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·综述·

偏头痛前驱症状的生物学内涵

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摘　要：近年来，偏头痛前驱期因其可能的头痛预测作用及早期头痛干预机会为人所重视。打呵欠、疲乏、颈强直、感知觉超敏症状（畏光、畏声、畏嗅）均是常见的偏头痛前驱症状。然而，关于偏头痛前驱症状的预测效能及其可能机制，目前结论尚未统一。偏头痛前驱症状可分为感知觉超敏症状、睡眠及认知相关症状、自主神经症状和其他症状。前驱症状与触发因素及偏头痛伴随症状的准确区分，目前仍未达成统一。疲乏、情绪变化、颈强直是青少年期患者常见的前驱症状。目前对偏头痛前驱症状的病理生理机制研究仍处于初步阶段。打呵欠是偏头痛具有预测意义的前驱症状之一，通常认为与多巴胺能神经元改变密切相关，在偏头痛病理生理中，可由多巴胺能D1、D2、D3受体介导。颈强直是偏头痛常见前驱症状，与多巴胺、5-羟色胺能神经元激活有关。下丘脑在偏头痛前驱期激活，可能是导致前驱期颈强直的重要原因。恶心作为偏头痛患者常见前驱症状，其病理生理学起源仍存在争议。目前的研究表明，前驱期恶心与5-羟色胺代谢改变有关。感知觉超敏症状包括皮肤异常性疼痛和畏光、畏声、畏嗅，在前驱期中丘脑激活已被证实与皮肤异常性疼痛和畏光相关。　[国际神经病学神经外科学杂志, 2021, 48(6): 559–563.]

关键词：偏头痛；前驱症状；感知觉超敏；打呵欠；颈强直；恶心

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Biological connotation of premonitory symptoms in migraine

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Abstract: In recent years, the premonitory stage of migraine has attracted much attention due to its role in prediction of headache and intervention of early-stage headache. Yawning, fatigue, neck stiffness, and sensory hyper excitability (photophobia, phonophobia, and osmophobia) are common premonitory symptoms in migraine. However, no unified conclusion has been reached on the predictive performance of premonitory symptoms in migraine and possible mechanism. The premonitory symptoms in migraine can be classified as sensory hypersensitivity symptoms, sleep- and cognition-related symptoms, autonomic symptoms, and other symptoms. No consensus has been reached on the precise distinction between premonitory symptoms/triggers and associated symptoms of migraine. Fatigue, mood changes, and neck stiffness are common premonitory symptoms in adolescents. At present, the research on the path physiological mechanism of premonitory symptoms in migraine is still in the preliminary stage. Yawning is one of the premonitory symptoms in migraine with predictive significance, which is generally believed to be closely associated with the changes in dopaminergic neurons, and in the path physiology of migraine, it can be mediated by dopaminergic D1, D2, and D3 receptors. Neck stiffness is a common premonitory symptom of migraine, which is associated with the activation of dopaminergic and serotonergic neurons, and the hypothalamusis activated in the premonitory phase of migraine, which may be an important cause of neck stiffness in the premonitory phase. Nausea is another common premonitory symptom in migraine, but there are still controversies over its pathophysiological origin, and

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current studies have shown that nausea in the premonitory phase is associated with the metabolic change in 5-hydroxytryptamine. The symptoms of sensory hyper excitability include cutaneous allodynia, photophobia, phonophobia, and osmophobia, and the activation of the thalamus in the premonitory phase has been proved to be associated with cutaneous allodynia and photophobia in migraine. [Journal of International Neurology and Neurosurgery, 2021, 48(6): 559-563.]

