

气味调控疼痛感知的行为及神经机制

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摘要 痛觉与嗅觉均为遗传学上古老且基本的感知系统, 在人类进化过程中发挥了核心作用, 为机体提供了重要的自我保护机制。由于嗅觉加工与疼痛加工在大脑神经通路和功能网络上存在显著重叠, 并与情绪、认知过程紧密耦合, 气味被认为能够调节个体的疼痛感知。本文系统梳理了气味调控疼痛感知的行为学与神经机制证据, 并在此基础上提出可供检验的潜在神经通路模型, 旨在为相关机制研究提供参考, 并为在临床情境下将气味干预作为辅助疼痛管理策略提供思路。现有行为学研究总体提示, 气味对疼痛的调节具有一定的维度特异性: 不同效价的气味通过诱发情绪状态变化, 较一致地作用于疼痛的情感-动机维度, 表现为对疼痛不愉悦度的调控; 而气味对疼痛感知-辨别维度(如疼痛强度、疼痛阈限等)的影响则不尽一致。神经机制证据进一步表明, 气味刺激可能通过情绪与奖赏、注意的神经机制, 参与调节疼痛的上行传导与下行抑制通路, 进而分别调控疼痛感知的情感-动机维度和感知-辨别维度。基于当前证据, 未来研究需在范式设计与指标体系上更精细地区分气味引发的情绪效应与注意效应, 并结合更严格的操控检验以进一步验证其维度特异性。此外, 结合脑脊同步功能磁共振成像等新技术, 未来研究有望直接评估气味调控疼痛在脊髓层面的作用, 从而揭示更完整的中枢调控通路。

关键词 痛觉, 嗅觉, 气味, 行为机制, 神经机制

痛觉是反应机体当下或潜在组织损伤的一种不愉悦感知和情绪体验^[1]。研究显示, 全球近五分之一的成年人患有持续性或慢性疼痛, 受急性疼痛困扰的人群数量则更为庞大^[2]。自2020年以来, 全球疼痛治疗市场预计以每年3.8%的速度增长, 到2027年市场规模将增至近920亿美元^[3,4]。寻找有效的镇痛方法以及缓解患者的痛苦情绪被视为医疗实践的核心^[5]。相较于传统药物治疗(如非甾体抗炎药、阿片类镇痛药物等), 采用非药物干预手段(如认知行为疗法、正念冥想、音乐疗法等)通常表现出更高的安全性、更低的成瘾和副作用风险以及更具成本效益的优势^[6-8]。

个体的疼痛体验通常被划分为两个相互联系但可区分的维度: 感知-辨别维度(sensory-discriminative dimension), 指对伤害性刺激物理属性的编码与辨别, 包括强度、部位、性质与持续时长; 情感-动机维度(affective-motivational dimension), 指疼痛刺激所引发的主观不愉悦或痛苦的情感体验及其驱动的逃避与防御动机^[9-11]。这两个维度的加工分别由疼痛的两条上行传导通路编码: 其一是外侧通路, 经新脊髓丘脑束、新三叉神经丘脑束、颈部束和脊髓后角束将疼痛信息从脊髓传递至躯体感觉皮层、外侧丘脑、顶叶岛盖和脑岛, 主要加工疼痛的强度、时间空间分辨信息; 另一条是

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内侧通路,经脊髓丘脑束、脊髓中脑束、脊髓网状束等将疼痛信息投射至前扣带回、脑岛、杏仁核、海马、旁臂核、蓝斑核、内侧丘脑核团等,主要形成了个体对疼痛的不愉悦感受^[11~13]。然而,疼痛的最终主观体验并非仅由上行输入决定,还会受到情绪与认知因素等自上而下因素的调节^[14]。研究表明,消极情绪通常会加剧疼痛感知,而积极情绪能发挥镇痛作用^[15]。例如,与无音乐的条件相比,在疼痛刺激过程中听愉悦或偏好音乐的受试者,其报告的主观疼痛强度降低,且伴随大脑边缘系统及下行疼痛调节系统(如导水管周围灰质和延髓头端腹内侧区)的活动变化^[16,17]。慢性疼痛患者在观看能诱发其愉悦情绪的亲人照片时,其主观疼痛强度也有所降低^[18]。此外,大量临床与实验研究表明,即使是简单的心理干预手段(如分心任务),也能显著调节个体对疼痛的主观体验^[14,19,20]。与执行低负荷任务相比,在接受疼痛刺激同时执行高负荷工作记忆任务的受试者报告其疼痛强度和不适感降低^[21]。另外,非沉浸式虚拟现实分心游戏也能显著缓解慢性腰痛患者在游戏期间及之后的疼痛强度,并减少其对疼痛持续关注的时间^[22]。

在这些多感官、非药物的干预途径中,鉴于嗅觉系统与情绪处理、痛觉系统在遗传机制及神经加工上的密切关联,由气味介导的疼痛感知调控及其临床转化应用受到越来越多的探索^[11,23,24]。分子生物学研究提示,痛觉与嗅觉在遗传机制上可能共享某些调控通路。研究发现,有26个基因在人类嗅球中表达的同时也与疼痛调控相关^[24,25]。SCN9A基因(sodium voltage-gated channel alpha subunit 9, SCN9A)编码的电压门控型钠通道Nav1.7,在痛觉受体和嗅觉神经元中均有表达^[25,26]。该通道功能的异常既可能导致先天性痛觉缺失伴随嗅觉障碍,也可引起个体对痛觉与嗅觉的敏感性同步增强^[27~30]。除了遗传机制外,嗅觉与痛觉在神经加工层面也存在显著的功能重叠。研究表明,处理这两种感官信息共同涉及包括杏仁核、脑岛(前、中、后部)、眶额皮层、顶叶以及丘脑区域^[24](图1)。其中,杏仁核、脑岛和眶额皮层主要负责情绪和高级认知加工^[31,32]。与其他感官不同的是,嗅觉系统与人类边缘系统有直接连接投射,且嗅觉信息通常能被快速且毫不费力地知觉为正性或负性刺激,诱发强烈的情绪响应。气味因此常被认为是实验室情绪诱发的最佳材料^[33~35]。基于此,现有研究已将气味刺激的这一特性作为切入点开始探索不同效价(愉悦、不愉悦)的气味

