blood and not in LBV blood. These patients likely experienced tissue hypoperfusion because ΔSOFA effectively reflects the degree of organ dysfunction over time.[7] Hypothetically, differences between PA and LBV blood might reveal renal and splanchnic hypoperfusion. Ho and colleagues[8] reported a negative correlation between the cardiac output and S_{O_2} difference between central and mixed venous blood in patients affected by circulatory failure. However, P_{CO_2} and S_{O_2} of the LBV mainly reflect cerebral blood flow, with the brain receiving 20% of the cardiac output while the entire compartment drained by the SVC receives 35%. P_{CO_2} and S_{O_2} values of LBV blood were less affected by moderate low cardiac output states, which do not seriously impair cerebral perfusion.[9,10]

The main limitations of this study were the inability to measure P_{CO_2} and S_{O_2} in the inferior vena cava and coronary sinus, and the assumption that P_{CO_2} and S_{O_2} values were equal in left and right brachiocephalic veins.

In conclusion, CVC blood should be collected from the right atrium to provide information on the whole-body perfusion, including renal and splanchnic areas. Further studies are needed to investigate whether any useful information can be obtained by analysing LBV blood and, in general, SVC blood, which may be mainly representative of cerebral perfusion.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Gutierrez G. Central and mixed venous O_2 saturation. *Turk J Anaesthesiol Reanim* 2020; **48**: 2–10
2. van Beest PA, Lont MC, Holman ND, Loef B, Kuiper MA, Boerma EC. Central venous-arterial pCO_2 difference as a tool in resuscitation of septic patients. *Intensive Care Med* 2013; **39**: 1034–9
3. Dubin A, Pozo MO, Kanoore Edul VS, Vazquez AR, Enrico C. Poor agreement in the calculation of venoarterial PCO_2 to arteriovenous O_2 content difference ratio using central and mixed venous blood samples in septic patients. *J Crit Care* 2018; **48**: 445–50
4. Cavaliere F, Zamparelli R, Martinelli L, et al. Blood from the right atrium may provide closer estimates of mixed venous saturation than blood from the superior vena cava. A pilot study. *Minerva Anestesiol* 2014; **80**: 11–8
5. Cavaliere F, Antoniucci ME, Arlotta G, et al. Is the pCO_2 gap obtained from the superior vena cava in agreement with that from the pulmonary artery? *Minerva Anestesiol* 2019; **85**: 1308–14
6. Peebles K, Celi L, McGrattan K, Thomas K, Ainslieet PN. Human cerebrovascular and ventilatory CO_2 reactivity to end-tidal, arterial and internal jugular vein PCO_2. *J Physiol* 2007; **584**: 347–57
7. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Crit Care* 2019; **23**: 374
8. Ho KM, Harding R, Chamberlain J. A comparison of central venous-arterial and mixed venous-arterial carbon dioxide tension gradient in circulatory failure. *Anaesth Intensive Care* 2007; **35**: 695–701
9. Mohiaddin RH, Wann SL, Underwood R, Duranteau J. Vena caval flow: assessment with cine MR velocity mapping. *Radiology* 1990; **177**: 537–41
10. Torbey MT, Bhardwaj A. Cerebral blood flow physiology and monitoring. In: Suarez JI, editor. *Critical care Neurology and neurosurgery. Current clinical neurology*. Totowa, NJ: Humana Press; 2004. p. 23–35

doi: 10.1016/j.bja.2021.01.018
Advance Access Publication Date: 23 February 2021

Mechanistic insights into spinal neurones involved in neuraxial opioid-induced pruritus

Eileen Nguyen[1,2], Grace Lim[3,4] and Sarah E. Ross[1,*]

[1]Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [2]Medical Scientist Training Programme, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [3]Department of Anaesthesiology & Perioperative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA and [4]Department of Obstetrics, Gynaecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

*Corresponding author. E-mail: saross@pitt.edu

Keywords: itch; morphine; neuraxial opioid; opioid; pruritus; spinal disinhibition

Editor—Neuraxial administration of opioids consistently evokes clinical pruritus, which is reported in nearly half of obstetric patients who receive neuraxial opioids for labour or Caesarean delivery anaesthesia and analgesia.[1] Historically, pruritus has been assumed to result from a direct effect of opioids within the neuraxis; in particular, it has been

proposed that neurones in the spinal cord dorsal horn are responsible for mediating opioid-induced pruritus.[2,3] Only recently have advancements in mouse genetic models allowed for the selective manipulation of distinct spinal circuits to finally interrogate their role in the context of opioid-induced itch behaviours. These mechanistic studies in rodents have contributed significant, new insights to the neural circuitry of somatosensation and mechanisms for opioid-induced itch.

