•综述•

# 靶向Nav1.7的镇痛药物开发: 临床试验进展与选择性抑制剂发现

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**摘要**: 电压门控钠离子通道亚型Nav1.7在伤害性感觉神经元中高表达, 是多种人类遗传性疼痛综合征的关键致病靶点。近年来, 大量研究表明Nav1.7在炎性、神经病理性及伤害性刺激诱发的疼痛中具有重要作用。因此, 靶向抑制Nav1.7是新型镇痛药研制的新策略和热点。本文介绍了Nav1.7的结构与功能、在疼痛中的调节作用, 重点总结了临床试验中Nav1.7小分子抑制剂的开发进展, 并对临床前Nav1.7高专一性抑制剂的开发进行了分析, 以期为Nav1.7镇痛药物的开发提供参考。

**关键词**: Nav1.7; 疼痛; 镇痛药物; 临床研究; 选择性抑制剂

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# Development of analgesic drugs targeting Nav1.7: advances in clinical trials and discovery of selective inhibitors

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**Abstract**: The voltage-gated sodium channel subtype Nav1.7 is highly expressed in nociceptive sensory neurons and is a key pathogenic target in several human hereditary pain syndromes. In recent years, a large number of studies have shown that Nav1.7 plays an important role in inflammatory, neuropathic, and nociceptive pain. Therefore, targeting Nav1.7 is a new strategy and hotspot for the development of novel analgesics. This review introduces the structure and function of Nav1.7, its regulatory role in pain, highlights the development progress of small-molecule Nav1.7 inhibitors in clinical trials, and analyzes the preclinical development of highly specific Nav1.7 inhibitors, with a view to providing reference for the development of Nav1.7 analgesic drugs.

**Key words**: Nav1.7; pain; analgesic drug; clinical trial; selective inhibitor

电压门控钠离子通道 (voltage-gated sodium channels, VGSCs) 由一个$\alpha$亚基 (260 kDa) 和一个或多个$\beta$亚基 (30～40 kDa) 组成, 广泛分布于人体, 是调控钠离子选择性滤过的多亚基跨膜蛋白[1,2]。目前已鉴定出9种哺乳动物的钠通道$\alpha$亚基, 即Nav1.1～Nav1.9[3,4]。Nav1.7由*SCN9A*编码, 主要在小直径外周感觉神经元、交感神经节神经元、三叉神经节感觉神经元、迷走神经感觉神经元中表达[5-8]。Nav1.7通过响应膜电位去极化, 介导动作电位的产生和重复放电, 在伤害性感觉神经元电信号传导中发挥核心作用[9]。

## 1 Nav1.7的基本结构

Nav1.7的$\alpha$亚基由3个细胞内环 (intracellular loops, L1～L3) 连接的4个同源 (但不相同) 结构域 (domain I～domain IV, DI～DIV) 组成。$\alpha$亚基的每个结构域包含6个跨膜螺旋片段 (S1～S6), 其中S1～S4构成电压敏感区域 (voltage-sensing domain, VSD), S5、S6及其细胞外连接环 (P-loop) 构成孔道结构域 (pore domain, PD)[3,10]。每个VSD中的S4螺旋分布着高度保守带正电荷的精氨酸和赖氨酸, 灵敏地响应电压变化,

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构成Nav1.7的电压敏感性; S5和S6之间的pore-loops组成选择性滤器 (selectivity filter, SF), 在钠离子的通透过程中发挥重要作用。

细胞膜电位的变化引起Nav1.7通道带电荷的氨基酸在细胞膜上移动, 诱导通道在3种构象之间转换: 静息、开放和失活[11,12]。在静息膜电位下, 4个VSD朝向膜的细胞内侧, 通道处于非导电闭合状态, 即静息状态。当膜电位降低 (去极化) 时, 带正电荷的S4跨膜螺旋片段朝细胞外移动, 改变通道构象, 在短时间 (小于1毫秒) 打开通道孔并允许钠离子进入, 通道进入激活状态。去极化发生过程中, 失活球快速插入通道的孔道区, 堵塞孔道从而阻止钠离子内流, 通道进入失活状态。失活球由位于DIII和DIV之间L3上的异亮氨酸 (I)、苯丙氨酸 (F)、甲硫氨酸 (M) 和苏氨酸 (T) 组成。在细胞膜复极化过程中, 钠离子通道从失活状态恢复, S4片段回到初始静息状态位置, 为下一次去极化做准备[11,13]。$\alpha$亚基单独表达即可在体外形成功能性钠通道[14], 但它们在体内通常与辅助性$\beta$-亚基结合, 通过共价或非共价相互作用形成多蛋白信号复合物。$\beta$亚基可以调节钠通道的动力学、电压依赖性等门控特性及其表达和运输[1], 并影响调节剂与Nav1.7的作用[3,15] (图1)。长期以来, 高分辨率三维结构的缺乏限制了Nav1.7构象机制的深入认识和靶向Nav1.7的药物开发。2022年, 颜宁团队联合潘孝敬团队、申怀宗团队, 首次报告了与$\beta$1和$\beta$2亚基复合的hNav1.7 (野生型) 高分辨率冷冻电镜结构 (2.2 Å), 揭示了数个先前难以辨认的胞质片段结构; 进一步深入研究与两种毒素结合的Nav1.7 (E406K) 结构, 确定了DIV S6中参与调节PD区域门控的两种不同构象[16]。颜宁团队与潘孝敬团队[17]通过构建11个Nav1.7致病突变体, 进一步解析了hNav1.7突变体的冷冻电镜结构, 为电压门控钠离子通道的机电耦合机制提供了重要的见解, 并为与疼痛相关的突变提供了分子病理机制的解释。

