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Dorsal root ganglion: a key to understanding the therapeutic effects of the erector spinae plane (ESP) and other intertransverse process blocks?

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Received 2 July 2023
Accepted 22 August 2023

To cite: Sørenstua M, Leonardsen A-CL, Chin KJ. *Reg Anesth Pain Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/rapm-2023-104816

ABSTRACT

Since its description in 2016, the erector spinae plane block (ESPB) has become a widely employed regional anesthetic technique and kindled interest in a range of related techniques, collectively termed intertransverse process blocks. There has been ongoing controversy over mechanism of action of the ESPB, mainly due to incongruities between results of cutaneous sensory testing, clinical efficacy studies, and investigations into the neural structures that are reached by injected local anesthetic (LA). This paper reviews the spread of LA to the paravertebral and epidural space and the cutaneous anesthesia in ESPB, with specific emphasis on the dorsal root ganglion (DRG). We hypothesize that the DRG, due to its unique and complex microarchitecture, represents a key therapeutic target for modulation of nociceptive signaling in regional anesthesia. This paper discusses how the anatomical and physiological characteristics of the DRG may be one of the factors underpinning the clinical analgesia observed in ESPB and other intertransverse process blocks.

INTRODUCTION

Since its description in 2016,[1] the erector spinae plane block (ESPB) has become a widely employed regional anesthetic technique and kindled interest in a range of related techniques, collectively termed intertransverse process blocks.[2] There has been ongoing controversy over these blocks, particularly the ESPB, mainly pertaining to the specific mechanisms of their analgesic effect. This largely springs from the fact that the body of evidence that supports clinical analgesic efficacy in the territory supplied by thoracoabdominal spinal nerves, has not always been congruent with studies investigating injectate spread or cutaneous sensory changes.[3] Some early cadaveric studies only found spread restricted to the dorsal rami, whereas more recent work confirms that spread to the paravertebral space can and does occur.[4 5] Imaging studies in live subjects generally show injectate spread to the dorsal rami, the paravertebral space, neural foramina, and the epidural space, although the last is more inconsistent.[3 6] The extent of detectable cutaneous sensory block associated with this spread is variable and tends to underestimate its magnitude.[6] In this paper, we present a novel perspective on the possible mechanisms by which clinically significant analgesia can be achieved with the ESPB and other intertransverse process blocks, despite the apparently modest spread of local anesthetic (LA) to the paravertebral and epidural space and the absence of dense cutaneous anesthesia. We hypothesize that the dorsal root ganglion (DRG) represents a key therapeutic target for these regional anesthetic techniques in the modulation of nociceptive signaling.

DISCUSSION

Fractional distribution of LA to the neural foramen and DRG

The DRG is an enlargement of the dorsal root of each spinal nerve and sits within the intervertebral neural foramen in the transition zone between the paravertebral and epidural space. Recent work using sophisticated micro-CT scanning in cadavers has found that the intervertebral foramina containing each DRG are in direct communication with the interfascial compartment deep to the erector spinae muscle and superficial to the superior costotransverse ligament (the 'retro-SCTL space') (figure 1).[5] LA injected deep to the erector spinae muscle or into the intertransverse tissue complex can thus reach the DRG by a combination of bulk flow and simple diffusion. The physical extent of this spread to the neural foramina, paravertebral, and intercostal spaces, and the consistency with which it occurs, has been recently confirmed by MRI in human subjects.[6] It should be noted that only a fraction of the total LA dose reaches the neural structures in these locations, and that this fraction will vary between individuals depending on the unique interplay of factors influencing physical spread.[7] This can lead to the phenomenon of differential block, which accounts for the discrepancy between detectable cutaneous sensory block and clinical analgesia that is often observed with the ESPB but also other fascial plane blocks.[8] The basis for differential block has been summarized elsewhere,[7] but in brief, different nerve fiber types exhibit different sensitivities to LA conduction block that is inversely proportional to their diameter. Notably, the majority of nociception (particularly long-latency 'second' pain) is transmitted in the smallest C-fibers; however, pinprick sensation is transmitted in larger Aδ-fibers.[9] Thus, the pattern of sensory block will vary depending on the LA concentration achieved at the neural structure in question, and the absence of dense or detectable cutaneous sensory loss does not preclude meaningful analgesia.