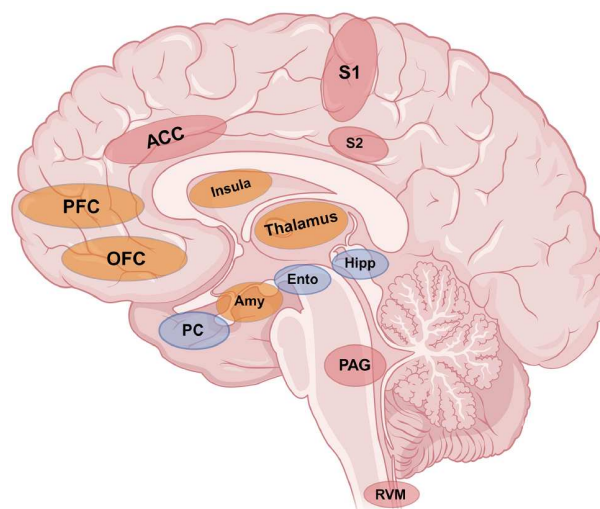


图1 (网络版彩色)嗅觉与痛觉加工脑区。红色区域表示疼痛加工特异性脑区,蓝色区域表示嗅觉加工特异性脑区,橙色区域表示痛觉与嗅觉加工共同涉及的脑区。ACC,前扣带皮层;Amy,杏仁核;Ento,内嗅皮层;Hipp,海马;OFC,眶额皮层;PAG,中脑导水管周围灰质;PC,梨状皮层;PFC,前额叶皮层;RVM,延髓头端腹内侧区;S1,初级躯体感觉皮层;S2,次级躯体感觉皮层(使用BioRender.com制图)

Figure 1 (Color online) Brain regions involved in olfactory and pain processing. Red areas indicate brain regions specifically involved in pain processing. Blue areas indicate regions specifically involved in olfactory processing. Orange areas indicate regions commonly involved in both pain and olfactory processing. ACC, anterior cingulate cortex; Amy, amygdala; Ento, entorhinal cortex; Hipp, hippocampus; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PC, piriform cortex; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex; S2, secondary somatosensory cortex (created with BioRender.com)

对于个体疼痛感知的调控,并将其应用于临床镇痛情境^[11,15,36~43]。除了诱发个体的情绪反应以外,气味作为一种显著性刺激,也能分散个体的注意力^[41]。有研究表明,气味诱发的情绪效应和注意效应能分别调控个体的疼痛不愉悦度和疼痛强度感知,对应疼痛的情感-动机维度和感知-辨别维度^[15,41]。

现有研究显示,不同效价的气味对个体疼痛感知的调控效果存在较大不一致性,其影响程度及主要作用维度尚未明确,相关神经机制亦有待揭示。探究气味调控疼痛的内在机制,不仅能深化我们对疼痛处理中多感官交互的理论认知,更有望为开发非药物镇痛策略提供新思路,从而为对药物敏感或存在用药禁忌的疼痛患者提供治疗替代方案。为此,本文旨在系统梳理最新研究进展:首先以疼痛体验的两维度为框架重新整合分散证据并评估气味在临床与非临床情境下调控个体疼痛感知的效果;进而结合脑成像研究,阐释其背

后的神经机制,并提出可供检验的通路模型。

1 气味调控疼痛的行为学证据

1.1 疼痛研究常用行为学指标

当前实验室诱发疼痛的范式主要包括冷热温度痛觉、电刺激痛觉、机械痛觉(压力、针刺)、化学刺激诱发痛觉(辣椒素诱发皮肤灼烧疼痛、嗅觉刺激诱发三叉神经疼痛等)、生理性痛觉(例如缺血性疼痛)^[11,44]。常用的行为学指标包括:疼痛阈限(pain threshold)、疼痛耐受(pain tolerance)、疼痛强度(pain intensity)、疼痛不愉悦度(pain unpleasantness)。其中,疼痛阈限是指个体由“非痛”过渡为“疼痛”时所对应的最低刺激强度,多采用心理物理学方法测得,例如在热痛、压痛、电刺激等范式中使用极限法(method of limits)、阶梯法(staircase)等测定阈限,并以对应的温度、压力或电流强度等作为阈限值^[45]。疼痛耐受指个体在安全范围内愿意忍受疼痛的最大刺激水平或最长持续时间,多在冷压痛(cold pressor pain)、热痛或机械压力疼痛任务中记录个体自行终止刺激的潜伏期(坚持时间)或其可接受的最大刺激强度^[45]。与之不同,疼痛强度与疼痛不愉悦度主要基于个体主观报告获得,通常在0~10或0~100的数字评分量表(numerical rating scale, NRS)或视觉模拟量表(visual analogue scale, VAS)上获得相应评分:前者反映疼痛感觉“有多强/多痛”,后者反映疼痛带来的情绪性不适与厌恶体验。在疼痛维度划分的框架下,研究中通常将疼痛阈限与疼痛强度视为疼痛感知-辨别维度的主要行为指标;将疼痛耐受与疼痛不愉悦度视为疼痛的情感-动机维度的主要行为指标^[11]。

1.2 气味对痛觉感知-辨别维度的调控

1.2.1 气味对疼痛强度的调控

关于气味刺激对疼痛强度的调控,当前行为学研究结果较不一致。在基于冷热温度痛觉的研究中,有学者发现相比中性和愉悦气味(橙子)条件,不愉悦气味(“呕吐物”气味,丁酸)会显著增加个体所感知的疼痛强度^[36]。类似地,在一项探讨不同效价的气味对疼痛回缩反射调控的研究中发现,个体疼痛强度感知以及回缩反射信号的振幅在愉悦的香草气味刺激中显著降低,在不愉悦的戊酸气味刺激中显著升高^[37],与Masaoka等人^[46]和Riello等人^[47]的研究结果一致。Marchand等人^[48]则在46~48℃水浴诱发的热痛刺激下发现,愉悦气

味能诱发男性和女性相同程度的积极情绪,但只降低了女性的疼痛强度感知。而一项整合了热痛、机械痛及缺血性疼痛的研究发现,芳香精油的气味(薰衣草、迷迭香)只能显著降低男性受试者对总体疼痛强度的主观评分^[49]。在临床疼痛情境下,较多证据表明愉悦气味(尤其是薰衣草)能够有效降低痿管穿刺术后疼痛、分娩疼痛、神经痛及牙齿疾病疼痛等多种病理性疼痛的强度感知^[42,50~52]。此外,针对新生儿的研究表明,母乳气味尤其是亲生母亲的母乳气味可显著降低新生儿检查(如足跟采血)过程中反映疼痛的各项行为及生理指标^[53~58]。另有研究则发现薰衣草气味同样能有效降低新生儿在足跟采血时的疼痛感知^[59]。

