危险因素[1-2]。现有多项证据表明，肥胖的发生和发展与食物奖赏（food reward）密切相关[3-5]。食物奖赏是指在摄入适口性食物，尤其是高糖和高脂食物后，个体获得愉悦和满足感的美好体验，通常伴有持续性进食倾向[6]。高能量密度食物作为天然奖赏激动剂，强烈吸引个体在饱腹情况下仍然主动进食[7]。短期摄入适口性食物将不断强化与食物奖赏相关脑区/核团对这种外源性刺激的敏感性，提高突触传递效能，令个体再次面对美味食物时产生进食欲望[8-9]；然而长期摄入这些食物将导致奖赏环路发生神经适应性改变和突触重塑，诱导奖赏阈值提高，迫使机体只能通过增加进食量来弥补缺失的快感[10-12]。最近研究表明，由于营养和能量过剩引起的代谢性炎症（metaflammation）可通过扰乱多巴胺（dopamine，DA）神经元活动、影响递质代谢、诱导突触功能异常等影响食物奖赏[13-15]。因此，推测代谢性炎症可能是诱导食物奖赏异常的重要神经病理学基础。故深入探讨肥胖、食物奖赏以及代谢性炎症之间的关系，总结代谢性炎症诱导食物奖赏异常的可能机制，可为防治肥胖提供新的思路和理论支持。

1 食物奖赏异常与肥胖

肥胖是机体长期处于能量摄入高于能量消耗的结果，食物奖赏在其中发挥着重要作用[16-17]。生理状态下，能量摄入受内稳态性食欲和享乐性食欲调节，前者负责维持机体的能量平衡，后者则与食物奖赏有关，二者相互作用共同调节进食[18]。进化理论认为，机体对食物线索的高度敏感，并尽可能多地摄入能量有利于应对饥荒和疾病[19]。随着食品行业的高度工业化，美味、高能量密度食物的种类和来源极其丰富。受食物奖赏驱使，个体倾向选择食用美味适口性食物，这样不仅能够满足机体对能量的需求，同时还能享受摄食带来的快感。有文献报道，体质量指数（body mass index，BMI）与高脂高糖的奶昔喜好呈正相关，提示肥胖个体对

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** 通讯联系人。
Tel：18931871518，E-mail：heyuxiu@hebtu.edu.cn
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高能量密度食物的渴求度更高[20-21]。然而这种摄食偏好的转变将重塑奖赏环路，迫使自体能量调节稳态失衡，促进肥胖的发展[11，22]。

食物奖赏由“享乐价值（liking）”、“进食动机（wanting）”以及“学习与记忆（learning and memory）”3部分组成，每个环节均由相应的神经通路支配[6]。中脑皮质边缘系统（mesocorticolimbic system，MS）是参与调控食物奖赏的重要环路。MS由腹侧被盖区（ventral tegmental area，VTA）发出的DA神经元投射至伏隔核（nucleus accumbens，NAc）、前额叶皮质（prefrontal cortex，PFC）、杏仁核、海马体等多个脑区/核团构成[23]。其中，NAc负责奖赏权衡，调控进食行为和动机[24]，PFC参与进食的决策执行，整合与摄食相关的情绪和感官信息（视觉、味觉、嗅觉等）[25]，杏仁核和海马负责将食物线索（口味、颜色、形状、气味）与愉快/不愉快的刺激相关联，并强化机体对食物认知、感官信息及情绪之间的联结[26]。影像学研究显示，与正常体重/超重受试者相比，肥胖人群左侧杏仁核/海马体静息态活动与高热量食物线索诱导的激活呈正相关，并且这两项指标均与BMI有关[26]；同样，在观察其他脑区/核团中发现，肥胖人群在饮用奶昔期间，PFC、视觉皮质（visual cortex）、下丘脑、中脑及脑干之间的神经元连接和信号传递减弱[27]。这些证据表明，肥胖与食物奖赏相关的神经环路可塑性关系密切。值得注意的是，上述神经环路很可能在肥胖形成之前就已经发生了适应性改变。因为在正常饮食基础上，持续8周每天额外两次摄入高脂肪/高糖酸奶降低了正常体重人群对低脂食物的偏好，同时增加了大脑对食物的反应以及独立于食物线索或奖赏的联想学习。这种神经可塑性并不伴有脂肪含量、体重和代谢标志物的变化，说明美味食物对重塑奖赏环路产生了直接影响，而这一结果可能与NAc功能有关[11]。

VTA-NAc通路是MS的核心部分，负责将摄食产生的神经冲动传递至NAc促进DA大量释放，从而使个体产生觅食动机并在进食后获得奖赏[24，28-29]。在肥胖未形成时，过量摄入高脂肪食物可刺激VTA-NAc-DA神经元放电和递质释放提高欣快感[8]；相反，长期高脂膳食（high food diet，HFD）将导致NAc微小兴奋性和抑制性突触后电流频率下降、DA释放减少、摄取效率降低，进而导致奖赏效应不足引发强迫性进食[10，30-32]（图1）。人和动物实验表明，这种强迫性进食与药物成瘾个体在行为表现上十分相似，例如对食物的渴求、进食失控、节食失败等[33-34]。然而有观点认为，虽然两者在机制上均涉及VTA-NAc通路调控，但目前尚无法完全将这种现象认定为“食物成瘾”，因为符合评价标准的个体也可独立于肥胖发生，所以在命名上目前仍存有争议[35-36]。需要强调的是，这种特殊进食行为与肥胖的关系已被学术界广泛

