靶向Nav1.8的镇痛药物研发进展

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摘要: 电压门控钠通道亚型Nav1.8主要分布于外周伤害性感觉神经元, 在神经病理性疼痛等多种疼痛的发生与维持中发挥关键调控作用。2025年1月苏泽曲林 (suzetrigine), 首个以Nav1.8为靶点的镇痛药物获得美国FDA批准上市, 标志着Nav1.8靶向镇痛药物研发取得重大突破。这一里程碑事件引发了国内外对Nav1.8镇痛抑制剂研发的广泛关注。本文系统综述了Nav1.8的结构特征、生理功能及其系列镇痛药物开发进展, 重点阐述了Nav1.8的电生理特性、疼痛调控机制以及选择性抑制剂的临床研究, 旨在为Nav1.8镇痛药物的开发提供参考。

关键词: Nav1.8; 电生理特性; 疼痛; 镇痛药物; 临床研究

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Advances in the development of Nav1.8-targeted analgesics

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Abstract: The voltage-gated sodium channel isoform Nav1.8 is predominantly distributed in peripheral injurious sensory neurons and plays a key regulatory role in the development and maintenance of acute and chronic pain and neuropathic pain. In January 2025, suzetrigine, the first analgesic drug targeting Nav1.8, was approved for marketing in the United States FDA, marking a major breakthrough in the development of Nav1.8-targeted pain therapeutics. The successful development of the first analgesic for Nav1.8 has led to a global interest in the development of Nav1.8 analgesic inhibitors. This article reviews the structure, physiological function, and drug development of Nav1.8. We focus on summarizing the electrophysiological properties of Nav1.8, its role in pain, and the clinical studies of selective inhibitors, aiming to provide a reference for the development of Nav1.8 analgesics.

Key words: Nav1.8; electrophysiological property; pain; analgesic drug; clinical trial

电压门控钠通道 (voltage-gated sodium channels, VGSCs) 是经典局部麻醉剂的作用靶点, 然而该类药物因缺乏亚型选择性, 导致心脏毒性和神经系统不良反应等毒副作用, 限制了其在镇痛领域的临床应用。近年来, 针对钠通道亚型Nav1.8的高选择性抑制剂开发取得重大突破, 展现出疼痛治疗的巨大潜力, 有望成为阿片类镇痛药物的重要替代与辅助。

1 Nav1.8的基本结构

人类Nav1.8由1 956个氨基酸组成, 分子质量为220 kDa[1], 由位于人类3号染色体p22～24区域的基因*SCN10A*编码[2], 与*SCN5A* (编码Nav1.5) 和*SCN11A* (编码Nav1.9) 来自同一个进化源。Nav1.5、Nav1.8、Nav1.9仅能被高浓度的河豚毒素 (tetrodotoxin, TTX) 抑制, 属于TTX抵抗型 (TTX-resistant, TTX-R) 钠通道[3]。

Nav1.8的α亚基由4个同源结构域 (domain I～IV, DI～DIV) 组成, 每个结构域由6个跨膜螺旋段 (S1～S6) 构成。S1～S4这4个跨膜螺旋段环绕形成一个中

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央孔道, 称为电压敏感区域 (voltage-sensing domain, VSD), S4 片段上带正电的精氨酸 (arginine, R) 和赖氨酸 (lysine, K) 残基作为门控电荷载体在细胞去极化至阈值电位时向细胞膜外方向位移, 引起 Nav1.8 通道构象变化从而激活通道的开放[4,5]。DI 与 DIV 之间存在钠通道的失活闸门, 由位于细胞内环上的异亮氨酸 (isoleucine, I)、苯丙氨酸 (phenylalanine, F) 和甲硫氨酸 (methionine, M) 3 个氨基酸残基构成, 成为 IFM 模序 (IFM motif)。S5～S6 及其细胞外连接环 (P-loop) 构成孔道结构域 (pore domain, PD), P 环负责离子选择性, 其中一个关键区域是选择性过滤器 (selectivity filter), 由一组保守的氨基酸残基构成: DI 中的天冬氨酸 (aspartic acid, D)、DII 中的谷氨酸 (glutamic acid, E)、DIII 中的赖氨酸 (lysine, K) 和 DIV 中的丙氨酸 (alanine, A), 是钠通道选择性地允许 Na^+ 通过通道的结构基础 (图 1)。不同的成孔 α 亚基决定 VGSC 亚型不同的功能表达, 其在体外即可单独表达出钠通道的所有特征性结构[6,7], 体内通过共价或非共价作用与辅助性 β 亚基相互作用形成多蛋白信号复合物。

Nav1.8 通道包含 5 种不同的 β 亚基 (β_1、β_{1B}、β_2、β_3 和 β_4), 它们在调节 α 亚基的表达和膜运输、通道激活和失活以及配体结合方面都发挥重要作用[6]。Navβ 亚基同时是免疫球蛋白超家族的成员, 调节细胞黏附和迁移[8]。2022 年, 颜宁及潘孝敬团队[9]利用冷冻电镜技术测定了人类 Nav1.8 以及其与选择性抑制剂 A-803467 结合的结构, 研究发现 Nav1.8 通道的第一电压感应域 (voltage-sensing domain I, VSDI) 具有 3 种不同的构象, 并且 VSDI 与 PD 之间的胞外连接部分决定了 Nav1.8 的高电压依赖性激活。

A-803467 是 Abbott Laboratories 公司研发的一个高选择性, 强抑制活性的 Nav1.8 阻滞剂[10], 对处于失活状态的 Nav1.8 通道阻断效力更强[11], 与其他钠通道亚型相比, A-803467 对 Nav1.8 的选择性超过 100 倍。A-803467 结合于 Nav1.8 孔结合域的中央腔 (site C),

