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变应性鼻炎与情绪障碍共病的神经-免疫机制及中医药干预研究进展

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【摘 要】变应性鼻炎(allergic rhinitis,AR)是一种全球高发的慢性鼻黏膜炎症性疾病,近年来临床与基础研究均提示其与焦虑、抑郁等情绪障碍存在显著共病关系,严重影响患者生活质量与社会功能。目前,二者共病的病理机制尚未完全阐明,尤其缺乏基于"神经-内分泌-免疫(neuro-endocrine-immune,NEI)网络"的系统性整合分析,临床缺少针对共病的有效干预策略。本文系统综述了AR与情绪障碍共病的多层次发病机制,内容涵盖:①免疫失衡机制,包括辅助性T细胞2(T helper 2 cell,Th2)免疫偏移、上皮屏障损伤与警报素[胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin,TSLP)、白细胞介素(interleukin,IL)-25、IL-33等]释放;②神经内分泌机制,涉及下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA轴)功能紊乱及神经肽[如P物质(substance P,SP)、降钙素基因相关肽(calcitonin gene-related peptide,CGRP)、血管活性肠肽(vasoactive intestinal peptide,VIP)]分泌异常;③"鼻-脑轴"双向通讯机制,阐释外周炎症通过嗅觉通路影响中枢神经系统,诱发神经炎症与情绪障碍,并形成"外周-中枢-外周"的恶性循环。在治疗方面,重点探讨了中医药干预该共病的多途径潜力:除内服中药及针刺疗法可通过调节免疫、神经内分泌及相关信号通路发挥作用外,芳香疗法也显示出独特优势。然而,现有研究仍较为分散,尤其缺乏针对共病的高质量临床证据与机制整合研究。本文旨在为深入理解AR与情绪障碍共病的NEI网络机制、推动中医药多靶点整合治疗策略的研发提供理论参考与研究思路。

【关键词】变应性鼻炎;情绪障碍;共病机制;神经-内分泌-免疫网络;鼻-脑轴;中医药治疗
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Research advances in the neuro-immune mechanisms of comorbidity of allergic rhinitis and mood disorders and related traditional Chinese medicine interventions

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【**Abstract**】Allergic rhinitis (AR) is a globally prevalent chronic inflammatory disorder of the nasal mucosa. Recent clinical and basic studies have shown that it is significantly comorbid with mood disorders such as anxiety and depression, severely affecting the quality of life and social functioning of patients. The pathological mechanisms underlying this comorbidity remain unclear at present, with a lack of systematic integration analysis based on the neuro-endocrine-immune (NEI) network, and there is also a lack of effective intervention strategies for this comorbidity in clinical practice. This article systematically reviews the multi-level pathogenesis of AR comorbid with mood disorders from the following aspects: (1) immunological imbalance mechanisms, including Th2-skewed immunity, epithelial barrier disruption, and the release of alarmins (such as thymic stromal lymphopoietin, interleukin-25, and interleukin-33); (2) neuroendocrine mechanisms, involving the dysfunction of the hypothalamic-pituitary-adrenal axis and abnormal secretion of neuropeptides (e.g., substance P, calcitonin gene-related peptide, and

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vasoactive intestinal peptide); (3) bidirectional communication mechanisms via the "nose-brain axis", clarifying how peripheral inflammation influences the central nervous system through olfactory pathways, induces neuroinflammation and mood disorders, and forms a vicious "peripheral-central-peripheral" cycle. As for treatment, this article explores the multi-pathway potential of traditional Chinese medicine in managing this comorbidity: oral administration of herbal formulations and acupuncture therapy can exert a therapeutic effect by regulating immunity, neuroendocrine, and related signaling pathways, and aromatherapy has also demonstrated unique advantages. However, existing research remains fragmented, especially with a lack of high-quality clinical evidence and integrated mechanistic studies targeting this comorbidity. This article aims to provide a theoretical reference and research ideas for deepening the understanding of the NEI network mechanisms underlying the comorbidity of AR and mood disorder and promoting the development of multi-target integrated traditional Chinese medicine treatment strategies.