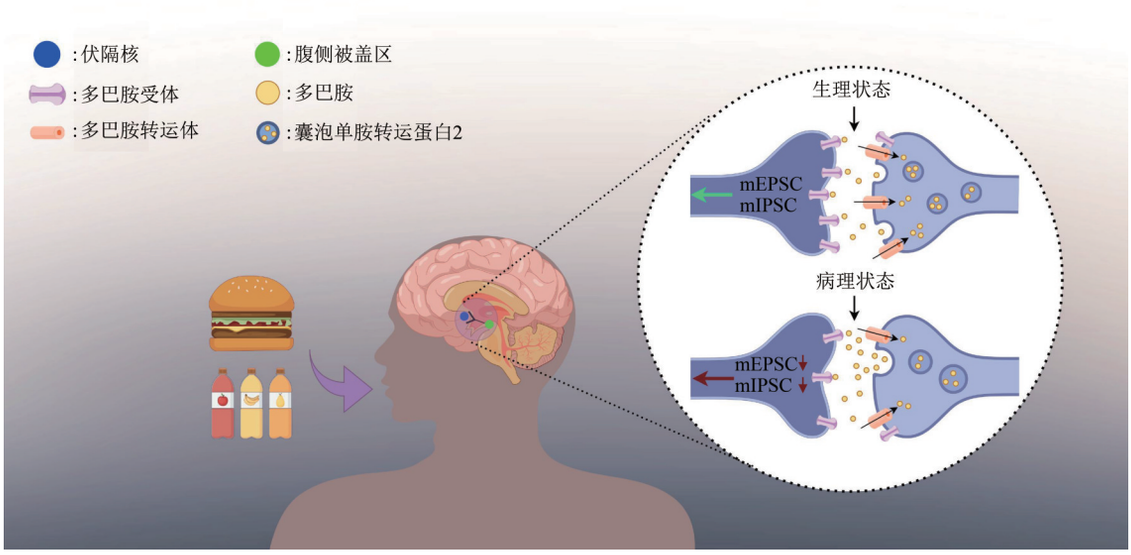

Fig. 1　HFD induces synaptic remodeling in the VTA−NAc−DA pathway

图1　HFD诱导VTA−NAc−DA通路突触重塑

mEPSC：微小兴奋性突触后电流（miniature excitatory postsynaptic current）；mIPSC：微小抑制性突触后电流（miniature inhibitory postsynaptic current）。本图由Figdraw绘制，授权码ID：SOUOA49704。

认可[37-38]。

综上，根据现有证据表明，长期暴露于高能量密度饮食导致的食物奖赏异常是肥胖形成与发展的重要原因之一，但是其中的机制问题仍有待深入研究。

2　肥胖诱导代谢性炎症

代谢性炎症被认为是慢性的、不典型和低度的全身无菌性炎症，虽然它与经典炎症在分子机制上相似，但其并不伴有红（rubor）、肿（tumor）、热（calor）和痛（dolor）等症状，是区别于经典炎症的“独立炎症”[39]。Hotamisligil等[40]首次提出，能量过剩是诱发代谢性炎症的主要原因，涉及外周及中枢两个方面。

2.1　外周系统炎症

长期高脂高糖膳食和静坐少动的生活方式使体内多余的葡萄糖转化为甘油三酯过度沉积于脂肪细胞内部，导致细胞体积增大和数量增多[39]。为了应对肥胖，脂肪细胞会分泌如单核细胞趋化蛋白1（monocyte chemotactic protein 1，MCP-1）、肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）、白介素-6（interleukin-6，IL-6）以及白介素-1β（interleukin-1β，IL-1β）等促炎因子减少脂质含量[41-42]。随着脂肪组织不断扩张，脂肪细胞内环境逐渐缺血缺氧并诱导细胞凋亡，进而激活大量巨噬细胞和T淋巴细胞浸润，以清除坏死的脂肪细胞，维持脂肪组织功能[43-44]。然而，促炎因子的持续释放和缺血缺氧诱导的氧化应激（oxidative stress，OS）将进一步招募更多的巨噬细胞进入脂肪组织，并且促进巨噬细胞由M2型抗炎细胞转化为M1型促炎细胞持续产生免疫反应，从而使机体长期处于慢性炎症状态[45-47]。另外，随着肥胖程度增加，血浆中游离脂肪酸（free fatty acid，FFA）水平显著上升，这些FFA经血液循环异位沉积于肝脏、骨骼肌、心脏和胰腺等器官内部并产生脂肪毒性（如糖脂代谢紊乱、OS），进一步促进全身炎症[48]。与此同时，中枢神经系统（central nervous system，CNS）同样会出现类似情况[14-15]。

