

新型冠状病毒感染中味觉障碍及防治

郑欣, 徐欣, 周学东, 彭显[△]

口腔疾病研究国家重点实验室 四川大学华西口腔医院(成都 610041)

【摘要】 人味蕾中味觉细胞接受刺激后产生味觉信号, 传导至中枢神经系统产生味觉, 有助于机体鉴别营养物质和有毒有害物质, 对人和其他哺乳动物的生存具有重要意义。多项临床研究及荟萃分析表明味觉障碍是新型冠状病毒感染的重要并发症之一, 严重危害患者营养摄入与生活质量。根据味觉感知的生理学过程, 味觉障碍的直接病因包括味觉感受器功能受损以及味觉神经系统损伤, 间接病因包括遗传因素、增龄性变化、细菌与病毒感染、肿瘤化疗等。味觉障碍致病因素错综复杂, 且部分机制尚不明确, 一些发现与结论有待考证, 对临床病因诊断与针对性治疗产生极大挑战。本文就味觉感知生理过程、新型冠状病毒诱发味觉障碍的可能机制及防治策略进行综述, 为建立并完善新型冠状病毒感染并发味觉障碍的综合管理提供理论帮助。

【关键词】 新型冠状病毒 味觉障碍 味觉感知 味蕾 味觉受体

Mechanisms and Management of COVID-19-Associated Taste Disorders ZHENG Xin, XU Xin, ZHOU Xue-dong, PENG Xian[△]. State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

[△] Corresponding author, E-mail: pengx@scu.edu.cn

【Abstract】 The taste buds in the human tongue contain specialized cells that generate taste signals when they are stimulated. These signals are then transmitted to the central nervous system, allowing the human body to distinguish nutritious substances from toxic or harmful ones. This process is critical to the survival of humans and other mammals. A number of studies have shown that dysgeusia, or taste disorder, is a common complication of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which can severely affect patients' nutritional intake and quality of life. Based on the physiological process of taste perception, the direct causes of dysgeusia include dysfunction of taste receptors and damage to the taste nervous system, while indirect causes include genetic factors, aging-related changes, bacterial and viral infections, and cancer treatments such as radiotherapy and chemotherapy. The pathogenic factors of dysgeusia are complicated, further research is needed to fully understand the underlying mechanisms, and some of the reported findings and conclusions still need further validation. All these form a great challenge for clinical diagnosis of the cause and targeted treatment of dysgeusia. Herein, we reviewed published research on the physiological process of taste perception, the potential mechanisms of taste disorders related to SARS-CoV-2 infection, and strategies for prevention and treatment, providing theoretical support for establishing and improving the comprehensive management of COVID-19 complicated by taste disorders.

【Key words】 COVID-19 Taste disorders Taste perception Taste buds Taste receptor

味觉是重要的人体化学感官之一, 对食物的摄入与选择至关重要^[1-2]。2019新型冠状病毒(SARS-CoV-2)为β属冠状病毒, 机体一旦感染SARS-CoV-2, 部分患者的味觉发生改变, 导致味觉减退、味觉丧失等^[3-7]。味觉障碍(dysgeusia), 亦称味觉异常(taste disorder), 包括味觉减退(hypogeusia)、味觉亢进(hypergeusia)、味觉倒错(parageusia)、失味症(ageusia)及幻味症(phantogeusia)。味觉障碍虽不致命, 但直接影响食物与营养摄入, 对能量代谢、免疫功能等具有潜在危害, 极大影响患者生活质量, 是不容忽视的临床问题^[8]。目前研究发现引发味觉障碍的因素众多, 包括遗传因素、增龄性改变、细菌感染与

炎症、神经系统受损及药物使用等^[9-13]。目前对于味觉障碍的病因及机制仍缺乏系统认识, 一些因素引发味觉障碍的机制仍较为缺乏, 甚至完全不明, 导致临床上对味觉障碍的病因诊断较为困难, 缺乏针对性治疗手段。人味觉感知机制及味觉障碍病因及机制的深入研究将有助于味觉障碍的临床诊断与治疗, 具有重大现实意义。

1 味觉感知

人味觉系统经历了上百万年的进化, 针对食物选择与趋避而形成了甜、鲜(umami)、苦、咸、酸五种基本味觉^[2]。甜味与鲜味通常意义上是人所偏好的基本味觉, 大部分甜味物质为碳水化合物, 而鲜味物质均为氨基酸类,

[△] 通信作者, E-mail: pengx@scu.edu.cn

分别是重要的碳源和氮源。自然界的苦味物质多数来源于植物,是植物防御系统的重要手段,因此也往往代表了毒性,故而苦味是哺乳动物所趋避的,仅仅较低程度的苦味为人所接受或喜好。咸味的产生与进化过程中哺乳动物维持体内钠离子浓度平衡有关。酸味往往由未成熟的果实或因过度发酵而腐败的食物所产生,通常为哺乳动物所趋避^[8]。需要注意的是,味觉的偏好与趋避是进化过程中所形成的一种简化系统,实际上甜味物质不一定都对人体具有益处,苦味物质并非都有毒性。近年来研究还提出了厚味(kokumi)、脂肪味(fat)、金属味(metallic)等新的味觉,但目前对于这些味觉的存在与形成机制仍有争论^[14]。

1.1 味觉感受器——味蕾

基本味觉信号均由味觉感受器——味蕾接受相应刺激所形成^[15]。味蕾主要分布于舌上皮,在人软腭、会厌及咽部上皮也存在味蕾。舌上皮中存在四种舌乳头,轮廓乳头(circumvallate papilla)、叶状乳头(foliate papilla)、菌状乳头(fungiform papilla)与丝状乳头(filiform papilla)。轮廓乳头位于舌背界沟前,数量较少,但每个乳头上皮中包含数千个味蕾;叶状乳头分布于舌侧后缘,包含数十个味蕾;菌状乳头分布于舌前2/3,数量较多,每个乳头上皮内包含少量味蕾;丝状乳头均匀分布于舌背,数量最多,但上皮内不含味蕾^[15]。需要注意的是,虽然舌乳头分布具有区域性,但其上皮内包含的味蕾功能相同,均能够感知各类味觉,以往提出的“舌背味觉地图”理论,即舌背特定区域负责特定味觉的理论,目前已被认为是错误的。

1.2 味觉受体

味蕾中的味觉细胞可表达不同味觉受体,从而接受刺激形成味觉信号。目前发现的味觉受体主要有两类:G蛋白偶联受体(G protein-coupled receptors, GPCRs)及离子通道类受体。

