

进食行为的迷走神经调控机制

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摘要

进食行为是一个高度复杂的动态过程，需要整合机体内稳态信号与环境中的享乐信号，以实现自适应平衡。肠神经系统(ENS)作为人体的“第二大脑”，通过肠-脑轴与中枢神经系统(CNS)进行信号交换，在调节进食行为中发挥重要作用，其中迷走神经(VN)作为肠脑对话的关键纽带，调控着进食的稳态与享乐过程。本文综述了迷走神经在稳态进食中的两大核心系统——内感受系统和外周饱腹系统，以及在享乐进食中的两类驱动线索——感官愉悦线索和营养价值线索的作用机制。同时，结合现代食物环境下的肥胖易感性，探讨了迷走神经相关的干预策略，为优化进食行为调控提供理论依据与实践指导。

关键词

迷走神经，稳态进食，享乐进食，内感受，食物奖赏

Vagal Regulatory Mechanism of Feeding Behavior

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Abstract

Eating behavior is a highly complex and dynamic process that requires the integration of homeostatic signals and hedonic cues from the environment to achieve adaptive balance. The enteric nervous system (ENS), known as the “second brain,” plays a vital role in regulating eating behavior by exchanging signals with the central nervous system (CNS) via the gut-brain axis. The vagus nerve (VN), as a key mediator of gut-brain communication, governs both homeostatic and hedonic aspects of eating. This review examines the role of the vagus nerve in regulating homeostatic eating through two major systems—the interoceptive system and the peripheral satiety system—and its involvement

in hedonic eating via sensory pleasure and nutritional value cues. Additionally, the susceptibility to obesity in the modern food environment and vagus nerve-based intervention strategies are discussed, providing theoretical insights and practical guidance for optimizing the regulation of eating behavior.

Keywords

Vagus, Homeostatic Feeding, Hedonic Feeding, Interception, Food Reward

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1. 引言

进食行为(eating behavior)是一项高度复杂的动态进程, 需要根据机体与环境线索整合内稳态信号和享乐信号以实现自适应平衡[1]-[5]。其中, 稳态的部分确保我们在饥饿时进食, 一旦饱足就停止进食, 从而使食物摄入量与能量消耗相匹配。而享乐的部分则是由眼下丰富的食物环境所创造, 是一种快乐驱动的进食方式, 并伴随偏好高度可口食物的持续供应和频繁消费的潜在后果。

肠神经系统(enteric nervous system, ENS)又称人体“第二大脑”, 在调节进食行为方面起着重要作用, 并通过肠-脑轴(gut-brain axis)与中枢神经系统(central nervous system, CNS)交换多种进食信号。近年来, 迷走神经在肠脑对话中的纽带作用日益凸显, 越来越多的神经科学和心理学者关注到了肠-脑迷走神经在进食行为中的作用机制[2][6][7]。迷走神经(vagus nerve, VN)是第十对脑神经, 也是脑神经中行轨最长、分布最广的一对。在颈部水平由大约 80%的传入纤维和 20%的传出纤维组成, 而在膈下水平包含高达 30%的传出纤维[8][9], 经颈胸腹长程完成肠脑信号的双向通讯。迷走神经支配消化系统的绝大部分器官, 负责感知并向大脑传递“吃饱(饥饿感和饱腹感)”和“吃好(营养物质和能量)”的信号, 调控消化行为和营养吸收。

在此, 本文对肠-脑迷走神经回路在进食行为中的作用进行综述(见图 1), 重点关注由迷走神经介导调控稳态进食的两大系统——内感受系统和外周饱腹系统, 以及由迷走神经介导驱动享乐进食的两大线索——感官愉悦线索和营养价值线索, 并进一步探讨现代食物环境下的肥胖易感性及其迷走神经干预策略。