此外,有另一部分研究表明,气味对个体疼痛强度的调控可能并无显著效果,或得到相反结论。Kiecolt-Glaser等人^[39]发现,在薰衣草气味和柠檬气味条件下,个体对冷压痛强度的感知与无气味条件相比并无显著差异。类似地,Prescott与Wilkie的研究发现,受试者无论暴露于食物相关的愉悦气味(焦糖味)、非食物相关的愉悦气味(须后水味)、不愉悦气味还是无气味条件下,其对冷压痛强度的感知亦未有显著差别^[60]。同样的,在探讨不同效价的气味对辣椒素诱发的皮肤灼烧疼痛和尼古丁诱发的鼻内灼烧疼痛感知强度的研究中,没有显示气味的调控作用^[38,61]。另外,Martin等人^[62]要求受试者接受持续15 min的冷压痛(3~4℃)刺激,发现无论接受愉悦(柠檬)还是不愉悦(机油)气味干预,受试者的疼痛强度无差别且显著高于无气味条件。值得一提的是,该研究采用的是被试间设计,且并未报告各条件组间被试的嗅觉功能与疼痛感知特征是否进行了合理匹配,这可能削弱了研究结论的可靠性。此外,临床研究发现,愉悦气味对于慢性口腔灼烧疼痛患者的疼痛强度感知并未表现出显著缓解作用^[40]。

Villemure等人^[15,41]则在分离了气味刺激带来的情绪和注意效应后发现,气味的效价并未影响热痛强度感知,而受试者对气味的注意可以降低疼痛强度感知。据我们所知,这是目前该领域唯一一项区分气味的注意效应与情绪效应的研究。研究结果提示,气味诱发的情绪唤起可能并不直接作用于个体的疼痛强度感知,这也进一步解释了当前气味对疼痛强度调控行为学研究结果的异质性。类似地,在使用其他非气味干预手段,例如视频、催眠等方法诱发积极或消极情绪的实验中,个体的疼痛强度感知并没有随着积极或消极情绪的唤起而改变^[63~65]。然而,有多数研究表明,当个体能将注

意力从疼痛上转移开时,其感受到的疼痛强度会降低,且该注意力调控机制甚至能发生于脊髓背角层面^[20,66]。由此可见,与情绪调节相比,分散注意力对个体疼痛强度的调控可能更为显著。这种模式也可能适用于气味刺激对疼痛的调控作用。值得一提的是,气味刺激常伴随快速且强烈的情绪唤起,分离气味带来的情绪和注意效应可能比较困难。未来仍需更多巧妙的研究设计将二者分离,并分别探讨其在调节疼痛感知中的作用^[20,67]。

1.2.2 气味对疼痛阈限的调控

目前,探讨气味刺激对疼痛阈限影响的研究相对较少,已有的实验室研究多表明,气味对个体的疼痛阈限无明显影响。类似的研究结果出现于涵盖了热痛、压力痛、缺血性疼痛和电刺激痛等多种疼痛类型的实验中^[47,49]。然而,也有一项研究发现绿叶气味会使个体机械痛觉的阈限升高,但该实验缺少对样本数量和实验程序的描述,因此其研究结果的可靠性尚难以得到有效验证^[11,68]。此外,也有少量研究进一步考察了通过嗅觉训练(olfactory training, OT)改善疼痛症状的可能性。嗅觉训练通常指在数月内,个体以相对固定的频次重复、结构化地嗅闻一组气味,以促进嗅觉感受神经元的生长或增强其活性表达^[69,70]。经典的OT方案通常持续约4~6个月,每日2次,每次依次嗅闻4种代表性气味(花香、果香、辛香和树脂中各一种气味)^[69]。既往元分析研究表明,OT能显著改善健康和临床个体的嗅觉阈限、识别与辨别等多维嗅觉功能^[69,71]。在疼痛领域,部分研究表明OT不仅能提高个体的嗅觉阈限,还能有效提高青少年原发性头痛患者和慢性腰痛患者的电刺激疼痛阈限^[23,72]。鉴于嗅觉加工与情绪加工的密切关联,OT可能通过促进情绪调节与相关认知过程的改善,进而降低疼痛敏感性并缓解疼痛体验;这一推测与既往在健康人群及抑郁患者中研究观察到OT可改善情绪相关功能的发现相一致^[71,73,74]。这些初步结果揭示了长期嗅觉干预在临床上改善疼痛症状的潜在有效性与应用前景,未来有必要开展更多高质量的研究以进一步验证这一治疗方式的效果和机制。

1.3 气味对痛觉情感-动机维度的调控

1.3.1 气味对疼痛不愉悦度的调控

目前,气味调控个体疼痛不愉悦度感知的研究结果较为一致。多数研究表明,愉悦气味通常能够降低个体的疼痛不愉悦感知,而不愉悦气味则会增强疼痛的

不愉悦体验。在诱发热痛的实验中,无论是接触性热痛刺激还是46~48℃水浴热痛刺激,相较于中性气味或不愉悦气味,愉悦气味显著降低了受试者对疼痛不愉悦度的评分^[15,36,41,48]。类似的调控效应亦见于电刺激和化学刺激疼痛(如辣椒素诱发疼痛)研究中^[38,46,47]。此外,一项整合热痛、机械压力痛及缺血性疼痛的研究发现,愉悦的芳香精油气味(薰衣草)能够显著降低个体对多种疼痛刺激的总体不愉悦度评分^[49]。在临床疼痛患者群体,如神经性疼痛和口腔灼烧疼痛患者中,愉悦气味同样表现出降低疼痛不愉悦度的效应^[40,42]。Villemure等人^[15,41]则在排除气味刺激引发的注意效应后发现,气味的效价(愉悦、不愉悦)能单独调控个体疼痛不愉悦度感知而非疼痛强度感知。这提示,不同效价气味刺激诱发的情绪改变,可能可以单独调控痛觉的情感-动机维度,尤其是疼痛不愉悦体验。此外,Masaoka等人^[46]探讨了安慰剂效应与气味刺激对疼痛感知的协同作用,结果显示,当受试者被告知愉悦气味具有镇痛效果时,其疼痛不愉悦度感知进一步降低。

1.3.2 气味对疼痛耐受的调控

与气味调控疼痛阈限的研究类似,关于气味刺激调控疼痛耐受度的研究数量相对较少。已有研究表明,不同效价的气味对热刺激、电刺激及机械压力刺激引发的疼痛耐受度无显著影响^[47,49]。然而,Prescott与Wilkie^[60]的研究发现,虽然气味对个体冷压痛疼痛强度评分无显著调控作用,但相较于不可食用的愉悦气味(须后水气味)和不愉悦气味(海狸气味),可食用的甜味气味(焦糖气味)显著提高了个体对冷压痛的耐受能力,使个体手部放置于冷水浴的时长增加。该现象可能与可食性气味诱发的味觉甜味感受相关的镇痛机制有关^[75]。然而,目前相关研究较为有限,未来需进一步系统探讨不同类别气味对疼痛耐受的影响机制及其潜在作用路径。