甜、鲜、苦信号由II型味觉细胞形成,均由G蛋白偶联受体所介导。I型味觉受体家族(taste receptor type 1, TAS1R)包含TAS1R1~3三种亚型,其中TAS1R2与TAS1R3形成异二聚体介导甜味信号形成,被称为甜味受体^[16];鲜味受体为TAS1R1与TAS1R3形成的异二聚体^[17]。2型味觉受体家族(taste receptor type 2, TAS2R)为苦味受体,人具有25种TAS2R亚型,与结构各异的苦味物质结合而介导苦味信号^[18]。甜、鲜、苦受体下游信号传导通路相似,由G蛋白转导素(gustducin)及磷脂酶PLCB2等参与,详细分子传导机制详见笔者团队其他相关综述^[19-21]。甜、鲜、苦受体信号通路激活后可使味觉细胞开放瞬时电位离子通道TRPM5,使细胞产生动作电位,释放神经递

质ATP^[22]。

酸味与咸味感知受体与机制目前尚无定论。以往研究发现酸味信号由表达PKD2L1的III型味觉细胞所产生,ASIC、HCN、KCNK及K_{IR}2.1等离子通道被认为可能是酸味受体^[23-26];近期研究证明选择性离子通道OTOP1为酸味感知所必需的酸味受体^[27]。低浓度与高浓度NaCl触发咸味的机制不同:目前认为ENaC离子通道介导了低咸感知,是否有其他受体介导低咸感知、负责高咸感知的味觉细胞类型及受体尚不明确^[28]。

味觉受体不仅在味觉细胞中存在,近年来众多高水平研究证明甜味受体、苦味受体在肠道、呼吸道等组织位点存在,与宿主代谢、固有免疫功能密切相关^[29-30]。笔者研究团队研究发现苦味受体表达于牙周组织,与口腔微生物群落及口腔感染性疾病发生发展密切相关^[19-20, 31-33]。以上研究发现提示:味觉受体功能异常所导致的味觉障碍可能对全身健康产生不利影响,需要进一步深入研究。

1.3 味觉信号传导及编译

味蕾内味觉细胞接受刺激形成味觉信号后,释放神经递质传导至传入神经纤维。面神经分支鼓索神经及岩浅大神经分别负责舌前2/3和软腭区域产生的味觉刺激传递,舌咽神经传递负责舌后1/3区,迷走神经支配会厌处味蕾^[34]。近期研究发现甜、鲜、苦、酸、咸对应味觉信号经初级感觉纤维传递至神经节后,由对应类型的味觉神经元进行处理,这种外周味觉信号编译(taste coding)模式被称为标记信道(labelled-line)模式^[35]。这些味觉信号最终传输至中枢神经系统而产生味觉感知。人大脑皮层中处理味觉信号的区域与负责内脏功能、记忆、情感与语言的区域相近,因此人味觉感知的过程可能受到众多先天与后天因素的影响,对临床上味觉障碍的诊断造成挑战。

2 味觉障碍的病因与机制

味觉与味道/风味(flavor)概念不同。味道/风味是味觉、嗅觉以及其他感觉(例如辣、质感等)的综合。临床上患者所描述的“味觉异常”多实际为味道/风味异常,其中多数合并嗅觉异常与味觉异常^[36]。这种综合感觉的异常亦是临床诊断难点之一。本文仅对味觉障碍进行讨论。

味觉障碍可分为程度(quantity)与性质(quality)两方面的异常。前者表现为完全无法感知味觉的失味症、味觉减退及味觉亢进;后者包括味觉错乱,例如甜味错误感知为苦味等情况,还包括幻味症,即未接受相应味觉刺激时仍能产生特定的味觉感知。以上味觉障碍分类主要依

据临床表现。

2.1 SARS-CoV-2感染导致味觉障碍的机制研究

大量临床研究发现味觉障碍是SARS-CoV-2感染后常见的临床症状之一,荟萃分析显示约40%患者SARS-CoV-2感染后出现味觉障碍^[6-7]。SARS-CoV-2导致味觉障碍的可能机制主要包括:①病毒直接感染味觉细胞而造成直接损伤;②病毒感染所致神经系统损伤;③抑制味蕾中味觉信号传导相关蛋白的唾液酸修饰;④病毒感染导致的唾液腺功能障碍;⑤引发局部组织缺锌。

SARS-CoV-2可通过刺突蛋白与宿主细胞表面受体相互作用而感染味觉细胞和味觉神经,导致味觉障碍。宿主细胞表达的SARS-CoV-2受体主要为血管紧张素转换酶2(angiotensin-converting enzyme 2, ACE2)。研究指出ACE2舌上皮表达丰度较高^[37],可能是SARS-CoV-2患者常出现味觉障碍的原因之一。另一项研究发现II型味觉细胞表达ACE2,是SARS-CoV-2直接感染味觉细胞的有力证据;同时该研究发现SARS-CoV-2感染后菌状乳头内干细胞更新受损,此损伤在症状出现后6周仍未完全恢复^[38]。SARS-CoV-2还能够导致神经系统受损,或破坏神经元支持细胞,从而可导致味觉障碍^[39]。

唾液酸是唾液黏蛋白的基本成分,唾液酸修饰能够保护味蕾内的味觉信号传导蛋白不被过早降解^[40]。唾液中唾液酸减少与味觉减退相关^[41]。有学者提出SARS-CoV-2的刺突蛋白可能抑制唾液酸修饰及功能,可能是导致味觉障碍的原因之一^[42-43]。

唾液腺中ACE2高表达^[37],故SARS-CoV-2可能直接感染唾液腺而诱导功能障碍,影响唾液成分和分泌量,导致味觉障碍。其原因包括:①唾液分泌减少降低了化学物质与味觉受体的接触效率^[44];②唾液对于保护味蕾免受干燥和细菌感染非常重要,小鼠颌下腺移除会导致菌状味蕾的丧失及形态异常,手术切除唾液腺可导致舌上皮角化过度、味蕾萎缩、细菌渗入味觉细胞顶端等病理改变^[45]。

SARS-CoV-2感染引起体内锌从血液重新分布到肝脏,导致其他组织局部缺锌。缺锌是明确的味觉障碍致病因素^[46]。锌在各种基本代谢途径中发挥重要作用,是多种金属酶的组成部分,包括味觉转导素G蛋白,对味觉感知至关重要^[47]。另一方面,唾液腺组织局部缺锌将抑制锌依赖性碳酸酐酶(zinc-metalloenzyme carbonic anhydrase)活性,对唾液分泌功能产生不利影响^[48],亦可能间接损害味觉感知。

除以上已报道的可能机制外,SARS-CoV-2感染可能通过推动其他味觉障碍致病因素,或与其他因素相互叠

加,从而影响味觉障碍的发生与发展。这些因素包括遗传因素、增龄性变化、细菌感染与炎症、神经系统损伤、肠道微生物等。下文将对以上致病因素进行全面总结,为后续研究进一步揭示SARS-CoV-2感染相关味觉障碍机制提供思路。