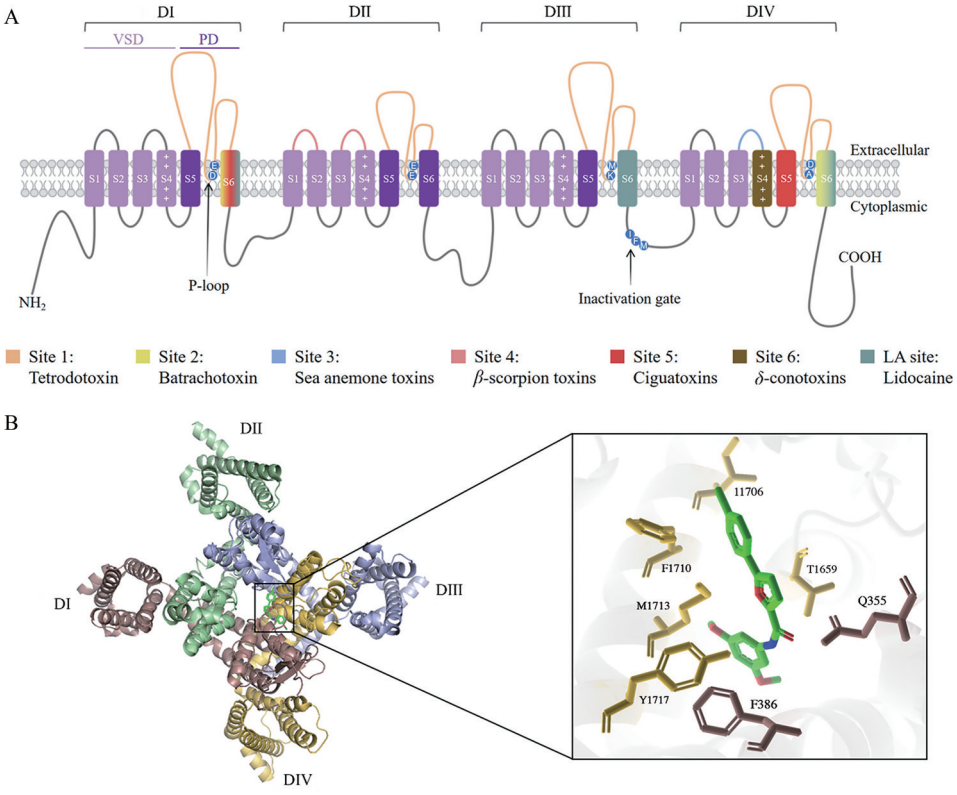


Figure 1 Schematic diagram of molecular structure and pharmacology of voltage-gated sodium channels (VGSCs). A: Voltage gated sodium channel structure; B: 2.7 Å resolution cryo-EM structure of human Nav1.8 with A-803467 complex. Inset: the amino acids in the human Nav1.8 channel that bind to A-803467. DI−DIV: Four homologous domains; S1−S6: Six transmembrane helices; ++: Basic amino acids as voltage-sensor gating charges; VSD: Voltage-sensing domain; PD: Pore domain; TTX: Tetrodotoxin; Blue circles: DEKA (inner), EEDD (outer) and IFM located on the intracellular loop connecting domains DI−DIV, constitute the proposed neurotoxin receptor site 1 for the TTX, the selectivity filter that determines Na^+ passage and the IFM motif that folds into the channel pore to block it during sustained cell depolarization; Blocks of different colors: Different neurotoxin binding sites and local anesthetic binding sites, with representative inhibitors for each binding site

其羰基通过Gln355形成唯一直接氢键相互作用, 但其亚型选择性主要由Thr397与Gly1406两个远端位点通过别构机制决定[12](图1)。A-803467亦对心肌钠通道Nav1.5有一定的抑制作用, 有助于治疗由*SCN5A*基因突变引起的长QT综合征3型心律失常[13], 但这也成为A-803467在后期开发中的心脏不良反应的机制之一。研究表明, 在临床可达浓度下, A-803467也可抑制人类T型钙通道[14]。尽管A-803467在动物疼痛模型中显示出良好的镇痛效果, 但该分子未能进入临床试验。其主要原因可能是由于A-803467存在较低的口服生物利用率和较高的血浆蛋白结合率, 这些药代动力学特性限制了其临床应用的可行性[15]。

2 Nav1.8独特的电生理特性

VGSCs具有典型的门控机制, 通道上具有激活闸门 (activation gate) 和失活闸门 (inactivation gate) 并存在静息态 (resting)、激活态 (activated) 和失活态 (inactivated) 3种状态[16]。与其他VGSCs相比, Nav1.8具有更高的去极化激活电压阈值, 当细胞去极化到一定电压时, 其他VGSCs通道会因失活而无法继续响应电刺激, Nav1.8通道依然能够保持开放状态。Nav1.8的缓慢失活特性允许其在长时间内保持开放, 在持续电流条件下维持钠离子的流入[17-19]。这些特性使得Nav1.8成为伤害感受器动作电位的上行相期间钠电流的主要贡献通道[20]。Han等[21]进一步了探讨人和大鼠Nav1.8的生理特性, 以及Nav1.8在背根神经节 (dorsal root ganglion, DRG) 神经元中对动作电位发放的影响(图2)。Nav1.8独特的生物物理特性, 为伤害性感受神经元在长时间或高频刺激下的兴奋性提供了重要支持[22], Nav1.8的开放与关闭对神经元的兴奋性至关重要, 其调节功能的异常导致慢性疼痛、神经性疼痛等多种疼痛疾病。因而针对Nav1.8的靶向抑制, 已成为镇痛药物开发的新策略。

3 Nav1.8在疼痛调节中的关键作用

Nav1.8是感觉神经元特异性表达的通道, 主要分布在DRG和三叉神经节 (trigeminal ganglion, TG) 的神经元中, 亦在小直径无髓鞘的伤害性感觉神经元中高表达[23]。相比于大直径DRG神经元 (直径44～50 μm), Nav1.8在小直径 (直径18～25 μm) 的C类纤维和Aδ纤维中的电流具有更高的去极化阈值 (约高30 mV)[24]。疼痛的生理病理学研究表明, Nav1.8在炎症性疼痛、神经病理性和冷痛中发挥着关键调控作用[25]。

3.1 Nav1.8在炎症性疼痛的调节 炎症性疼痛由炎症引起的组织损伤导致, 炎症介质如细胞因子、激肽、生长因子和前列腺素等会敏化伤害感受器上的Aδ和C类纤维[26], 引发DRG神经元激活电压的轻微超极化位移和对刺激的反应性增加以及自发异位放电, 这些改变导致痛觉超敏、异常性疼痛和自发性持续疼痛的发展[27]。炎症介质通过多种不同的第二信使途径共同作用于Nav1.8, 或直接磷酸化Nav1.8通道, 进而调控通道的电生理特性[28]。炎性介质可增加Nav1.8通道介导的TTX-R电流幅度, 引起其激活曲线向超极化方向位移, 降低激活阈值并增强动作电位的生成, 使神经元对刺激的反应性增加[29]。研究表明, Nav1.8基因敲除小鼠 (*Nav1.8*$^{-/-}$) 对神经生长因子 (nerve growth factor, NGF) 诱导的热痛觉过敏反应显著减弱[30]; 其结肠内注射炎症和伤害性感受器致敏剂辣椒素和芥末油后疼痛行为相较于野生型小鼠显著减少[31]。在重复注射前列腺素E_2 (prostaglandin E_2, PGE_2) 引起的持续性痛觉过敏中, 大鼠Nav1.8的mRNA表达水平显著增加。不仅在急性疼痛期间显著表达, 在完全弗氏佐剂诱发的大鼠慢性痛觉持续期的小直径DRG神经元中Nav1.8蛋白表达显著增加[32]。给予大鼠环氧合酶抑制剂, 抑制炎症介质的生成, 并可减少Nav1.8通道的表达进而缓解炎症性疼痛[33]。