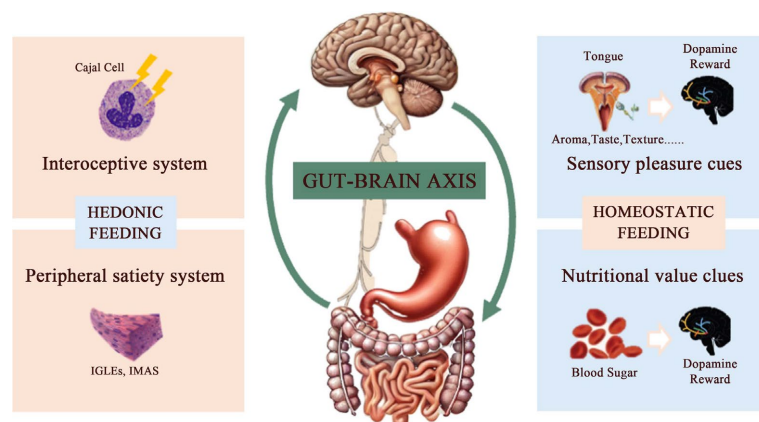


Figure 1. Feeding regulatory pathways in the gut-brain vagal system

图 1. 肠-脑迷走神经系统中的进食调控路径

2. 迷走神经介导的稳态进食

稳态进食(homeostatic feeding)是一种由机体能量需求直接驱动的进食行为,通过控制食物摄入平衡内感受系统(interception system)中的饥饿感和饱腹感信号,以维持正常体重和代谢功能[4]。

作为主要的内感受信号传输媒介,迷走神经的感觉神经元(vagal sensory neurons)能够将外周消化器官的信号,如静息放电(电信号)、胃肠蠕动(机械信号)、消化吸收(化学信号)等,经脑干孤束核(Nucleus tractus solitarius, NTS)传递给食欲中枢下丘脑,进一步通过下丘脑整合饥饿感和饱腹感等食欲信息,并特异性地调整食物摄入数量和质量以维持身体的稳态[9]-[11]。这种由迷走神经介导的稳态进食主要涉及两大系统:内感受系统和外周饱腹系统。

2.1. 迷走神经电信号介导的内感受系统

内感受系统对于能量稳态非常重要。作为副交感神经系统的一部分,迷走神经可以通过外周器官与脑干之间的信号传递调节自主神经功能的内感受性[12]。研究表明,迷走神经纤维携带的信号还可以越过脑干继续上传至复杂的大脑区域,这揭示了大脑中一个更为广泛的内感受网络[9] [13] [14],也意味着大脑可以通过迷走神经对多样且繁多的内感受信号做出表征和响应。例如,Rebollo 等人首次在人类被试上确定了胃网络(gastric network)的存在[15],即一种与胃 Cajal 间质细胞发出的基础电节律(0.05 Hz, 20 s/cycle)相位延迟耦合的新静息状态网络,这表明进食过程中的内感受活动与自发的大脑活动之间存在联系。迷走神经的作用不仅依赖于其传递信号的解剖路径,还与其不同分支的功能特化密切相关。迷走神经的传入纤维占其总神经纤维的 80%~90%,主要分为三个关键分支:① 胃肠道分支,主要调控消化过程,感知胃张力和肠激素信号;② 肺分支,监测呼吸模式,与饥饿和能量消耗密切相关;③ 心血管分支,调控心率变异性,与进食诱发的自主神经平衡调整有关。传出信号则通过迷走神经的分泌作用影响胰岛素、胰高血糖素和胃排空等外周过程。不同分支通过各自的靶器官影响全身能量稳态,并通过迷走神经核团(如孤束核, NTS)进行整合。随之, Müller 等人使用非侵入性的经皮耳迷走神经刺激(taVNS)来模拟内感受信号的激活[14],发现 taVNS 增加了 NTS 和中脑的胃脑耦合,同时促进了整个大脑的耦合。在这一过程中,神经递质的作用不可忽视。迷走神经的传入信号主要通过谷氨酸(兴奋性递质)在孤束核投射到高级脑区,同时 γ -氨基丁酸(GABA)则在孤束核内起到局部调控作用。此外,多巴胺能和去甲肾上腺素能通路也通过迷走神经核团影响奖励驱动的进食行为。而胃肠道内源性激素(如 CCK 和 PYY)则通过其受体亚型(如 CCK-A 受体和 Y2 受体)与迷走神经末端作用,可调节信号传递效率,并对食物摄入产生抑制效应。至关重要的是,在皮层中, taVNS 诱导的耦合变化主要发生在跨模态区域,并与作为主观代谢状态指标的饥饿等级变化相关。这表明,迷走神经传入刺激有助于将来自单模态表征的代谢信息整合到跨模态延伸的胃网络中,从而协调行为适应,以确保长期的能量稳态。

2.2. 迷走神经机械-化学信号介导的外周饱腹系统

迷走神经也参与稳态进食的食欲调控,对外周饱腹信号的响应十分迅速。早期的解剖学和电生理学研究将胃肠道迷走神经传入神经细分为两种主要类型:支配肌肉层并对胃肠道扩张做出反应的机械感受器 IGLs 和 IMAs,以及响应肠内分泌细胞(enteroendocrine cell, EEC)激素释放的化学感受器。这些由迷走神经支配的机械感受器和化学感受器特异性地分布于整个胃肠道,支配着肠腺、肠绒毛、肠道、胃和门静脉系统[9] [16],可以直接将食物摄入后胃扩张的感觉和肠道营养信息,经脑干 NTS 传递至下丘脑弓状核(arcuate nucleus of hypothalamus, ARC)的两大类食欲神经元[4] [17]-[19]——一类是促进食欲神经肽 Y(neuropeptide Y, NPY)和刺鼠肽基因相关蛋白(agouti-related peptide, AgRP)神经元;一类是抑制食欲阿黑皮素原(POMC)神经元——进而调节饥饿感和饱腹感以控制进食量、进食频率等行为。