1.4 气味调控疼痛感知的行为学研究小结

综合现有研究,从行为学角度来看,气味刺激对疼痛感知的调控表现出维度特异性:对于疼痛的情感-动机维度,现有研究结果较为一致地表明愉悦气味可显著降低个体疼痛感知的不愉悦度,而不愉悦气味会增加个体的疼痛情绪体验,这一调控效应也存在于多种疼痛类型与情境中;而气味对个体疼痛感知-辨别维度(如疼痛强度)的调控尚未形成较一致的结论。现有行为学研究结果的不一致性可能源于以下几方面。首先,大

多实验中仅使用单一愉悦性或厌恶性气味,容易引发嗅觉适应,从而削弱其对疼痛的调节效应^[76]。其次,多数研究未对气味的唤醒度进行测量或控制,而个体的唤醒水平可能影响疼痛感知。研究发现,诱发交感神经的兴奋可加剧复杂性区域疼痛综合征患者的疼痛评分^[77]。由蓝斑介导的心理性唤醒水平的改变可能产生镇痛或痛觉增敏效应,而痛觉增敏在慢性疼痛患者中尤为显著^[78]。此外,由气味刺激引发的情绪效应与注意效应在疼痛感知调节中所起的作用尚待进一步区分。目前仅有一项研究将气味刺激对疼痛感知调控的情绪和注意效应分离^[15]。结果显示,气味带来的情绪变化可能主要作用于调节疼痛的情感-动机维度,改变个体的疼痛不愉悦感知,相反,气味引发的注意力分散可能主要参与调节疼痛的感知-辨别维度,改变个体的疼痛强度感知。然而,针对疼痛阈限和耐受度的调控,仅有少量证据支持气味在特定条件下可以改变个体的疼痛阈限或耐受性。

值得注意的是,气味与安慰剂效应、年龄、性别差异等因素结合也可能共同影响气味对疼痛感知的调控效果。研究表明,除气味本身的化学特性与情绪效价外,个体对“某种气味具有镇痛、放松或治疗作用”的信念与预期也可以通过自上而下的调控影响疼痛体验^[46]。该过程可能与嗅觉诱发的情绪改变相互作用:积极预期有望放大愉悦气味带来的情绪改善并增强镇痛,而消极预期则可能抵消甚至改变气味调控方向^[79]。此外,多项研究显示,女性的嗅觉功能(包括嗅觉阈限、识别及辨别力)通常显著优于男性^[80,81]。同时,女性对气味愉悦度的感知也更为极端,即对愉悦气味评价较男性更积极,对不愉悦气味评价更消极。这一性别差异趋势与听觉、视觉刺激下的情绪反应表现相一致^[82,83]。上述嗅觉功能与对气味的情绪反应差异,可能使气味对疼痛的调控作用存在一定的性别特异性。同时,不同年龄群体可能存在气味调控疼痛感知效果的差异。研究表明,嗅球中的纤维数量以及嗅觉受体随着年龄的增长而显著减少;老年人群体的嗅觉功能普遍降低明显,且在嗅闻气味时梨状皮层、杏仁核以及眶额皮层的激活减少^[84]。此外,与年轻人相比,老年人对一系列相同强度的愉悦气味的积极感受较低^[85]。因此,老年人嗅觉功能的下降与气味愉悦体验的下降均可能削弱气味对其疼痛的调节效力。目前,不同效价的气味是否能调节老年人的疼痛感知仍待考究。未来研究可考虑纳入多个年龄段样本,增加标准化的嗅觉功能评估(如

Sniffin' Sticks嗅觉阈限、识别、辨别力测试),并将年龄与嗅觉功能作为潜在调节变量纳入分析,以提高结论的外推性与临床可转化价值。

综上所述,未来研究可更系统地揭示气味对疼痛感知的行为调控机制,包括探索气味刺激的情绪与注意效应分离、性别差异及其他个体差异机制,并扩展至多种实验性与临床疼痛情境中,从而更深入理解气味刺激调控疼痛感知的内在机制及其临床应用前景。此外,仅基于行为学的研究,我们无法揭示气味刺激如何通过具体的脑神经通路调控疼痛感知,深入探讨其脑神经机制将有助于更全面理解气味调节疼痛感知的神经原理。

2 气味调控疼痛感知的神经机制

2.1 痛觉与嗅觉感知加工的神经机制

大脑中与疼痛处理相关的广泛脑区被称为“疼痛矩阵”(pain matrix)^[86,87],包括但不限于初级和次级躯体感觉皮层(primary and secondary somatosensory cortices, S1/S2)、脑岛(insula)、前扣带皮层(anterior cingulate cortex, ACC)、中央导水管周围灰质(periaqueductal gray, PAG)和丘脑等^[87-91]。需要明确的是,疼痛矩阵中的这些区域不仅仅处理疼痛信息,也处理其他的显著性刺激,即其他引起注意力和情绪反应的非疼痛刺激,例如听觉、视觉刺激等^[11,92]。尽管疼痛矩阵并非特异性处理疼痛信息,但它的提出有利于将机体对于疼痛刺激的躯体感觉和情感体验区分显示出来。研究表明,初级和次级躯体感觉皮层、后脑岛(posterior insula, PI)及部分前脑岛(anterior insula, AI)和主要负责加工疼痛刺激的躯体感觉,例如对疼痛强度、时间的分辨和疼痛空间信息的加工^[86,87,93,94]。而前扣带回尤其是背侧前扣带回(dorsal anterior cingulate cortex, dACC)和脑岛等边缘系统区域主要负责加工疼痛的不愉快体验^[86,95-97]。疼痛的躯体感觉和情感体验涉及疼痛加工的两条上行传导通路,其中一条是外侧通路,经新脊髓丘脑束、新三叉神经丘脑束、颈部束和脊髓后角束将疼痛信息传递至躯体感觉皮层、外侧丘脑、顶叶岛盖和脑岛;另一条是内侧通路,经脊髓丘脑束、脊髓中脑束、脊髓网状束等将疼痛信息传递至前扣带回、脑岛、杏仁核、海马、旁臂核、蓝斑核、内侧丘脑核团等^[12,13]。外侧通路将有关疼痛强度、疼痛时间空间分辨的信息传递至初级和次级躯体感觉皮层;而内侧通