【Key words】 allergic rhinitis; mood disorders; comorbidity mechanisms; neuro-endocrine-immune network; nose-brain axis; traditional Chinese medicine treatment

变应性鼻炎(allergic rhinitis, AR)是特应性个体接触致敏原后,由免疫球蛋白E(immunoglobulin E, IgE)介导、多种细胞因子参与的鼻黏膜Ⅰ型变态反应,主要临床表现为打喷嚏、流涕、鼻塞等[1-2]。AR影响全球5%~15%的儿童与10%~40%的成年人,其患病率持续上升[3]。除典型鼻部症状外,AR亦是焦虑、抑郁等情绪障碍的重要风险因素,不仅显著降低患者的生活质量,也带来了沉重的家庭与社会负担[4]。值得注意的是,情绪障碍也可反向通过神经生理机制加剧AR症状,形成恶性循环[5-6]。因此,深入探究AR与情绪障碍的共病机制至关重要。然而,现有研究多局限于流行病学关联分析或单一机制探讨,缺乏基于"神经-内分泌-免疫(neuro-endocrine-immune, NEI)网络"的系统阐释,未充分总结中医药干预该共病的价值与研究现状。本文旨在基于病理生理学框架,系统探讨AR与情绪障碍共病的可能机制及中医药治疗现状。

1 AR发病机制研究

AR的发病核心是由IgE介导的鼻黏膜Ⅰ型变态反应。这一过程始于变应原首次进入鼻腔:树突状细胞捕获并提呈抗原,驱动初始T细胞(naive T cell)或Th0细胞向辅助性T细胞2(T helper 2 cell, Th2)方向极化。活化的Th2细胞分泌关键细胞因子白细胞介素(interleukin, IL)-4,进而诱导B细胞产生变应原特异性IgE。IgE通过与肥大细胞(mast cells, MCs)和嗜碱性粒细胞表面的高亲和力免疫球蛋白E受体(high-affinity IgE receptor, FcεRI)结合,使机体处于致敏状态[7]。当变应原再次进入时,会与细胞表面结合的IgE发生交联,触发MCs等效应细胞脱颗粒,释放组胺、白三烯、前列腺素等炎症介质,引发打喷嚏、流涕、鼻痒等典型AR症状[8-10]。

鼻黏膜上皮屏障是抵御外界刺激的第一道物理和免疫防线,其完整性对维持局部免疫稳态至关重要[11]。当屏障完整性受损时,上皮细胞释放"警报素",包括胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin, TSLP)、IL-25和IL-33,这些细胞因子在启动和放大2型免疫反应中发挥关键作用,诱导气道病理改变,是AR免疫致病机制中的重要调节因子[12]。其中,TSLP是一种IL-7样细胞因子,可诱导Th2反应失调,是AR的标志性特征[13]。IL-25通过与异二聚体受体结合并激活核因子κB(nuclear factor kappa B, NF-κB)信号通路,促进Th2细胞因子表达[12]。IL-33是IL-1细胞因子家族的新成员,可调控Th2反应并刺激MCs释放促炎介质[14]。此外,NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)兼具核转录功能与细胞质炎性小体功能,通过调控IL-33等警报素的表达,与上皮源性细胞因子协同激活2型先天淋巴细胞(group 2 innate lymphoid cell, ILC2),经NF-κB、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等信号通路促进Th2型细胞因子分泌,直接参与炎症调控,构成AR的关键病理机制[15]。研究发现,泛素特异性蛋白酶25可能通过调控肿瘤坏死因子受体相关因子3(TNF receptor-associated factor 3, TRAF3)的稳定性抑制鼻上皮细胞中TSLP信号传导,减轻AR炎症[16]。而长链非编码RNA FOXD3-AS1可通过调节鼻上皮细胞中IL-25的表达,抑制AR患者Th2型免疫反应[17]。