Unique characteristics of the DRG

It is increasingly evident that the DRG has a unique and complex microarchitecture that underpins

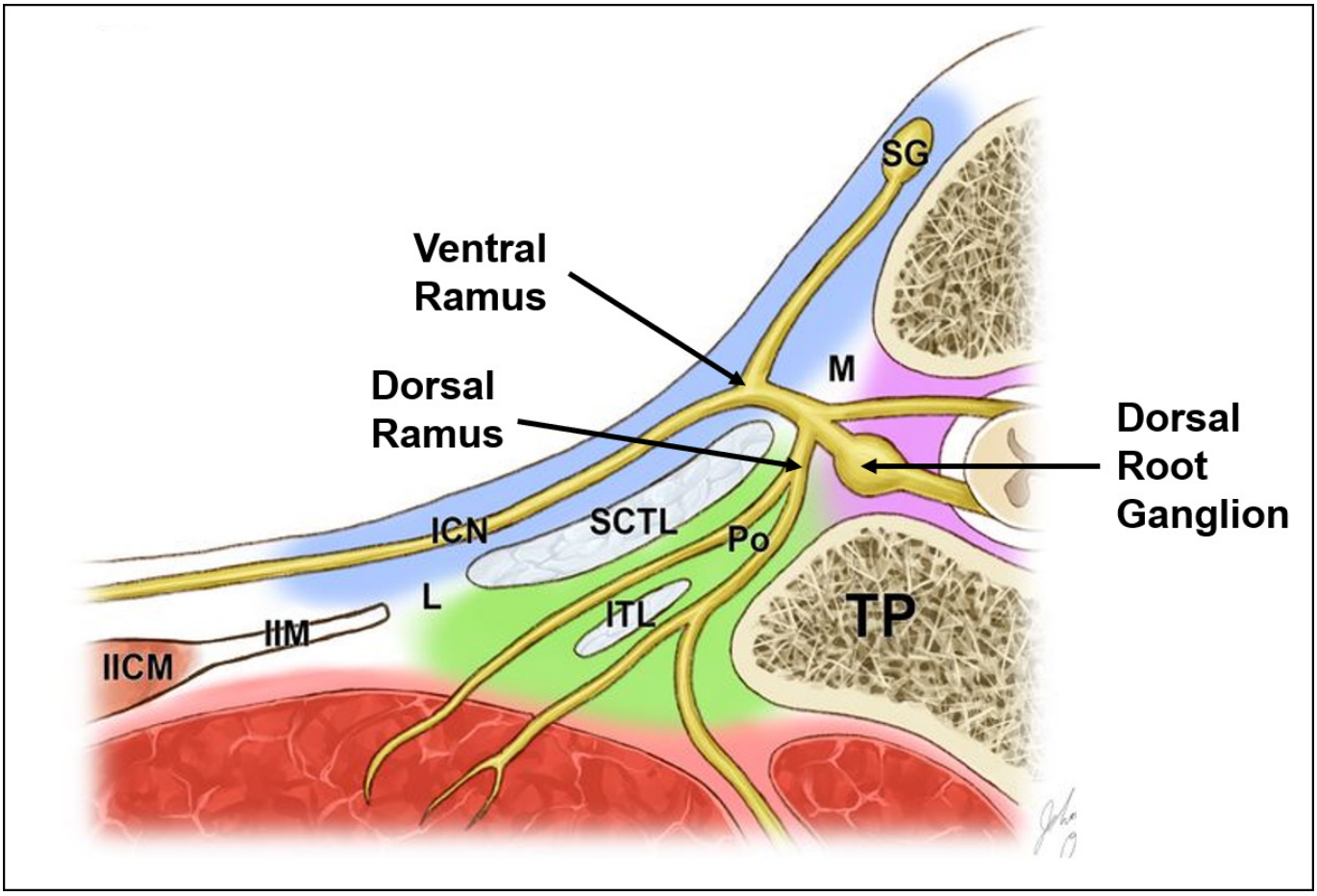

Figure 1 Different tissue compartments and anatomical pathways of communication between them, including fenestrations in the superior costotransverse ligament (SCTL), have been demonstrated in the thoracic paravertebral area using micro-CT scanning techniques. In an erector spinae plane block or intertransverse process block, local anesthetic is injected into the erector spinae plane compartment (red) and retroSCTL space (green), from where it can flow toward the neural foramina and intervertebral space (pink), and into the thoracic paravertebral space (blue). The dorsal root ganglion sits within the intervertebral foramen and space. ICN, intercostal nerve; IICM, internal intercostal muscle; ITL, intertransverse ligament; L, lateral slit; M, medial slit; SG, sympathetic ganglion; TP, transverse process of vertebra (reproduced with permission from Cho *et al*[5]).

its role in transmission and modulation of sensory input from the periphery to the central nervous system (CNS). The DRG contains the somas (cell bodies) of almost all somatic and visceral afferents from peripheral tissues and organs (low-threshold and higher-threshold mechanosensory fibers, the Aβ, Aδ, and C-fibers).[10] DRG neurons are pseudounipolar—each soma has a protruding stem axon, which divides into a peripheral axonal process and a central axonal process. The central process extends into the dorsal horn of the spinal cord, while the peripheral process extends out into the periphery where its terminal endings respond to external and internal stimuli. The division point of the stem axon is called the T-junction.[10] The microarchitecture of the T-junction has relevance for the DRG's role in nociception and LA action at this site. When a peripheral nociceptor registers noxious stimuli, a train of action potentials (APs) is generated that travels up the peripheral axonal process, through the T-junction and into the central process and dorsal horn of the spinal cord.[11] Each electrical AP represents an 'all-or-nothing' depolarization of the cell membrane. The amplitude of change in the resting membrane potential is fixed, and increasing intensity of noxious stimuli is encoded by increasing frequency of APs.[12] The frequency, pulse duration, and timing of sequential APs is a critical feature of neural sensory signaling, and is referred to as the rate code.