3.2 Nav1.8在神经病理性疼痛的调节 神经病理性疼痛是由周围或中枢神经系统的损伤或疾病引起的持续性或间歇性的疼痛, 其主要特征为神经系统本身的异常活动或功能改变。受损的周围神经会导致轴突病变和脱髓鞘, 触发了受损神经元的膜重塑进而引起细胞兴奋性增加, 这一病理改变与钠通道的表达和运输异常有关, 可能还伴随着钠通道动力学性质的变化[34]。受损神经元表现出自发放电和异位放电, 构成了神经病理性疼痛的主要信号, 维持了中枢敏化从而放大了感觉输入, 导致如触觉异常性疼痛等症状[34]。在大鼠第5和第6腰椎脊神经结扎 (L5/L6 spinal nerve ligation, L5/L6 SNL) 模型中, 鞘内注射特异性针对Nav1.8的反义寡脱氧核苷酸能显著减少DRG神经元中Nav1.8的表达, 同时也能缓解大鼠的神经病理性疼痛行为[35]。Dib-Hajj等[36]发现, Nav1.8可能是通过其在邻近未受伤的神经元中表达上调来促进神经性病理疼痛的发展。对大鼠单独进行L5 SNL模型造模后, Nav1.8通道蛋白在L5受损神经元中表达下调, 并且重新分布到受损轴突邻近的未受损轴突上, 同时Nav1.8电流增加[37]。然而, 在慢性疼痛的后期, 受损轴突中的Nav1.8通道表达可能会重新上调并集聚在神经损伤部位[38,39]。

糖尿病神经病理性疼痛是一种常见的周围神经病变, 高血糖引发的外周神经损伤会导致神经纤维的自发性活动异常和机械敏感性[40]。糖尿病患者体内过度糖酵解及糖醛还原酶的还原能力不足, 导致积累过

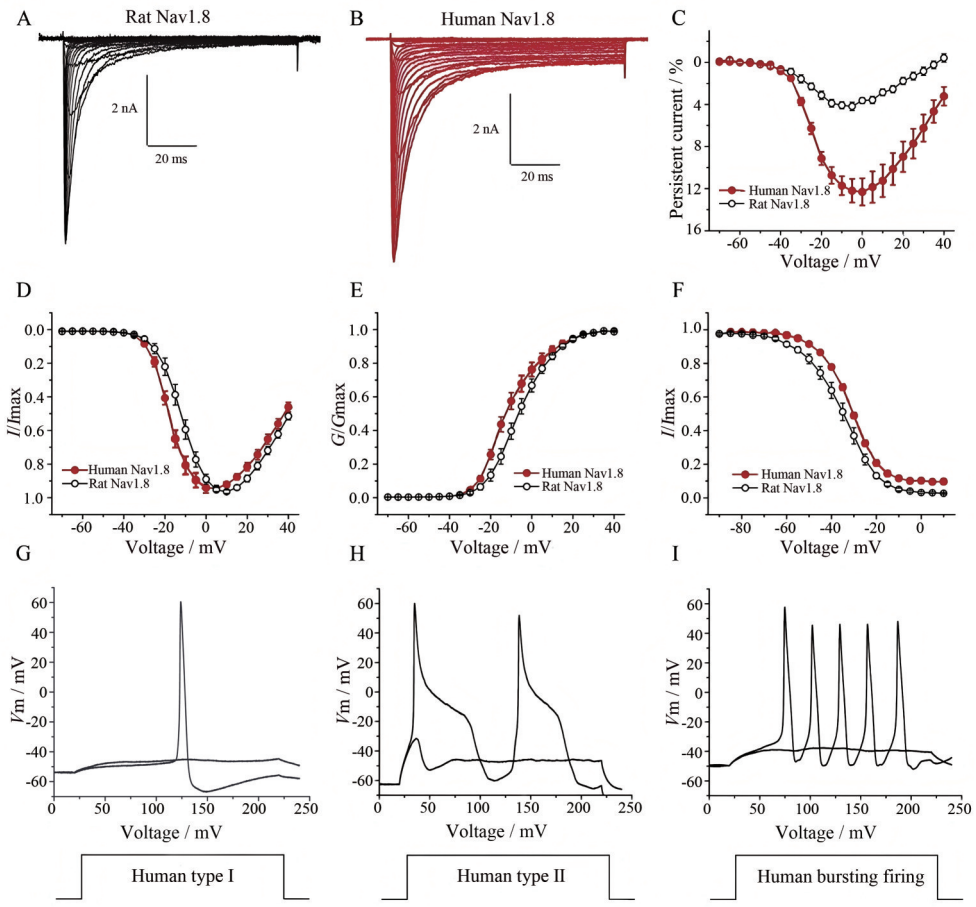


Figure 2 Comparison of persistent currents and electrophysiological parameters in Nav1.8-knockout mouse DRG neurons transfected with human or rat Nav1.8 channels. A, B: Representative traces of Nav1.8 currents recorded from mouse *Nav1.8*-knockout DRG neurons expressing rat (A) or human (B) Nav1.8 channels. Voltage was held at −70 mV and stepped from −70 to +40 mV in 5 mV increments for 100 ms; C: Absolute value of persistent currents between rat and human Nav1.8 channels; D: Normalized current-voltage (*I*−*V*) relationships of human and rat Nav1.8 channels; E: Comparison of voltage-dependent activation, showing a ~5 mV hyperpolarizing shift in human Nav1.8 activation compared to rat Nav1.8. *G*/*G*max represents normalized sodium conductance; F: Fast inactivation of human Nav1.8 is depolarized by 3.7 mV relative to rat Nav1.8, indicating differences in channel gating properties; G−I: Human Nav1.8 channels in transfected *Nav1.8*-knockout mouse DRG neurons generate different firing patterns; G: Representative type I response: a 200 ms depolarizing stimulus induces a single action potential, with a half-width of less than 10 ms; H: Representative type II response: the first action potential has a half-width greater than 10 ms; I: Representative bursting firing response: the first all-or-none response is followed by a burst of multiple spikes. Adapted from Han et al[21]. DRG: Dorsal root ganglion

多的葡萄糖代谢产物甲基乙二醛[41]。甲基乙二醛与Nav1.8结合后诱导其翻译后修饰, 使得Nav1.8通道的电压敏感性发生变化, 导致神经元电生理兴奋性的增加及感觉神经元放电的增强[42]。在甲基乙二醛诱导的代谢性痛觉过敏动物模型中, Nav1.8基因敲除小鼠并未引发热性和机械性的疼痛行为, 甲基乙二醛对Nav1.8的修饰是动物痛觉过敏的病因, 也是糖尿病患者产生异常疼痛的原因[41]。链脲佐菌素诱导的糖尿病大鼠模型表现出痛觉过敏与异常, Nav1.8通道阻滞剂A-803467通过腹腔注射 (系统性给药) 或足底注射 (局部给药) 显著减轻糖尿病大鼠的异常疼痛感觉, 其效果优于利多卡因[43]。

多发性硬化症是一种中枢神经系统的慢性脱髓鞘疾病, 主要表现为神经功能障碍[44]。Nav1.8在正常状态下不表达于小脑, 而在多发性硬化症患者和相关动物模型中, Nav1.8会在小脑的浦肯野细胞中异位表达[45]。实验性自免疫性脑脊髓炎 (experimental autoimmune encephalomyelitis, EAE) 小鼠模型中, Nav1.8基因敲除小鼠只表现出轻微的神经功能障碍, 对野生型EAE小鼠进行A-803467脑室给药发现, A-803467可以部分逆转浦肯野神经元的快速、不同步电信号, 给药后神经功能障碍的部分症状, 如步态不稳和肢体姿势异常等均