Previous views suggested that opioids elicit itch through the suppression of pain. This was supported by the finding that nociceptive stimuli inhibit neuronal responses to itch-evoking agents.[4] However, the idea that opioid-induced pruritus arises as a result of the inhibition of pain was challenged by Liu and colleagues[5]. Using targeted knockdown studies to investigate the differential contributions of distinct splice isoforms of the mu opioid receptor (MOR), they showed that opioids drive itch through a process independent of analgesia. In particular, small interfering RNA knockdown of the MOR1 isoform revealed that this isoform is required for morphine-induced analgesia, but not morphine-induced itch.[5] In animals in which the MOR1 gene is disrupted, the analgesic effects of morphine are lost, but scratching persists, suggesting that morphine-induced itch occurs through an active process that is separate from pain.

For nearly a decade, this study by Liu and colleagues[5] also appeared to settle the question of how morphine elicits itch. The authors suggested that neuraxial morphine causes itch through activation of excitatory spinal neurones that promote itch. They proposed that morphine-induced itch could be driven by glutamatergic spinal neurones expressing both the MOR1D isoform and the gastrin-releasing peptide receptor (GRPR). In mice lacking GRPR, morphine-induced itch was significantly attenuated; furthermore, intrathecal morphine-induced itch was inhibited when morphine was co-administered with a GRPR antagonist. Lastly, it was argued that neuraxial morphine induced heterodimerisation of MOR1D with GRPR, activating the PLCβ3 and IP3R3 pathway, thereby resulting in itch. However, these conclusions are considered controversial for two main reasons. First, recent molecular sequencing studies have revealed a lack of overlap between GRPR and MOR expression in spinal neurones.[6] Secondly, mechanistically, binding of morphine to the MOR generally causes hyperpolarisation, rather than activation, of neurones. Thus, the idea that opioids cause itch through heterodimerisation of MOR and GRPR in excitatory spinal neurons remains contested.

A recent study by Wang and colleagues,[7] suggested that opioids cause itch through a mechanism of neuronal disinhibition (Fig. 1). Selective knockdown of the MOR from inhibitory (GABAergic) neurones abolished opioid-induced itch in a mouse model.[7] These striking behavioural findings in Wang and colleagues[7] emphasise the role of inhibitory neurones in the spinal cord as the crucial mediators of opioid-induced itch. Electrophysiological recordings from individual inhibitory neurones in the presence of a mu agonist are consistent with the canonical view that opioids typically signal through Gαi-coupled G-protein-coupled receptors to inhibit neuronal activity, and, in contrast to the mechanism proposed by Liu and colleagues,[5] provide support for how spinal disinhibition could be responsible for neuraxial opioid-induced itch.[8]

Wang and colleagues[7] also determined that the expression of MOR on *TRPV1* in somatostatin sensory neurones, which are thought to be involved in itch signalling, is not involved in morphine-induced itch. This further implicates the specific role of spinal neurones, rather than sensory fibres, as the crucial mediators of opioid-induced itch. Wang and colleagues[7] also uncovered a potential circuit for opioid-induced itch in a series of detailed pharmacological studies. Administration of neuropeptide Y (NPY) reduces morphine-induced itch, supporting the role of NPY neurones in the inhibition of itch.[9] Chemical ablation of GRPR neurones eliminated morphine-induced itch, which supports the findings of Liu and colleagues[5] by proposing that morphine acts on downstream pathways involving GRPR neurons to signal itch. However, the circuit now proposed by Wang and colleagues[7] suggests that MOR and GRPR neurones comprise two distinct neuronal populations. Reconciling the existing evidence reported by Liu and colleagues[5] and Wang and colleagues,[7] it can be concluded that morphine inhibits a subpopulation of itch-inhibiting (GABAergic) spinal neurones, leading to the downstream disinhibition of GRPR excitatory neurones (Fig. 1).