2.2 遗传因素

一些遗传病患者可表现出味觉障碍。家族性自主神经功能异常(赖利-戴综合征)是一种遗传性疾病,患者缺乏舌乳头,可表现为失味症或味觉减退^[49]。另一方面,味觉受体的遗传多态性(genetic polymorphism)是影响味觉受体功能、味觉感知和饮食的重要因素。目前较多研究报道TAS1R与TAS2R的单核苷酸多态性(single nucleotide polymorphism, SNP)与味觉感知或饮食习惯具有相关性^[50],可能导致SARS-CoV-2感染所致味觉障碍的临床表现与易感性不同。

2.3 增龄性变化

现有证据表明,年龄增长影响味蕾中味觉细胞更新^[51-53]和味觉神经反应^[54]。动物实验与人体组织研究报道味蕾增龄性变化表现为数量减少及包含味觉细胞减少^[51-53],其原因可能与衰老导致味觉祖细胞/干细胞数量下降相关,从而降低味蕾自主更新与损伤修复能力^[55],但具体机制不明。动物实验发现:衰老可致鼓索神经对NaCl的反应减弱^[54],延迟味觉神经损伤恢复^[53],提示神经功能下降是增龄导致味觉衰退的另一个原因。

2.4 细菌感染与炎症

舌背细菌生物膜重量与味觉敏感性呈负相关^[56],机械清洁后味觉敏感性显著恢复^[57-58],提示舌背细菌生物膜物理屏障可能通过限制化学物质与味觉受体接触而减弱味觉感知。

口腔微生物群落中链球菌、放线菌、乳酸杆菌可将碳水化合物降解为有机酸,普雷沃氏菌、卟啉单胞菌可将蛋白质降解为氨基酸和短链脂肪酸^[59]。菌群代谢活动可改变舌背微环境中化学物质成分(例如糖、氨基酸及有机酸等)与浓度而影响味觉感知^[56]。口腔微生物群落对蔗糖的代谢方式与个体甜味敏感性相关,微生物群落三羧酸循环代谢活性高的个体甜味敏感较高,而微生物群落糖酵解活性高则个体甜味敏感性较低^[60]。

脂多糖(lipopolysaccharide, LPS)是革兰阴性细菌的重要毒力因子,有研究表明腹腔注射LPS可升高小鼠味蕾炎症因子的表达量,可能通过影响味觉前体细胞增殖而诱发味觉障碍^[61]。笔者团队研究发现LPS感染可上调TAS1R2非功能性可变剪接体的表达,从而降低小鼠甜味感知能力^[62]。

2.5 神经系统损伤

神经系统损伤是味觉障碍的常见病因,能够直接影响味觉神经信号传导与编译,亦可能抑制味蕾更新与重建功能。

面神经分支岩浅大神经、鼓索神经、舌咽神经及迷走神经均参与味觉神经信号传导与编译。鼓索神经引起的味觉障碍常见于病毒感染(如贝尔麻痹)、慢性中耳炎以及医源性损伤^[63]。颈动脉壁血肿压迫导致舌咽神经受损能够造成味觉障碍^[64]。中枢损伤(主要包括脑干、丘脑以及大脑皮层受损)会导致味觉障碍。脑干受损所致味觉障碍表现为同侧偏瘫或偏侧味觉减退,常见原因是脱髓鞘或脑血管疾病^[65]。研究发现中风患者在丘脑梗塞的同侧或对侧可发生味觉障碍^[66-67]。癫痫、脑血管疾病、肿瘤、帕金森综合征^[68]及阿尔茨海默病^[69]等可引起大脑皮层功能受损,可导致味觉障碍。

味蕾的发育和重建可能依赖于味觉神经^[70],可能的机制是味觉神经末梢可释放营养因子支持味觉细胞。有研究报道味觉神经末梢能释放刺猬因子(sonic hedgehog, SHH)维持味蕾细胞的更新和再生^[71-72]。动物实验发现味觉神经切断导致味蕾数量、大小和味觉细胞数量减少^[73]。小鼠鼓索、舌神经切断后 14 d,味蕾数量减少70%,体积缩小60%^[74]。

2.6 肠道微生物

近年来微生物-肠-脑轴(microbiota-gut-brain axis)研究发现,肠道微生物能够通过影响味觉感知等多种机制改变宿主饮食习惯。微生物代谢产生多种神经化学物质(γ -氨基丁酸、5-HT)改变食欲^[75]。在缺乏必需氨基酸饮食的情况下,肠道共生醋酸菌可提供支链氨基酸,诱导肠细胞分泌CNMa多肽与神经元交互作用而改变食欲^[76]。以上肠道微生物对饮食的影响可能与味觉感知并无关系。

肠道微生物的改变与味觉感知的变化存在相关性^[77-78]。研究报道肠道激素可影响味觉感知:瘦素(leptin)、胰高血糖素样肽-1(GLP-1)、内源性大麻素可影响甜味敏感性^[79-81],胆囊收缩素(CCK)、酪酪肽(PYY)可影响苦味感知^[82-83],食欲刺激素(ghrelin)增强咸、酸味感知^[84]。一方面肠道微生物合成多肽可能与上述某些肠道激素结构与功能相似^[78],另一方面肠道微生物来源短链脂肪酸可调节肠内分泌细胞释放激素和神经肽(如GLP-1和PYY)^[85-87],是肠道微生物影响宿主味觉感知的可能机制。

2.7 灼口综合征

根据国际口腔面部疼痛分类指南(The International Classification of Orofacial Pain),灼口综合征(burning

mouth syndrome, BMS)定义为“每日反复出现2 h以上、持续3个月以上的口腔内灼烧感或触物痛感,口腔检查未发现其他明确病因”^[88]。BMS患者常主诉躯体感觉异常,其中据估计11%~68%的患者表现出味觉敏感性变化、幻味症在内的味觉障碍^[89]。关于BMS相关味觉障碍的致病机制目前有去抑制(disinhibition)学说、味敏者(supertaster)学说、 γ -氨基丁酸抑制味觉学说等,明确机制尚无定论^[90]。BMS患者唾液减少亦可能是导致味觉障碍的原因之一。

2.8 其他因素

吸烟可能导致菌状乳头血管化及味蕾形态改变,从而减弱味觉感知能力^[47]。主动和被动吸烟与呼吸道感染、口腔疾病等相关,亦可能对味觉感知产生间接影响^[47]。酗酒也是味觉障碍的潜在风险因素:酗酒者甜味敏感性较低,以及倾向于高蔗糖饮食^[91]。酗酒可能通过干扰维生素A、B以及锌的吸收、唾液腺损伤以及味蕾形态变化等机制而影响味觉感知^[47]。