具体而言,食物摄入首先会导致胃扩张,这可以刺激胃肠道平滑肌层中受迷走神经支配的机械感受器 IGLs 和 IMAs [20]。刺激这些肠道机械感受器足以激活脑干中的饱腹感促进途径,并抑制下丘脑中的饥饿促进 AgRP 神经元。即使在缺乏营养的情况下,增加肠容量也足以抑制食物摄入和 AgRP 神经元活动[6]。其次,食物摄入还会诱导 EEC 释放多种食欲激素,如胰高血糖素样肽-1 (GLP-1)、肽 YY 3-36 (PYY3-36)、胆囊收缩素(CCK)及胃源性瘦素(Leptin) [21]-[23]。这些激素可以直接调节肠粘膜内靠近(或直接突触接触)化学感受器的迷走神经传入神经元的神经末梢[24],以响应能量摄入。这种来自肠的营养物质的迷走神经信号与胃扩张信号相结合,有助于在进餐期间出现饱腹感。

有趣的是,研究发现迷走神经传入终末不仅能感觉到食物的摄取量[19] [20],而且还能感知到食物的营养类型[19] [24]-[27]。如脂肪通路从上肠开始,通过迷走神经将增强信号传递到右侧结状神经节、后脑、中脑和背侧纹状体[26] [28];碳水化合物的直接途径仍然未知,然而在转化为葡萄糖后,糖和淀粉被氧化为细胞过程提供燃料,这时的迷走神经传感器就可能位于门静脉中[29] [30],预计会激活最终到达纹状体的脊髓传入神经。值得注意的是,虽然这些发现在临床研究中已得到化学或手术消融方法(如,完全膈下迷走神经传入阻滞术)的技术支持,但对于这种与外周器官广泛联结的混合神经,单纯以器官特异性的方式将其传入神经完全分离,实际上限制了迷走神经不同的终末结构和胃肠道对应位置的特定功能的进一步清晰化[7] [25] [30]。

3. 迷走神经介导的享乐进食

享乐进食(hedonic feeding)是一种由食物奖赏(food reward)线索驱动的进食行为,并通过对食物奖赏价值的学习建立稳定的肠-脑奖赏回路[1] [2] [31]。在现代食品环境的背景下,享乐进食易打破前馈自适应(adaptive feedforward)下的内稳态机制而引起体重的增加,进一步引发超重肥胖等健康问题。

根据享乐进食是否能被意识到,可以将食物奖赏线索分为两种情况,一种是能够直接进行主观报告的感官愉悦线索(sensory pleasure cues),一种是基于内隐处理的营养价值信号(nutritional value cues) [2]。在肠-脑奖赏系统中,两者参与了独立的迷走神经回路。

3.1. 感官愉悦线索下的迷走神经调控机制

食物的摄入首先触发个体对食物多种感官特性的感知。虽然大部分体验都是基于鼻后嗅觉和味觉线索的整合[32],但食物的温度和质地(texture),以及给口腔带来的感官刺激,以及触觉、听觉和视觉线索在内的多模态感知都有助于我们对食物的整体体验。

早期小鼠双瓶测试(two-bottle choice)首先在行为表征上验证了这种基于感官愉悦线索下享乐进食模式,即风味-风味联结(flavor-flavor association)。研究者通过使用人工甜味剂选择性地操纵食物的感官特征,并在营养成分没有变化的前提下,将两种风味搭配在一起,发现小鼠更喜欢与更高浓度糖精搭配的任何一种风味[33],即对未知或中性风味的偏好将根据对与之搭配呈现的风味的现有偏好而变化。这也是为什么食物的营养信息或能量密度在食物到达肠道之前不会被检测到,但仍然会影响口味偏好。