2.2　中枢系统炎症

早期观点认为：脑是免疫特权器官，不能与外周免疫双向通信[49]。随后的研究结果更正了前人观点，证实中枢免疫与外周免疫间确实存在联系[50-51]。关于能量过剩引起CNS炎症的第一篇报道出现于2005年[52]。该研究表明，与普通膳食对照组相比，连续16周HFD大鼠下丘脑TNF-α、IL-1β、IL-6等促炎因子表达显著增加，并且伴有胰岛素信号受损，说明在外周代谢组织中激活的炎症途径也可以在CNS重现。此后，越来越多的研究发现，其他脑区/核团也会受到炎症侵袭，包括大脑皮层[53]、海马[54]、杏仁核[55]、VTA[14]和NAc[56]等。有多项研究证据表明，来自外周的炎性介质可促进CNS炎症的发生与发展，促炎因子如IL-6、免疫细胞如巨噬细胞、肠道内毒素如脂多糖（lipopolysaccharide，LPS）等均能够破坏血脑屏障（blood brain barrier，BBB）进入下丘脑、海马、纹状体等脑区/核团，从而影响神经元功能和突触可塑性[57-61]。

除了外周免疫系统输入外，驻留脑内的小胶质细胞和/或星型胶质细胞可被直接激活，并分泌促炎因子和神经毒素（如活性氧）诱导CNS炎症[62-64]。动物实验发现，25周HFD促进了肥胖大鼠黑质纹状体产生炎症和OS，表现为小胶质细胞激活、星形胶质细胞增生、TNF-α水平升高[65]。Mizoguchi等[66]报道，HFD饲养3 d的雄性小鼠VTA *IL-1β*基因表达升高，饲养7 d后，TNF-α、IL-1β、IL-6和小胶质细胞激活标志物离子钙结合衔接分子1（ionized calcium-binding adapter molecule 1，Iba-1），以及簇状分化抗原11b（cluster of differentiation 11b，CD11b）的基因表达与普通膳食对照组相比存在统计学差异。这可能与饱和脂肪酸（saturated fatty acids，SFA）通过与各种Toll样受体（toll-like receptors，TLRs）结合直接激活小胶质细胞引发的CNS免疫反应有关[67-68]。离体实验证实，BV-2细胞和原代小胶质细胞中SFA以Toll样受体4（TLR4）依赖的方式激活核因子κB（nuclear factor-κB，NF-κB）通路，导致促炎因子和活性氧水平升高，而将NF-κB信号阻断后逆转了SFA诱导的小胶质细胞激活[69]。此外，当小胶质细胞功能障碍时，星形胶质细胞可代偿性发挥吞噬作用引发免疫反应[63]。在HFD和肥胖情况下，星形胶质细胞过度增生并产生TNF-α、IL-1β和IL-6多种促炎因子，这些细胞因子可以影响邻近的小胶质细胞、神经元和星形胶质细胞本身[70]。究其原因可能与星形胶质细胞中骨髓巨噬细胞分化因子88（myeloid differentiation primary response 88，Myd88）表达增加有关，因为特异性Myd88敲除改善了高热量膳食诱导的肥胖相关代谢表型，同时减少了促炎因子分泌[71]。这些结果说明，尽

管没有外周免疫系统输入，小胶质细胞和/或星形胶质细胞也可通过内源性途径诱发CNS炎症。综上，肥胖可诱导外周（脂肪组织、心脏、肝脏、胰腺等）和中枢（下丘脑、海马、纹状体等）产生代谢性炎症，而炎症信号将破坏机体内环境稳态平衡影响食物奖赏，进而促进肥胖的发展（图2）。

