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·综 述·

特异性促炎症消退介质在围手术期神经认知障碍中的研究进展

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[摘 要] 围手术期神经认知障碍(perioperative neurocognitive disorders，PND)是老年患者术后常见的并发症，包括谵妄和术后长期记忆障碍。PND可导致患者住院时间延迟长，病死率增高，预后较差。炎症是PND的重要病理机制，炎症不能及时消退与认知功能障碍密切相关。目前认为炎症消退与炎症发生一样，是主动程序性过程，其主要由多不饱和脂肪酸衍生的特异性促炎症消退介质(specialized pro-resolving mediators，SPMs)介导。SPMs可通过减少炎症细胞浸润，调节小胶质细胞表型及星形胶质细胞活性等方式减轻围手术期中枢神经系统炎症，有望为PND的治疗提供新的策略。

[关键词] 特异性促炎症消退介质；围手术期神经认知障碍；炎症消退

Research progress of specialized pro-resolving mediators on perioperative neurocognitive disorders

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ABSTRACT Perioperative neurocognitive disorders (PND) are the common postoperative complications in the elderly patients, including delirium and postoperative long-term memory impairment. PND can lead to prolonged hospital stay, increased mortality, and poor prognosis. Inflammation is an important pathological mechanism of perioperative neurocognitive impairment, and the timely resolution of inflammation is closely related to cognitive dysfunction. It is currently believed that resolution of inflammatory response is an active procedural process, which is mainly mediated by polyunsaturated fatty acid-derived specialized pro-resolving mediators (SPMs). SPMs can reduce perioperative central nervous system inflammation by ameliorating infiltration of inflammatory cells,

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modulating microglia phenotype and astrocyte activity, which is expected to provide a new strategy for the treatment of PND.

KEY WORDS specialized pro-resolving mediators; perioperative neurocognitive disorders; inflammation resolving

手术是以治疗为目的，但围手术期可能会出现严重并发症，尤其是年老体弱患者。围手术期神经认知障碍(perioperative neurocognitive disorders，PND)，也称为术后认知功能障碍(postoperative cognitive dysfunction，POCD)，包括认知功能的急性变化(即谵妄)和长期记忆障碍[1]。PND严重影响患者预后，导致手术患者病死率升高，并使患者面临更大的并发症风险，包括永久性痴呆[2]。围手术期神经炎症是PND的重要致病因素。炎症是机体的主动防御反应，但炎症过度或炎症消退障碍会造成患者器官功能恢复延迟，机体受损。当炎症发展到一定阶段，炎症开始逐渐消退，最近研究[3-4]发现炎症消退和炎症发生一样，是机体主动程序性过程，该过程由一系列促炎症消退介质介导，其中最主要的一类是由多不饱和脂肪酸衍生而来的脂性介质，也被称为特异性促消退介质(specialized pro-resolving mediators，SPMs)。当SPMs产生不足或通路受阻时，会导致炎症迁延不愈，器官功能恢复障碍。研究[3-4]发现：SPMs可通过调节中性粒细胞、巨噬细胞、淋巴细胞等免疫细胞促进炎症消退，加速围手术期器官功能恢复。本文就围手术期神经炎症以及SPMs对围手术期神经认知障碍的作用进行综述。

1 围手术期炎症与PND

在手术过程中，除了麻醉药物对中枢神经系统(central nervous system，CNS)的直接影响外，创伤和无菌损伤引发的急性炎症也可对大脑功能产生影响，导致PND样变化[5]。炎症反应是机体的主动防御反应，但炎症反应失调会导致广泛的器官功能障碍和组织损伤。促炎细胞因子、警报素及白三烯等介质的释放可对大脑产生长期影响，导致神经炎症、神经毒性和随后的记忆障碍。全身炎症影响CNS功能的机制尚未完全阐明。全身性细胞因子通过不同的免疫信号途径(包括体液、神经元和胶质细胞途径[6])进入大脑。在骨科手术PND模型中，促炎细胞因子，包括白细胞介素(interleukin，IL)-1β和肿瘤坏死因子(tumor necrosis factor，TNF)-α，对介导手术引起的神经炎症和术后认知功能下降起关键作用[7-8]。另外，非CNS手术诱导的外周炎症细胞因子也可破坏血脑屏障(blood-brain barrier，BBB)，从而激活TNF-α/核转录因子κB(nuclear transcription factor-κB，NF-κB)信号通路促进外周免疫细胞(包括巨噬细胞)向脑实质的迁移[9-10]。BBB稳态在外周炎症与中枢神经炎症之间的沟通中起着重要的基础性作用。在小鼠剖腹手术模型中发现，手术可导致紧密连接明显减少，BBB渗透性增加，老年小鼠认知功能下降[11]。