Toll样受体(Toll-like receptors, TLRs)作为重要的模式识别受体,在鼻黏膜的天然免疫防御中起哨兵作用[18]。TLRs广泛表达于鼻黏膜的树突状细胞、巨噬细胞和MCs等免疫细胞表面[19]。目前TLRs家族中TLR2和TLR4是变应性疾病研究较多的成员。外界病原体或组织损伤刺激TLR后,可通过衔接蛋白髓样分化因子88(myeloid differentiation primary response 88, MyD88)激活下游信号,经系列激酶触发核因子κB抑制蛋白激酶β亚单位(inhibitor of nuclear factor kappa-B kinase subunit β, IKK-β)介导的核因子κB抑制蛋白(inhibitor of NF-κB, IκB)磷酸化,释放转录因子NF-κB(p65/p50二聚体)入核[20]。活化的NF-κB可诱导IL-4、IL-5、IL-13、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、IL-6等多种炎症因子基因转录,打破Th1/Th2平衡,促进MCs脱颗粒,从而驱动AR炎症反应[21]。AR的发病机制远不仅涉及系统性免疫失衡,更包含复杂的"神经-免疫"交互作用。研究还发现,变应原刺激破坏鼻黏膜屏障所释放的P物质(substance P, SP),除了直接作用于MCs上的神经激肽-1

受体(neurokinin-1 receptor,NK-1R)外,还可能作为一种内源性危险信号被TLR2和TLR4识别,激活NF-κB信号通路,启动和加剧AR反应。下调SP,可抑制MCs上游的TLR2、TLR4及下游的NF-κB p65信号通路,进而抑制MCs脱颗粒,缓解AR症状[22]。

鼻黏膜上皮作为物理屏障与信号枢纽,富含感觉及交感、副交感神经纤维,可分泌乙酰胆碱、去甲肾上腺素、SP等神经递质。这些神经信号与上皮细胞分泌的IL-25、IL-33、TSLP等警报素共同构成了神经-免疫互作的分子基础[23-24]。变应原与IgE交联激活MCs脱颗粒,释放的炎症介质可直接激活感觉神经末梢,引发打喷嚏、鼻痒等症状。同时,MCs表达NK-1R、降钙素基因相关肽受体(calcitonin gene-related peptide receptor,CGRPR)等神经肽受体,可被神经元释放的SP、降钙素基因相关肽(calcitonin gene-related peptide,CGRP)、胃泌素释放肽(gastrin-releasing peptide,GRP)激活,进一步促进其脱颗粒,形成炎症正反馈环路[25]。此外,AR释放的炎症细胞因子可激活下丘脑-垂体-肾上腺轴(the hypothalamic-pituitary-adrenal axis,HPA),促进糖皮质激素分泌[26]。长期或过量的糖皮质激素可对海马等边缘系统产生负面影响,导致神经元损伤和糖皮质激素受体水平改变,进而诱发情绪失调和抑郁[27]。这可能是AR患者并发情绪障碍的重要NEI机制。

2 AR伴情绪障碍发病的NEI机制研究

2.1 AR与HPA轴

HPA轴是机体应对应激、维持内稳态的核心系统,在AR的发病进程中起着关键的调控作用。长期环境应激可导致HPA轴过度活跃,释放过量的内源性糖皮质激素(glucocorticoid,GC)。GC与T细胞糖皮质激素受体结合,增强相关信号转导,促使免疫应答向Th2方向偏移,加剧变态反应[28-29]。动物实验提供了直接证据:肾上腺切除术阻断HPA轴功能,降低血清皮质酮(corticosterone,CORT)水平,进而降低IL-10、IgE,升高干扰素-γ(interferon-gamma,IFN-γ),并显著抑制花粉症发作[30];同样,在AR模型小鼠中,双侧肾上腺切除不仅降低症状评分和血清特异性IgE水平,还减少了鼻黏膜中嗜酸粒细胞(eosinophils,EOS)和MCs的浸润,这表明低水平的CORT削弱了其与免疫细胞受体的结合能力,减轻Th2反应[31];此外,CORT减少还可降低MCs表面IgE受体的表达,延缓IgE介导的过敏反应[32]。以上结果证实,HPA轴通过调控MCs活化与Th1/Th2平衡,参与AR的发病进程。