有显著的改善[46]。

3.3 Nav1.8在内脏疼痛中的调节 Nav1.8在DRG神经元和迷走神经节 (vagal ganglion, VG) 神经元中均有表达。Nav1.8的功能传统上与痛觉传递密切相关, 但其在迷走神经传入纤维中的高表达, 提示Nav1.8可能还参与调节非伤害性刺激的反应。在胃肠道中, Nav1.8阳性神经纤维主要分布于黏膜和肌层, 特别是在胃、十二指肠和肠道的肌间神经丛及黏膜下层。此外, 肝脏、胆囊、胰腺等代谢相关组织以及部分血管周围也存在表达Nav1.8的传入神经纤维[47]。Nav1.8通过介导内脏感觉神经元中的TTX-R钠电流, 促进与炎症和损伤相关的疼痛信号传递。研究表明, 在结肠炎小鼠模型中, DRG神经元中Nav1.8的表达显著上调[48]; 在应激诱导的内脏高敏感性大鼠模型中, TTX-R钠通道电流密度和Nav1.8蛋白表达均显著增加[49]; 而在糖尿病性肠神经病变大鼠中, 肠道感觉传入神经出现过度兴奋, DRG神经元中的Nav1.8表达亦显著上调[50]。在Nav1.8缺失小鼠中, 对结肠内辣椒素刺激的疼痛反应显著减弱[38], 通过巴西日圆线虫 (*Nippostrongylus brasiliensis*) 诱导的短暂性空肠炎模型中, 感染后小鼠DRG神经元的兴奋性显著增加, 但Nav1.8-null小鼠则未表现出这种过度兴奋[51]。进一步的研究发现, *SCN10A*基因中的突变体A1073V与机械性疼痛阈值的增加相关。在对121名炎症性肠病患者和86名健康对照者进行*SCN9A*、*SCN10A*和*SCN11A*的靶向外显子测序及TaqMan基因分型后, 研究者发现A1073V纯合突变是导致炎症性肠病患者出现低痛觉的一个潜在原因[52]。此外, 在乙状结肠切除术患者中, A1073V纯合突变患者的术后疼痛评分显著低于正常*SCN10A*基因型患者[53]。这些结果表明, *SCN10A*突变在炎症性肠病及相关疾病中的低痛觉表型中可能扮演重要角色。

3.4 Nav1.8在冷痛感觉中的调节 感知外界温度能够使哺乳动物维持体温稳态, 并能有效避免由异常温度引起的组织损伤, 在低温环境下, Nav1.8通道对于伤害感受器的持续兴奋至关重要[54]。研究表明, 低温条件下TTX-S钠通道的电流幅度显著减弱, 而TTX-R钠通道所受影响较小, 这是由于Nav1.8通道具有对低温不敏感的慢失活特性[55], 是唯一在低温下仍能正常工作的电压门控钠通道[56]。此外, 低温能够降低钠通道的激活阈值并提高细胞膜电阻, 放大膜电流引起的电压变化, 进一步增强了Nav1.8在低温环境下的兴奋性和动作电位的生成能力[56]。Nav1.8的缺失不会影响小鼠对轻度冷刺激 (≥ 5 ℃) 的行为反应, 而在极端冷刺激 (−5 ℃) 的冷板实验中, Nav1.8敲除小鼠完全缺乏痛觉反应。通过荧光激活细胞分选和基因芯片分析, 解释了在低温下不表达Nav1.8的神经元是感知温和冷刺激和急性冷刺激的主要功能单位, 而表达Nav1.8的神经元则主要负责长时间极端冷刺激的信号转导[57]。上述研究表明, Nav1.8是冷痛调节的关键离子通道。

4 Nav1.8镇痛药物的临床研究

Nav1.8独特电生理特性使其在疼痛信号传导中发挥关键作用, 近年来, 已成为新型镇痛药物开发的热门靶点。本文通过查阅相关文献与统计ClinicalTrials网站、国家药物临床试验登记与信息公示平台及相关制药公司的公开信息, 总结了处于临床研究阶段的Nav1.8抑制剂相关信息及研究进展 (表1、图3)。

氨溴索 (ambroxol, **1**) 是一种黏膜活性药物, 自1979年起被广泛应用于治疗各种急性和慢性上呼吸道和下呼吸道疾病[58]。研究发现, 在DRG神经元中氨溴索以剂量依赖性方式抑制TTX-R钠通道电流[59], 并在多种动物模型中减轻神经病理性疼痛[60,61]。临床中, 氨溴索能缓解咽炎相关疼痛是由于其具有局部麻醉的作用, 它优先阻断Nav1.8钠通道亚型[62,63]。但在2019年开始的一项III期临床试验结果显示, 口服氨溴索剂和安慰剂的3和24 h内, 患者的疼痛缓解程度并未达到统计学差异 (NCT03583658)[64]。氨溴索作为Nav1.8抑制剂其IC_{50}在微摩尔级别, 显著高于现有药物, 作为靶向1.8的镇痛药物开发意义与价值并不突出。

Pfizer公司研发的PF-01247324 (**2**), 是在对钠通道抑制剂拉莫三嗪 (lamotrigine) 的一系列分子结构改造中发现的一种高效的Nav1.8选择性阻滞剂。PF-01247324在大鼠体内表现出低清除率和高口服生物利用度 (91%), 大鼠SNL模型中具有显著的镇痛效果。电生理实验中, PF-01247324对Nav1.8的抑制相较于其他钠离子通道具有50倍以上的选择性[65]。PF-01247324对Nav1.8的选择性主要源于Gly1406残基的较小侧链, 从而为PF-01247324分子上的*N*-甲基酰胺基团与通道site C结合提供了空间适配性。其他钠通道亚型 (如Nav1.7) 的同源位置上由Ser1445取代, 丝氨酸的侧链与PF-01247324产生空间排斥效应, 从而降低了PF-01247324与其他钠通道的结合亲和力[66]。然而, 对PF-01247324的开发止步于临床前研究。Pfizer公司在PF-01247324的基础上进一步优化得到化合物PF-04531083 (**3**), 在芳香基团和酰胺基团上进行改进。PF-04531083对大鼠和人类DRG神经元中的TTX-R电流表现出频率依赖性和状态依赖性, 在大鼠神经病理性的胫神经横断损伤的疼痛模型中, 显示出与普瑞巴林相似的疼痛缓解作用。此外, PF-04531083能够穿过血脑屏障, 并且能够在不影响大鼠的水平和垂直运动的情况下达到有效血药浓度[65]。PF-04531083进

Table 1 Summary of novel clinical trials of Nav1.8 inhibitors. PID: Pain intensity difference; SPID: Summed pain intensity difference; HPTT: Heat pain tolerance threshold; TOTPAR: Total pain relief; AEs: Adverse events; SAEs: Serious adverse events; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; NPRS: Numeric pain rating scale; ADPS: Average daily pain score