路形成了个体感知疼痛的不愉快体验,诱发个体产生保护性应答^[11~13]。此外,疼痛感知的加工还包括一条重要的下行抑制通路。该下行通路可起始于背外侧前额叶皮层(dorsolateral prefrontal cortex, dlPFC)、膝前部前扣带回(pregenual anterior cingulate cortex, pgACC)、杏仁核等高级大脑皮层区域,并将疼痛相关信号传递至PAG。随后,PAG将这些信号继续下行传递至延髓头端腹内侧区(rostral ventromedial medulla, RVM),最终到达脊髓背角(dorsal horn)^[98~100]。这条下行性疼痛抑制通路反映了大脑调控急性或持续疼痛的能力,并与两条上行传导通路共同构成了人类疼痛感知的整体机制^[7]。

嗅觉感受途径始于嗅觉感受器细胞,由挥发性气味分子激活后经嗅神经传递至嗅球(olfactory bulb, OB)。梨状皮层、前嗅核、嗅结节、杏仁核周围灰质皮层、杏仁核、外侧内嗅皮层、腹侧顶盖区和外侧嗅束直接接受嗅球的投射,这些结构构成初级嗅觉皮层,其中梨状皮层是初级嗅觉皮层中最大的区域且是嗅球投射的最主要区域^[101,102]。同时,经由梨状皮层,来自嗅球的信息还可以间接投射于内嗅皮层、背内侧丘脑核、下丘脑、腹侧苍白球、眶额皮层(orbitofrontal cortex, OFC)、杏仁核和脑岛,这些区域构成次级嗅觉皮层^[103]。气味刺激的知觉常伴随情绪的强烈唤起。一项基于激活似然性估计(activation likelihood estimation, ALE)的脑成像元分析研究显示,愉悦气味在双侧杏仁核以及梨状皮层处诱发强激活^[104~107]。此外,Royet等人^[108]利用正电子发射断层扫描(positron emission tomography, PET)技术发现,情绪性视觉、听觉、嗅觉刺激均能使左半球眶额皮层、颞极和额上回的局部脑血流量(regional cerebral blood flow, rCBF)增加;嗅觉与视觉情绪刺激额外激活下丘脑和胼胝体下回;而仅嗅觉刺激能引发双侧杏仁核的rCBF显著升高。此外,研究表明愉悦气味刺激也在眶额皮层、右侧脑岛、左侧苍白球、左侧壳核和中央岛盖区域诱发了较强的激活^[104]。眶额皮层和脑岛在嗅觉信息加工中负责嗅觉信息整合以及多模态信息整合,同时也涉及对气味情绪效价的高级加工^[107,109~111]。

2.2 气味调控疼痛的情绪与奖赏机制

由于疼痛加工与嗅觉加工均与情绪密切相关,情绪在气味对个体疼痛感知的调控中可能发挥核心作用。Villemure等人^[15]在一项同时呈现热痛与气味刺激的实

验中,分别设置了温度辨别和气味强度辨别任务,调控个体的注意力,以分离气味的情绪效应与注意效应。结果发现,相较于不愉悦气味条件,愉悦气味诱发的情绪状态显著降低了个体疼痛不愉悦度评分,并伴随着ACC、内侧丘脑、初级及次级躯体感觉皮层等疼痛加工相关脑区的激活减少,其中ACC区域激活降低的程度最大。此外,ACC与外侧下额区(lateral inferior frontal cortex, Linff)及PAG之间的任务态功能连接呈正相关关系。其中,ACC与内侧丘脑属于疼痛上行内侧通路的关键脑区,主要负责处理疼痛引起的不愉快感受,而PAG则在下行抑制通路中发挥重要作用。这表明,嗅觉诱发的情绪变化可能主要参与影响疼痛的内侧通路及下行抑制通路,进而影响大脑整体对疼痛刺激的响应。另外,嗅觉信息的加工与杏仁核有直接的联系,嗅球和嗅觉皮层的突触广泛投射于杏仁核多个核团^[112,113],提示气味刺激引起的情绪变化可直接影响杏仁核的激活状态。在Jo等人^[36]的研究中,相比于愉悦气味,不愉悦气味增强了左侧杏仁核与右侧缘上回的功能连接强度;而相比于无气味条件,愉悦气味增强了右侧杏仁核与左侧额上回的功能连接强度,且该功能连接强度与个体疼痛不愉悦度评分成正相关关系。已有文献表明,右侧缘上回和左侧额上回主要与主观疼痛体验相关,而非简单对热痛刺激的物理属性响应^[88,114]。在小鼠模型中,Tashiro等人^[115]、Yoshida等人^[116]和Sakurai等人^[117]发现,下丘脑食欲素神经元接受来自杏仁核各个核团的突触输入并大量投射至PAG,提示杏仁核可能介导了芳樟醇气味激活下丘脑食欲素神经元的镇痛通路。

除杏仁核外,腹侧纹状体(ventral striatum, VST)亦在气味刺激调控疼痛中发挥重要作用。VST包括伏隔核(nucleus accumbens, NAc)、腹侧尾状核和腹侧壳核(ventral putamen)^[118]。与杏仁核偏向于处理负性情绪不同,VST主要参与正性情绪和奖赏加工^[119~122]。研究发现,愉悦气味带来的镇痛效果(疼痛不愉悦度的降低)与双侧VST的激活呈正相关关系^[43]。功能连接的结果显示,VST的激活与PAG呈正相关关系,而与内侧前额叶(medial prefrontal cortex, mPFC)、背内侧丘脑(medial dorsal thalamus, mdTH)、腹外侧前额叶皮层(ventro-lateral prefrontal cortex, VLPFC)、背侧前扣带回(dorsal anterior cingulate cortex, dACC)呈负相关。另外,食欲素神经元也能够通过调节腹侧被盖区(ventral tegmental area, VTA)至伏隔核通路的兴奋性,进一步参与疼痛下

行抑制传导通路^[115]。这提示,正性的嗅觉刺激可能主要激活奖赏刺激加工回路,继而增强疼痛下行抑制通路,降低大脑对疼痛刺激的响应。最新一项针对小鼠大脑中前外侧杏仁核(posterolateral cortical amygdala, plCoA)下游投射靶点的研究发现,plCoA的主要投射靶点——内侧杏仁核(medial amygdala, MeA)和NAc分别与感知厌恶刺激(如不愉悦气味)和奖赏刺激加工有关,揭示plCoA在加工嗅觉刺激效价中的重要作用及其功能分离^[123]。由此可得,愉悦和不愉悦的嗅觉刺激可能通过不同机制对疼痛感知进行调控:不愉悦的嗅觉刺激主要通过杏仁核参与疼痛的内侧通路和下行抑制通路的调节,而愉悦的嗅觉刺激通过杏仁核可额外激活奖赏回路进而参与疼痛刺激加工的调节(图2)。然而,也有部分研究认为通过情绪调节个体的疼痛感知不会涉及疼痛的下行抑制通路,因其调控的时间进程较内源性阿片系统镇痛机制短且消退速度快^[20,124]。未来研究可采用脑脊同步磁共振成像技术,直接验证气味刺激的情绪调节效应是否能到达脊髓层面,从而为其是否参与下行通路机制提供关键实验证据。