一些食物可能引起味觉异常:如松子综合征(pine nut syndrome, PNS),其特点是在食用一种华山松的松子后,会产生一种苦涩的金属味,通常会因食用其他食物而加剧,持续时间可长达4周^[92]。PNS发病机制不明,可能与遗传因素相关^[92]。

3 味觉障碍的防治

SARS-CoV-2感染导致的味觉障碍,大多数人可以在2~4周内恢复^[93],有的会持续更久,甚至无法恢复,需要及时对症治疗。详细的病史记录与全面的临床检查将有助于区分味觉障碍与其他化学感官异常,同时可提示味觉障碍的诱发病因与直接病因,以便制定治疗计划,可针对性通过口腔护理、食物调节、激素治疗、中医中药、感官刺激等方式促进味觉恢复。对于一些无法明确病因的患者,通过保证充足睡眠时间、加强运动等方式,提高个人的免疫力和抵抗力也是行之有效的方法。

3.1 口腔护理

改善口腔卫生在一定程度上可以纠正味觉障碍,尤其是有效去除舌背生物膜,能够改善口腔异味,也对味觉感知恢复有帮助^[57]。对于SARS-CoV-2感染导致唾液腺损伤而出现唾液减少的患者,可使用人工唾液进行治疗。人工唾液和保湿剂被用于改善患者口腔舒适度和黏膜功能^[94]。人工唾液能有效促进味觉刺激物与味蕾的接触效率从而促进味觉感知能力恢复,但目前还缺乏研究来评估唾液替代品对味觉障碍的疗效。除此之外,使用拟胆碱能药物如毛果芸香碱,或咀嚼口香糖,刺激自然唾液的

分泌亦可能是有效方法^[95]。

3.2 营养支持与改善饮食

对于微量元素缺乏而发生味觉障碍的患者,针对性地补充微量元素能够缓解味觉障碍。例如,对于最常见缺锌和缺铁所导致的味觉障碍,服用补锌剂、补铁剂能够有效改善^[96]。对于一些微量元素缺乏,改善饮食也是有效的手段。例如可以多吃一些富含锌元素的食物(海产品、肝脏、鱼类等)。此外,味觉障碍患者应当避免过多食用刺激性强的食物,避免食用过热过冷食物,戒烟戒酒。

3.3 激素疗法

针对SARS-CoV-2感染伴发味觉障碍的一项随机对照研究表明曲安奈德漱口水处理显著改善了实验组味觉感知功能^[97]。个别病例报道甲状腺激素治疗纠正了味觉与嗅觉障碍^[98]。

3.4 中医中药

味觉异常在中医学中被称为“失味症”,是五脏之气失和的外在表现。味觉、嗅觉障碍与肺、脾、胃有关,脾胃不和、脾气亏虚,口淡无味,也可能因为湿热之邪导致口唇舌苔厚腻而导致食不知味。中医认为“五脏不和则五味无以入,故不知五味”,可见调理脏器之和是中医治疗味觉异常的关键。通过穴位针灸能疏通经络,调节神经,促使味觉恢复^[99]。研究发现眼针埋针疗法联合体针对周围性面瘫的疗效显著,并可改善面瘫引起的味觉障碍^[100]。除此之外,也可以在专业医生指导下采用方药治疗味觉障碍,如白术厚朴汤、甘露饮加广藿香、苓术饮、清透遏膜方、口淡方等^[101]。总结中药治疗SARS-CoV-2感染的经验与研究发现,祛湿类方剂可以有效抑制炎症因子的表达^[102],因此中医治疗SARS-CoV-2感染后味觉异常可以以祛湿为基础。也可以通过中医的辨证施治,个性化中药治疗。

4 展望

味觉感知与味觉异常的基础研究涉及发育分子生物学、神经科学及动物行为学等众多交叉领域,味觉障碍缺乏动物研究模型,临床上亦缺乏对味觉障碍的客观评价标准,是基础研究的难点所在。根据味觉感知的生理学过程,单纯的味觉障碍的直接因素包括味觉感受器功能受损以及味觉神经系统损伤,间接因素包括遗传因素、年龄性变化、微生物感染、药物使用、营养缺乏等等,致病因素错综复杂,且部分机制尚不明确,一些发现与结论有待考证,对临床病因诊断与针对性治疗产生挑战。未来研究应进一步深入探究味蕾发育重建机制、味觉信号外

周及中枢编译机制,从导致味觉障碍的直接病因入手,建立并完善味觉障碍诊断与治疗体系。

* * *

利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

- [1] LINDEMANN B. Receptors and transduction in taste. *Nature*, 2001, 413(6852): 219–225. doi: 10.1038/35093032.
- [2] CHANDRASHEKAR J, HOON M A, RYBA N J, *et al.* The receptors and cells for mammalian taste. *Nature*, 2006, 444(7117): 288–294. doi: 10.1038/nature05401.
- [3] THOMAS D C, CHABLANI D, PAREKH S, *et al.* Dysgeusia: a review in the context of COVID-19. *J Am Dent Assoc*, 2022, 153(3): 251–264. doi: 10.1016/j.adaj.2021.08.009.
- [4] MAHMOUD M M, ABUOHASHISH H M, KHAIRY D A, *et al.* Pathogenesis of dysgeusia in COVID-19 patients: a scoping review. *Eur Rev Med Pharmacol Sci*, 2021, 25(2): 1114–1134. doi: 10.26355/eurrev_202101_24683.
- [5] AZIZ M, PERISETTI A, LEE-SMITH W M, *et al.* Taste changes (dysgeusia) in COVID-19: a systematic review and meta-analysis. *Gastroenterology*, 2020, 159(3): 1132–1133. doi: 10.1053/j.gastro.2020.05.003.
- [6] AGYEMAN A A, CHIN K L, LANDERSDORFER C B, *et al.* Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc*, 2020, 95(8): 1621–1631. doi: 10.1016/j.mayocp.2020.05.030.
- [7] TONG J Y, WONG A, ZHU D, *et al.* The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*, 2020, 163(1): 3–11. doi: 10.1177/0194599820926473.
- [8] BRESLIN P A. An evolutionary perspective on food and human taste. *Curr Biol*, 2013, 23(9): R409–418. doi: 10.1016/j.cub.2013.04.010.
- [9] PELLEGRINI M, MERLO F D, AGNELLO E, *et al.* Dysgeusia in patients with breast cancer treated with chemotherapy--a narrative review. *Nutrients*, 2023, 15(1): 226. doi: 10.3390/nu15010226.
- [10] JAFARI A, ALAEE A, GHODS K. The etiologies and considerations of dysgeusia: a review of literature. *J Oral Biosci*, 2021, 63(4): 319–326. doi: 10.1016/j.job.2021.08.006.
- [11] CHI W J, MYERS J N, FRANK S J, *et al.* The effects of zinc on radiation-induced dysgeusia: a systematic review and meta-analysis. *Support Care Cancer*, 2020, 28(12): 1–12. doi: 10.1007/s00520-020-05578-8.
- [12] MORTAZAVI H, SHAFIEI S, SADR S, *et al.* Drug-related dysgeusia: a systematic review. *Oral Health Prev Dent*, 2018, 16(6): 499–507. doi: 10.3290/j.ohpd.a41655.
- [13] SYED Q, HENDLER K T, KONCILJA K. The impact of aging and medical status on dysgeusia. *Am J Med*, 2016, 129(7): 753.e1–6. doi: 10.1016/j.amjmed.2016.02.003.