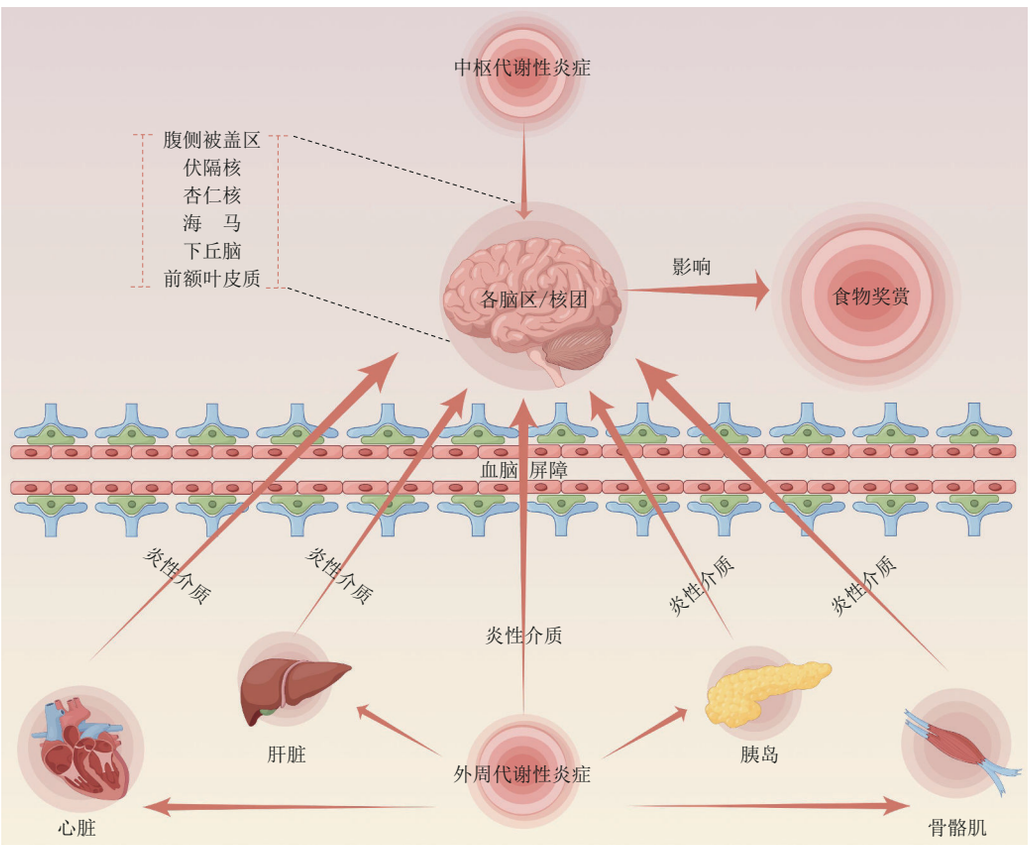

Fig. 2　Central and peripheral metabolic inflammation affect food reward

图2　中枢和外周代谢性炎症影响食物奖赏

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3　代谢性炎症诱导食物奖赏异常

既往在抑郁[72]、药物滥用[73]以及酒精依赖[74]等研究中发现，炎症与奖赏密切相关。一项涉及152人的影像学研究表明[75]，精加工食品的摄入量与抑郁症呈显著正相关，其中肥胖人群表现出更高的抑郁倾向，与非肥胖人群相比，前者左腹侧壳核（属于腹侧纹状体）体积与精加工食品摄入量之间存在更高的负相关性，而白细胞数量是摄入量与抑郁症状之间的重要中介变量。另外，在酒精依赖和药物滥用个体中发现，长期过量服用阿片类药物或酗酒将激活神经胶质细胞释放促炎细胞因子影响神经元功能，并且破坏DA、γ氨基丁酸（gamma-aminobutyric acid，GABA）等神经递质的突触传递促进成瘾行为[76-77]。然而抑制神经胶质细胞活性可以减弱NAc中吗啡诱导的DA释放，并且改变小鼠对吗啡和甲基苯丙胺诱导的条件位置偏好（conditioned place preference，CPP）[78-79]。与之相似，对大鼠注射吲哚美辛（抗炎药）后发现，酒精诱导的大脑皮质和海马体中炎性介质，包括环氧合酶2（cyclooxygenase-2，COX-2）和诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）表达被完全抑制，并且减轻了大鼠与成瘾有关的行为障碍[80]。综合分析认为，炎症可能在奖赏调节过程中发挥重要作用，同时这些结果也为解释代谢性炎症诱导食物奖赏异常提供了前期依据。

近来有大量研究认为，因能量过剩引起的代谢性炎症可能会通过与药物滥用或酒精依赖等类似途径诱导食物奖赏异常，从而促进肥胖的发生与发展。人体研究表明[81]，暴露于2周高饱和脂肪膳食的健康人群血浆中IL-6和IL-1β水平显著升高，并且与负责参与调控奖赏的基底神经节（尾状核和壳核）激活程度增加有关。Décarie-Spain等[56]报道，12周高饱和脂肪膳食（含有50%kcal棕榈油）小鼠血浆中C反应蛋白、TNF以及IL-1β水平明显增加，NAc中Iba-1、胶质纤维酸性蛋白（glial fibrillary acidic protein，GFAP）的基因表达，以及干扰素γ和热休克蛋白含量均显著增加，并且小鼠表现出对蔗糖的强迫性寻求行为。考虑到NF-κB通路在促炎基因表达中发挥重要作用，研究者对小鼠NAc注射IKKβ抑制剂阻断IKKβ-NF-κB通路后发现，小鼠对蔗糖的奖赏寻求行为被显著抑制。此外，Cheng等[15]在2022年《自然》杂志子刊*Nature Neuroscience*上发表的一项动物实验结果显示，在伴有足部电击的情况下，仍然不妨碍HFD小鼠对蔗糖奖赏的寻求，当研究者探讨这种行为背后的脑机制时发现，与普通膳食小鼠相比，HFD小鼠在强迫性寻求蔗糖后，前丘脑室旁核（anterior paraventricular thalamus，aPVT）中的神经元激活程度更高，然而这种现象与aPVT中小胶质细胞激活有关。随后利用PLX3397抑制剂耗尽小胶质细胞后发现，HFD小鼠aPVT中神经元兴奋性降低，并且抑制了小鼠强迫性寻求蔗糖行为。上述这些研究从不同角度证明了外周或中枢代谢性炎症均能诱导食物奖赏异常。有趣的是，后两项研究表明，炎症侵袭不同脑区可表现出同样的蔗糖强迫性寻求行为，分析其中的原因可从两方面解释。首先，由于食物奖赏环路并不是单一通路，涉及多个脑区/核团调控，其中任意一个环节受到干扰后均有可能导致奖赏回路产生级联反应；其次，食物奖赏也可以被细化为“liking”、“wanting”以及“learning and memory”成分，然而涉及参与调节这些成分的脑区/核团功能各有不同，炎症可能从不同方面，例如：动机（渴望）或条件线索（喜爱/厌恶）等干扰奖赏信号传导，进而外显为同一种表现，因此在讨论机制时还需辩证看待。此外，除上述已经报告的脑区/核团外，仍有大量研究报道，炎症也可以侵袭诸如PFC、VTA、杏仁核以及海马体等位置诱导食物奖赏异常[14，82-84]。