在动物模型和临床前研究中，先天免疫途径的整体激活以及促炎细胞因子可能是认知功能下降的致病因素。有研究[7,12]通过在动物模型中干预炎症因子信号评估其对神经炎症和PND的影响，例如：选择性靶向关键促炎细胞因子(如抗TNF-α和IL-1受体激动剂)可预防神经炎症并抑制动物术后认知功能下降。巨噬细胞特异性κB抑制因子激酶(inhibitor of κB kinase，IKK)β缺失可抑制NF-κB通路的激活，减轻手术后BBB损伤并减少巨噬细胞在海马浸润，从而抑制术后神经炎症和认知功能下降[9]。尽管这些措施可以在动物实验水平减少术后神经炎症并抑制PND的发生，但该治疗策略存在过度抑制免疫系统，增加感染和伤口愈合延迟等风险。因此，在不抑制全身免疫功能的情况下，寻找更安全的治疗策略来预防过度的神经炎症至关重要。

2 炎症消退与SPMs

急性炎症反应可分为开始和消退2个阶段。在炎症反应开始后，炎症消退也启动[13]。炎症消退由一系列促炎症消退介质介导，促炎症消退介质的合成和释放是平衡和协调整体免疫反应所必需的过程，其中最主要的一类促炎症消退介质是SPMs，其具有限制炎症信号的功能[14]。SPMs包括二十碳五烯酸和二十二碳六烯酸来源的消退素、保护素和maresins，以及由花生四烯酸衍生的脂氧素[15]。

在多种急慢性模型中发现SPMs具有抗炎作用和

免疫调节特性。SPMs抑制中性粒细胞在损伤部位的过度浸润，并增强天然免疫细胞对病原微生物的清除能力[3-4]。SPMs还可作为“炎症消退激活剂”，调节急性炎症并限制慢性炎症的发展；重要的是，SPMs无免疫抑制作用[13]。中风、神经退行性变和慢性疼痛等多种神经炎症性疾病都存在炎症消退障碍。使用膳食鱼油补充剂进行的临床研究[16-17]表明Ω-3多不饱合脂肪酸在急性和慢性炎症中都有很好的调节作用。SPMs在促进神经炎症消退和神经保护方面的作用也逐渐被发现。在阿尔茨海默病(Alzheimer’s disease，AD)患者大脑组织中，循环SPMs及其受体表达均减少[18]。这些研究[16-18]提示SPMs及其通路参与神经炎症。

3 SPMs的促炎症消退作用的机制

在炎症消退过程中，SPMs抑制中性粒细胞募集，增强巨噬细胞清除细胞碎片。SPMs对巨噬细胞吞噬功能的调节可能是通过巨噬细胞表型转换介导[19]。SPMs可将巨噬细胞由M1炎症型转换为M2促炎症消退型[19]。Maresin-1可以抑制脂多糖(lipopolysaccharide，LPS)诱导的原代骨髓源性巨噬细胞TNF-α释放、NF-κB核易位、超氧化物生成和M1样表型表面标志物表达[20]。这些对巨噬细胞功能或表型的调节作用可能是SPMs抑制手术诱导的BBB损伤、神经炎症和认知功能下降的关键机制[20]。SPMs同时具有抗炎和促炎症消退作用，因此它们对终止炎症至关重要，同时也能促进组织修复，这对于围手术期器官功能恢复非常关键。已有研究[21-22]证实消退素D1可以加速糖尿病患者伤口愈合。消退素E1通过增加肠上皮细胞的迁移和增殖促进肠黏膜愈合[23]。笔者所在研究组[24-25]发现：脂氧素A4和消退素D1还能促进上皮细胞修复，加速肺泡液体清除，从而减轻急性肺损伤。这些研究[19-25]提示SPMs可通过调节免疫细胞功能促进围手术期器官功能恢复。

4 SPMs对小胶质细胞的作用

小胶质细胞是CNS主动免疫防御系统的重要参与者，可维持脑内稳态。然而，小胶质细胞活化可诱导促炎细胞因子和反应性氧化物质的过度产生，从而导致持续性炎症并加剧CNS的病理变化[26-27]。在PND中，小胶质细胞活性影响术后BBB通透性和单核细胞浸润，通过调节其活性的治疗策略可用于治疗PND。