与此同时,HPA轴也是连接AR与情绪障碍(如焦虑和抑郁)的关键神经内分泌桥梁。AR相关炎症反应产生的细胞因子(如IL-1β、IL-4)可穿透血脑屏障,激活HPA轴并刺激GC过度释放。长期高水平的GC会导致海马等脑区糖皮质激素受体(glucocorticoid receptor,GR)的表达或功能下调,破坏GR介导的负反馈机制,致使HPA轴持续亢进。这不仅损害海马和边缘系统功能,诱发情绪与认知障碍,还可能反向加重AR的鼻部症状[33-34]。因此,上调海马神经元GR表达或增强其亲和力,恢复GC的敏感性,是修复HPA轴负反馈功能、改善情绪共病的潜在途径[35]。研究提示,鼻黏膜菌群失调可能通过影响HPA轴间接调控AR。变应性鼻黏膜的菌群紊乱可破坏上皮屏障,使炎症因子通过嗅觉通路进入中枢,激活HPA轴并加剧免疫炎症[36]。多中心随机对照试验结果及大量前期文献支持,中度或重度持续性AR患者会长期处于身心双重压力状态。这种持续高刺激会过度激活HPA轴,导致激素分泌异常,选择性抑制Th1细胞功能,打破Th1/Th2平衡,加剧过敏性炎症;而HPA轴的长期激活可能导致其疲劳与功能失调,最终导致过敏性炎症失控并持续加重[37]。综上,AR可能通过释放炎症介质影响中枢神经系统,导致神经内分泌失调,这构成了AR与情绪障碍共病的重要神经内分泌-免疫机制。

针刺可通过免疫调节与神经内分泌双重机制改善AR症状,其作用途径与HPA轴的调控密切相关[38]。实验选取60只8周龄健康雄性SD大鼠,随机分为5组:空白对照组、模型对照组、针刺组、针刺+RU486组及RU486组,每组12只。针刺干预选取大椎(Governor Vessel 14,GV14)、双侧肺俞(Bladder 13,BL13)及双侧足三里(Stomach 36,ST36)穴,每5 min捻针1次,留针20 min,隔日治疗,持续14 d。实验结果提示,针刺能显著改善AR大鼠的过敏行为,具体机制包括:免疫调节方面,针刺下调血清IL-4、IL-5、IL-13等Th2型细胞因子,上调IFN-γ,从而恢复Th1/Th2平衡,发挥抗炎作用;神经内分泌方面,针刺显著降低HPA轴相关激素[CORT、促肾上腺皮质激素释放激素(corticotropin-releasing hormone,CRH)、促肾上腺皮质激素(adrenocorticotropic hormone,ACTH)]水平,且该效应可被糖皮质激素受体拮抗剂RU486部分阻断,提示针刺可能通过糖皮质激素受体途径调控HPA轴功能。此外,针刺可增强室旁核(paraventricular nucleus,PVN)神经元c-Fos表达,表明其通过激活PVN神经元,影响CRH释放,参与HPA轴功能调节。国内临床研究证实,整体取穴针刺可缓解AR患者的鼻部伴随症状、情绪障碍、睡眠障碍,并提升生活质量,其机制可能与下调血清白细胞介素水平、上调IFN-γ,以及降低血清CORT、CRH和ACTH水平相关[39]。

2.2 AR与神经肽

鼻黏膜存在复杂的神经调控网络,由交感、副交感及感觉神经末梢密集分布构成[40]。交感神经释放去甲肾上腺素与神经肽Y(neuropeptide Y,NPY),促进鼻血管收缩,减少分泌物;副交感神经释放乙酰胆碱和血管活性肠肽(vasoactive intestinal peptide,VIP)等,引起血管舒张与腺体分泌,导致鼻塞;感觉神经则可释放SP、CGRP等神经肽,引发喷嚏、流涕等防御反应[41]。电镜观察显示,神经细胞和MCs之间存在膜-膜附着结构,其空间间隙约为20 nm甚至更小,且MCs表面表达多种神经肽受体[42],在过敏性炎症状态下,鼻上皮屏障完整性受损,感觉神经末梢暴露,释放的SP、CGRP及VIP等神经肽可与MCs结合,促使其活化与脱颗粒,释放组胺、白三烯等炎症介质,加剧鼻部症状[43-44]。同时,局部产生的TNF-α、IL-5等炎症因子可透过血脑屏障,作用于边缘叶、海马等情绪相关脑区,参与情绪调节过程[5]。