综上所述,气味刺激可以通过情绪和奖赏系统相关脑区的调节,参与疼痛感知尤其是疼痛不愉悦度的加工。这一结论与现有的行为学研究结果对应:由于气味刺激主要引起情绪改变,其对疼痛不愉悦度感知的调控表现出较为稳定和一致的结果。然而,目前相关研究数量较少,上述气味调节疼痛感知的情绪与奖赏神经通路尚未在人类研究中完整揭示,其参与下行抑制通路调控的直接证据亦亟待补充。此外,慢性疼痛等临床患者常伴随情绪、记忆及认知功能的改变^[14],其气味调控疼痛的情绪-奖赏神经通路是否区别于健康人群,仍有待进一步考察。

2.3 气味调控疼痛的注意机制

气味刺激作为一种显著性刺激,不仅能够引起情绪变化,还可以影响个体的注意资源分配,进而影响疼痛感知。已有大量研究表明,注意分散可以有效减弱疼痛感知,例如音乐、视觉刺激,以及认知任务等都能通过分散注意力来实现镇痛效果,且当个体将更多的注意力资源集中在其他刺激或任务而非疼痛刺激上时,疼痛的感知强度往往会进一步减弱^[125,126]。Hauck等人^[127]发现,音乐刺激能够显著减弱由激光痛诱发的大脑delta波活动,这一变化定位于中扣带皮层和前脑岛区域。该delta波活动主要反映晚期激光诱发电位成分,

且这些成分的振幅会因注意分散而减小^[128]。此外,Bantick采用Stroop范式干扰任务发现,注意分散可以有效降低个体对疼痛强度的评分,同时减少个体脑岛、丘脑和中扣带回区域的激活^[129]。在使用气味刺激调控疼痛感知的实验中,Villemure等人^[15]通过控制受试者完成温度分辨任务或气味强度分辨任务来操控注意分配。结果表明,在疼痛刺激的呈现下,个体对气味的注意能够使疼痛强度评分显著降低,同时伴随着前脑岛激活的减少。任务态功能连接分析进一步表明,前脑岛与上顶叶(superior parietal, SPP)的激活呈正相关关系。前人研究显示,顶叶是疼痛感知加工外侧通路的相关脑区,在注意定向和注意控制中发挥重要作用^[15,130]。上顶叶的激活能够增强感觉皮层的活动,并通过同步相关神经元的放电强化对被注意目标的神经表征^[131]。在疼痛感知的过程中,个体对疼痛刺激的注意会增加上顶叶以及前脑岛的激活水平,从而导致疼痛强度感知的增强。

这些研究结果提示,脑岛,尤其是前脑岛可能在嗅觉刺激调控疼痛的注意机制中起到了关键作用。前脑岛激活的改变可能可以通过参与调控疼痛的外侧通路,进而影响个体疼痛体验的感知-辨别维度,尤其是疼痛强度感知。此外,研究发现前脑岛不仅可以作为注意、预期或信念等认知过程的中继站,通过改变前额叶、前扣带回、额顶叶等脑区的激活来塑造疼痛感知,还可以将信号传递至PAG进而调节疼痛的下行抑制通路^[132,133]。Ploner等人^[134]研究发现,双侧前脑岛的激活水平可以预测个体将刺激感知为疼痛的程度,并且在刺激呈现前,前岛叶与PAG的功能连接能够显著影响个体是否将刺激感知为疼痛的判断。因此,气味刺激调控疼痛的注意机制也可涉及疼痛的下行抑制通路,并最终改变大脑皮层加工疼痛的激活状态(图2)。

综上所述,气味刺激能够通过分散注意力调控个体的疼痛感知,其机制主要涉及前脑岛的激活变化,进而调节疼痛的外侧通路和下行抑制通路。然而,目前相关研究仍较为稀少,且现有实验未能完全区分情绪效应与注意效应的独立作用。Villemure等人^[41]的实验设计虽然能在一定程度上分离气味的情绪和注意效应,但其使用了阈上的愉悦和不愉悦气味刺激,使得气味不仅携带不同的效价信息,也伴随着较高的唤醒度与显著性,从而难以在严格意义上完全分离气味的情绪与注意对疼痛感知的交织影响。未来研究可进一步结合阈下或接近阈值的嗅觉刺激,在控制气味效价一致