No.	Compound	Company	Clinical trial phase	Condition/disease	Primary endpoint	Primary outcome measure	Status of study	Study start to last update	Ref.
1	Ambroxol	Sanofi	Phase III	Pharyngitis	Relief sore throat pain in patients with acute pharyngitis	Change from baseline in PID within 3 h	Completed (no study results posted)	2018/06-2022/04	NCT03583658
3	PF-04531083	Pfizer	Observational	Healthy individuals	Safety, tolerance and pharmacokinetics	Pharmacokinetic parameters at 240 h post-dose	Completed (no study results posted)	2009/08-2009/12	NCT00992316
			Phase I	Healthy individuals	Safety, tolerance and pharmacokinetics	Pharmacokinetic parameters from 1 to 15 d post-dose	Completed (no study results posted)	2009/11-2010/04	NCT01012310
			Phase I	Healthy individuals	Pharmacokinetics of multiple doses of PF-04531083 tablets	Concentration in the blood on day 1 and day 8 post-dose	Completed (no study results posted)	2010/05-2010/08	NCT01119235
			Phase I	UVB-Induced heat pain	Reduce the heat by ultraviolet light	HPTT in the area of UVB-induced erythema endpoint at 2, 4, 6 and 24 h	Completed (no study results posted)	2010/06-2010/09	NCT01127906
			Phase II	Post-surgical dental pain	Relief post-surgical dental pain	Change from baseline in TOTPAR score from 0 to 6 h	Terminated (futility)	2011/10-2013/06	NCT01512160
4	PF-06305591	Pfizer	Phase I	Healthy individuals	Safety, tolerance and pharmacokinetics	Pharmacokinetic parameters and number of AEs and SAEs	Completed (no study results posted)	2012/11-2013/05	NCT01747941
			Phase I	Healthy individuals	Multiple doses of safety, tolerance and pharmacokinetics	Pharmacokinetic parameters and number of AEs and SAEs	Completed (no study results posted)	2013/04-2013/12	NCT01776619
			Phase I	Capsaicin/heat induced neurogenic flare	Effect on capsaicin and capsaicin/heat-induced neurogenic flare	Mean blood perfusion between 40 and 60 min post administration of capsaicin	Completed (no study results posted)	2013/04-2013/08	NCT01797796
			Phase I	Cold pain	Effects on cold pain	Change from baseline in VAS within 24 h	Completed (no study results posted)	2013/06-2013/09	NCT01812265
5	VX-150	Vertex Pharmaceuticals	Phase II	Osteoarthritis	Treatment of osteoarthritis pain	Change from baseline in WOMAC at day 14	Completed (no study results posted)	2015/12-2020/09	NCT02660424
			Phase II	Small fiber neuropathy	Treatment of pain caused by small fiber neuropathy	Pain intensity per night for 6 weeks	Completed (met primary endpoint)	2017/09-2021/11	NCT03304522
			Phase II	Acute pain	Treatment of acute pain following bunionectomy	SPID between 0 and 24 h after the first dose	Completed (met primary endpoint)	2017/06-2021/02	NCT03206749
			Phase II	Acute pain	Dose-response relationship and safety	SPID between 0 and 24 h after the first dose	Completed (met primary endpoint)	2018/12-2022/02	NCT03764072
7	VX-548	Vertex Pharmaceuticals	Phase III	Acute pain	Efficacy and safety in treating acute pain after an abdominoplasty	SPID from 0 to 48 h	Completed (met primary endpoint)	2022/10-2025/07	NCT05558410
			Phase III	Acute pain	Efficacy and safety for acute pain after a bunionectomy	SPID from 0 to 48 h	Completed (met primary endpoint)	2022/10-2025/08	NCT05553366
			Phase III	Acute pain	Safety and effectiveness in treating acute pain	Pharmacokinetic parameters and number of AEs and SAEs	Completed (met primary endpoint)	2023/01-2025/07	NCT05661734
			Phase II	Painful lumbosacral radiculopathy	Efficacy and safety for painful lumbosacral radiculopathy	Change from baseline in the weekly average of daily leg pain intensity on NPRS	Completed (no study results posted)	2023/12-2024/10	NCT06176196

Continued

No.	Compound	Company	Clinical trial phase	Condition/disease	Primary endpoint	Primary outcome measure	Status of study	Study start to last update	Ref.
8	VX-993	Vertex Pharmaceuticals	Phase I	Healthy individuals	Safety, tolerance and pharmacokinetics	Pharmacokinetic parameters and number of AEs and SAEs	Completed (no study results posted)	2024/01-2024/07	NCT06226454
9	VX-973	Vertex Pharmaceuticals	Phase I	Healthy individuals	Multiple doses of safety, tolerance and pharmacokinetics	Pharmacokinetic parameters and number of AEs and SAEs	Completed (no study results posted)	2023/05-2024/05	NCT05866055
10	LTG-001	Latigo Biotherapeutics	Phase I	Healthy individuals	Safety, tolerance, pharmacokinetics	Pharmacokinetic parameters	Recruiting	2023/10-2025/05	NCT06049095
11	LTG-305	Latigo Biotherapeutics	Phase I	Healthy individuals	Safety, tolerance, pharmacokinetics	Pharmacokinetic parameters	Completed (no study results posted)	2024/08-2025/07	NCT06554574
13	HRS4800	Jiangsu Hengrui Pharmaceuticals Co., Ltd.	Phase I	Healthy individuals	Safety, tolerance, pharmacokinetics and effect of food on pharmacokinetics	Pharmacokinetic parameters and food effect	Completed (no study results posted)	2020/11-2022/03	NCT04573036
			Phase I	Healthy individuals	Safety, tolerance and pharmacokinetics	Pharmacokinetic parameters	Recruiting	2021/07-2021/09	CTR20211682
			Phase II	Pain	Efficacy and safety of HRS4800 tablets for postoperative analgesia after teeth extraction	SPID within 8 h	Completed (no study results posted)	2022/01-2022/04	NCT05318846
			Phase II	Post-surgical dental pain	Relief post-surgical dental pain	Change from baseline in TOTPAR score from 0 to 8 h	Completed (no study results posted)	2022/01-2022/03	CTR20220048
14	JMKX-000623	Jemincare	Phase II	Diabetic peripheral neuropathic pain	Efficacy and safety for diabetic peripheral neuropathic pain	Change from baseline in ADPS within 12 weeks	Recruiting	2024/03-2024/04	NCT06221241
			Phase II	Diabetic peripheral neuropathic pain	Efficacy and safety for diabetic peripheral neuropathic pain	Change from baseline in ADPS within 12 weeks	Completed (no study results posted)	2024/03-2025/06	CTR20240670
15	HBW-004285	Chengdu Haibowei Pharmaceutica Co., Ltd.	Phase I	Healthy individuals	Safety, tolerability, pharmacokinetics	Pharmacokinetic parameters	Recruiting	2023/04-2023/11	CTR20231148
16	JKN23061	Guangzhou Fermion Technology Co., Ltd.	Phase I	Healthy individuals	Safety, tolerability, pharmacokinetics	Pharmacokinetic parameters	No yet recruiting	2024/02-2024/02	CTR20240574
17	FZ008-145	Guangzhou Fermion Technology Co., Ltd.	Phase I	Healthy individuals	Safety, tolerability, pharmacokinetics	Pharmacokinetic parameters	Recruiting	2024/11-2025/07	NCT06685809
18	KHN702	Chengdu Kanghong Pharmaceutical Co., Ltd.	Phase I	Healthy individuals	Safety, tolerability, pharmacokinetics	Pharmacokinetic parameters	No yet recruiting	2025/06	CTR20252159
			Phase I	Healthy individuals	Safety, tolerability, pharmacokinetics	Pharmacokinetic parameters	No yet recruiting	2025/06-2025/07	NCT07044960