[13] Information about sensory stimuli is represented by different firing patterns (rate codes) which in turn are interpreted by the higher centers of the CNS. Any modulation of the firing pattern (frequency, duration, and timing) of the APs transmitted to the dorsal horn will alter how these stimuli are perceived. One firing pattern of particular significance for nociception comprises high-frequency trains of short-duration APs grouped in bursts; these are transmitted with high synaptic reliability, and are perceived by human subjects as being more painful than lower-frequency tonic APs, even when the average firing rate is the same.[11 12 14] These high-frequency bursts of APs are also implicated in dorsal horn neuronal plasticity and development of chronic pain.[15]

The branch point of any nerve is a favorable location for modulating AP transmission, and the DRG T-junction is a prime example of this. There is a minimum voltage threshold for propagation of an AP along an axon—the excitation threshold—and any rise in membrane potential in excess of this is referred to as the 'safety factor'. The safety factor is lower at the T-junction and other branch points, increasing the propensity for interruptions of AP propagation and neural transmission. Modulation of neural transmission at the T-junction of DRG neurons also results from an impedance mismatch between the larger-diameter peripheral process (lower impedance) and smaller-diameter central process (higher impedance).[11 16] This transition of electrical signaling

from the low-impedance to high-impedance axonal fibers causes slowing of high-frequency APs.[17] The overall implication is that the T-junctions of DRG neurons can potentially act as a protective switch or a low-pass filter for high-frequency APs that encode noxious stimuli, and thus provide a defensive mechanism for attenuating pain perception.[17 18]

The ion channel blocking effects of LA applied to the DRG will further inhibit AP propagation beyond the T-junction and augment antinociception.[17] Once again, the microarchitecture of the DRG may render it more susceptible to the effects of LA. Most notably, the DRG is enveloped by a connective tissue capsule that is analogous to the perineurium that ensheathes peripheral nerve fascicles but, unlike the perineurium, lacks tight junctions.[19] The presence of tight junctions in the perineurium means that LA molecules have to diffuse through, rather than between, the flat cells of the basal laminae.[20] The molecular weight and lipid solubility of the LA agent is thus a determinant of its potency with regard to conduction block of peripheral nerves.[21] In contrast, the lack of tight junctions in the DRG capsule means that it is more permeable to LA molecules.[19 22] The implication is that the DRG will be more sensitive to conduction block by an equivalent concentration of LA in the interstitial space, compared with a peripheral nerve. This may be another explanation for the clinically apparent analgesia produced by the relatively small mass of LA that reaches the interforaminal region following an ESPB.