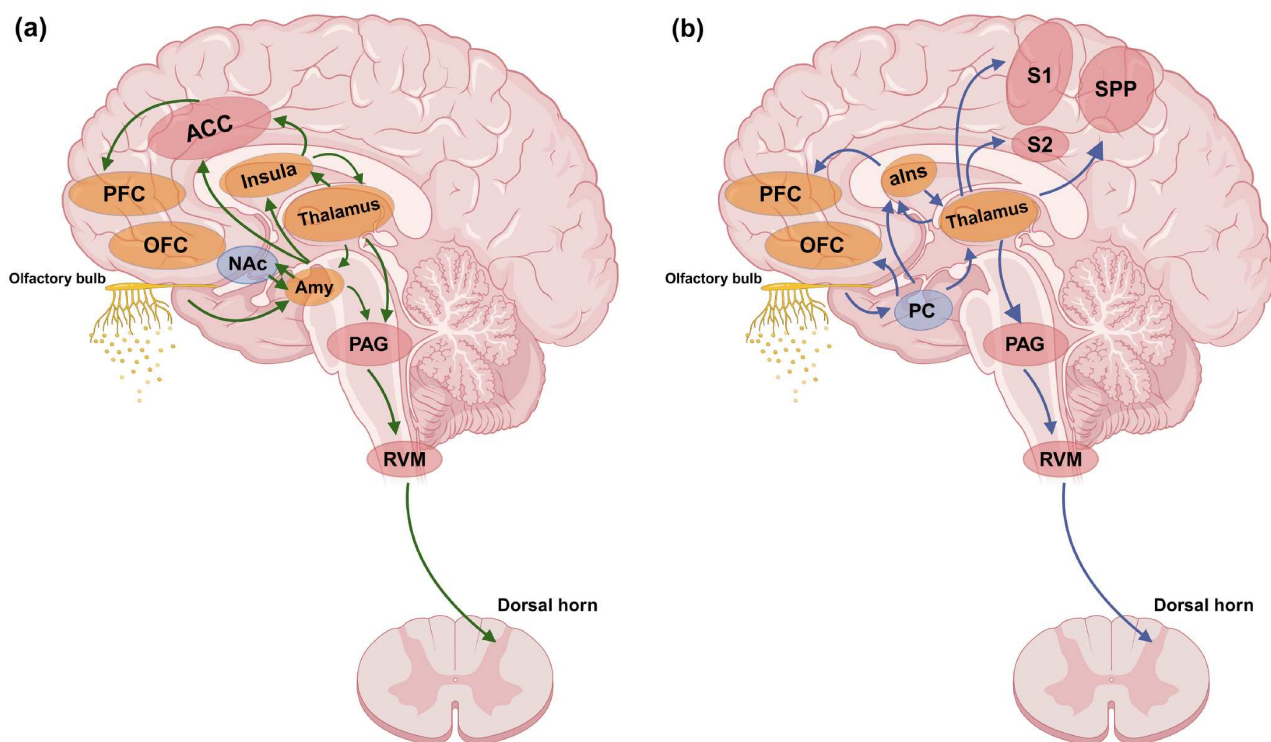


图2 (网络版彩色) 气味调控疼痛的神经机制. (a) 气味调控疼痛的情绪与奖赏机制; (b) 气味调控疼痛的注意机制. 红色区域表示处理疼痛加工特异性脑区, 蓝色区域表示处理嗅觉加工特异性脑区, 橙色区域表示痛觉与嗅觉加工共同涉及的脑区. ACC, 前扣带皮层; aIns, 前脑岛; Amy, 杏仁核; NAc, 伏隔核; OFC, 眶额皮层; PAG, 中脑导水管周围灰质; PC, 梨状皮层; PFC, 前额叶皮层; RVM, 延髓头端腹内侧区; S1, 初级躯体感觉皮层; S2, 次级躯体感觉皮层; SPP, 上顶叶(使用BioRender.com制图)

Figure 2 (Color online) Neural mechanisms of odor modulation on pain. (a) Emotional and reward mechanisms of odor modulation on pain; (b) attentional mechanisms of odor modulation on pain. Red areas indicate brain regions specific to pain processing, blue areas indicate brain regions specific to olfactory processing, and orange areas indicate brain regions commonly involved in both pain and olfactory processing. ACC, anterior cingulate cortex; aIns, anterior insula; Amy, amygdala; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PC, piriform cortex; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SPP, superior parietal lobule (Created with BioRender.com)

(并尽量匹配强度、唤醒度及潜在三叉神经刺激性)的前提下, 系统比较同一效价气味在阈上与阈下浓度时对疼痛强度与疼痛不愉悦度的影响差异以及不同效价气味在阈下浓度时对疼痛的影响. 在这一框架下, 阈上气味更具显著性, 可能更容易通过注意捕获或注意资源再分配影响疼痛加工; 而阈下气味则可在相对弱化显性注意转移的条件下, 更接近检验气味的自动化情绪启动对疼痛的贡献. 研究表明, 阈下的气味刺激仍可诱发个体与情绪相关的行为与生理反应^[135~137]. 例如, 阈下呈现的愉悦、不愉悦、中性气味可在被试缺乏意识觉察的情况下偏置其对中性面孔的喜好评价, 并伴随心率等自主神经指标的相应变化^[136]. Hummel等人^[137]发现, 个体的脑岛和前扣带回区域对混合气味中的阈下目标成分能表现出差异性神经激活. 这提示, 阈下嗅觉信息可在不进入意识报告的情况下参与影响情

绪加工通路并触发情绪性生理反应. 因此, 引入阈下嗅觉刺激并结合更精细的注意操控, 可能可以为分离气味的情绪效应与注意分散效应对疼痛感知的影响提供新的实验思路. 未来研究仍需在更创新且可操作化的范式中, 结合严谨的行为学操控检验与多模态生理、神经指标, 共同揭示气味刺激调控疼痛感知的完整神经生理机制.

3 总结与展望

从行为学研究层面来看, 气味刺激对痛觉在感知-辨别维度(疼痛强度、疼痛阈限)和情感-动机维度(疼痛不愉悦度、疼痛耐受)的调控存在明显的维度特异性. 现有研究表明, 气味对疼痛感知-辨别维度的调控结果较不一致, 气味刺激诱发的情绪改变可能并不直接作用于调节个体的疼痛强度感知, 对气味的注意则

可能会降低个体疼痛强度感受,但目前缺乏充分实验证据证实。相反,当前研究较为一致地反映了气味刺激对疼痛不愉悦感知的调控,具体而言,个体在愉悦的气味条件下倾向于感受到较低的疼痛不愉悦体验,在不愉悦的气味条件下则感受到较高的疼痛不愉悦体验。以上行为学结果的出现可能是由于气味刺激能够直接且强烈地诱发个体情绪反应,嗅觉与痛觉重叠的脑区也主要涉及情绪加工的脑区(例如,杏仁核、脑岛、眶额皮层),因此气味刺激对疼痛的调控可能主要还是经由情绪效应调节,并且在脑机制层面反映为对疼痛感知内侧通路的激活影响。当前仅有Villemure等人^[15,41]的研究结果表明了气味刺激带来的注意分散和情绪唤起会特异性分别调控疼痛的强度和不愉悦度感知,并且在脑神经机制上反映为对不同脑区激活的影响。未来仍需能有效分离气味刺激的注意和情绪效应的研究,进一步证实气味刺激对疼痛感知两个维度调控的异质性。

神经机制层面,本文结合现有脑神经机制研究提出并探讨了气味刺激对疼痛感知调控可能的两条神经机制通路,进一步解释了行为学的研究结果。其中一条通路是情绪与奖赏神经机制通路,气味刺激通过杏仁核和腹侧纹状体主导的情绪及奖赏加工脑区参与改变疼痛上行内侧通路和下行抑制通路激活,从而调控疼痛感知的不愉悦体验;另一条是注意神经机制通路,气味刺激作用于前脑岛,协同额顶注意网络参与改变疼痛上行外侧通路和下行抑制通路的激活,从而调控主观疼痛强度感知。值得注意的是,有部分研究认为通过情绪调节个体的疼痛感知不会涉及疼痛的下行抑制通路,未来研究可以结合脑脊同步磁共振成像技术,直接验证气味刺激的情绪调节效应是否能到达脊髓层面,从而为其是否参与下行通路机制提供关键实验证据。