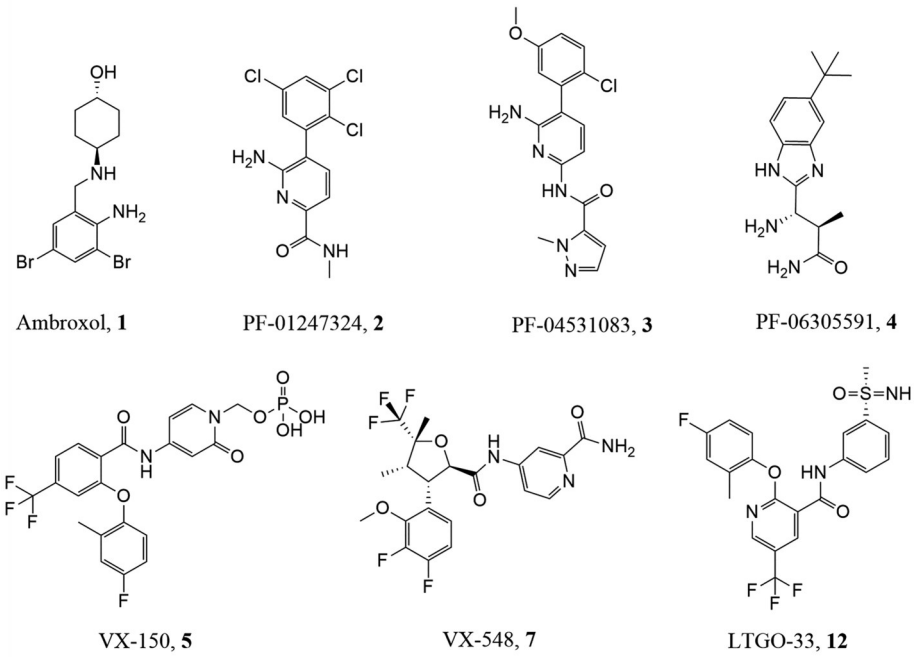


Figure 3 The molecular structures of clinically disclosed Nav1.8 inhibitors

行了3项I期临床试验、1项II期临床试验及1项剂量实验。PF-04531083的安全性实验 (NCT00992316)、药物代谢动力学试验 (NCT01012310)、其片剂的口服生物利用度实验 (NCT01119235) 以及PF-04531083对照射紫外线引起热痛的影响 (NCT01127906) 4项临床研究项目均未公布研究结果, PF-04531083用于治疗术后牙痛的II期临床试验 (NCT01512160), 由于未能达到6 h内疼痛减轻的主要结果而终止。其口服生物利用度及药代动力学试验结果并未公布, 推测其难以达到有效的血药浓度并汇集于疼痛部位, 导致其抑制作用未能转化为显著的临床镇痛效果。然而, Pfizer公司并未止步于此。

Pfizer公司以苯并咪唑类化合物PF-04531083作为新的研究起点, 在对Nav1.8的选择性阻断剂进行结构优化和活性提升后开发出了PF-06305591 (**4**)。PF-06305591相较于PF-04531083具有更高的溶解度和更低的体内清除率, 这意味着PF-06305591在体内的代谢更为稳定, 能够达到更高的血药浓度, 从而可能提高疗效。此外, PF-06305591对Nav1.8通道的选择性提高, 同时降低了其对hERG通道的相互作用, 这有助于减少潜在的不良反应[67]。对PF-06305591进行了4项I期临床试验, 包括对PF-06305591的安全性、耐受性和药代动力学的研究 (NCT01747941)、重复剂量的安全性、耐受性和药代动力学的研究 (NCT01776619)、PF-06305591对辣椒素和热诱导的伤害性疼痛中的影响研究 (NCT01797796) 和在冷痛中发挥作用的研究 (NCT01812265), 这些临床试验均未发布最终的研究结果。尽管PF-06305591在临床前研究中表现出对Nav1.8的高选择性和较优的药代动力学特性, 但截至目前, 相关研究结果尚未正式发布, 且未见其进入II期临床试验的报告。

Vertex公司开发了一系列吡啶酮酰胺类选择性Nav1.8小分子抑制剂, VX-150 (**5**) 作为一种前药, 通过快速转化为其活性成分从而发挥作用。一项I期临床试验 (EudraCT2017-003557-42) 评估了VX-150在健康成年男性中的镇痛作用、安全性、耐受性和药代动力学。结果显示, VX-150在多种诱发疼痛测试中显示出镇痛效果, 尤其在冷痛和热痛中表现显著, 服药后4 h内冷痛阈值显著提高。VX-150总体耐受良好, 研究期间未发现显著的安全问题, 报告的不良事件多为轻度或中度, 常见的不良反应为头痛[68,69]。2015年, Vertex公司进行了一项II期临床试验 (NCT02660424), 评估VX-150在124名膝关节炎患者中的镇痛疗效, 并未公布正式研究结果。2017年, 另一项II期临床试验评估了VX-150治疗小纤维神经病变患者的有效性和安全性 (NCT03304522), 虽然Vertex公司在其新闻稿中称此项研究达到主要研究目的, 即接受治疗的患者在第6周时疼痛得到显著缓解, 但并未进行后续相关临床实验。同时Vertex公司还对VX-150在拇囊炎切除术后急性疼痛中的治疗效果和镇痛中的剂量范围开展两项II期临床试验 (NCT03206749、NCT03764072), 结果显示VX-150能缓解拇囊炎切除术后急性疼痛患者的

疼痛反应。

2017年, 在VX-150之后Vertex公司开始对VX-128 (**6**) 进行临床试验研究, 在一项I期随机、双盲的临床研究 (EudraCT2017- 003557- 42) 中, 评估了VX-128的单剂量和多剂量在健康成年受试者中的安全性、耐受性、药代动力学和药效动力学。在单剂量下VX-128出现头痛的不良反应, 多剂量下会导致皮疹以及1位受试者出现血管性水肿, 在2018年因安全性问题终止临床试验[70]。VX-128临床试验过程中, 给药剂量和给药频率可能未能合理优化, 进而导致多种毒副作用的产生。同时, 临床试验中出现的不良反应凸显了药物研发过程中关注药物安全性和耐受性的重要性。特别是在神经病理性疼痛需要长期治疗的情况, 长期使用可能导致药物蓄积或其他潜在的不良反应, 因而现有及潜在的不良反应问题使得VX-128的开发被迫终止。