多种SPMs可以调节小胶质细胞活性。在小胶质细胞系BV-2进行的体外研究[28-29]发现：消退素D1和E1可通过调节miRNA表达和NF-κB信号通路抑制LPS诱导的*TNF-α*、*IL-6*和*IL-1β*基因表达。在人小胶质细胞中脂氧素A4、maresin-1和消退素D1可以减轻β-淀粉样蛋白(Aβ)42诱导的炎症[29-31]。除了减少小胶质细胞M1样标志物表达外，在小鼠小胶质细胞BV2细胞中，消退素D1和脂氧素A4还促进M2样标志物精氨酸1和Ym1的表达[32-33]。这些体外研究[28-33]结果表明：SPMs直接参与调节小胶质细胞的炎症水平，可能对CNS炎症性疾病具有治疗作用。在手术诱导的小胶质细胞激活模型中，脂氧素和消退素都可以通过抑制促炎细胞因子的释放来改善神经炎症[34-36]。其他类型的炎症消退信号也可以调节PND模型中的神经炎症。在深低温停循环的体外循环大鼠模型中，膜联蛋白A1能够改善大鼠认知功能，并通过抑制NF-κB p65转录活性及其下游细胞因子产生来调节小胶质细胞的活性[37]。在小鼠骨科手术模型中，maresin-1可以抑制手术后的小胶质细胞激活以BBB的开放，减少巨噬细胞在海马的浸润[20]。因此，包括SPMs在内的促炎症消退介质可通过调节小胶质细胞表型减轻神经炎症，从而改善围手术期认知功能障碍。但目前还有许多SPMs在PND中的作用还未证实，其作用的具体机制还需进一步研究。

5 SPMs对星形胶质细胞的作用

除小胶质细胞外，星形胶质细胞在维持CNS稳态方面也起着关键作用，包括调节脑血流[38]、突触功能[39]、细胞外离子浓度[40]，以及与内皮细胞相互作用以维持BBB[41]。星形胶质细胞也具有免疫调节的作用[42]。作为CNS中的一种主动免疫调节细胞，该细胞感知刺激和危险信号，通过释放递质与神经元进行通信。它们可以与小胶质细胞一起进一步激活适应性免疫防御[42]。在脑损伤或神经退行性疾病中，星形胶质细胞发生明显的转化，称为“星形胶质细胞增生”。星形胶质细胞增生有助于CNS的修复[43]。但这种表型改变可通过上调IL-17受体和1-磷酸鞘氨醇的表达而变得有害[44-45]，这进一步诱发促炎细胞因子和趋化因子的产生，从而导致神经炎症和神经退行性变的加剧[46]。

研究[46-47]表明：星形胶质细胞的促炎活性可能由小胶质细胞通过细胞因子、趋化因子、补体激活、生长因子和其他信号分子调节。Xu等[47]发现星形胶质细胞中CCL2表达的增加可以激活小胶质细胞并导

致学习障碍。因此，星形胶质细胞增生可能间接调节小胶质细胞的活性。在神经炎症期间，星形胶质细胞的活动状态可能由局部环境中的危险信号决定，且随炎症不同阶段而发生变化[46]。SPMs对星形胶质细胞的作用尚未完全阐明。在骨科手术诱导的PND模型中，星形胶质细胞形态发生变化[20,36]。星形胶质细胞增生与基础谷氨酸突触传递增加、海马短期可塑性和长期强化的下降有关[36]。星形胶质细胞的这些病理变化可以通过阿司匹林触发的消退素D1(aspirin-triggered resolvin D1，AT-RvD1)或maresin-1预防性治疗[20]，但AT-RvD1和maresin-1对围手术期星形胶质细胞作用的确切机制仍需进一步探讨。

6 展 望

促炎症消退介质在围手术期疾病和术后恢复中的作用逐渐被人们认识到，但其作用机制还需进一步研究，以评估各种SPMs对不同类型CNS细胞的确切作用机制，以及特定介质是否可以更好地靶向手术创伤引发的免疫反应。SPMs在人类脑脊液中被检测到，且其表达水平与神经功能相关，可能作为临床PND等神经疾病进展的生物标志物。另外，SPMs可通过饮食干预进行补充，例如补充Ω-3多不饱和脂肪酸，从而在围手术期提供有效的干预，促进SPMs产生。研究围手术期神经炎症以及SPMs对神经认知障碍的影响有望为SPMs作为神经炎症标志物提供理论基础，也为PND的治疗提供新的策略。

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