## 2 Nav1.7在痛觉调控中发挥关键作用

《中国疼痛医学发展报告 (2020)》指出我国慢性疼痛患者已超过3亿, 且以每年近2 000万的速度增长, 疼痛已成为继心脑血管疾病、肿瘤之后的第三大健康问题[18]。阿片类药物是目前最有效也最常用的疼痛治疗药物。然而, 由于阿片类药物存在成瘾、呼吸抑制等突出的不良反应, 以及滥用导致了严峻的社会问题, 现已成为严格管控的药物[19]。因此, 针对新型靶点, 开发安全有效的非阿片类药物是镇痛药物研制的前沿和热点。

**2.1 Nav1.7的电生理特性** Nav1.7通道可快速激活和快速失活, 具有较慢关闭态失活特性, 能响应阈下刺激, 并促进细胞膜进一步去极化, 被认为是动作电位产生的阈值通道。快速激活的Nav1.7能够诱发再生电流, 是疼痛产生的重要病因机制。Nav1.7在伤害性感觉神经元中的表达高于非伤害性感觉神经元, 并分布在无表皮神经末梢到突触前中枢末梢的整个长度上[20]。Nav1.7在相对超极化的膜电位下激活, 以及缓慢闭合状态下失活的生物物理特性, 使其能够响应缓慢去极化的阈下刺激, 增加伤害感受器神经元膜电位

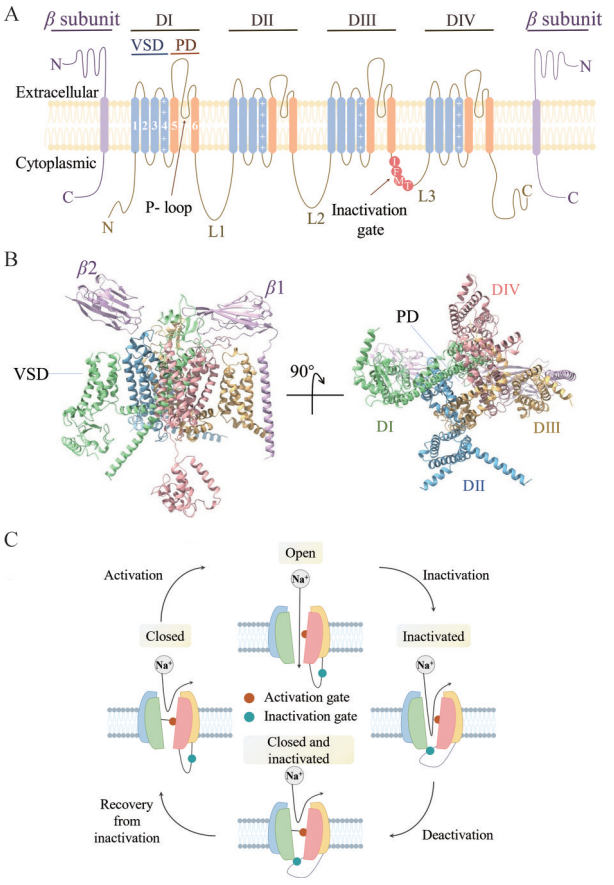


**Figure 1** Overall structures and typical open-closed-inactivated cycle of voltage-gated sodium channels. A: VGSCs structural topology. VSD and PD are represented in different colors while $\beta$ subunits are shown in purple. Domain I−domain IV, P loop, and L1−L3 are labeled along with a diagram of the inactivation gate; B: 2.2 Å resolution cryo-EM structure of WT human Nav1.7-$\beta$1-$\beta$2 complex. Side view and top view of Nav1.7 and two $\beta$ subunits with four domain represented in a different color (PDB: 7W9K)[16]. The four homologous domains contain the VSD and PD. This high-resolution structure of wild-type Nav1.7 provides an accurate template for mechanistic studies and drug discovery; C: Typical gating mechanism of VGSCs: open-closed-inactivation cycle. Figure adapted from Deuis et al and Xu et al[11,12]. VGSCs: Voltage-gated sodium channels; VSD: Voltage-sensing domain; PD: Pore domain; L1−L3: Intracellular loop 1−intracellular loops 3; DI−DIV: Domain I−Domain IV

到达动作电位产生阈值的概率[20-22]。

**2.2　Nav1.7与遗传性疼痛**　近年来, 人类遗传学与基因组检测技术的发展使人们能够识别基因变异和疼痛感知个体差异之间的关系。遗传学研究发现, Nav1.7与人类复发性疼痛或无法感知疼痛为特征症状的痛觉异常密切相关。Nav1.7的功能获得性突变会导致极度疼痛症状, 如遗传性红斑肢痛症 (inherited erythromelalgia, IEM)[23,24]、阵发性极度疼痛障碍 (paroxysmal extreme pain disorder, PEPD) (又名家族性直肠疼痛综合征)[25]及小纤维神经病 (small fiber neuropathy, SFN)[26,27]。IEM是一种以四肢阵发性疼痛、红斑、发热为特征的常染色体显性遗传病, 患者疼痛多伴有"灼烧感", 通常由高温、长时间站立、运动或酒精引起, 低温可缓解[28,29]。PEPD也是一种常染色体显性遗传病, 其特征是直肠、眼睛或下颌骨的阵发性灼痛和自主神经症状, 包括皮肤发红和心动过缓[30]。SFN是一种以有髓鞘 (A$\delta$ fibers)、无髓鞘 (C-fibers) 神经纤维轴突和表皮内神经纤维损伤为特征的疾病, 常伴有阵发性疼痛与自主神经症状[31]。目前发现的大多数Nav1.7功能获得性突变以错义突变为主[32], 通常通过增强Nav1.7的激活、影响其稳态快速失活或稳态慢速失活特性, 从而使神经元过度兴奋产生疼痛症状[25,32-35]。相反, Nav1.7的功能丧失型隐性突变导致先天性疼痛不敏感 (congenital insensitivity to pain, CIP), 这类患者不能感受疼痛但具有触觉和压力敏感性, 常伴有嗅觉丧失, 对组胺诱导的瘙痒没有反应[36,37]。