其中,SP是中枢和周围神经系统以及免疫系统中的重

要介质。AR患者SP水平显著升高，其与NK-1R结合，直接诱导MCs脱颗粒；而抑制NK-1R的表达则可减轻AR临床症状及鼻黏膜EOS浸润[45]。此外，SP还能通过NF-κB通路或MyD88通路调节MCs中IL-6和TNF-α表达，诱导MCs释放组胺。值得注意的是，MCs和EOS亦能合成并释放SP[46]，形成正反馈环路，进一步放大炎症反应。CGRP则作为强效血管扩张剂，加重黏膜水肿与鼻塞[47]。VIP则可能协同乙酰胆碱，促进腺体分泌与血管舒张[48]。这些神经肽通过与MCs、T细胞及B细胞等的相互作用，共同调控鼻黏膜过敏性炎症的进程[49]。

综上，外周神经释放的神经肽可通过激活MCs等免疫细胞，直接参与AR的发病；而AR炎症介质又可经血脑屏障影响中枢情绪相关脑区。这为阐释AR伴随情绪障碍提供了另一条“神经-免疫”交互通路。

研究表明，部分药物可通过干预这一通路发挥治疗作用。例如，醒鼻凝胶滴鼻剂（徐长卿、蝉蜕、人工牛黄、天然冰片组成）给予AR大鼠50 μL/次，2次/d，连续治疗12 d后，能减少AR大鼠鼻黏膜EOS浸润，抑制SP、VIP等促炎神经肽释放，上调NPY，并降低IgE、转化生长因子-β1（transforming growth factor-beta 1，TGF-β1）等免疫因子表达，提示其可能通过Fyn信号通路调节“鼻黏膜-海马”神经免疫机制，改善AR行为及学习记忆功能[50]。槲皮素具有多靶点调控作用，既能抑制鼻黏膜感觉神经轴突末端钙离子异常内流，也可通过抑制神经肽产生、纠正Th1/Th2失衡及抑制EOS活化等途径缓解AR[51-52]。

1项国内随机对照试验探讨了针刺对中重度持续性AR患者的临床疗效及可能机制。该研究将135例患者随机分为3组：西药组（单用布地奈德鼻喷雾剂）、鼻内针刺组（布地奈德+针刺内迎香、鼻丘穴）和联合组（在鼻内针刺组基础上加用调神针，取百会、四神聪等八穴），治疗1次/d，疗程均为2周。结果显示，治疗后3组患者的鼻部症状[鼻症状总分（total nasal symptom score，TNSS）、非鼻症状总分（total non-nasal symptom score，TNNSS）]、生活质量[鼻结膜炎生活质量问卷（Rhinoconjunctivitis Quality of Life Questionnaire，RQLQ）]、情绪状态[焦虑自评量表（Self-Rating Anxiety Scale，SAS）、抑郁自评量表（Self-Rating Depression Scale，SDS）]以及实验室指标（血清IgE、SP、VIP及外周血EOS计数）均较前显著改善，血清NPY水平升高（均$P<0.05$）。其中，鼻内针刺组疗效优于西药组，而联合组各项指标改善更为全面，总有效率高达88.89%，显著优于其他2组（$P<0.05$）。研究表明，鼻内针刺联合调神针的治疗策略，不仅能缓解中重度AR患者的鼻部症状、抑制过敏反应（降低IgE、EOS）并调节神经肽平衡（降低SP、VIP，升高NPY），同时还可改善焦虑与抑郁情绪，为AR整合治疗提供了临床依据[53]。

2.3 鼻-脑轴的双向机制

鼻-脑轴是连接鼻腔与中枢神经系统的双向调控网络，通过感觉神经、激素和免疫信号实现信息传递与反馈[45]。AR状态下，鼻黏膜炎症介质（如IL-1β、TNF-α）可经受损血脑屏障或嗅觉通路进入中枢，尤其易影响嗅球（olfactory bulb，OB）及嗅觉皮层等区域，激活小胶质细胞与星形胶质细胞，诱发神经炎症[54-56]。多项研究为此机制提供了直接证据：AR小鼠模型中，应激可激活OB区小胶质细胞P2X7受体，诱发抑郁样行为[57]。而抑制TLR4/MyD88/NF-κB通路可减轻OB神经炎症与细胞凋亡，并显著改善AR小鼠的嗅觉功能[58]。AR大鼠中，海马内SP、TNF-α、IL-6等炎症介质表达上调，影响血清素、多巴胺等神经递质代谢，可能导致情绪障碍[33]，研究还发现，AR模型动物嗅球-前额叶皮层神经回路出现theta/gamma耦合增强等电生理改变，与焦虑样行为密切相关[6]。此外，环境刺激（如PM2.5暴露）可通过增强三叉神经瞬时受体电位香草酸亚型1（transient receptor potential vanilloid 1，TRPV1）敏感性，影响脑干谷氨酸代谢，经鼻-脑轴加剧全身炎症反应，加重AR症状[59]。神经炎症不仅直接损伤嗅觉神经元，导致嗅觉功能障碍[60]，其产生的细胞因子还可扩散至海马、前额叶等情绪调控脑区，诱发情绪障碍[5,57]。反之，中枢功能失调（如应激、神经炎症）也可通过自主神经下行通路，释放乙酰胆碱、SP、CGRP等，作用于鼻黏膜免疫细胞与上皮细胞，加剧局部Th2免疫应答和神经源性炎症[43-44,61]。综上，AR可通过“鼻-脑轴”形成“外周炎症驱动中枢神经炎症—中枢功能障碍加重外周炎症”的自我强化循环，这为阐释AR常伴发情绪障碍提供了关键的神经免疫机制依据。