4　代谢性炎症诱导食物奖赏异常的可能机制

4.1　代谢性炎症影响DA信号传递

众所周知，DA在传递奖赏信息、调控奖赏动机中发挥关键作用。进食会引起DA释放，使个体感到愉悦和满足。这种正向强化被认为有利于提高个体对食物的渴望和摄取[85]，然而，随着进食量增加，体重也随之上涨，由此产生的代谢性炎症可通过侵扰DA合成、释放、再摄取，以及DA受体功能和表达等多个生理过程诱导食物奖赏异常。

4.1.1　DA合成

DA合成依赖于其前体物质L-3,4-二羟基苯丙氨酸（L-3, 4-dihydroxyphenylalanine，L-DOPA）。苯丙氨酸羟化酶（phenylalanine hydroxylase，PAH）和酪氨酸羟化酶（tyrosine hydroxylase，TH）是合成L-DOPA所必需的辅酶，这两种酶都需要借助酶辅助因子四氢生物蝶呤（tetrahydrobiopterin，BH4）的参与才能发挥正常功能。因此，BH4的活性及可用性对DA合成极为重要[86]。分子及人体实验表明，中枢或外周炎性介质如IL-6，可通过降低BH4的生物活性使PAH与TH功能受损，导致DA合成减少[87-89]；此外有报道称，炎症能够引起iNOS活性增加使BH4可用性下降，从而导致一氧化氮合酶（nitric oxide synthase，NOS）“解偶联”生成超氧化物诱发OS[90]；然而OS将诱导BH4被氧化还原为无活性的二氢生物蝶呤，导致DA含量进一步减少[91]。Kitagami等[92]报道，大鼠肌肉内注射干扰素α（interferon-alpha，IFN-α）可诱导一氧化氮穿过BBB，并抑制杏仁核等区域BH4和DA合成，抑制NOS后发现，IFN-α对BH4和DA浓度的抑制作用得到逆转。这些结果表明，代谢性炎症可能通过降低BH4的生物活性及可用性减少DA生成，进而导致食物奖赏异常。

4.1.2　DA释放和再摄取

DA神经元兴奋后产生动作电位使电压门控钙离子通道开放，随后钙离子进入细胞质内促使囊泡单胺转运蛋白2（vesicular monoamine transporter 2，VMAT2）包裹DA转运至突触前膜并释放。在此过程中，IL-6和TNF-α能够降低NAc-VMAT2表达减少DA释放[93]。有研究表明，小鼠被注射垂体腺苷酸环化酶激活多肽（具有抗炎作用）后发现，纹状体神经炎症和OS明显减轻，VMAT2表达增

加，同时改善了慢性甲基苯丙胺诱导的DA神经毒性[94-95]。此外，炎症也能够通过影响DAT转运体（dopamine transporter，DAT）表达增加对突触间隙中DA再摄取，进而降低DA可用性[96]。这可能与炎症信号分子刺激丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）增加了DAT活性有关，因为给予大鼠纹状体突触MAPK抑制剂后DA再摄取能力下降[97]。

4.1.3 多巴胺受体功能及表达

多巴胺受体（dopamine receptor，DR）属于G蛋白偶联受体，至少有5种亚型，分为D_1样受体家族（D_1R；D_1，D_5）和D_2样受体家族（D_2R；D_2，D_3，D_4）[98]；其中，D_2R与食物奖赏功能障碍关系密切[31]。一项荟萃分析显示，纹状体D_2R可用性降低与肥胖人群体重呈显著负相关，并且他们更加倾向产生强迫性进食行为[99]。Narayanaswami等[100]报道，与肥胖抵抗大鼠相比，肥胖易感（obesity prone）大鼠8周HFD导致纹状体D_2受体密度降低42%，同时表现出更高的进食动机；影像学研究显示，肥胖者纹状体D_2R可用性显著下降，体内C反应蛋白水平显著上升[101-102]。这些结果提示，炎症诱导食物奖赏异常的机制可能与D_2R功能及表达降低有关。

4.2 代谢性炎症影响μ阿片受体功能

如前文所述，VTA-NAc通路在调控奖赏功能中发挥重要作用。μ阿片受体（μ-opioid receptor，MOR）在VTA和NAc中大量表达，激活VTA-MOR能够增加NAc-DA释放，提高欣快感[103]。相反，长期抑制NAc-MOR信号传导会显著减轻大鼠体重，并减少对适口性食物的摄入量。然而，当VTA-MOR功能失调时，NAc-DA释放将发生剂量依赖性改变，并且增加大鼠对高剂量（≥5.0 mg/kg）海洛因的摄入[104]。研究表明，NAc中TNF-α浓度升高会减弱吗啡诱导的奖赏效应，并与MOR脱敏有关[105-106]；同样，在重度抑郁患者中发现，MOR表达水平也与IL-6和IL-10增加密切相关[107]。这些研究表明，炎症可通过影响MOR功能诱导奖赏异常。然而其背后的分子机制可能与炎性介质通过调节MOR表观遗传修饰有关。此观点可在Cruz-Carrillo等[108]研究中得到间接支持。他们发现，HFD诱导NAc中IL-6基因表达增加与大鼠食物成瘾行为和NAc壳中全基因组DNA甲基化相关。此外，超过15周的HFD增加了肥胖小鼠NAc甲基CpG结合蛋白2（methyl CpG-binding protein 2，MeCP2）与*MOR*基因启动子区域的结合，导致*MOR*转录受到抑制，从而对小鼠奖赏功能产生负面影响[109]。因此，基于以上证据推测，肥胖诱导的代谢性炎症很可能通过调节MOR-DNA甲基化诱导MOR功能障碍，进而导致食物奖赏异常。