与临床发现一致, Nav1.7敲除小鼠成年后表现出与CIP完全相似的表型[38]。最近, 一项对来自Nav1.7基因敲除小鼠DRG神经元的转录和蛋白质组学分析表明, 抑制DRG神经元中的Nav1.7通道可能会导致内源性脑啡肽的上调, 从而表现出阿片类药物的镇痛效果, 而不会产生中枢神经系统的不良反应。与这一假设相一致的是, 纳洛酮 (一种阿片受体拮抗剂) 可恢复Nav1.7基因敲除小鼠的热敏感性和机械敏感性, 一名CIP患者使用纳洛酮药物后首次体验到有害的热刺激[39]。这些研究发现为Nav1.7成为非阿片依赖性的镇痛治疗靶点, 提供了强有力的遗传与功能学证据。

## 3　Nav1.7镇痛药物的临床试验研究

**3.1　Nav1.7抑制剂临床应用现状**　基于Nav1.7在疼痛发生过程中的关键作用, 选择性Nav1.7抑制剂的研发已成为学术界与制药公司的关注重点, 以期望开发出安全有效且非成瘾性的镇痛药物。目前应用于Nav1.7的抑制剂有两大类: 物理堵塞通道PD部分阻止钠离子进入的孔道阻滞剂 (pore blockers), 另一类是与一个或多个VSD结合并将其捕获在特定构象状态来变构调节通道的门控调节剂 (gating modifiers)[3,12,40,41]。由于孔结构域的高度保守性, 与门控调节剂相比, 孔道阻滞剂往往具有较低的亚型选择性。如目前临床上常用的非选择性钠通道阻滞剂: 小分子局部麻醉药 (利多卡因、苯佐卡因)、I类抗心律失常药物 (美西律)、抗惊厥药物 (卡马西平)[42], 结合在通道孔的内腔中, 包括DI、DIII和DIV的S6上较为保守的氨基酸残基[43,44]。因此临床使用发现诸多不良反应, 包括抑制Nav1.4与Nav1.5通道活性引起的骨骼肌和心脏不良反应[45]、抑制Nav1.1、Nav1.2和Nav1.3引起中枢癫痫发作和意识改变[46]。近10多年来, 已陆续开发出多种选择性和强效的Nav1.7抑制剂, 包括小分子化合物、天然毒素及其衍生物和单克隆抗体。颜宁团队及多名研究学者, 通过解析Nav1.7与多肽毒素, 以及代表性小分子抑制剂的高分辨率冷冻电镜结构, 为靶向Nav1.7的药物设计与优化改造奠定了基础[16,47,48] (图2)。统计Clinical-Trials网站、Cortellis数据库及部分国际制药公司公开的信息, 目前开发的Nav1.7抑制剂40余种。本文重点关注临床研究阶段以及正在临床前早期开发的Nav1.7选择性抑制剂。

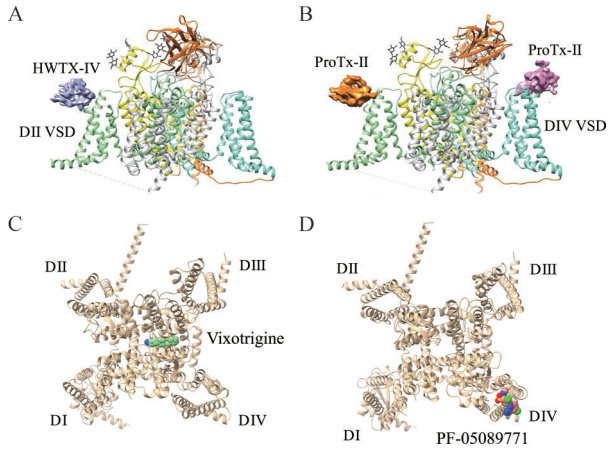


**Figure 2**　Structural diagram of Nav1.7 interaction with different compounds. A: Structure of Nav1.7 in complex with the specific toxin HWTX-IV; B: Structure of Nav1.7 in complex with the specific toxin ProTx-II. (A) and (B) reprinted and adapted from Shen et al[3]; C: Structure of human Nav1.7 in complex with vixotrigine from the top view (PDB: 8I5Y)[48]; D: Structure of human Nav1.7 in complex with PF-05089771 from the top view (PDB: 8I5G)[48]

**3.2　临床研究阶段的Nav1.7抑制剂**　目前, 临床试验阶段的Nav1.7抑制剂以小分子化合物为主 (表1)。Ralfinamide是Newron公司在研的一类$\alpha$-氨基酰胺类小分子化合物, 通过抑制Nav1.7, 非选择性抑制其他钠通道亚型、N型$Ca^{2+}$通道和NMDA受体来介导其在炎