Vertex公司研发的VX-548 (**7**), 是目前全球Nav1.8抑制剂临床研究进展最快的药物, 分别于2022年7月与2023年2月被美国FDA授予急性疼痛治疗的突破性疗法和快速通道的资格, 2024年7月, 美国FDA受理了VX-548的新药上市申请, 2025年1月, 该分子已被FDA批准成功上市, VX-548已成为近20年来首款用于治疗急性疼痛的非阿片类药物。截止到目前, VX-548已完成3项III期临床试验: 一项治疗腹部整形术后急性疼痛的随机对照试验、一项治疗拇囊炎切除术后急性疼痛的随机对照试验以及在治疗急性疼痛中的安全性和有效性试验 (NCT05558410、NCT05553366、NCT05661734)。在评估VX-548治疗腹部整形术和拇囊炎切除术后急性疼痛的两项试验中, 共招募了577名参与者, 临床实验的主要目的是评估不同剂量的VX-548组、酒石酸氢可酮和对乙酰氨基酚 (hydrocodone bitartrate/acetaminophen, HB/APAP) 组和安慰剂组在48 h内的疼痛程度的不同。低剂量VX-548未显示出显著的镇痛效果, 高剂量VX-548在48 h内显著减轻了疼痛, 但不良事件较为常见, 包括头痛和便秘[71,72]。虽然VX-548能达到缓解疼痛的主要临床研究目的, 但并未达到与阿片类药物HB/APAP相比更好镇痛作用的次要研究目的。一项评估腰椎神经根病的II期临床试验目前已完成, 但未公布具体结果 (NCT06176196)。VX-548作为一种非阿片类止痛药物, 避免了传统阿片类药物常见的不良反应, 包括成瘾性、呼吸抑制和镇静等, 这使得VX-548在急性疼痛的治疗中具有更好的安全性[73]。近期, 在药代动力学和代谢的研究表明, VX-548表现出显著的性别差异, 静脉给药后雌性大鼠的清除率远低于雄性大鼠, 口服给药中雌性大鼠的口服生物利用度为96%, 而雄性大鼠的口服生物利用度仅为11%。这可能是因为在雄性大鼠中表达更高的CYP3A2酶会更快地将VX-548代谢为无活性产物[74]。VX-548之后Vertex公司并未停止对Nav1.8抑制剂的进一步研发, 第三代Nav1.8抑制剂VX-993 (**8**) 和VX-973 (**9**) 均已进入I期临床 (NCT06226454、NCT05866055)。

2023年10月, 一家专注于疼痛药物开发的美国公司Latigo Biotherapeutics开始了Nav1.8选择性抑制剂LTG-001 (**10**) 安全性的I期临床试验 (NCT06049095)。2024年8月, 该公司开始LTG改构化合物LTG-305 (**11**) 的I期临床试验 (NCT06554574)。2024年1月, Latigo Biotherapeutics公司公布了一项重要研究成果, 首次披露其所开发的一种具有高选择性的小分子Nav1.8抑制剂LTGO-33 (**12**)。该化合物在纳摩尔效力范围实现对人源Nav1.8的强效抑制, 对其他钠通道亚型的选择性超过600倍[75]。与既往多数依赖通道失活状态结合位点的Nav1.8抑制剂不同, LTGO-33对静息态和失活态通道均表现出相近的抑制效力, 呈现出无状态依赖性 (state-independent) 特点。其作用位点位于电压感应结构域II (voltage-sensing domain II, VSDII) 的胞外区域, 尤其是S3和S4环[12]。这一作用模式在先前所有已知Nav1.8小分子抑制剂中属首次报道。LTGO-33对多种与人类遗传性疼痛表型相关的Nav1.8突变体 (S242T、L554P、V1073A、A1304T、G1662S及I1706V) 依然保有抑制效力[75]。目前, 该化合物尚处于临床前研究阶段, 有望成为下一代外周神经病理性疼痛治疗的重要候选药物。

Nav1.8抑制剂的研发前景可观, 国内也有多家公司积极进行相关开发, 由恒瑞医药研发的HRS4800 (**13**), 已有2项I期临床及2项II期临床试验, 涉及的适应症包括急性疼痛和牙科手术后疼痛 (NCT04573036、CTR20211682、NCT05318846、CTR20220048)。济民可信开发的JMKX-000623 (**14**) 于2022年3月在国内获批临床, 并于2024年3月开展II期临床试验, 用于治疗糖尿病神经病变 (NCT06221241、CTR20240670)。由海博为药业开发的HBW-004285 (**15**) 于2023年4月在国内获批临床, 目前正在开展I期临床试验 (CTR20231148)。广州费米子科技有限责任公司于2024年2月进行JKN23061 (**16**) 的I期临床试验 (CTR20240574)。此外, FZ008-145 (**17**, 广州费米子科技有限责任公司开发) 于2024年11月在澳大利亚获批临床试验 (NCT06685809)。成都康弘药业集团股份有限公司开发的KHN702 (**18**) 于2025年6月获批临床实验 (CTR20252159、NCT07044960)。

Nav1.8通道成孔结构域的中央腔 (site C) 为众多小分子抑制剂提供了核心结合位点[76,77], Gly1406的侧

链特性为PF-01247324提供了与Nav1.8通道结合的空间基础。Gly1406还作为A-803467与Nav1.8结合的远端别构调控位点，其可能是决定Nav1.8选择性抑制的重要因素。VSDII作为Nav1.8上小分子结合的新型位点，该位点富含Nav1.8独有的氨基酸残基（如Val746、Lys748、Lys749与Gly750），组成了一个亚型特异的药物结合腔体[12]。Pfizer公司在Nav1.8镇痛抑制剂的开发进行了大量工作，但其PF系列化合物并未有效通过II期临床试验，推测与该类化合物作用于Nav1.8较为保守的孔道区（site C）相关，从而导致选择性与安全性不能满足进一步开发的需求。近期作者实验室的研究表明位于DII S3-S4区域的数个氨基酸是VX系列化合物的关键作用位点。DII S3-S4是site 4多肽毒素作用的区域，该区域在钠通道亚型中具有一定差异，结合此位点脱离了传统的孔道阻断策略，推测将是Nav1.8镇痛药物开发的重点关注位点。此外，细胞外环区域作为电压门控钠通道中序列保守性最低的结构单元[78]，相较于Nav1.5，Nav1.8在此位点上存在关键氨基酸的缺失和替换，这为避免作用于其他钠通道亚型和降低潜在心脏毒性提供了结构依据（图4）。

5 Nav1.8抑制剂临床研发的展望

疼痛影响全球超过20%的人口，其病因复杂多样，病程长期且易复发，给个人带来了巨大的经济压力和心理负担。目前，阿片类药物虽然在镇痛方面具有显著疗效，但因其成瘾性、耐药性及呼吸抑制等严重不良反应，其临床应用受到了较大限制[47,79]。随着全球对非阿片类镇痛药物需求的增加，Nav1.8抑制剂作为一种新型的疼痛治疗靶点，提供了更安全的替代方案。由于Nav1.8在疼痛信号传导中的关键作用以及其独特的电生理特性，多家制药公司正在开发针对Nav1.8的选择性抑制剂。全球范围内已有多款Nav1.8抑制剂进入不同的开发阶段，其中Vertex公司的VX-548已在美国成功上市。

Nav1.8抑制剂的开发具有巨大的临床潜力，尤其是在疼痛治疗方面。综合基础研究与临床数据，目前一些未能取得积极进展的Nav1.8镇痛分子通常具有一些共同的特点：① 这些分子大多存在选择性不足的问题，无法专一性地抑制Nav1.8通道，这种非特异性抑制不仅降低了疗效，也增加了不良反应的风险；② 抑制Nav1.8的效力不够强，这可能是靶点占位不够，体内镇痛活性不显著的原因；③ 部分临床分子在体内的药代动力学表现不佳，面临着较差的口服生物利用度和较短的半衰期，这使得其在临床应用中缺乏持续的治疗效果。VX-548的开发过程中，尽管其在临床试验中展现了相对良好的止痛效果，但也暴露出一些潜在的不良反应。常见消化系统的不良反应，包括恶心、呕吐及腹泻，参与者还报告了头痛及头晕症状，这表明VX-548具有一定程度的中枢神经系统副作用。