The DRG neurons are enveloped and supported by two types of glial cells, the satellite glial cells (SGCs) and the Schwann cells (figure 2).[23] SGCs are unique to the DRG and are only found around the soma and proximal portion of the stem axon; whereas the Schwann cells envelope the distal part of the stem axon as well as the peripheral and central processes.[23] Peripheral nerve damage and inflammation induces activation changes in SGCs and there is increasing evidence that this contributes to ectopic activity in DRG neurons, the associated mechanical and thermal hypersensitivity, and pain perception.[24] This may in turn be one of the mechanisms underlying the chronification of acute pain.[25] Low concentrations of lidocaine at the DRG have been shown to suppress ectopic discharges and microglial

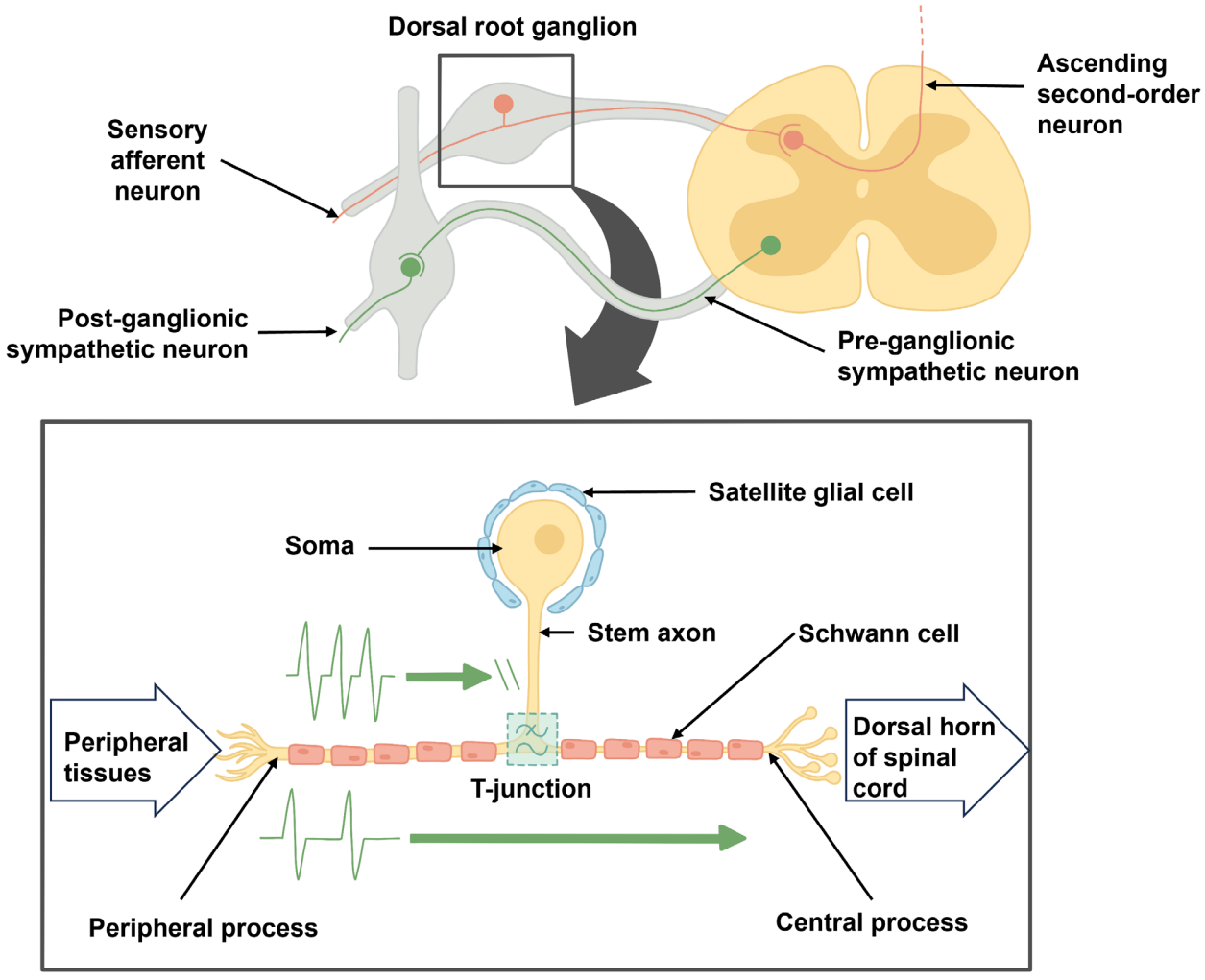

Figure 2 Organization of a dorsal root ganglion (DRG) neuron. The DRG neuron is a pseudounipolar sensory afferent neuron that transmits action potentials (APs) from the periphery via a peripheral process (axon). The soma (cell body) of DRG neurons is contained within the dorsal root ganglion of each spinal nerve that sits within the intervertebral foramen. The soma has a protruding stem axon that divides at the T-junction into the peripheral process and central process. The central process extends into the dorsal horn of the spinal cord to synapse with second-order neurons. The T-junction is a site of potential neuromodulation, acting as a low-pass filter to impede transmission of higher-frequency APs.[18] The soma is enveloped by a supporting structure of satellite glial cells, rather than the Schwann cells that sheath the peripheral and central axonal processes (reproduced with permission from KJ Chin Medicine Professional Corporation).