**Table 1** Summary of novel clinical trials of Nav1.7 inhibitors

| Drug | Company | Condition or disease | Phase | Registration number | Status of study | Last update posted |
|---|---|---|---|---|---|---|
| Ralfinamide (NW-1029) | Newron Pharmaceutical | Pain<br>Neuropathic pain | Phase 3 | NCT01019824 | Completed | 2017/9/15 |
| Vixotrigine (GSK-1014802; CNV-1014802; raxatrigine; BIIB074) | Biogen | Small fiber neuropathy; diabetes mellitus | Phase 2 | NCT03339336 | Terminated (sponsor decision to close study early; not due to safety concerns) | 2021/5/5 |
| | | Trigeminal neuralgia | Phase 3 | NCT03070132<br>NCT03637387 | Withdrawn (sponsor decision) | 2023/5/6 |
| PF-05089771 | Pfizer | Painful diabetic neuropathy | Phase 2 | NCT02215252 | Completed | 2017/5/5 |
| | | Primary (inherited) erythromelalgia (IEM) | Phase 2 | NCT01769274 | Completed | 2019/11/19 |
| | | Postoperative dental pain | Phase 2 | NCT01529346 | Completed | 2018/6/1 |
| Funapide (XEN402; TV45070; XPF-002) | Teva Branded | Postherpetic neuralgia | Phase 2 | NCT02365636 | Completed | 2018/10/23 |
| | | Osteoarthritis of the knee | Phase 2 | NCT02068599 | Completed | 2021/11/9 |
| | Xenon | Primary erythromelalgia; inherited erythromelalgia | Phase 1 & Phase 2 | NCT01486446 | Completed | 2014/4/14 |
| ANP-230 (DSP-2230) | AlphaNavi Pharma Inc. | Familial infantile patients with episodic limb pain<br>Peripheral neuralgia | Phase 2 | | | |
| ANP-390 (DSP-3905) | AlphaNavi Pharma Inc. | Peripheral neuralgia | Phase 1 | | | |
| DWP-17061 (iN1011-N17) | Daewoong Pharmaceutical Co., Ltd. | Arthritis pain | Phase 1 | ACTRN12620001253998 | | 2020/10/23 |
| | iN Therapeutics Co., Ltd. | Osteoarthritis<br>Pain | Phase 1 | NCT05496205 | Completed | 2023/12/19 |
| | | Post herpetic neuralgia pain<br>Osteoarthritis<br>Neuropathic pain<br>Chronic pain | Phase 1 | NCT06218784 | Recruiting | 2024/1/23 |
| Lohocla-201 (Kindolor) | Lohocla Research Corporation | Chronic pain | Phase 1 | NCT06243835 | Not yet recruiting | 2024/2/6 |
| AZD-3161 | AstraZeneca | Peripheral neuropathic pain; nociceptive pain | Phase 1 | NCT01240148 | Completed | 2011/4/12 |
| GDC-0276 | Genentech, Inc. | Healthy volunteer | Phase 1 | NCT02856152 | Withdrawn (the molecule is no longer in development) | 2018/2/19 |
| GDC-0310 | Genentech, Inc. | Healthy volunteer | Phase 1 | NCT02742779 | Completed | 2020/2/20 |
| PF-05241328 | Pfizer | Healthy volunteer | Phase 1 | NCT01165736 | Completed | 2010/8/24 |
| ASP 1807 (CC-8464) | Chromocell Therapeutics & Astellas Pharma Inc. | Neuropathic and inflammatory pain | Phase 1 | | | |
| ST-2427 | SiteOne Therapeutics, Inc. | Acute, post-operative pain | Phase 1 | NCT04475198 | Terminated (strategic decision) | 2023/8/3 |
| BIIB-095 | Biogen | Diabetic neuropathies | Phase 1 | NCT04106050 | Withdrawn (sponsor decision) | 2021/3/22 |
| | | Healthy volunteer | Phase 1 | NCT03454126 | Completed | 2019/5/16 |
| OLP-1002 | OliPass Corporation | Pain | Early phase 1 | NCT03760913 | Completed | 2021/8/26 |
| | | Osteoarthritis | Phase 1 | NCT04677933 | Completed | 2020/12/24 |
| | | | Phase 2 | NCT05216341 | Recruiting | 2023/1/17 |

症和神经性疼痛动物模型中的镇痛活性[49,50]。目前ralfinamide已在英国、德国、意大利、波兰、罗马尼亚和印度进行神经病理性疼痛的III期临床试验[51]。Vixotrigine是百健公司在研的一种用于治疗糖尿病性、特发性小纤维神经病变和三叉神经痛等神经病理性疼痛疾病的药物。2013年7月, vixotrigine已被美国FDA批准为用于治疗三叉神经痛的孤儿药。功能分析显示其不影响Nav1.7激活特性, 但可通过稳定失活状态, 加速失活并延迟失活恢复, 从而抑制Nav1.7通道[52]。最新发现vixotrigine是一种广谱钠通道抑制剂, 100 μmol·L$^{-1}$ vixotrigine能抑制不同钠通道亚型90%以上的峰电流, 且各种亚型之间$IC_{50}$的值差异变化在10倍以内[53]。体内研究表明, vixotrigine具有大脑渗透性, 因而该药物的抗伤害感受被认为可能是由中枢神经系统钠通道亚型的抑制所介导, 与局部给药相比, 全身给药的镇痛疗效更好[54]。Vixotrigine在癫痫发作和精神分裂症动物模型中也表现出镇静作用和疗效[53]。在治疗腰骶神经根病引起的神经病理性疼痛的II期临床研究中, 因未达到其主要或次要疗效终点, vixotrigine在该适应症的临床研究 (NCT02957617) 已被终止[55]。有研究者提出, 疼痛病理机制的复杂性调控了钠通道的不同状态, 限制了vixotrigine作用于去极化或过度活跃神经元中的失活钠通道[53,56]。大量的临床前及临床研究表明, vixotrigine仍可作为一种潜在的镇痛药物应用于特殊的神经病理性疼痛[54,57], 需要寻找合适的疼痛类型进行该化合物的临床镇痛研究。2021年5月, vixotrigine在特发性或糖尿病相关疼痛性SFN的疗效和安全性的II期临床研究已提前结束, 显示安全性良好[58]; 虽然vixotrigine在三叉神经痛患者的III期安慰剂对照、双盲随机戒断研究被撤回, 但患者对其良好的耐受性及镇痛疗效 (患者的阵发性疼痛发作次数和平均每日疼痛评分明显减少) 支持其进一步的临床研究[59]。PF-05089771是辉瑞公司开发的Nav1.7高选择性的芳基磺酰胺类化合物 ($IC_{50}$约11 nmol·L$^{-1}$)[60], 可以与VSD发生相互作用, 稳定通道的失活构象从而抑制去极化的Nav1.7通道[61]。截止到2015年, PF-05089771已经完成多项疼痛治疗的I期临床试验 (NCT01365637、NCT01690351、NCT01934569、NCT01854996、NCT01529671、NCT01259882、NCT02349607、NCT05935280)。在术后牙痛与IEM的II期临床试验中, PF-05089771表现出显著的镇痛疗效; 然而在糖尿病神经病理性疼痛的随机双盲研究中, 疼痛评分或睡眠质量没有统计学上的显著改善, 且患者报告出现胆固醇水平升高。可能由于高血浆蛋白结合特性, 以及易从Nav1.7通道解离的脱靶效应, 导致作用部位药物浓度过低, 影响了这种磺胺类药物的镇痛疗效[62,63]。目前辉瑞公司已停止对该化合物的开发。Funapide是一种由Teva和Xenon公司开发的局部应用的Nav1.7选择性阻滞剂 ($IC_{50}$约80 nmol·L$^{-1}$)[64]。最初被报道可有效缓解IEM患者的疼痛症状[64], 目前临床试验以治疗原发性膝关节骨性关节炎、IEM、带状疱疹后遗神经痛为主。虽II期临床试验结果显示, funapide仅可改善部分糖尿病神经病变患者的疼痛症状, 但因其表现出良好安全性和耐受性, 且没有出现与药物相关的中枢神经系统或心脏毒性, 仍然有较好的开发前景[65]。