随着技术的进步,越来越多神经层面的证据表明食物风味信息处理过程中同样也需要依赖迷走神经来接收与整合食物的多模态感官属性[8]。从分支功能的角度来看,迷走神经在味觉与风味信息的处理上展现了显著的特异性:舌咽支和喉支主要负责味觉和口腔内感受信息的传递,而肠道相关分支则对食物的后续消化吸收过程进行监测。具体地,迷走神经通过支配舌根、会厌和喉部等进食相关的消化前外周器官,将食物多种感觉信息经脑干孤束核中的迷走神经结状神经节(nodose ganglion, NG) [8] [34] [35]。在孤束核中,这些信号通过迷走神经结状神经节(nodose ganglion, NG)整合后,进一步传递至前岛叶皮层[8] [36]-[38],完成风味信息的复杂加工,最终构建对食物的整体体验。例如, Jin 等人最近通过遗传学手段

发现了小鼠脑干孤束核吻部(rNST)中的甜味和苦味偏好性神经元[35]。具体而言,通过顺行示踪病毒注射发现味觉皮层的苦味中枢主要下行投射到对侧 rNST 中的苦味敏感性神经元,少量投射到同侧 rNST,而杏仁核中央核的甜味中枢则基本投射到同侧 rNST 中的甜味敏感性神经元。两类神经元虽然作为相互独立的风味感知通路,但在 rNST 中部分混合,这也可能与迷走神经在外周器官中的不对称性投射有关。此外,孤束核作为风味感知与情绪调节的关键节点,与杏仁核和前岛叶的双向连接支持了食物风味与情绪之间的交互作用。例如,杏仁核对风味的情绪化评价通过迷走神经的舌咽支传回孤束核,影响味觉中枢的感知敏感性,而前岛叶则通过孤束核实现对风味愉悦体验的强化效应。

3.2. 营养价值线索下的迷走神经调控机制

此外,摄食后入的营养结果也是驱动享乐进食的关键线索。在动物模型中,Holman 开创性地将风味与营养价值相关联[33],发现经过一定周期的喂养的大鼠更喜欢与胃内(intragastric, IG)葡萄糖输注配对的调味溶液(CS^+),而不是与非热量输注配对的替代风味(CS^-) [39] [40]。这一结果首次证明享乐进食中的食物选择确实会随摄食后营养感知的价值信号而发展,即风味-营养联结(flavor-nutrient association)。有意思的是,虽然风味-营养调节会延迟,但非常强大,以至于在一定程度上可以超越风味-风味调节。例如,通过 IG 输注个别常量营养素(碳水化合物、脂肪、蛋白质)可以将对苦味或酸味的先天厌恶转化为强烈的偏好,甚至产生持久的偏好[41] [42]。这些发现表明,食物的感官特征与潜在强化中的营养价值比是次要的[2]。正如使用光纤光度记录 Ca 活动的研究表明,下丘脑中的饥饿神经元在糖分等营养物质进入肠道后的几秒钟内就会受到抑制[43]。因此,即使食物的感官愉悦线索提高了短期摄入量,摄入后的营养价值线索也会通过更大程度地刺激餐后饱腹感而抑制食欲。

而这种享乐途径的关键靶点在于中脑多巴胺奖赏环路[4] [31] [44] [45]。与此同时,大脑还进化出了一些有趣的神经递质让我们享受进食的乐趣——特别是两种,多巴胺(dopamine, DA)和外周内源性大麻素(endocannabinoids, eCBs)。其中,在纹状体复合体和中脑边缘多巴胺系统驱动的享乐进食中[4] [46],迷走神经在其间可作为外周奖赏感受器,整合奖赏神经递质,协调肠-脑轴来调控享乐进食。在经过完全迷走神经切断术和化学传入神经阻滞处理的小鼠模型中,研究者证实了迷走神经在肠-脑奖赏回路中对多巴胺能的消除作用[47]。而近期通过光遗传学方法,研究者们进一步鉴定出了肠-脑迷走神经机制下食物奖励性神经元群[26],补充了迷走神经元充当肠-脑奖赏回路外周感受器的证据。具体而言,右侧迷走神经支配的结状神经节将外周感觉神经元与大脑奖赏神经元群联结起来,激活背外侧臂旁黑质通路,并诱导多巴胺在黑质神经元释放,使小鼠持续产生更多的自我刺激行为(识别奖赏神经元的标志性试验),以及味觉偏好和位置偏好的调节。此外,另一种驱动享乐进食的代谢信使——外周内源性大麻素——也需要通过迷走神经来协调参与非稳态适应的 DA 依赖肠-脑奖赏回路,改变能量稳态效应和诱导的暴饮暴食行为[48] [49] [50]。通过建立享乐进食驱动的暴食小鼠模型,研究者选择性抑制外周内源性大麻素受体 CB1R,发现受体完全依赖于迷走神经多突触回路,引起下丘脑活动增加、调节代谢效率、削弱中脑缘的多巴胺回路活动[48],这些共同作用可抑制享乐性进食。