neuroinflammatory responses, and are postulated as mechanisms for an analgesic effect of plasma-borne LA.[26] The macroscopically visible spread of injectate achieved with an ESPB[6] should produce LA concentrations at the DRG that would at least equal, if not exceed, that of systemic administration; and thus the same mechanisms of analgesic effect will apply.

CONCLUSION

In conclusion, the current evidence indicates that some fraction of LA injected into the retro-SCTL space in ESPB and other intertransverse process blocks will reach the neural foramen and the DRG contained therein. The neurophysiology and microarchitecture of the DRG render it uniquely susceptible to modulation of nociceptive impulses, and it may represent an important site of LA action. The LA concentration achieved at the DRG and other branches of the spinal nerve within the paravertebral space may not always be high enough to produce detectable sensory loss to conventional testing modalities. Clinically significant analgesia may nevertheless result from differential blockade of C-fiber mediated nociception, and the same molecular mechanisms proposed for the lower target-site concentrations that systemically administered LA would produce. Future research using a wider range of nociceptive stimuli, for example, thermal quantitative sensory testing, may be able to further elucidate the contribution of the DRG to the effect of the ESPB in acute and chronic pain conditions.

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Acknowledgements We thank Rachel Wei Ying Chin for her assistance in producing the illustration in figure 2.

Contributors MS stands as guarantor for the overall content. All authors participated in the manuscript writing and reviewed all references. MS, KJC and A-CLL approved the final manuscript.

Funding Funding was provided by institutional and/or departmental sources in Ostfold Hospital Trust.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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REFERENCES