Keywords: migraine; prodrome symptom; sensory hyper excitability; yawning; neck stiffness; nausea

偏头痛是临床常见的原发性头痛，具有高度致残性，其病因和发病机制仍未完全阐明。前驱期（prodrome phase or premonitory phase）指无先兆偏头痛的头痛发作前或有先兆偏头痛的先兆出现前的症状期，最长可持续48 h[1]，部分偏头痛患者在前驱期即可根据既往前驱症状一定程度预测头痛发作，为偏头痛的早期用药提供了可能靶点。本文将从偏头痛前驱症状分类、前驱症状与触发因素（trigger）的鉴别、青少年前驱症状表型及常见前驱症状病理生理学机制等方面进行综述，以进一步阐述偏头痛前驱期生物学内涵。

1 偏头痛前驱症状概述

1.1 前驱症状分类

目前，已知的前驱症状包括：①感知觉超敏症状（sensory hyperexcitability）：皮肤异常性疼痛（cutaneous allodynia）和畏光（photophobia）、畏声（phonophobia）、畏嗅（osmophobia）；②情绪、睡眠和认知相关症状：焦虑、抑郁、激惹、疲乏、注意力集中困难、嗜睡、早醒、多动等；③自主神经症状：腹胀、恶心、多尿、竖毛、面色苍白、口渴等；④其他症状：打呵欠（yawning）、颈强直（neck stiffness）、对特定食物（如巧克力、红酒）的渴望、眼部不适等[2-5]。

在回顾性研究中，打呵欠、心情改变、疲乏、颈部症状（颈痛、颈强直）、畏光是常见的前驱症状，且前驱症状越重，偏头痛程度也越严重[6]。早期研究认为，打呵欠、情绪变化、阅读和写作困难是最具有预测性的前驱症状[2]，近来则认为畏光、嗜睡、打呵欠、口渴和视力模糊的预测意义较高[7]。较为罕见的前驱症状如竖毛、腹胀等，可能与患者的个体易感性差异有关。偏头痛患者个体之间潜在的头痛诱发因素和前驱症状存在高度异质性，进一步强调了偏头痛个体化管理和治疗的重要性[8]。在垂体腺苷酸环化酶激活肽-38（pituitary adenylate cyclase-activating peptide-38, PACAP38）静脉注射诱导的偏头痛临床实验中，疲乏、恶心和打呵欠是偏头痛样发作患者报告的最常见的非头痛症状[9]。硝酸甘油也可诱导偏头痛患者药物源性前驱症状，如疲乏、打呵欠、颈强直[10]。

1.2 前驱症状、触发因素与伴随症状

关于偏头痛前驱症状的争论一直存在。一方面，畏光、畏声、恶心等症状既是国际头痛协会认定的偏头痛伴随症状[1]，也是常见的前驱症状，二者之间难以明确界定。另一方面，触发因素和前驱症状之间或有重合，如何准确区分和界定，仍有待商榷。例如，颈强直是常见的偏头痛前驱症状[6]，可增加49%的偏头痛发生风险[8]，但也有学者认为颈强直更有可能是偏头痛发作特征，而非前驱症状[11]。将偏头痛患者暴露于常见触发因素（如闪光、特定的食物和气味），认为头痛由上述触发因素引起的患者，在前驱期更倾向于出现畏光、食物渴望和畏嗅等前驱症状[12]。对于偏头痛前驱期和前驱症状的准确定义，目前仍存在争议，更进一步的前驱期影像学和分子生物学研究，或许有助于准确定义分期。

1.3 青少年前驱症状

由于儿童和青少年在病史采集、交流和认知、躯体表型等方面与成年人存在一定差异，这类人群中前驱症状调查相对少见。早期研究中儿童最常见的前驱症状是面部变化（面色苍白、黑眼圈）、疲乏和易激惹，其中面部变化是儿童较特征的前驱症状[13]，可能与儿童神经调节较弱有关。在18岁以下儿童中报告的偏头痛前驱症状，其总体临床表型与成人相当，疲乏、情绪变化和颈强直是最常见的前驱症状[14]。最近的研究印证了疲乏和情绪变化在儿童前驱症状中的高比例，并指出焦虑与前驱症状显著相关[15]。