- [14] FINGER T E, BARLOW L A. Cellular diversity and regeneration in taste buds. *Curr Opin Physiol*, 2021, 20: 146–153. doi: [10.1016/j.cophys.2021.01.003](https://doi.org/10.1016/j.cophys.2021.01.003).
- [15] DULAC C. The physiology of taste, vintage 2000. *Cell*, 2000, 100(6): 607–610. doi: [10.1016/s0092-8674\(00\)80697-2](https://doi.org/10.1016/s0092-8674(00)80697-2).
- [16] NELSON G, HOON M A, CHANDRASHEKAR J, *et al.* Mammalian sweet taste receptors. *Cell*, 2001, 106(3): 381–390. doi: [10.1016/s0092-8674\(01\)00451-2](https://doi.org/10.1016/s0092-8674(01)00451-2).
- [17] ZHAO G Q, ZHANG Y, HOON M A, *et al.* The receptors for mammalian sweet and umami taste. *Cell*, 2003, 115(3): 255–266. doi: [10.1016/s0092-8674\(03\)00844-4](https://doi.org/10.1016/s0092-8674(03)00844-4).
- [18] CHANDRASHEKAR J, MUELLER K L, HOON M A, *et al.* T2Rs function as bitter taste receptors. *Cell*, 2000, 100(6): 703–711. doi: [10.1016/s0092-8674\(00\)80706-0](https://doi.org/10.1016/s0092-8674(00)80706-0).
- [19] XI R, ZHENG X, TIZZANO M. Role of taste receptors in innate immunity and oral health. *J Dent Res*, 2022, 101(7): 759–768. doi: [10.1177/00220345221077989](https://doi.org/10.1177/00220345221077989).
- [20] DONG H, LIU J, ZHU J, *et al.* Oral microbiota-host interaction mediated by taste receptors. *Front Cell Infect Microbiol*, 2022, 12: 802504. doi: [10.3389/fcimb.2022.802504](https://doi.org/10.3389/fcimb.2022.802504).
- [21] 陆洋宇, 席苒琀, 郑欣, 等. 味觉受体信号转导机制及对微生物的调控. *华西口腔医学杂志*, 2017, 35(5): 549–554. doi: [10.7518/hxkq.2017.05.020](https://doi.org/10.7518/hxkq.2017.05.020).
- [22] IWATA S, YOSHIDA R, NINOMIYA Y. Taste transductions in taste receptor cells: basic tastes and moreover. *Curr Pharm Des*, 2014, 20(16): 2684–2692. doi: [10.2174/13816128113199990575](https://doi.org/10.2174/13816128113199990575).
- [23] LIU L, SIMON S A. Acidic stimuli activates two distinct pathways in taste receptor cells from rat fungiform papillae. *Brain Res*, 2001, 923(1/2): 58–70. doi: [10.1016/s0006-8993\(01\)03190-0](https://doi.org/10.1016/s0006-8993(01)03190-0).
- [24] STEVENS D R, SEIFERT R, BUFE B, *et al.* Hyperpolarization-activated channels HCN1 and HCN4 mediate responses to sour stimuli. *Nature*, 2001, 413(6856): 631–635. doi: [10.1038/35098087](https://doi.org/10.1038/35098087).
- [25] BELTRAN L R, DAWID C, BELTRAN M, *et al.* The effect of pungent and tingling compounds from *piper nigrum* L. on background K^+ currents. *Front Pharmacol*, 2017, 8: 408. doi: [10.3389/fphar.2017.00408](https://doi.org/10.3389/fphar.2017.00408).
- [26] YE W, CHANG R B, BUSHMAN J D, *et al.* The K^+ channel KIR2.1 functions in tandem with proton influx to mediate sour taste transduction. *Proc Natl Acad Sci U S A*, 2016, 113(2): E229–38. doi: [10.1073/pnas.1514282112](https://doi.org/10.1073/pnas.1514282112).
- [27] ZHANG J, JIN H, ZHANG W, *et al.* Sour sensing from the tongue to the brain. *Cell*, 2019, 179(2): 392–402.e15. doi: [10.1016/j.cell.2019.08.031](https://doi.org/10.1016/j.cell.2019.08.031).
- [28] NOMURA K, NAKANISHI M, ISHIDATE F, *et al.* All-electrical Ca^{2+} -independent signal transduction mediates attractive sodium taste in taste buds. *Neuron*, 2020, 106(5): 816–829.e6. doi: [10.1016/j.neuron.2020.03.006](https://doi.org/10.1016/j.neuron.2020.03.006).
- [29] MCGINTY J W, TING H A, BILLIPP T E, *et al.* Tuft-cell-derived leukotrienes drive rapid anti-helminth immunity in the small intestine but are dispensable for anti-protist immunity. *Immunity*, 2020, 52(3): 528–541.e7. doi: [10.1016/j.immuni.2020.02.005](https://doi.org/10.1016/j.immuni.2020.02.005).