ANP-230是日本住友制药公司开发的Nav1.7和Nav1.8阻滞剂。2013年进行了I期临床试验 (ISRCTN80154838和ISRCTN07951717)[66], 但目前缺乏该药物的文献和临床试验信息, 仅在该公司公开信息中表述已进入家族性婴儿发作性肢体疼痛患者和周围神经痛的II期临床试验, 该公司目前在研的另一Nav1.7抑制剂ANP-390已进入I期临床试验。DWP-17061是大熊制药研发的Nav1.7小分子抑制剂。目前该分子已开始I期临床试验, 用于治疗带状疱疹后遗神经痛、骨关节炎等神经痛与慢性疼痛, 但缺乏较为详细的试验信息。Lohocla-201 (Kindolor) 是由Lohocla研究公司研发的一种新型二苯基脲类的抗痛觉过敏药物[67], 可激动$\delta$-阿片受体, 并抑制谷氨酸兴奋系统的NMDA受体、Nav1.8和Nav1.7的功能[68]。Lohocla-201对福尔马林所致的小鼠早期急性疼痛没有影响, 但可将后期炎症阶段疼痛降低至福尔马林注射前的水平。Lohocla-201可改善慢性疼痛的痛敏, 而不影响正常疼痛反应[68]。Lohocla-201主要作用于周围神经系统, 对中枢神经系统影响小。2024年, Lohocla已在美国开展其用于治疗慢性疼痛的I期临床试验[69]。

部分化合物, 虽在早期的综述论文中描述对Nav1.7具有抑制作用, 但仍停滞在I期临床试验中, 没有进一步的进展报告, 有些已终止研究。如AZD-3161是阿斯利康公司开发的一种选择性Nav1.7阻滞剂, 于2011年进行了I期临床试验, 但目前该分子的进一步临床研究信息未见报道[13]。GDC-0276是基因泰克公司研发的选择性Nav1.7抑制剂, 在I期临床研究后撤回。原因可能与安全性有关, 如肝转氨酶表达升高和低血压[70]。GDC-0310是在GDC-0276结构基础上通过优化不稳定的苄基位置来改善代谢稳定性的*N*-苄基哌啶类化合物, 能够抑制Nav1.7, 已进行I期临床试验, 目前无后续进展[71]。PF-05241328是由辉瑞公司研发的Nav1.7小分子抑制剂, 2010年I期临床试验中缺乏良好的药代动力学特性, 表现出高血浆蛋白结合、高

血浆清除率、较短的体内半衰期, 并未进行后续临床研究[72]。

另有部分化合物仅在ClinicalTrials网站或制药公司公开信息中查到其在临床试验所处阶段, 未能检索到试验药物化合物结构等信息的相关文献。如ASP 1807 (CC-8464) 是由Chromocell和Astellas制药共同研发的一种Nav1.7选择性抑制剂, 其主要作用于外周, 优先作用于受伤或发炎的组织, 在多种动物疼痛模型中有效, 而对未受伤/健康组织中的Nav1.7通道影响小, 可用于治疗特发性小纤维神经病变相关的神经病理性疼痛。2016年10月FDA已授予ASP 1807开发项目的快速通道资格, 但目前无后续进展报告。ST-2427是由Siteone Therapeutics研发的Nav1.7抑制剂, 2023年8月宣布用于治疗急性疼痛和术后疼痛I期临床研究终止。BIIB-095由百健公司研发, 2020年10月用于治疗糖尿病神经病变的I期临床研究被撤回。

CRISPR/Cas9系统在基因组编辑和基因组调控领域的成功应用, 促进了针对Nav1.7的基因治疗[73]。临床前的研究发现CRISPR/Cas9系统可下调*SCN9A*, 从而抑制背根神经节内的Nav1.7表达, 有效改善炎症性疼痛的热性痛敏、神经病理性疼痛的触觉异常性疼痛, 而对小鼠正常运动功能无影响[74]。OliPass公司开发了一种基于DNA靶向的表观遗传调控的基因疗法: OLP-1002是*SCN9A*的反义寡核苷酸, 可以选择性地抑制神经元细胞中Nav1.7钠通道的表达, 从而模拟*SCN9A*基因无义突变CIP患者的部分表型。OLP-1002已于2021年完成了I期临床试验, 并于2023年在澳大利亚开启II期临床试验, 旨在评估OLP-1002皮下注射减轻髋关节及膝关节骨关节炎引起的中度至重度疼痛的疗效、安全性和耐受性, 该研究的中期结果显示, OLP-1002具有强效镇痛效果和长效治疗镇痛的特点。