此外,对于不同常量营养素营养感知的肠-脑迷走神经机制也有所不同。例如,有研究表明,一些称为神经足细胞(neuropod cells)的肠道感觉上皮细胞可以在十二指肠内检测到葡萄糖,并分泌释放谷氨酸释至迷走神经传入神经元上[24] [29] [51]-[54],同时激活对糖敏感的孤束核尾部(cNST)神经元还可以产生特定的嗜糖偏好[54]。无独有偶,将脂肪信号从肠道传输到 cNST 形成脂肪偏好同样需要迷走神经。通过基因敲除技术,研究者发现存在两个独立的肠-脑回路用于肠-脑脂肪传感,即仅由脂肪刺激激活的迷走神经通路和综合感知常量营养素的迷走神经通路[28]。

4. 肥胖易感性与迷走神经刺激

当前丰富多产的现代进食环境对于杂食属性的人类来说是具有挑战性的。首先，持续食用高度可口的饮食也会引起神经适应，从而使过度消费模式长期存在。而当对食物刺激的异常奖赏相关反应超越了稳态过程，就会导致体重增加。例如，来自动物模型和人类的数据表明，饮食中接触高糖、高脂或高盐会改变对更高浓度的偏好[55]-[61]，这可能会使生物体偏向于选择这些化合物含量较高的食物。因为这些食物的热量更高，这可能会促进体重增加和代谢疾病，这可能会进一步破坏化学感应和奖励回路以加强它们的选择。其次，致肥环境也助长了肥胖流行，其特点是廉价而深加工的高脂高糖食品的广泛供应。这些因素增加了肥胖的风险和其他随之而来的对健康的不利影响[62]。如，越来越多的证据表明，过度摄入可口的高糖食物可能导致类似成瘾的行为[62] [63]。

进食行为的健康管理受到肥胖易感与迷走神经功能障碍的双向掣肘。一方面，肥胖会引起迷走神经信号功能障碍。饮食诱导的肥胖模型提供了大量证据表明迷走神经传入神经元对外周信号的敏感性变得迟钝，使得动物肆意消费更多的可口的、能量密集的食物。例如，与瘦小鼠相比，肥胖小鼠响应胃肠道上皮收缩扩展的机械负荷的迷走神经传入放电减少，以及对胃肠道食欲激素的迷走神经传入敏感性显著降低[25] [30]。另一方面，迷走神经传入信号的破坏又会促进食欲过盛和肥胖。例如，完全膈下迷走神经切断术、辣椒素或膈下传入神经阻滞对迷走神经的损坏都能改变膳食模式，导致进餐量增加，但导致对体重和每日食物摄入量的影响不大。值得注意的是，这些消融技术存在相当大的局限性，可能没有完全区分传出信号和传入信号，而这些信号之间的作用可能彼此相反，从而掩盖了其中一种或另一种在能量稳态中的重要作用[30]。利用新的遗传工具，就能发现迷走神经传入信号的中断足以导致食物过度消耗和体重增加。

与此同时，越来越多的证据表明，以迷走神经为靶点的神经调节可以治疗肥胖。在临床应用中，迷走神经刺激(vagus nerve stimulation, VNS)是一种既定的大脑刺激方法，可用于多种疾病，如癫痫、失眠、慢性疼痛等[64]-[66]。值得注意的是，VNS 已显示出治疗超重肥胖和食物成瘾的潜力，如动物研究表明，慢性 VNS 能减少了体重增加、食物消耗和对甜食的渴望[67]，而急性 VNS 具有强化特性可通过多巴胺能机制调节食物偏好[26]。在人体被试中同样发现在接受 VNS 后体重明显减轻，有趣的是，接收较高频率 VNS 刺激的被试体重减轻最多。然而，这些试验都是在接受癫痫或抑郁症治疗的患者身上进行的，因此不能代表肥胖人群，患者之间的参数差异很大，刺激部位也不是减肥的最佳位置。其次，这也是一种需要麻醉和手术风险的侵入性方法，其长期安全性和有效性的研究仍然有限。在这种情况下，非侵入性的经耳迷走神经刺激(transcutaneous auricular VNS, taVNS)似乎是一种潜在补充治疗选择。通常，taVNS 是通过在耳朵上放置电极来对迷走神经耳支施加电刺激，刺激会在此处引起远场电位[68] [69]。在临床前研究中，研究者发现左侧急性 taVNS 刺激能够降低胃的肌电频率[70]，并促进对食物奖励的寻求，这为肥胖治疗铺平了道路。

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