基于上述机制，天然芳香挥发油制剂在缓解AR及其伴随情绪症状方面具有潜在价值。以苍艾挥发油（Cang-Ai volatile oil，CAVO）为例：在AR治疗方面，口服CAVO（剂量分别为20.59、41.18及82.36 mg/kg，连续2周）可缓解卵清蛋白（ovalbumin，OVA）诱导的AR大鼠鼻部炎症与过敏症状。其机制为调节Th1/Th2平衡，即增强Th1反应（上调IFN-γ、T-box转录因子（T-box transcription factor TBX21，T-bet））并抑制Th2反应（下调IL-4、GATA结合蛋白3（GATA binding protein 3，GATA3））[62]；在情绪调节方面，经鼻吸入CAVO（高剂量20.8 μL/kg、低剂量5.2 μL/kg，1次/d，连续4周）可改善慢性应激（chronic unpredictable mild stress，CUMS）诱导的大鼠抑郁样行为。该效应与其调节脑内多巴胺和5-羟色胺代谢有关，且在双侧OB损伤后作用减弱，提示CAVO可能通过“鼻-脑轴”依赖途径影响中枢神经递质系统[63]。临床研究进一步支持吸入芳香疗法对AR患者的综合效果。1项针对常年性AR患者的随机对照试验发现，2次/d、每次5 min吸入含有檀香木、天竺葵等混合精油（持续7 d），能显著改善TNSS，尤其在缓解鼻塞方面效果突出；同时，患者的生活质量、疲劳感及情感功能均得到显著改善[64]。

3 讨 论

AR与情绪障碍共病已成为影响全球健康的重要临床问题，其发生发展与NEI网络的整体失调密切相关。基于上述机制分析，本文提出“NEI网络动态调控模型”，系统阐释AR与情绪认知障碍共病的核心机制。在AR发病过程中，过敏原破坏鼻黏膜上皮屏障，诱导TSLP、IL-33与IL-25等警报素释放，引起Th1/Th2/调节性T细胞（T regulatory cell，Treg）/辅助性T细胞17（T helper 17 cell，Th17）功能失衡及TNF-α、

IL-4、IL-5等炎症因子大量释放[65-66]；这些炎症介质可穿透血脑屏障，激活HPA轴促使糖皮质激素过度释放，长期高水平GC导致海马等脑区糖皮质激素受体表达或功能下调，形成糖皮质激素抵抗，削弱其对HPA轴的负反馈抑制，进而加剧局部免疫应答，构成“免疫-内分泌”双向调控的病理环路[34]。同时，激活的鼻腔感觉神经末梢释放SP、NPY、VIP等神经肽，进一步招募并活化EOS等免疫细胞，活化的免疫细胞又可影响感觉神经，形成“神经-免疫”正反馈环路，协同放大炎症信号[67-68]。这些外周紊乱信号通过“鼻-脑轴”双向传递：其一，细胞因子等经血脑屏障的体液途径作用于中枢；其二，三叉神经与嗅神经的直接投射将感觉与化学信号传递至OB、海马及前额叶皮层等高级脑区，诱发神经炎症反应与突触可塑性改变[4]，临床表现为情绪障碍与认知功能障碍；而中枢功能异常又可通过神经内分泌及自主神经下行通路，反向增强外周炎症反应，最终形成“外周炎症-中枢功能障碍-外周炎症加重”的闭合性病理循环网络，为共病的系统性干预提供了理论依据。