The work of both Liu and colleagues[5] and Wang and colleagues[7] has provided key insights into the neuronal basis for opioid-induced itch. Future work that accounts for genetic polymorphisms of the MOR may guide the development and targeting of opioid analgesics that treat pain, but do not cause itch. Nearly 20 splice variants of the MOR have been identified in humans, which may explain the varied effects of opioid medications on patient self-reported measures of opioid

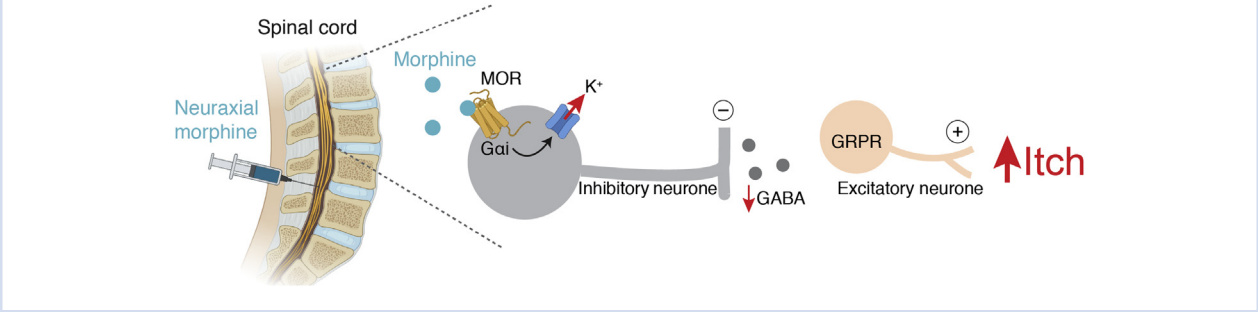

Fig 1. Spinal mechanism of neuraxial opioid-induced pruritus. Neuraxial morphine elicits itch through a mechanism of neuronal disinhibition in the dorsal horn of the spinal cord. Morphine inhibits GABAergic neurons upon binding to the mu opioid receptor (MOR). This has a permissive effect on excitatory neurones expressing the gastrin-releasing peptide receptor (GRPR), thereby evoking itch.

analgesia and opioid-related side effects.[10] The studies conducted by Liu and colleagues[5] have paved a roadmap by which to test the differential contributions of MOR isoforms on analgesia and pruritus. Although it is not clear whether the MOR1D isoform identified by Liu and colleagues[5] may be involved in pruritus in humans, the ability to identify and test distinct isoforms of the MOR in mice now presents unique opportunities to uncover novel analgesic treatments that do not evoke pruritus in future clinical and translational studies.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: a review. *J Clin Anesth* 2003; **15**: 234–9
2. Ko M-C. Neuraxial opioid-induced itch and its pharmacological antagonism. *Handb Exp Pharmacol* 2015; **226**: 315–35
3. Kumar K, Singh SI. Neuraxial opioid-induced pruritus: an update. *J Anaesthesiol Clin Pharmacol* 2013; **29**: 303–7
4. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci* 2006; **7**: 535–47
5. Liu X-Y, Liu Z-C, Sun Y-G, et al. Unidirectional cross-activation of GRPR by MOR1D uncouples itch and analgesia induced by opioids. *Cell* 2011; **147**: 447–58
6. Häring M, Zeisel A, Hochgerner H, et al. Neuronal atlas of the dorsal horn defines its architecture and links sensory input to transcriptional cell types. *Nat Neurosci* 2018; **21**: 869–80
7. Wang Z, Jiang C, Yao H, et al. Central opioid receptors mediate morphine-induced itch and chronic itch via disinhibition. *Brain Adv Access* 2020. https://doi.org/10.1093/brain/awaa430. Published December 27
8. Nguyen E, Lim G, Ding H, Hachisuka J, Ko M-C, Ross SE. Morphine acts on spinal dynorphin neurons to cause itch through disinhibition. *Sci Transl Med* 2021; **13**, eabc3774
9. Bourane S, Duan B, Koch SC, et al. Gate control of mechanical itch by a subpopulation of spinal cord interneurons. *Science* 2015; **350**: 550–4
10. Pasternak GW. Molecular insights into mu opioid pharmacology: from the clinic to the bench. *Clin J Pain* 2010; **26**(Suppl 10): S3–9

doi: 10.1016/j.bja.2021.02.009
Advance Access Publication Date: 11 March 2021