1 Forero M, Adhikary SD, Lopez H, *et al*. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. *Reg Anesth Pain Med* 2016;41:621–7.
2 El-Boghdadly K, Wolmarans M, Stengel AD, *et al*. Standardizing nomenclature in regional anesthesia: an ASRA-ESRA delphi consensus study of abdominal wall, paraspinal, and chest wall blocks. *Reg Anesth Pain Med* 2021;46:571–80.
3 Chin KJ, El-Boghdadly K. Mechanisms of action of the erector spinae plane (ESP) block: a narrative review. *Can J Anesth/J Can Anesth* 2021;68:387–408.
4 Cho T-H, Kwon H-J, O J, *et al*. The pathway of Injectate spread during thoracic intertransverse process (ITP) block: micro-computed tomography findings and anatomical evaluations. *J Clin Anesth* 2022;77:110646.
5 Cho T-H, Kim SH, O J, *et al*. Anatomy of the thoracic paravertebral space: 3D micro-CT findings and their clinical implications for nerve blockade. *Reg Anesth Pain Med* 2021;46:699–703.
6 Sørenstua M, Zantalis N, Raeder J, *et al*. Spread of local anesthetics after erector spinae plane block: an MRI study in healthy volunteers. *Reg Anesth Pain Med* 2023;48:74–9.
7 Chin KJ, Lirk P, Hollmann MW, *et al*. Mechanisms of action of fascial plane blocks: a narrative review. *Reg Anesth Pain Med* 2021;46:618–28.
8 Støving K, Rothe C, Rosenstock CV, *et al*. Cutaneous sensory block area, muscle-relaxing effect, and block duration of the transversus abdominis plane block: a randomized, blinded, and placebo-controlled study in healthy volunteers. *Reg Anesth Pain Med* 2015;40:355–62.
9 Magerl W, Fuchs PN, Meyer RA, *et al*. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain* 2001;124(Pt 9):1754–64.
10 Esposito MF, Malayil R, Hanes M, *et al*. Unique characteristics of the dorsal root ganglion as a target for neuromodulation. *Pain Med* 2019;20(Suppl 1):S23–30.
11 Gemes G, Koopmeiners A, Rigaud M, *et al*. Failure of action potential propagation in sensory neurons: mechanisms and loss of afferent filtering in C-type units after painful nerve injury. *J Physiol* 2013;591:1111–31.
12 Lundberg LE, Jørum E, Holm E, *et al*. Intra-neural electrical stimulation of cutaneous nociceptive fibres in humans: effects of different pulse patterns on magnitude of pain. *Acta Physiol Scand* 1992;146:41–8.
13 Ponulak F, Kasinski A. Introduction to spiking neural networks: information processing, learning and applications. *Acta Neurobiol Exp (Wars)* 2011;71:409–33.
14 Krahe R, Gabbiani F. Burst firing in sensory systems. *Nat Rev Neurosci* 2004;5:13–23.
15 Lisman JE. Bursts as a unit of neural information: making unreliable synapses reliable. *Trends Neurosci* 1997;20:38–43.
16 Suh YS, Chung K, Coggeshall RE. A study of axonal diameters and areas in lumbosacral roots and nerves in the rat. *J Comp Neurol* 1984;222:473–81.
17 Sundt D, Gamper N, Jaffe DB. Spike propagation through the dorsal root ganglia in an unmyelinated sensory neuron: a modeling study. *J Neurophysiol* 2015;114:3140–53.
18 Zhou L, Chiu SY. Computer model for action potential propagation through branch point in myelinated nerves. *J Neurophysiol* 2001;85:197–210.
19 Abram SE, Yi J, Fuchs A, *et al*. Permeability of injured and intact peripheral nerves and dorsal root ganglia. *Anesthesiology* 2006;105:146–53.
20 Iwanaga T, Takahashi-Iwanaga H, Nio-Kobayashi J, *et al*. Structure and barrier functions of the perineurium and its relationship with associated sensory corpuscles: a review. *Biomed Res* 2022;43:145–59.
21 Taylor A, McLeod G. Basic pharmacology of local anaesthetics. *BJA Educ* 2020;20:34–41.
22 Byröd G, Rydevik B, Johansson BR, *et al*. Transport of epidurally applied horseradish peroxidase to the endoneurial space of dorsal root ganglia: a light and electron microscopic study. *J Peripher Nerv Syst* 2000;5:218–26.
23 Nascimento AI, Mar FM, Sousa MM. The intriguing nature of dorsal root ganglion neurons: linking structure with polarity and function. *Prog Neurobiol* 2018;168:86–103.
24 Zheng Q, Dong X, Green DP, *et al*. Peripheral mechanisms of chronic pain. *Med Rev (Berl)* 2022;2:251–70.
25 Du J, Yi M, Xi D, *et al*. Satellite glial cells drive the transition from acute to chronic pain in a rat model of hyperalgesic priming. *Front Mol Neurosci* 2023;16:1089162.
26 Hermanns H, Hollmann MW, Stevens MF, *et al*. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. *Br J Anaesth* 2019;123:335–49.