## 4 临床前Nav1.7抑制剂的开发

**4.1 小分子类化合物** 电压门控钠离子通道亚型孔道区 (PD) 高度保守, 为提高选择性, 研究者致力于开发在PD外结合的小分子化合物。此类化合物中多具有磺胺结构, 通过与DIV VSD的S2和S3相互作用来稳定通道的失活状态, 抑制快速失活的恢复, 并优先靶向已激活的通道[75]。因此, 目前Nav1.7小分子抑制剂的研究多以先前报道的磺酰胺类化合物为模板, 通过对其结构的优化改造, 提高化合物对Nav1.7的抑制活性和亚型选择性, 并降低血浆蛋白结合率与改善药代动力学特性[76-78]。安进公司采用此策略对Nav1.7小分子抑制剂的研发主要分为两个系列: 酰基磺酰胺类和芳基磺酰胺类化合物[79], 目前已报道的分子有AM-2099[80]和AM-0466[81], 在体外和体内疼痛模型中均显示镇痛活性。Xenon公司探索将酰基磺酰胺羰基环化到芳香环上, 开发出以新型三唑结构为核心的GNE-131[82], 在小鼠、大鼠和狗中表现出优异的镇痛效果、良好的体外代谢稳定性和低体内清除率, 并在诱导疼痛的转基因小鼠模型中也显示出优异的疗效。Xenon公司基于结构和配体的设计原理, 发现了一系列新型哌啶基铬烷芳基磺酰胺类Nav1.7抑制剂, 最终得到了一种高效力、代谢稳定、高选择性的Nav1.7抑制剂GNE-616, 可用以评估Nav1.7抑制在慢性疼痛治疗中的效用[77]。GX-201和GX-585是基因泰克与Xenon公司联合开发的Nav1.7抑制剂, 在伤害性疼痛、炎症性疼痛及神经病理性疼痛模型中镇痛效果良好, 且具有较长的半衰期[62]。另外, 辉瑞公司开发了系列磺酰胺类化合物, 虽然没有进入临床试验, 但在临床前研究中起到了重要作用, 如在临床前实验中提供对照作用的PF-05198007[60,83]以及PF-05153462[84]。2020年, Chandra等[85]基于计算机技术, 将150万种化合物与Nav1.7的DIV VSD区域进行分子虚拟对接及分子动力学模拟筛选出了DA-0218, 其对Nav1.7的电流抑制80%, $IC_{50}$为0.74 μmol·L$^{-1}$, 并在福尔马林诱导的炎症性疼痛模型、紫杉醇诱导的神经病理性疼痛模型、组胺诱导的瘙痒模型和小鼠淋巴瘤慢性瘙痒模型中显示良好的抑制作用。最近, Karanjule等[86]根据辉瑞公司研发的Nav1.7选择性抑制剂酰基磺酰胺衍生物开发了一种新型的*N*-芳基吲哚衍生物DS43260857, 表现出对人和小鼠Nav1.7的强抑制活性, 对Nav1.1、Nav1.5和hERG具有高选择性。青岛大学开发的QLS-81是以ralfinamide为基础合成的丙酰胺类化合物, 抑制Nav1.7活性是ralfinamide的10倍, 在电生理特性上引起Nav1.7快速和慢速失活向超极化偏移, 减慢了通道的失活恢复, 从而抑制小鼠DRG神经元放电, 有效缓解脊髓神经损伤引起的神经病理性疼痛和福尔马林诱导的炎症性疼痛, 而对豚鼠心电图没有显著影响[51]。代表性小分子来源Nav1.7抑制剂的活性与钠通道亚型选择性如表2[51,62,77,80-82,84-86]所示。

**4.2 天然毒素来源的Nav1.7抑制剂** 动物毒液来源的活性多肽是Nav1.7抑制剂的重要来源, 其中强效和选择性的抑制剂主要来源于蜘蛛毒素多肽, 如GpTx-1[87]、ProTx-II[88]、JZTX-V[89]、HWTX-IV[90]、Pn3a[91]、HNTX-III[92]。这些多肽的相对分子量多在3～4.5 kDa, 包含3对二硫键, 形成抑制剂胱氨酸结或knottin折叠。尽管具有潜在的缺点, 如膜通透性有限、潜在的免疫原性和缺乏口服生物利用度, 但与小分子药物相比, 毒素多肽对Nav1.7具有更好的选择性和更高的效力。因此

**Table 2** *In vitro* Nav1.7 subtype selectivity of small molecule compound inhibitors. $IC_{50}$ values in nmol·L$^{-1}$; n.r.: Not reported

| Compound | Nav1.1 | Nav1.2 | Nav1.3 | Nav1.4 | Nav1.5 | Nav1.6 | Nav1.7 | Nav1.8 | Nav1.9 | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| AM-2099 | 7 300 | 2 100 | 21 000 | 17 000 | 16 000 | 3 700 | 140 | >30 000 | n.r. | [80] |
| AM-0466 | >42 500 | >42 500 | >42 500 | >42 500 | >42 500 | 650 | 6 | n.r. | n.r. | [81] |
| GNE-131 | 45 | 7 | n.r. | n.r. | 110 | 92 | 3 | n.r. | n.r. | [82] |
| GNE-616 | >1 000 | 12 | >1 000 | >1 000 | >1 000 | 29 | 0.38 | n.r. | n.r. | [77] |
| GX-201 | 192 | 41 | n.r. | n.r. | 705 | 464 | 3.2 | n.r. | n.r. | [62] |
| GX-585 | 100 | 33 | n.r. | n.r. | 435 | 890 | 15.1 | n.r. | n.r. | [62] |
| PF-05153462 | 82 | 134 | 246 | 246 | 820 | 138 | 12.2 | >82 | n.r. | [84] |
| DA-0218 | n.r. | n.r. | n.r. | n.r. | n.r. | n.r. | 740 | n.r. | n.r. | [85] |
| DS43260857 | 6 600 | n.r. | n.r. | n.r. | 14 000 | n.r. | 15 | n.r. | n.r. | [86] |
| QLS-81 | n.r. | n.r. | n.r. | 37 300 | 15 400 | n.r. | 3 500 | n.r. | n.r. | [51] |