在治疗方面，中医药具有通过多途径、多靶点干预该共病的潜力。中药单体与复方可通过调节免疫平衡、修复黏膜屏障、抑制炎症信号通路等改善AR症状；同时，部分研究提示中药成分（如槲皮素等）及复方（如醒鼻凝胶滴鼻剂）具有调节神经肽、改善学习记忆与情绪行为的神经保护作用。针刺疗法可通过调节HPA轴及相关免疫-神经通路缓解AR伴随情绪症状。除内服中药与针刺疗法外，芳香疗法作为中医药外治法的特色，在调节“鼻-脑轴”方面具有独特优势，基于中医理论的吸入芳香疗法，通过调节嗅觉黏膜中沉默信息调节因子1（Sirtuin 1，SIRT1）/FK506结合蛋白5（FK506 binding protein 5，FKBP5）/GR/NF-κB信号通路，减轻炎症反应，促进嗅觉神经再生，实现对“鼻-脑轴”功能的双向调节，从而可能改善AR伴随情绪障碍的病理状态[69]。这些发现为AR伴随情绪障碍的整合治疗提供了新思路。

然而，目前研究仍存在明显局限：共病机制研究多呈“碎片化”，缺乏对NEI网络动态整合的系统阐释；中医药干预研究多集中于AR本身，针对共病、尤其是基于“鼻-脑轴”机制的研究尚处于起步阶段，作用机制尚未完全阐明，且缺乏高质量临床证据。

4 未来研究方向

基于AR与情绪障碍共病的“NEI网络”失调机制及中医药干预潜力，未来研究需构建从机制解析到精准治疗的完整体系。

4.1 系统解析“鼻-脑轴”网络调控与共病机制

借助网络药理学、多组学（转录组、蛋白质组、代谢组）和空间质谱成像整合分析、高分辨率神经影像[如功能性磁共振成像（functional magnetic resonance imaging，fMRI）、正电子发射断层扫描（positron emission tomography，PET）]及神经环路特异性调控技术（如光遗传学、化学遗传学），系统绘制“鼻-脑轴”双向通讯的动态调控图谱。重点阐明外周炎症信号（如IL-1β、TNF-α、神经肽）如何经由嗅觉通路与体液途径影响OB、海马及前额叶皮层，诱发神经炎症与突触可塑性改变，并揭示中枢功能失调如何通过自主神经及HPA轴下行反馈加重外周炎症的闭环机制。同时，拓展研究视野至“肠-鼻-脑轴”，探讨肠道菌群及其代谢产物如何通过免疫-神经途径参与共病机制，以深化对网络失调的系统认识。

4.2 构建“病-证-效”证据链并发展精准干预模式

通过大规模前瞻性队列研究，整合症状、情绪量表、神经内分泌指标、嗅觉功能及中医四诊等多维数据，识别共病的临床亚型与证候规律。在此基础上，开展两阶段临床试验：第一阶段以机制为导向，动态评估中药复方、针刺或芳香疗法等对NEI网络关键节点（如HPA轴激素、神经肽谱、小胶质细胞活化标志物）的调控效应；第二阶段推进以“鼻部症状缓解率联合情绪功能改善”为复合终点的大规模、多中心随机对照试验（randomized controlled trial，RCT），积累高级别循证证据。同时，重点探索鼻腔局部给药、中药内服、针刺调神及芳香疗法等多途径整合方案的协同效应，并基于共病特征、中医证型及生物标志物谱构建“病-证-法-药对应”的精准决策模型，推动诊疗向个体化、精准化发展。

利益冲突 所有作者声明均不存在利益冲突

作者贡献声明 陈凤：提出论文选题，完成文献检索与分析，撰写论文初稿；周晓媛：参与文献筛选与资料整理，协助撰写相关章节；牛志超：查阅文献，参与论文部分内容的撰写；解宇环：参与论文结构设计与内容审阅，提出修改建议；熊磊：参与论文框架设计与学术指导，审阅并修订全文；李刚：负责研究整体构思与设计，指导论文撰写与修改，最终审阅并定稿

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