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GPR177-WNT5a-TRPV1 pathway in dorsal root ganglia as a potential therapeutic target for diabetic neuropathic pain

Aim: To investigate whether and how the GPR177-WNT5a signal axis contributes to the development of diabetic neuropathic pain (DNP).
Methods: The distribution of the orphan G protein–coupled receptor 177 (GPR177) in mouse dorsal root ganglia (DRGs) was examined via in situ hybridization. The influence of GPR177 ablation on neuronal hyperexcitability and neuropathic pain was evaluated using behavioural tests in diabetic mice. The mechanism by which WNT5a (member of WNT family of proteins) contributed to DNP and revealed its direct activation on transient receptor potential vanilloid receptor-1 (TRPV1) channel was examined using calcium imaging and patch-clamp recordings.
Results: The authors reported that GPR177, expressed in large-diameter A-fiber DRG neurons, is required for the development of DNP in mice. Mechanistically, the activation of GPR177 resulted in WNT5a secretion from A-fiber DRG neurons into cerebrospinal fluid (CSF) and subsequent activation of TRPV1 ion channel. In rodents, the authors demonstrated that the pharmacological blockade of the interaction between WNT5a and TRPV1 eliminated DNP. Further, human DRG neurons were confirmed to co-express GPR177/WNT5a and WNT5a secretion in CSF was elevated in subjects with DNP compared to diabetic patients without DNP.
Conclusions: These results identify the GPR177-WNT5a-TRPV1 signaling axis in DRG neurons and reveal its involvement in DNP pathogenesis in rodents.

Comments. DNP affects 25 to 30% of patients with diabetes. The pathogenic mechanisms mediating the development of DNP are not completely understood, and effective treatments are lacking. On this account, this article describes for the first time and in an elegant way a molecular signaling underlying the contribution of A-fiber neurons in DNP and the distinct cross-talk between A-fiber and C-fiber DRG neurons in diabetic mice. Using in vivo and in vitro studies, GPR177-WNT5a signaling was confirmed to play an important role in the pathophysiology of DNP by over activating TRPV1-positive nociceptive neurons. The unique findings of this article propose a potential future analgesic target that might relieve neuropathic pain in patients with diabetes. But until then, further research remains necessary to clarify the clinical relevance of these mechanisms in humans and in patients.

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Reference. Xie YK, Luo H, Zhang SX, Chen XY, Guo R, Qiu XY, Liu S, Wu H, Chen WB, Zhen XH, Ma Q, Tian JL, Li S, Chen X, Han Q, Duan S, Shen C, Yang F, Xu ZZ. GPR177 in A-fiber sensory neurons drives diabetic neuropathic pain via WNT-mediated TRPV1 activation. Sci Transl Med. 2022 Apr 6;14(639):eabh2557. doi: 10.1126/scitranslmed.abh2557. Epub 2022 Apr 6.
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