2 前驱症状相关机制

2.1 打呵欠

打呵欠是一种系统发育较为古老的定型行为，也是偏头痛最具有预测意义的前驱症状之一[2]，涉及包括多巴胺（dopamine, DA）在内的多种神经递质改变。与打呵欠相关的病理生理机制存在许多学说，其中多巴胺能学说受到广泛推崇。一项关于偏头痛与打呵欠相关性的横断面研究显示，在纳入的339例患者中，143例患者在前驱期出现至少一种多巴胺能下丘脑（hypothalamus）症状，其中打呵欠最常见（21.2%）[16]。

早期研究中，多巴胺D1/D2受体激动剂阿扑吗啡（apomorphine）可以在人和大鼠中引起打呵欠[17-18]，在患者中还观察到恶心、呕吐、眩晕、出汗等多巴胺能症状[17]，而在大鼠中存在阴茎勃起、生殖器梳洗等症状[18]。垂体切除可消除大鼠阿扑吗啡影响，证实打呵欠可由下丘脑—垂体多巴胺能通路经由D1/D2受体介导[18]。在雄性大鼠下丘脑室旁核中注射普拉克索和阿扑吗啡时，通过激活多巴胺D2受体，钙离子内流和一氧化氮释放而引起打呵欠和阴茎勃起[19]。多巴胺也可激活下丘脑室旁核产生催产素，通过D3多巴胺受体和随后的胆碱能传递引起打呵欠[20]。多巴胺还可通过调节下丘脑A11核的投射调

节三叉神经颈复合体(trigeminocervical complex, TCC)内神经元放电[21]。由此可见,不同多巴胺能通路激活均可导致打呵欠。临床病例报告中证实多巴胺可介导打呵欠—疲劳综合征(Yawning-Fatigue syndrome)[22],侧面印证了早期研究中多巴胺受体激动剂可诱导偏头痛患者恶心、呕吐、打呵欠[17]的结论。综上,打呵欠与多巴胺能神经元改变密切相关,而其在偏头痛前驱期中的具体机制,则有赖于未来进一步影像学和分子生物学研究。

2.2　颈强直

颈强直是另一项十分常见的前驱症状,存在于49.7%的偏头痛患者[2]。其与偏头痛之间的联系,不仅止于前驱期。经历发作期颈部不适(超过2/3的偏头痛患者头痛发作时颈部疼痛、酸胀或僵硬感)的偏头痛患者中有77%存在前驱期[23]。各种颈部不适症状中,颈强直在偏头痛患者中反映最多。下丘脑后部的A11核对通过多巴胺D2和5-羟色胺(5-hydroxytryptamine, 5-HT)1B/1D受体介导的伤害性三叉神经传递具有强直性抑制作用[21]。若偏头痛早期阶段存在下丘脑功能障碍,则可以消除这种抑制作用,从而有利于三叉神经痛觉传导。下丘脑在偏头痛前驱期的激活近年来已受到广泛关注,在头痛发作前24 h,下丘脑对三叉神经痛性刺激的反应性即开始增加,且与三叉神经脊束核(spinal trigeminal nuclei)和背侧桥脑(dorsal rostral pons)间功能耦合发生改变[24],为前驱期颈强直的发生提供进一步论证依据。由于三叉神经和C1-C2颈神经间存在中央连接,可以将其感觉为颈部不适感[25],表现为颈部肌肉收缩和僵硬感;而近期研究表明,C1-C2颈神经激活,可导致前额部疼痛[26],前额部同时也是偏头痛患者常见的头痛部位。在硝酸甘油诱导的发作性偏头痛(episodic migraine)患者前驱期进行扫描,下丘脑后外侧(posterolateral hypothalamus)、导水管周围灰质(periaqueductal grey, PAG)、背侧桥脑等在内的各种皮质区均存在激活[27];功能成像研究表明,脑桥与边缘叶连接方向改变可能也参与前驱期病理生理过程[28]。而下丘脑、边缘叶、导水管周围灰质等结构已在先前研究中证实与疼痛处理相关,这些结构的激活,可能是偏头痛患者前驱期颈强直的始动因素。