相比于Nav1.7镇痛剂的开发，Nav1.8抑制剂在多个方面展现了其独特的优势。Nav1.7广泛表达于周围神经系统和中枢神经系统，包括DRG、交感神经元以及嗅觉神经元，因其在非痛觉通路中的功能，针对Nav1.7的抑制剂可能带来非靶向的不良反应。Nav1.8的表达具有更高的特异性，主要分布在周围神经系统中的小直径伤害性感觉神经元，且高表达于无髓C类纤维和Aδ纤维，与疼痛传导直接相关，这种组织特异性降低了非靶向抑制对正常生理功能的干扰，可减少不良反应风险。Nav1.7在疼痛信号传导的启动阶段中发挥重要作用，但其失活速度较快，难以维持持续性信号的传递。Nav1.7抑制剂的疗效可能局限于急性疼痛类型，对慢性疼痛（如神经病理性疼痛）疗效有限。

Nav1.8的高激活阈值、缓慢失活及快速复原等特



Figure 4 Sequence alignment of the Nav1.8 selectivity-associated region with the corresponding segments of the other eight human voltage-gated sodium channel isoforms. Nav1.8-specific residues, Val746, Lys748, Lys749, Gly750, and Gly1406, are highlighted in red. The sequence logo above the alignment reflects conservation across isoforms and is color-coded according to amino acid physicochemical properties: pink indicates small hydrophobic residues, green indicates polar uncharged residues, purple indicates small polar residues, yellow indicates aromatic residues, blue indicates basic residues, and red indicates acidic residues. The residue numbers of Nav1.8 are shown at the top

性, 使其在持续去极化状态下仍可维持动作电位的发放, 从而参与慢性疼痛信号的持续传导[80]。炎症环境中, PGE_2和NGF可显著增强Nav1.8的表达与电流密度, 导致痛觉敏化; 而在神经病理状态下, Nav1.8在未受损神经元中异常上调与重新分布, 进一步放大了疼痛信号传导[81]。Nav1.8的表达特异性和电生理特性使其成为开发外周靶向、高选择性、低不良反应镇痛药物的理想候选靶点。

除钠通道外, 当前研究较多的镇痛药物开发靶点还包括阿片类受体、α_2-肾上腺素能受体、大麻素受体、γ-氨基丁酸 (gamma-aminobutyric acid, GABA) 受体、*N*-甲基-*D*-天冬氨酸 (*N*-methyl-*D*-aspartate, NMDA) 受体、瞬时受体电位香草酸亚型1 (transient receptor potential vanilloid 1, TRPV1) 通道、降钙素基因相关肽 (calcitonin gene-related peptide, CGRP) 受体以及环氧化酶 (cyclooxygenase, COX) 等。阿片类药物产生成瘾、耐受、呼吸抑制、便秘等严重不良反应, 仍是滥用与监管重点[82]。α_2-肾上腺素能受体激动剂虽在外周与脊髓水平均能发挥镇痛作用, 但其激活中枢α_{2A}和α_{2C}受体后易引发镇静、低血压、呼吸抑制等不良反应, 同时外周α_2B受体的激活还可诱导血管收缩和进一步心血管负担增加[83]。大麻素受体1 (cannabinoid receptors, CB1) 激动剂具有一定的镇痛潜力, 因其在中枢神经系统的广泛表达, 常引发运动障碍、认知损害及精神异常反应, 限制其临床应用[84]。GABA受体激动剂可逆转神经性疼痛模型中的痛觉过敏反应, 由于GABA在多个系统中参与生理功能, 其全身性激活往往伴随镇静、成瘾性和耐受性等不良反应[85]。NMDA受体拮抗剂可通过阻断中枢敏化机制, 增强阿片类药物的镇痛效能, 但其治疗窗口狭窄, 同时常伴意识障碍、幻觉、记忆缺陷等中枢精神不良反应, 剂量控制困难[86]。TRPV1通道作为炎症性与神经病理性疼痛中的伤害性感受器, 其可被低pH、有害热刺激和内源性脂质介质等激活。然而, TRPV1拮抗剂在临床上被发现会引发高体温和对热刺激感知受损等问题, 严重影响正常的伤害感知功能[87]。CGRP受体拮抗剂目前已广泛用于偏头痛的治疗, 由于CGRP具显著的血管舒张作用, 其适应症主要限于血管源性疼痛, 对其他类型慢性疼痛疗效有限[88]。此外, 非甾体抗炎药通过抑制COX发挥抗炎镇痛作用, 其中非选择性COX抑制剂易引发胃肠道损伤、出血等问题, 而选择性COX-2抑制剂则存在心肌梗死和血栓形成风险, 限制了其长期安全使用[89,90]。尽管非钠通道靶点展现出镇痛效能, 但其广泛分布及复杂的生理参与机制导致不良反应频发, 一定程度限制了其在慢性疼痛治疗中的长期应用价值。与此形成鲜明对比的是, Nav1.8因其高度组织特异性、电生理特性及在慢性疼痛状态中的动态表达调控, 展现出作为镇痛靶点的独特优势。

Nav1.8在疼痛信号的维持和传导过程中发挥关键调控作用, 尤其是在动作电位的上升相和持久性信号传递中具有独特优势。目前, Nav1.8选择性抑制剂作为新型镇痛药物已显示出良好的治疗前景, 但其临床转化仍面临诸多挑战, 包括分子选择性不足、抑制活性不强、药代动力学特性欠佳以及潜在的心血管系统不良反应等问题。针对这些挑战, 未来研究应着重于以下方面: ① 基于结构生物学方法优化配体–受体相互作用, 提高亚型选择性; ② 通过前药设计等策略改善化合物的吸收、分布、代谢和排泄特性; ③ 建立完善的临床前安全性评价体系。

为开发出更具成药潜力的Nav1.8抑制剂, 药代动力学优化是一个重要的研究内容, 优化目标包括提高药物的水溶性与膜通透性; 保持或增强Nav1.8的选择性抑制; 降低代谢清除率; 消除hERG通道抑制风险以提升安全性; 具备可控的体内半衰期与良好的生物利用度。基于Nav1.8与其他钠通道亚型之间的氨基酸序列差异, 尤其是VSDII特异性残基构成的空间结构, 可通过设计高度匹配的结合基团, 避免作用于心脏相关的Nav1.5等非靶通道或者受体, 从源头上降低潜在心脏毒性风险。通过引入含氮杂环、羟基或碱性胺等极性取代基, 提高分子水溶性, 同时通过调控pK_a值、极性表面积等, 优化膜通透性与代谢稳定性之间的平衡, 增强口服利用度与组织靶向性。随着基于结构的药物设计技术和精准医疗策略的不断发展, 新一代高选择性Nav1.8抑制剂有望为慢性疼痛治疗提供更安全有效的治疗方案。

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