- [30] O'LEARY C E, SCHNEIDER C, LOCKSLEY R M. Tuft cells—systemically dispersed sensory epithelia integrating immune and neural circuitry. *Annu Rev Immunol*, 2019, 37: 47–72. doi: [10.1146/annurev-immunol-042718-041505](https://doi.org/10.1146/annurev-immunol-042718-041505).
- [31] ZHENG X, TIZZANO M, REDDING K, *et al.* Gingival solitary chemosensory cells are immune sentinels for periodontitis. *Nat Commun*, 2019, 10(1): 4496. doi: [10.1038/s41467-019-12505-x](https://doi.org/10.1038/s41467-019-12505-x).
- [32] ZHOU Z, XI R, LIU J, *et al.* TAS2R16 activation suppresses LPS-induced cytokine expression in human gingival fibroblasts. *Front Immunol*, 2021, 12: 726546. doi: [10.3389/fimmu.2021.726546](https://doi.org/10.3389/fimmu.2021.726546).
- [33] 刘佳鑫, 郑欣, 徐欣. 簇细胞的信号传导机制及生物学作用. *中华微生物学和免疫学杂志*, 2022, 42(8): 647–651. doi: [10.3760/cma.j.cn112309-20210929-00321](https://doi.org/10.3760/cma.j.cn112309-20210929-00321).
- [34] GREEN B G. From receptors to the brain: psychophysical clues to taste physiology. *Curr Opin Physiol*, 2021, 20: 154–158. doi: [10.1016/j.cophys.2020.12.010](https://doi.org/10.1016/j.cophys.2020.12.010).
- [35] LEE H, MACPHERSON L J, PARADA C A, *et al.* Rewiring the taste system. *Nature*, 2017, 548(7667): 330–333. doi: [10.1038/nature23299](https://doi.org/10.1038/nature23299).
- [36] HUMMEL T, LANDIS B N, HUTTENBRINK K B. Smell and taste disorders. *GMS Curr Top Otorhinolaryngol Head Neck Surg*, 2011, 10: Doc04. doi: [10.3205/cto000077](https://doi.org/10.3205/cto000077).
- [37] XU H, ZHONG L, DENG J, *et al.* High expression of ACE2 receptor of SARS-CoV-2 on the epithelial cells of oral mucosa. *Int J Oral Sci*, 2020, 12(1): 8. doi: [10.1038/s41368-020-0074-x](https://doi.org/10.1038/s41368-020-0074-x).
- [38] DOYLE M E, APPLETON A, LIU Q R, *et al.* Human type II taste cells express angiotensin-converting enzyme 2 and are infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Am J Pathol*, 2021, 191(9): 1511–1519. doi: [10.1016/j.ajpath.2021.05.010](https://doi.org/10.1016/j.ajpath.2021.05.010).
- [39] ROMAN G C, SPENCER P S, REIS J, *et al.* The neurology of COVID-19 revisited: a proposal from the environmental neurology specialty group of the world federation of neurology to implement international neurological registries. *J Neurol Sci*, 2020, 414: 116884. doi: [10.1016/j.jns.2020.116884](https://doi.org/10.1016/j.jns.2020.116884).
- [40] WITT M, MILLER I J, Jr. Comparative lectin histochemistry on taste buds in foliate, circumvallate and fungiform papillae of the rabbit tongue. *Histochemistry*, 1992, 98(3): 173–182. doi: [10.1007/BF00315876](https://doi.org/10.1007/BF00315876).
- [41] PUSHPASS R G, PELLICCIOTTA N, KELLY C, *et al.* Reduced salivary mucin binding and glycosylation in older adults influences taste in an *in vitro* cell model. *Nutrients*, 2019, 11(10): 2280. doi: [10.3390/nu1102280](https://doi.org/10.3390/nu1102280).
- [42] MILANETTI E, MIOTTO M, Di RIENZO L, *et al.* In-silico evidence for a two receptor based strategy of SARS-CoV-2. *Front Mol Biosci*, 2021, 8: 690655. doi: [10.3389/fmolb.2021.690655](https://doi.org/10.3389/fmolb.2021.690655).
- [43] VAIRA L A, SALZANO G, FOIS A G, *et al.* Potential pathogenesis of ageusia and anosmia in COVID-19 patients. *Int Forum Allergy Rhinol*, 2020, 10(9): 1103–1104. doi: [10.1002/alar.22593](https://doi.org/10.1002/alar.22593).
- [44] Van OORT S, KRAMER E, De GROOT J W, *et al.* Taste alterations and cancer treatment. *Curr Opin Support Palliat Care*, 2018, 12(2):