近年来, 国际上制药公司开始对现有的Nav1.7多肽抑制剂进行活性改造及优化, 以提升对靶点的效力、选择性和体外镇痛效应。安进公司使用位置扫描模拟和核磁共振结构的组合分析, 设计了JZTX-V类似物AM-8145和AM-0422, 对Nav1.4和Nav1.5选择性提高到100～1 000倍, 其中AM-0422可抑制辣椒素诱导的大鼠DRG神经元和小鼠C纤维的动作电位发放[89]; 随后利用5-Br-Trp24替换JZTX-V的Trp24得到了AM-6120, 皮下给药后有效抑制组胺诱导的小鼠瘙痒症状[93]。Nguyen等[94]以ProTx-II-hNav1.7复合物的结构为基础模拟ProTx-II与hNav1.7的特定相互作用, 并使用Rosetta设计新的ProTx-II衍生物PTx2-3127和PTx2-3258, 对hNav1.7的$IC_{50}$分别为7和4 nmol·L$^{-1}$, 对人类Nav1.1、Nav1.3、Nav1.4、Nav1.5、Nav1.8和Nav1.9通道的选择性超过1 000倍, 其中PTx2-3127鞘内给药显著抑制由奥沙利铂诱导的大鼠慢性神经病理性疼痛及热板实验引起的热痛[94]。基于HNTX-III和hNav1.7的分子对接结果优化的HNTX-III突变体H4, 抑制Nav1.7的活力提高了30倍($IC_{50}$约7 nmol·L$^{-1}$), 对Nav1.4和Nav1.5的选择性>1 000倍, 在急性和慢性炎症性疼痛模型及神经病理性疼痛模型中也显示出强效镇痛作用[95]。

昆明动物研究所从中国红头蜈蚣 *Scolopendra subspinipes mutilans* 的毒液中鉴定出了一种具有3个二硫键的、由46个氨基酸残基组成的多肽Ssm6a, 对Nav1.7表现出高选择性和强抑制活性[96]。Ssm6a在减轻热和醋酸引起的疼痛的能力方面与吗啡相当, 并在福尔马林诱发的动物疼痛模型中, 有效性优于吗啡[96]。芋螺毒素也是一类作用于多种离子通道和神经受体的毒素多肽, 其中$\mu$-芋螺毒素以保守的半胱氨酸框架 (即CC-C-C-CC) 为特征, 通过孔道堵塞机制有效抑制电压门控钠离子通道[97,98]。在迄今为止表征的22种$\mu$-芋螺毒素中, 只有少数具有hNav1.7抑制活性, 如SxIIIC、SmIIIA、KIIIA, 但是缺乏亚型选择性[99]。根据结构设计优化的KIIIA-1类似物增强了Nav1.7抑制活性, 并在福尔马林诱导的疼痛模型中表现出了显著的镇痛活性[100]。多肽类药物易受到肾脏过滤和肝脏代谢的影响, 目前正在开发的几种修饰方法 (包括聚乙二醇化、糖基化以及与抗体等较大生物分子的修饰) 可以有效改善多肽的体内半衰期, 不同途径给药的剂型优化 (鞘内、皮下、鼻内) 可提高多肽的生物利用度[101]。此外, 动物毒素来源的小分子也是Nav1.7抑制剂的重要来源。如河豚毒素 (tetradotoxin, TTX) 和石房蛤毒素 (saxitoxin, STX)。Pajouhesh等[102]通过修饰STX, 获得了hNav1.7选择性孔道阻断剂ST-2262, 其对hNav1.7的选择性是hNav1.1-1.6和hNav1.8的200倍以上, 结合在Nav1.7 DIII细胞外孔环部分, 在急性热疼痛模型中具有显著的活性[102]。代表性天然毒素来源Nav1.7抑制剂的活性与钠通道亚型选择性如表3[87-96,100,102]所示。

**4.3　单克隆抗体及其他新型药物疗法**　自1986年FDA批准第一个抗体药物, 单克隆抗体因具有高特异性、低不良反应的特点, 已成为近年来药物开发的主要来源之一[103,104]。目前有研发团队期望将多肽抑制剂的高效力和选择性与单克隆抗体的长半衰期相结合, 尝试用毒素肽偶联非选择性抗体。Biswas等[105]尝试将GpTx I的类似物缀合到抗体上, 这一缀合虽影响了多肽毒素的体内镇痛活性, 但证明了具有体内长半衰期的毒素多肽–抗体偶联物可以到达神经纤维上的Nav1.7。随后, 该团队的进一步研究中, 将JZTX-V与抗体偶联, 对Nav1.7通道具有极佳的抑制活性(hNav1.7 $IC_{50}$约1.6 nmol·L$^{-1}$), 并在小鼠瘙痒症模型中具有中等程度的镇痛活性; 然而, 该偶联化合物只有在皮下注射高剂量时才能获得镇痛效果 (400 mg·kg$^{-1}$), 血清浓度 (370 nmol·L$^{-1}$) 比体外活性 (mNav1.7 $IC_{50}$约11 nmol·L$^{-1}$) 高34倍[106]。目前尚无靶向Nav1.7的单克隆抗体进入临床试验, Nav1.7抗体药物的开发有待进一步研究。Cai等[107]提出了一种间接调节Nav1.7的小分子药物, 通过抑制CRMP2-Ubc9相互作用来选择性靶向Nav1.7的苯甲酰哌啶基苯并咪唑类化合物 (194), 可抑制小鼠、大鼠、猪和人类DRG神经元中的Nav1.7