4.3 代谢性炎症影响谷氨酸兴奋性突触传递

谷氨酸信号通路突触可塑性变化与食物奖赏偏好密切相关[110]。谷氨酸受体可分为α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体（α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor，AMPA）、N-甲基-D-天冬氨酸受体（N-methyl-D-aspartic acid receptor，NMDA）以及代谢型谷氨酸受体，这3种类型受体均参与奖赏信号调节。炎症可减少和重塑VTA和NAc壳中的AMPA和NMDA受体、降低突触反应，减少谷氨酸诱发的神经传递来调节谷氨酸信号传导，从而对奖赏产生负面影响[111-112]。Lewitus等[113]在药物成瘾行为中发现，反复使用可卡因会诱导纹状体小胶质细胞激活产生TNF-α，进而抑制NAc核心的谷氨酸突触强度，限制行为敏化的发展；此外，Oliveira等[114]利用代谢型谷氨酸受体负性调节剂抑制谷氨酸受体5激活后发现，肥胖小鼠体重显著降低，脂肪组织炎症和暴饮暴食行为得到明显改善。因此，炎症可诱导谷氨酸兴奋性突触传递异常改变奖赏效应，这可能与促炎因子通过电压门控Na^+、Ca^{2+}和K^+通道的离子流动来影响谷氨酸能神经元兴奋性有关[115]。

4.4 代谢性炎症影响TLR4信号激活

TLR4作为先天免疫受体与炎症信号转导密切相关。实际上，在酒精依赖和药物滥用的研究中早有报道，TLR4诱导的炎症反应在促进成瘾行为过程中发挥重要作用[116]。例如：酒精可以激活TLR4触发PFC的炎症信号，进而影响小鼠对乙醇的偏好[117]；VTA内TLR4和IL-1β信号传递导致可卡因诱导的细胞外NAc-DA浓度升高，然而注射LTR4拮抗剂LPS-RS（来自紫硫红螺菌的脂多糖，lipopolysaccharide from *Rhodobacter sphaeroides*）可减弱可卡因诱导的NAc-DA增加，这表明TLR4激活是可卡因诱导的NAc-DA增加的原因，而这与可卡因奖赏和强化有关[118]；此外，TLR4是LPS和SFA结合的重要位点，而这与神经炎症和过度进食有关[69]。特异性敲除VTA-DA神经元上的TLR4能够显著减轻神经炎症、降低VTA-DA神经元活性和TH表达，进而调节NAc-DA水平[119-120]。总之，这些证据表明，代谢性炎症很可能通过TLR4诱导

食物奖赏效应发生改变，进而导致食物奖赏异常。

4.5　代谢性炎症影响中枢胰岛素/瘦素受体信号转导

脑是接受胰岛素和瘦素调节的敏感器官。通常情况下，胰岛素和瘦素能够通过主动转运穿越BBB进入CNS，并与DA神经元上对应受体结合，从而通过调节奖赏效应来抑制进食[121]。然而，随着肥胖程度增加，胰岛素和瘦素受体逐渐脱敏钝化，导致胰岛素/瘦素受体信号转导异常，并伴随奖赏效应改变[65，122]。

4.5.1　胰岛素受体信号转导异常

本课题组前期研究发现，12周HFD诱导的肥胖大鼠NAc-DA基础浓度降低，细胞外胰岛素信号传递减弱，并且对脂肪的摄入量明显增加[123]，分析原因可能与代谢性炎症有关。从机制来看，胰岛素与受体结合后导致受体自磷酸化，引起胰岛素受体底物（insulin receptor substrate，IRS）蛋白募集及其随后的磷酸化，磷酸化的IRS蛋白是激活磷脂酰肌醇3激酶（phosphoinositide 3-kinase，PI3K）-蛋白激酶B（protein kinase B，PKB）通路和MAPK-细胞外调节蛋白激酶（extracellular signal-regulated kinase，ERK）通路的关键节点[124]。一方面，促炎因子如TNF-α能够诱导胰岛素受体底物1（insulin receptor substrate-1，IRS-1）丝氨酸磷酸化，进而阻碍IRS-1酪氨酸磷酸化，降低IRS-1与胰岛素受体的结合能力，从而抑制胰岛素发挥作用[125]；另一方面，炎症也可能诱导应激激活蛋白激酶激活，如c-Jun激酶、p38激酶或IκB激酶（IκB kinase beta，IKKβ）影响MAPK-ERK通路的信号转导，产生胰岛素抵抗[126]。Sun等[14]报道，HFD诱导雌性小鼠VTA炎症会导致DA神经元功能障碍和胰岛素抵抗，同时伴有暴饮暴食行为，敲除IKKβ后，小鼠高脂食物的消耗量明显减少，VTA中PKB的磷酸化增加，DA神经元活性和炎症显著降低。