基于上述现状,未来研究可在多方面进行深化和拓展。在行为学层面,未来研究可以通过更精细的实验设计,系统分离嗅觉引发的情绪效应与注意效应,探讨其各自及交互作用对疼痛不同维度的调控机制。同时,未来研究还可以探讨性别及年龄差异对调控效应的影响,探索不同群体的差异性反应;还可以扩展至多种实验性疼痛模式及临床疼痛情境,以验证嗅觉刺激调控作用的广泛适用性和实际意义。另外,大量研究已揭示音乐、视觉情境线索以及虚拟现实(virtual reality, VR)技术等干预手段对疼痛感知的调节效果^[16,17,22]。在此基础上,将气味与上述视听或沉浸式技术进行多模态整

合可能会产生加和或协同效应,进一步调控个体的疼痛体验。例如,愉悦气味更可能优先影响疼痛的情感-动机维度,降低疼痛不愉悦度,而音乐与VR在分散注意、沉浸体验与情绪改善方面具有明确优势^[17,138];若二者在时间上同步、在语义或情境上保持一致(如海风气味与海边场景及舒缓音乐结合),可能增强多感官一致性与奖赏价值,进一步放大镇痛效应。未来研究可以进一步探讨气味与其他感官协同对个体疼痛感知的调节效果,丰富多模态整合调控疼痛感知的理论知识与应用。在神经机制研究层面,未来研究有望借助创新的脑影像技术(例如脑脊同步功能磁共振成像技术)和电生理手段,揭示气味刺激调控疼痛更全面的神经通路及脑网络机制。最后,从临床应用角度看,气味刺激作为一种非侵入性、易于实施的辅助镇痛手段,具有较好的可及性与转化潜力。愉悦气味在多种临床或病理情境下可一定程度缓解个体的疼痛感知,从而为其作为辅助性疼痛管理策略提供初步依据。值得注意的是,实验室研究与临床研究在气味呈现方式、实验控制程度及适用人群方面存在显著差异,因此实验室结论向临床推广时应保持审慎。具体而言,实验室情境下的研究多借助嗅觉仪对气味的浓度、流量、持续时间与呈现节律进行精确控制,并可与疼痛刺激严格时间同步,因而更有利于控制混杂因素;但此类研究通常纳入嗅觉功能相对稳定的健康受试者,其情绪状态、用药情况与疼痛病程的复杂性明显低于真实临床人群,生态效度与外部可推广性相对有限。相较之下,临床研究更常采用扩香仪、棉片吸入或病房环境暴露等方式营造持续气味体验,具有实施便捷、与护理流程兼容性强、生态效度较高等优势,更适合评估围手术期或操作性疼痛情境下的可行性与实际获益(如疼痛评分下降、镇痛药追加量减少、焦虑改善与满意度提升等)。然而,临床情境下气味暴露的实际吸入剂量难以精确量化,且通风条件、空间分布与共处环境等因素容易造成个体间暴露差异,进而增加疗效异质性并提升结果解释的复杂度^[50-52,78]。另外,尽管气味干预总体安全性较高,临床实施仍需重视潜在禁忌证与风险控制:例如既往对香料或精油过敏者、哮喘或气道高反应及慢性呼吸系统疾病患者、对气味高度敏感且易诱发头痛或恶心呕吐(如部分偏头痛或妊娠反应)的人群,均应谨慎使用或先行小剂量试闻,同时应关注病房通风与扩散范围,尽量避免对同室患者及医护人员造成不适。未来研究可在真实临床场景中引入更标准化、可量化

的气味递送与操纵检验,并结合患者嗅觉敏感性与情绪偏好探索个体化干预方案,同时与现有多模式镇痛策略协同评估,以优化疼痛管理效果并进一步提升患者生活质量.

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Summary for “气味调控疼痛感知的行为及神经机制”

Behavioral and neural mechanisms underlying odor modulation of pain perception

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Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Compared to traditional pharmacological treatments (such as non-steroidal anti-inflammatory drugs and opioid analgesics), non-pharmacological interventions (such as cognitive behavioral therapy, mindfulness meditation, and music therapy) for analgesia generally demonstrate higher safety, lower risks of addiction and side effects, and greater cost-effectiveness. Among these multisensory, non-drug approaches, odor-mediated modulation of pain perception and its clinical translation have attracted growing interest, owing to the close genetic and neural processing links between the olfactory system and the emotional and nociceptive systems. This review systematically synthesizes behavioral and neurobiological evidence on odor-induced modulation of pain and, on this basis, proposes testable models of potential neural pathways, with the aims of informing mechanistic research and providing insights into the clinical translation of odor-based interventions as adjunct strategies for pain management. From the perspective of behavioral research, odor stimulation exhibits distinct dimension-specificity in modulating pain across the sensory-discriminative dimension (pain intensity, pain threshold) and the affective-motivational dimension (pain unpleasantness, pain tolerance). Existing studies suggest that the modulation of odor on the sensory-discriminative dimension of pain shows relatively inconsistent outcomes. Odor-induced emotional changes may not directly regulate an individual's perception of pain intensity, while attention to odor may reduce perceived pain intensity, though conclusive experimental evidence for this is still lacking. In contrast, current research more consistently demonstrates that odor stimulation modulates the perception of pain unpleasantness. Specifically, individuals tend to report lower pain unpleasantness under pleasant odor conditions, and higher pain unpleasantness under unpleasant odor conditions. Further evidence from neural mechanisms suggests that olfactory stimuli may participate in modulating the ascending transmission and descending inhibitory pathways of pain through two potential neural pathways. One is the emotional and reward neural pathway, where odor stimulation engages emotion-and reward-processing brain regions, such as the amygdala and ventral striatum, to alter the activation of both the ascending medial pain pathway and the descending inhibitory pathway, thereby modulating the unpleasantness of pain. The other is the attentional neural pathway, where odor stimulation acts on the anterior insula and collaborates with the frontoparietal attention network to modify the activation of the ascending lateral pain pathway and the descending inhibitory pathway, thereby regulating the subjective perception of pain intensity. Building on the current evidence, future studies should more precisely dissociate odor-evoked emotional and attentional effects through refined paradigms and more stringent manipulation checks to further validate the dimension-specific nature of odor-induced pain modulation. Moreover, emerging techniques such as cortico-spinal synchronized functional magnetic resonance imaging may enable direct assessment of odor-related modulation at the spinal level, thereby delineating a more comprehensive central pathway underlying odor-induced pain regulation.

pain, olfaction, odor, behavioral mechanisms, neural mechanisms

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