- 162–167. doi: [10.1097/SPC.0000000000000346](https://doi.org/10.1097/SPC.0000000000000346).
- [45] GALANIHA L T, NOLDEN A A. The role of saliva in taste dysfunction among cancer patients: mechanisms and potential treatment. *Oral Oncol*, 2022, 133: 106030. doi: [10.1016/j.oraloncology.2022.106030](https://doi.org/10.1016/j.oraloncology.2022.106030).
- [46] YAGI T, ASAKAWA A, UEDA H, *et al*. The role of zinc in the treatment of taste disorders. *Recent Pat Food Nutr Agric*, 2013, 5(1): 44–51. doi: [10.2174/2212798411305010007](https://doi.org/10.2174/2212798411305010007).
- [47] RISSO D, DRAYNA D, MORINI G. Alteration, reduction and taste loss: main causes and potential implications on dietary habits. *Nutrients*, 2020, 12: 11. doi: [10.3390/nu12113284](https://doi.org/10.3390/nu12113284).
- [48] TSUCHIYA H. Gustatory and saliva secretory dysfunctions in COVID-19 patients with zinc deficiency. *Life (Basel)*, 2022, 12(3): 353. doi: [10.3390/life12030353](https://doi.org/10.3390/life12030353).
- [49] SMITH A, FARBMAN A, DANCIS J. Absence of taste-bud papillae in familial dysautonomia. *Science*, 1965, 147(3661): 1040–1041. doi: [10.1126/science.147.3661.1040](https://doi.org/10.1126/science.147.3661.1040).
- [50] CHAMOUN E, MUTCH D M, ALLEN-VERCOE E, *et al*. A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviors, and health. *Crit Rev Food Sci Nutr*, 2018, 58(2): 194–207. doi: [10.1080/10408398.2016.1152229](https://doi.org/10.1080/10408398.2016.1152229).
- [51] KANO M, SHIMIZU Y, OKAYAMA K, *et al*. Quantitative study of ageing epiglottal taste buds in humans. *Gerodontology*, 2007, 24(3): 169–172. doi: [10.1111/j.1741-2358.2007.00165.x](https://doi.org/10.1111/j.1741-2358.2007.00165.x).
- [52] MILLER I J, Jr. Variation in human taste bud density as a function of age. *Ann N Y Acad Sci*, 1989, 561: 307–319. doi: [10.1111/j.1749-6632.1989.tb20991.x](https://doi.org/10.1111/j.1749-6632.1989.tb20991.x).
- [53] SHIN Y K, CONG W N, CAI H, *et al*. Age-related changes in mouse taste bud morphology, hormone expression, and taste responsivity. *J Gerontol A Biol Sci Med Sci*, 2012, 67(4): 336–344. doi: [10.1093/geronol/glr192](https://doi.org/10.1093/geronol/glr192).
- [54] WHIDDON Z D, RYNBERG S T, MAST T G, *et al*. Aging decreases chorda-tympani nerve responses to nacl and alters morphology of fungiform taste pores in rats. *Chem Senses*, 2018, 43(2): 117–128. doi: [10.1093/chemse/bjx076](https://doi.org/10.1093/chemse/bjx076).
- [55] FENG P, HUANG L, WANG H. Taste bud homeostasis in health, disease, and aging. *Chem Senses*, 2014, 39(1): 3–16. doi: [10.1093/chemse/bjt059](https://doi.org/10.1093/chemse/bjt059).
- [56] FENG Y, LICANDRO H, MARTIN C, *et al*. The associations between biochemical and microbiological variables and taste differ in whole saliva and in the film lining the tongue. *Biomed Res Int*, 2018, 2018: 2838052. doi: [10.1155/2018/2838052](https://doi.org/10.1155/2018/2838052).
- [57] QUIRYNEN M, AVONTROODT P, SOERS C, *et al*. Impact of tongue cleansers on microbial load and taste. *J Clin Periodontol*, 2004, 31(7): 506–510. doi: [10.1111/j.0303-6979.2004.00507.x](https://doi.org/10.1111/j.0303-6979.2004.00507.x).
- [58] OHNO T, UEMATSU H, NOZAKI S, *et al*. Improvement of taste sensitivity of the nursed elderly by oral care. *J Med Dent Sci*, 2003, 50(1): 101–107.
- [59] TAKAHASHI N. Oral microbiome metabolism: from “who are they”? to “what are they doing”? *J Dent Res*, 2015, 94(12): 1628–1637. doi: [10.1177/0022034515606045](https://doi.org/10.1177/0022034515606045).
- [60] GARDNER A, SO P W, CARPENTER G H. Intraoral microbial metabolism and association with host taste perception. *J Dent Res*, 2020, 99(6): 739–745. doi: [10.1177/0022034520917142](https://doi.org/10.1177/0022034520917142).
- [61] FENG S, ACHOUTE L, MARGOLSKEE R F, *et al*. Lipopolysaccharide-induced inflammatory cytokine expression in taste organoids. *Chem Senses*, 2020, 45(3): 187–194. doi: [10.1093/chemse/bjaa002](https://doi.org/10.1093/chemse/bjaa002).
- [62] 朱健慧, 郑欣, 彭显, 等. 细菌脂多糖对甜味受体T1R2可变剪接与功能的调控作用. *华西口腔医学杂志*, 2021, 39(4): 469–474. doi: [10.7518/hxkq.2021.04.015](https://doi.org/10.7518/hxkq.2021.04.015).
- [63] 邓瑾成. 鼓索神经损伤引起味觉障碍临床分析. *中国实用神经疾病杂志*, 2015(11): 97–98. doi: [10.3969/j.issn.1673-5110.2015.11.066](https://doi.org/10.3969/j.issn.1673-5110.2015.11.066).
- [64] TAILLIBERT S, BAZIN B, PIERROT-DESEILLIGNY C. Dysgeusia resulting from internal carotid dissection. A limited glossopharyngeal nerve palsy. *J Neurol Neurosurg Psychiatry*, 1998, 64(5): 691–692. doi: [10.1136/jnnp.64.5.691](https://doi.org/10.1136/jnnp.64.5.691).
- [65] PASCUAL-LEONE A, ALTAFULLAH I, DHUNA A. Hemiageusia: an unusual presentation of multiple sclerosis. *J Neurol Neurosurg Psychiatry*, 1991, 54(7): 657. doi: [10.1136/jnnp.54.7.657](https://doi.org/10.1136/jnnp.54.7.657).
- [66] ONODA K, IKEDA M. Gustatory disturbance due to cerebrovascular disorder. *Laryngoscope*, 1999, 109(1): 123–128. doi: [10.1097/00005537-199901000-00024](https://doi.org/10.1097/00005537-199901000-00024).
- [67] ROUSSEAU M, MULLER P, GAHIDE I, *et al*. Disorders of smell, taste, and food intake in a patient with a dorsomedial thalamic infarct. *Stroke*, 1996, 27(12): 2328–2330. doi: [10.1161/01.str.27.12.2328](https://doi.org/10.1161/01.str.27.12.2328).
- [68] SHAH M, DEEB J, FERNANDO M, *et al*. Abnormality of taste and smell in Parkinson's disease. *Parkinsonism Relat Disord*, 2009, 15(3): 232–237. doi: [10.1016/j.parkreldis.2008.05.008](https://doi.org/10.1016/j.parkreldis.2008.05.008).
- [69] SCHIFFMAN S S, CLARK C M, WARWICK Z S. Gustatory and olfactory dysfunction in dementia: not specific to Alzheimer's disease. *Neurobiol Aging*, 1990, 11(6): 597–600. doi: [10.1016/0197-4580\(90\)90023-s](https://doi.org/10.1016/0197-4580(90)90023-s).
- [70] 郑欣, 徐欣, 何金枝, 等. 哺乳动物味蕾发育与重建的研究现状. *华西口腔医学杂志*, 2018, 36(5): 552–558. doi: [10.7518/hxkq.2018.05.016](https://doi.org/10.7518/hxkq.2018.05.016).
- [71] CASTILLO-AZOFEIFA D, LOSACCO J T, SALCEDO E, *et al*. Sonic hedgehog from both nerves and epithelium is a key trophic factor for taste bud maintenance. *Development*, 2017, 144(17): 3054–3065. doi: [10.1242/dev.150342](https://doi.org/10.1242/dev.150342).
- [72] LU W J, MANN R K, NGUYEN A, *et al*. Neuronal delivery of Hedgehog directs spatial patterning of taste organ regeneration. *Proc Natl Acad Sci U S A*, 2018, 115(2): E200–E209. doi: [10.1073/pnas.1719109115](https://doi.org/10.1073/pnas.1719109115).
- [73] GUAGLIARDO N A, HILL D L. Fungiform taste bud degeneration in C57BL/6J mice following chorda-lingual nerve transection. *J Comp Neurol*, 2007, 504(2): 206–216. doi: [10.1002/cne.21436](https://doi.org/10.1002/cne.21436).
- [74] OAKLEY B, LAWTON A, RIDDLE D R, *et al*. Morphometric and immunocytochemical assessment of fungiform taste buds after interruption of the chorda-lingual nerve. *Microsc Res Tech*, 1993, 26(3): 187–195. doi: [10.1002/jemt.1070260302](https://doi.org/10.1002/jemt.1070260302).