4.5.2　瘦素受体信号转导异常

生理状态下，瘦素通过激活Janus激酶2（janus kinase 2，JAK2）促使信号转导和转录激活因子3（signal transducer and activator of transcription 3，STAT3）的磷酸化来发挥抑制进食的生理作用[127]。STAT3的靶基因——细胞因子信号转导抑制因子3（suppressor of cytokine signaling 3，*SOCS3*）是瘦素信号转导通路中重要的负向调节因子，SOCS3能够通过与瘦素受体上酪氨酸位点Tyr985的特异性结合以及抑制JAK2的活性来阻碍瘦素受体信号转导。此外，蛋白质酪氨酸磷酸酶1B（protein tyrosine phosphatase 1B，PTP1B）也是瘦素受体信号转导通路的负向调节因子，它能够直接介导JAK2的去磷酸化进而导致瘦素抵抗。因此，STAT3、SOCS3以及PTP1B的异常表达通常被认为是CNS瘦素信号转导异常的主要原因[128]。值得注意的是，这3种蛋白质的表达均会受到炎症的影响。例如，IKKβ/NF-κB通路激活将诱导SOCS3表达，并且产生IL-1β、IL-6和TNF-α等多种促炎因子[129]，然而这些促炎因子促使SOCS3和PTP1B过表达，从而产生瘦素抵抗[130]。

综上所述，炎症信号可能通过各种生理途径诱导食物奖赏异常从而促进肥胖的发展（图3）。值得注意的是，HFD或肥胖是否会引起VTA出现瘦素抵抗的结果尚不完全一致，这可能与饲养周期有关[66，122]。因此当探讨瘦素抵抗在食物奖赏中的作用时，还需充分考虑饲养周期是否合理。

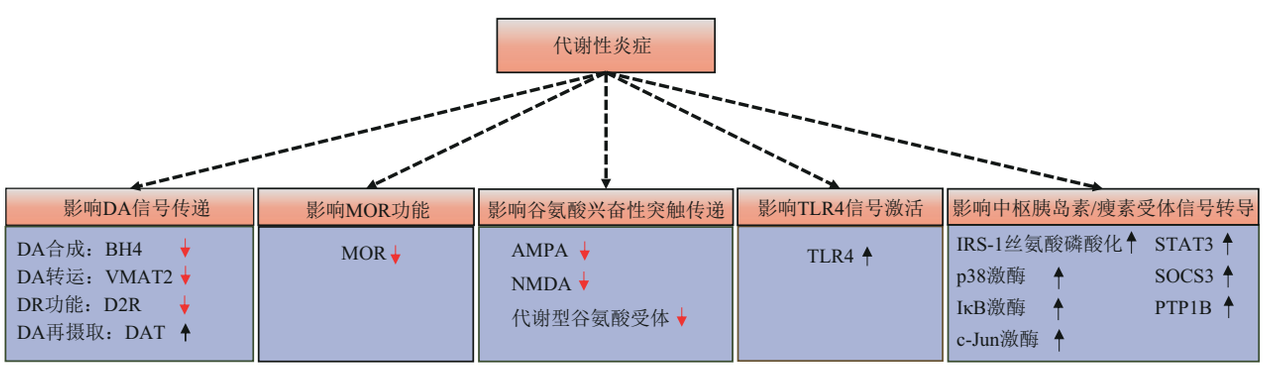

Fig. 3　The potential mechanisms of metaflammation induces food reward dysfuction

图3　代谢性炎症诱导食物奖赏异常的可能机制

5 总结与展望

食物奖赏异常是肥胖形成与发展的重要因素。因能量过剩产生的代谢性炎症可能通过影响DA信号传递、MOR功能、谷氨酸兴奋性突触传递、TLR4信号激活，以及中枢胰岛素/瘦素受体信号转导等生理途径破坏奖赏信号的正常传递，进而改变食物奖赏效应促进肥胖。目前，该领域仍然存有大量科学问题亟待解决。如：a. 代谢性炎症可发生于外周及中枢两方面，何种途径产生的炎症对食物奖赏相关的脑区/核团影响最为明显仍需深入探讨；b. 食物奖赏可进一步细化分为“liking”、“wanting”以及“learning and memory”3种成分，然而代谢性炎症对干扰/破坏这些成分中奖赏信号传递的确切机制尚不清楚，另外，代谢性炎症对哪种成分的奖赏信号传递影响较大仍然尚未可知；c. 是否存在某种手段，例如药物或运动能够将炎症有关的信号或通路作为潜在干预靶点，进而逆转其对食物奖赏的负面影响减轻肥胖，仍然值得进一步研究。总之，已有越来越多的证据指向代谢性炎症与肥胖食物奖赏关系密切，但仍需大量人体和动物实验对这一问题进行深入研究，并且对其中的机制问题给予更加明确的解释。