**Table 3** *In vitro* Nav1.7 subtype selectivity of natural toxin inhibitors. $IC_{50}$ values in nmol·L$^{-1}$

| Compound | Nav1.1 | Nav1.2 | Nav1.3 | Nav1.4 | Nav1.5 | Nav1.6 | Nav1.7 | Nav1.8 | Nav1.9 | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| GpTx-1 | n.r. | n.r. | 20.3 | 301 | 4 200 | n.r. | 4.4 | 12 200 | n.r. | [87] |
| ProTx-II | n.r. | 136 | 343 | 130 | 263 | 86 | 0.3 | 486 | n.r. | [88] |
| JZTX-V | n.r. | n.r. | n.r. | 2.2 | 2 350 | n.r. | 0.6 | n.r. | n.r. | [89] |
| HWTX-IV | n.r. | 5.8 | 13 | 15 | >385 | n.r. | 21 | n.r. | n.r. | [90] |
| Pn3a | 37 | 124 | 210 | 144 | 800 | 129 | 0.9 | 49 888 | 2 427 | [91] |
| HNTX III | 1 270 | 270 | 491 | >10 000 | >10 000 | n.r. | 232 | n.r. | n.r. | [92] |
| AM-8145 | n.r. | n.r. | n.r. | 145 | 3 000 | n.r. | 0.5 | n.r. | n.r. | [89] |
| AM-0422 | n.r. | n.r. | n.r. | 103 | 966 | n.r. | 0.8 | n.r. | n.r. | [89] |
| AM-6120 | n.r. | n.r. | n.r. | 104 | 6 640 | 604 | 0.8 | >1 000 | n.r. | [93] |
| PTx2-3127 | 16 970 | 5 040 | 20 040 | 11 530 | 137 090 | 608 | 6.9 | >150 000 | >150 000 | [94] |
| PTx2-3258 | 5 013 | 3 399 | 14 093 | 8 877 | 38 315 | 382 | 3.8 | 43 079 | 59 443 | [94] |
| H4 (HNTX III mutant) | n.r. | 13 | 32 | >1 000 | >1 000 | 23 | 7 | >10 000 | >10 000 | [95] |
| Ssm6a | 4 100 | 813 | >10 000 | >10 000 | >10 000 | >10 000 | 25 | >10 000 | n.r. | [96] |
| SxIIIC | 132 | 364 | 89 | 15 | >1 000 | 125 | 152 | >1 000 | n.r. | [100] |
| SmIIIA | 235 | 172 | 95 | 14 | >1 000 | 106 | 41 | >1 000 | n.r. | [100] |
| KIIIA | 136 | 186 | >1 000 | 67 | >1 000 | 762 | 379 | >1 000 | n.r. | [100] |
| ST-2262 | >1 000 | >1 000 | 65 300 | 80 700 | >1 000 | 17 900 | 72 | >1 000 | n.r. | [102] |

电流。化合物194在多种疼痛模型中可以剂量依赖性地缓解疼痛症状, 尤其是可显著改善神经损伤、慢性收缩损伤和紫杉醇诱导的周围神经病变引起的机械性疼痛, 而不影响运动活动和运动协调, 且不会导致焦虑抑郁行为和损伤嗅觉, 表现良好的安全性, 为抑制Nav1.7提出了一个安全有效的思路[107,108]。研究发现在慢性神经性疼痛中, 脑衰反应调节蛋白2 (collapsin response mediator protein 2, CRMP2) 的Lys374与类泛素蛋白修饰分子 (small ubiquitin-like modifier, SUMO) 1共价结合, SUMO化修饰可以调控Nav1.7的膜定位和电流密度[109,110], 阻止SUMO偶联E2酶Ubc9和CRMP2之间的相互作用, 可降低Nav1.7电流并减轻神经病理性疼痛[111]。

## 5 Nav1.7镇痛药物开发的展望

回顾Nav1.7镇痛抑制剂的开发过程, 从临床前研究到临床研究的转化并没有那么顺利。尽管已开发了多种Nav1.7高选择、高亲和力的抑制剂, 但其中大多在临床前的疼痛动物模型和人体临床试验中表现较差的镇痛活性。Nav1.7镇痛药物开发的困难可能由以下几个方面导致。首先, 靶点的差异。Nav1.7在体内可由一个或多个$\beta$亚基所调控, 这与只表达$\alpha$亚基进行药物筛选不同; 另外, 临床上的疼痛多为慢性疼痛, Nav1.7在慢性疼痛的病理条件被多种因素所调控, 如SUMO化修饰、PKC磷酸化修饰等[112-114], 区别于临床前研究的急性单次给药的动物模型中的Nav1.7特点。其次, 药物分子自身。由于渗透性低、体内半衰期短, 且与血浆蛋白结合率高, 从而导致药物在DRG神经元部位分布的浓度低而不能有效抑制Nav1.7。再者, 疼痛是一个多靶点介导的复杂病理过程。目前, 已报道在疼痛产生中发挥关键作用的靶点包括阿片受体、钙离子通道、瞬时感受器阳离子通道、大麻素受体等, 因而体内的疼痛反应是一个多靶点参与调控的过程, 仅抑制Nav1.7并不能阻断其他受体所介导的疼痛过程[115]。因此, 对于上述问题, 在药物筛选过程, 可考虑$\beta$亚基在通道功能中的作用, 评价药物在$\beta$亚基参与中的抑制活性; 同时, 临床前研究的疼痛动物模型的制备和给药方式, 应尽可能接近临床的真实情景; 此外, 多靶点的联合抑制可能是疼痛治疗的一种策略。本课题组长期关注并致力于靶向外周伤害性感觉神经元钠通道亚型的镇痛药物开发。近期, Nav1.8强效抑制剂VX-548顺利通过III临床试验, 显示出良好的镇痛活性。同为介导动作电位上升相产生的关键离子通道, Nav1.7仍是镇痛药物开发的优质靶点。因而, 利用多样化的分子策略, 包括小分子、活性多肽、抗体和基因编辑技术, 以及更加精准的体外抑制活性评价方法和疼痛动物模型, 并关注药物代谢动力学特征, Nav1.7镇痛药物的开发充满潜力。

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**利益冲突**: 本论文所有作者均不存在利益冲突。

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