- [75] TORRES-FUENTES C, SCHELLEKENS H, DINAN T G, *et al.* The microbiota-gut-brain axis in obesity. *Lancet Gastroenterol Hepatol*, 2017, 2(10): 747–756. doi: 10.1016/S2468-1253(17)30147-4.
- [76] KIM B, KANAI M I, OH Y, *et al.* Response of the microbiome-gut-brain axis in *Drosophila* to amino acid deficit. *Nature*, 2021, 593(7860): 570–574. doi: 10.1038/s41586-021-03522-2.
- [77] VASCELLARI S, MELIS M, COSSU G, *et al.* Genetic variants of TAS2R38 bitter taste receptor associate with distinct gut microbiota traits in Parkinson's disease: a pilot study. *Int J Biol Macromol*, 2020, 165(Pt A): 665–674. doi: 10.1016/j.ijbiomac.2020.09.056.
- [78] LEUNG R, COVASA M. Do gut microbes taste? *Nutrients*, 2021, 13(8): 2581. doi: 10.3390/nu13082581.
- [79] NAKAMURA Y, SANEMATSU K, OHTA R, *et al.* Diurnal variation of human sweet taste recognition thresholds is correlated with plasma leptin levels. *Diabetes*, 2008, 57(10): 2661–2665. doi: 10.2337/db07-1103.
- [80] SHIN Y K, MARTIN B, GOLDEN E, *et al.* Modulation of taste sensitivity by GLP-1 signaling. *J Neurochem*, 2008, 106(1): 455–463. doi: 10.1111/j.1471-4159.2008.05397.x.
- [81] YOSHIDA R, OHKURI T, JYOTAKI M, *et al.* Endocannabinoids selectively enhance sweet taste. *Proc Natl Acad Sci U S A*, 2010, 107(2): 935–939. doi: 10.1073/pnas.0912048107.
- [82] HERNES S, ZHAO F L, LU S G, *et al.* Expression and physiological actions of cholecystokinin in rat taste receptor cells. *J Neurosci*, 2002, 22(22): 10018–10029. doi: 10.1523/JNEUROSCI.22-22-10018.2002.
- [83] HURTADO M D, ACOSTA A, RIVEROS P P, *et al.* Distribution of Y-receptors in murine lingual epithelia. *PLoS One*, 2012, 7(9): e46358. doi: 10.1371/journal.pone.0046358.
- [84] SHIN Y K, MARTIN B, KIM W, *et al.* Ghrelin is produced in taste cells and ghrelin receptor null mice show reduced taste responsivity to salty (NaCl) and sour (citric acid) tastants. *PLoS One*, 2010, 5(9): e12729. doi: 10.1371/journal.pone.0012729.
- [85] LARRAUFIE P, MARTIN-GALLAUSIAUX C, LAPAQUE N, *et al.* SCFAs strongly stimulate PYY production in human enteroendocrine cells. *Sci Rep*, 2018, 8(1): 74. doi: 10.1038/s41598-017-18259-0.
- [86] CHRISTIANSEN C B, GABE M B N, SVENDSEN B, *et al.* The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. *Am J Physiol Gastrointest Liver Physiol*, 2018, 315(1): G53–G65. doi: 10.1152/ajpgi.00346.2017.
- [87] DALILE B, Van OUDENHOVE L, VERVLIET B, *et al.* The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol*, 2019, 16(8): 461–478. doi: 10.1038/s41575-019-0157-3.
- [88] [No author]. International Classification of Orofacial Pain, 1st edition (ICOP). *Cephalalgia*, 2020, 40(2): 129–221. doi: 10.1177/0333102419893823.
- [89] NASRI-HEIR C, SHIGDAR D, ALNAAS D, *et al.* Primary burning mouth syndrome: literature review and preliminary findings suggesting possible association with pain modulation. *Quintessence Int*, 2017, 49(1): 49–60. doi: 10.3290/j.qi.a39403.
- [90] KHAN J, NOMA N, KALLADKA M. Taste changes in orofacial pain conditions and coronavirus disease 2019: a review. *Front Oral Maxillofac Med*, 2021, 3: 5. doi: 10.21037/fomm-20-68.
- [91] SILVA C S, DIAS V R, ALMEIDA J A, *et al.* Effect of heavy consumption of alcoholic beverages on the perception of sweet and salty taste. *Alcohol Alcohol*, 2016, 51(3): 302–326. doi: 10.1093/alcal/agv116.
- [92] RISSO D S, HOWARD L, VANWAES C, *et al.* A potential trigger for pine mouth: a case of a homozygous phenylthiocarbamide taster. *Nutr Res*, 2015, 35(12): 1122–1125. doi: 10.1016/j.nutres.2015.09.011.
- [93] BOSCOLO-RIZZO P, BORSETTO D, FABBRIS C, *et al.* Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg*, 2020, 146(8): 729–732. doi: 10.1001/jamaoto.2020.1379.
- [94] CANON F, NEIERS F, GUICHARD E. Saliva and flavor perception: perspectives. *J Agric Food Chem*, 2018, 66(30): 7873–7879. doi: 10.1021/acs.jafc.8b01998.
- [95] CIFUENTES M, Del BARRIO-DÍAZ P, VERA-KELLET C. Pilocarpine and artificial saliva for the treatment of xerostomia and xerophthalmia in Sjögren syndrome: a double-blind randomized controlled trial. *Br J Dermatol*, 2018, 179(5): 1056–1061. doi: 10.1111/bjd.16442.
- [96] OSAKI T, OHSHIMA M, TOMITA Y, *et al.* Clinical and physiological investigations in patients with taste abnormality. *J Oral Pathol Med*, 1996, 25(1): 38–43. doi: 10.1111/j.1600-0714.1996.tb01221.x.
- [97] SINGH C V, JAIN S, PARVEEN S. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in dysgeusia in COVID-19 patients. *Am J Otolaryngol*, 2021, 42(3): 102892. doi: 10.1016/j.amjoto.2020.102892.
- [98] MCCONNELL R J, MENENDEZ C E, SMITH F R, *et al.* Defects of taste and smell in patients with hypothyroidism. *Am J Med*, 1975, 59(3): 354–364. doi: 10.1016/0002-9343(75)90394-0.
- [99] 罗冠宇, 李建强. 味觉缺失案. *中国针灸*, 2021, 41(5): 582. doi: 10.13703/j.0255-2930.20200601-k0004.
- [100] 康健, 邵妍. 眼针埋针疗法联合体针治疗急性期周围性面瘫味觉障碍临床疗效观察. *辽宁中医药大学学报*, 2023, 25(1): 35–38. doi: 10.13194/j.issn.1673-842x.2023.01.008.
- [101] 王兴丽, 杨向东, 张伟锋, 等. 白血病化疗相关味觉改变的中医综合施治研究. *湖北中医杂志*, 2021, 43(12): 53–55.
- [102] 李宇, 白莉, 苗明三. 基于数据挖掘的中药防范炎症因子过度表达致“炎症风暴”用药规律分析. *中药药理与临床*, 2020, 36(2): 32–35.

(2023-01-17收稿, 2023-01-20修回)

编辑 姜 恬