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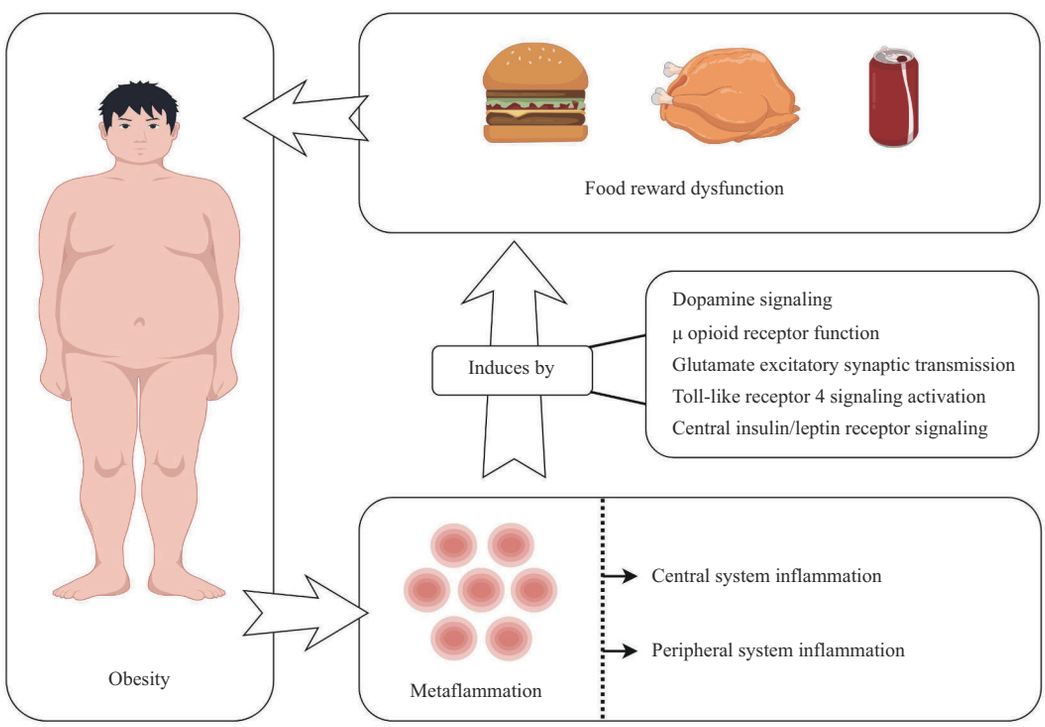
The Emerged Perspective on Obesity Etiology: Metaflammation Induces Food Reward Dysfunction*

DAI Yu-Xi[1)], HE Yu-Xiu[1,2)**], CHEN Wei[1,2)]

([1)]*School of Physical Education, Hebei Normal University, Shijiazhuang* 050024, China;

[2)]*Key Laboratory of Measurement and Evaluation in Exercise Bioinformation of Hebei Province, Shijiazhuang* 050024, China)

Graphical abstract



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Abstract　In recent years, obesity has emerged as a significant risk factor jeopardizing human health and stands out as an urgent issue demanding attention from the global public health sector. The factors influencing obesity are intricate, making it challenging to comprehensively elucidate its causes. Recent studies indicate that food reward significantly contributes to the genesis and progression of obesity. Food reward comprises three integral components: hedonic value (liking), eating motivation (wanting), and learning and memory. Each facet is

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** Corresponding author.

Tel：86-18931871518，E-mail：heyuxiu@hebtu.edu.cn

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governed by the corresponding neural pathway. The mesocorticolimbic system (MS) plays a pivotal role in regulating food reward, wherein the MS encompasses dopamine (DA) neurons originating from the ventral tegmental area (VTA) projecting into various brain regions or nuclei such as the nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala, and hippocampus. On one hand, prolonged consumption of palatable foods induces adaptive alterations and synaptic remodeling in neural circuits regulating food reward. This includes the attenuation of neuronal connections and signal transmission among the PFC, visual cortex, hypothalamus, midbrain, and brain stem, resulting in aberrant food reward and compelling the body to compensate for satisfaction deficiency by increasing food consumption. Studies involving humans and animals reveal that compulsive eating bears resemblance to the behavior observed in individuals with substance addictions, encompassing aspects such as food cravings, loss of eating control, and dieting failures. Propelled by food reward, individuals often opt for their preferred palatable foods during meals, potentially leading to excessive energy intake. Coupled with a sedentary lifestyle, this surplus energy is stored in the body, transforming into fat and culminating in obesity. While evidence supports the notion that prolonged exposure to a high-energy-density diet contributes to abnormal food reward, the internal mechanisms remain somewhat unclear. In previous research on depression, substance abuse, and alcohol dependence, it has been confirmed that there is a close connection between inflammation and reward. For example, obese people show a higher tendency toward depression, and white blood cell count is an important mediating variable between intake and depressive symptoms. In addition, it has been found in individuals with alcohol dependence and drug abuse that long-term opioid overdose or alcohol abuse will activate glial cells to release pro-inflammatory cytokines that affect neuronal function, and disrupt synaptic transmission of neurotransmitters to promote addictive behaviors. Comprehensive analysis suggests that inflammation may play an important role in the reward regulation process. Recent studies indicate that metaflammation within the central or peripheral system, triggered by excess nutrients and energy, can disrupt the normal transmission of reward signals. This disruption affects various elements, such as DA signaling (synthesis, release, reuptake, receptor function, and expression), mu opioid receptor function, glutamate excitatory synaptic transmission, Toll-like receptor 4 (TLR4) signal activation, and central insulin/leptin receptor signal transduction. Consequently, this disruption induces food reward dysfunction, thereby fostering the onset and progression of obesity. Building upon these findings, we hypothesized that obesity may be linked to abnormal food reward induced by metaflammation. This review aims to delve deeply into the intricate relationship between obesity, food reward, and metaflammation. Additionally, it seeks to summarize the potential mechanisms through which metaflammation induces food reward dysfunction, offering novel insights and a theoretical foundation for preventing and treating obesity.

Key words obesity, food reward, metaflammation
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