2.3　恶心

以恶心为前驱症状的偏头痛患者并不罕见,但前驱期恶心的起源仍未得到确切解释。曾有学者认为,恶心起源于头痛相关三叉神经核中三叉神经血管神经元与孤束核(nucleus tractus solitaris, NTS)和臂旁核(parabrachial nucleus)中神经元之间的相互连接[29],而近期正电子发射计算机断层显像(positron emission tomography, PET)研究则证实在以恶心为前驱症状的患者中,恶心的发生与NTS、迷走神经运动背核(dorsal motor nucleus of the vagus nerve)、疑核(the nucleus ambiguus)和PAG激活有关,而无此前驱症状的对照组未激活[30]。

也有学者认为前驱期恶心症状的存在与体内5-HT水平改变有关。在实验条件下可激活包括孤束核尾内侧核在内的三叉神经伤害性通路[31],而将5-HT 1B/1D受体激动剂曲普坦直接注入NTS可影响这一通路[32],从而引起恶心在内的多种症状。5-HT在胃肠道组织中的局部释放会激活迷走神经传入纤维,而其在血流中的水平升高则作用于化学感受器触发区,从而引起恶心[33]。最近的代谢组学研究也表明,偏头痛患者发作间期血清中色氨酸(5-HT前体物质)水平降低[34]。

2.4　感知觉超敏

偏头痛患者中常见各种感知觉超敏症状,包括皮肤异常性疼痛和畏光、畏声、畏嗅。感知觉超敏不但作为常见的伴随症状与头痛共存,在部分患者中也先于头痛发生,作为偏头痛前驱症状出现。

皮肤异常性疼痛的潜在机制被认为是由于丘脑后核(posterior thalamic nuclei)中的三级三叉神经血管神经元致敏引起。一项功能磁共振成像(functional magnetic resonance imaging, fMRI)研究探讨了与丘脑后部相关的有效连接途径,发现后丘脑(posterior thalamus, PTH)与参与疼痛处理的其他皮质或皮质下区域之间的有效连接途径被破坏[35],这可能与偏头痛中皮肤异常性疼痛的发生存在关联。

前驱期49%患者出现畏光[2],Noseda等[36]发现,硬膜敏感(对硬脑膜刺激存在反应性)光敏性非成像视网膜神经节细胞(intrinsically photosensitive retinal ganglion cells, ipRGCs)和三叉神经血管神经元投射到丘脑髓核,然后投射到枕叶皮质,证实了丘脑在偏头痛畏光中的作用。而光敏感性PET研究已证实前驱期畏光患者较无畏光患者,楔叶右视觉皮质(extrastriate visual areas, BA18)、右中央前回(right precentral gyrus, BA4)区域有显著激活[37]。前驱期畏光不依赖头痛及三叉神经伤害性传导,提示这种畏光可能由中枢驱动。静息态功能连接(resting-state functional connectivity, RSFC)磁共振成像研究发现,在PACAP38注射后,显著、感觉运动和默认模式网络连接模式均发生变化[38],即在偏头痛早期阶段,患者认知、情绪开始发生改变,侧面印证了偏头痛前驱期各前驱症状可能的中枢机制。

3　小结

打呵欠、疲乏、畏光、颈强直等均是成人中常见的前驱症状;而在儿童和青少年人群中相关研究数量较少。已知的具有代表性的青少年前驱症状包括疲乏、面部变化、颈强直。偏头痛各常见前驱症状的病理生理学机制仍未完全阐明。已知的可能病理生理学机制包括多巴胺能机制在打呵欠中发挥重要作用;包含下丘脑在内的多个脑区的前驱期激活与颈强直关系密切;恶心与5-HT能

神经元功能密切相关。未来的研究要进一步扩大样本量、精确捕捉前驱期和提高影像分辨率。前驱期表型、影像学及分子生物学的深入研究,有助于探索偏头痛的发生机制和进一步完善早期治疗方案。

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