Opioids, plasticity and phrenic motor performance: investigating the off-target effects of acute morphine administration

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Opioids, including morphine, are a class of analgesic drug used to treat pain. One of the mechanisms by which these compounds suppress pain is by inhibiting neurotransmitter release at presynaptic afferent neurons in ascending pain pathways. Despite their beneficial analgesic effects, therapeutic opioids can destabilise breathing culminating in respiratory side effects (Varga et al. 2020). Opioid effects on breathing are primarily mediated by μ-opioid receptor agonism within the respiratory control network. The abuse of opioids remains a significant threat to health worldwide and indeed respiratory depression can prove fatal in opioid overdose. While many studies in rodents have examined the consequences of chronic opioid administration on respiratory control, it is less well understood if therapeutic morphine has long-lasting effects on respiratory plasticity and stability of breathing.

The respiratory control system displays a remarkable capacity to adapt in the face of challenges, such as during exercise and exposure to low oxygen or in disease states, including neuromuscular disorders. The ability of the system to adapt in response to physiological and pharmacological stressors ensures adequate ventilation and the maintenance of blood gas and pH homeostasis. The term used to describe this phenomenon is respiratory plasticity, which is defined as a persistent change in the neural control system based on prior experience (for review, see Fuller & Mitchell, 2017). Of note, there are several distinct forms of structural and functional plasticity, which can occur at multiple sites of the respiratory control system.

One of the most well-studied models of respiratory plasticity is phrenic motor plasticity, also known as phrenic long-term facilitation (pLTF). The phrenic nerves originate in the cervical spinal cord and deliver action potentials to the diaphragm, facilitating contraction of the primary inspiratory pump muscle. pLTF can be evoked by exposure to moderate bouts of acute intermittent hypoxia (AIH), which stimulates episodic serotonin release in the cervical spinal cord (Fuller & Mitchell, 2017). Serotonergic activation of phrenic motor neurons initiates a downstream signalling cascade, culminating in the production of brain-derived neurotrophic factor (BDNF) and activation of its associated receptor, tropomyosin-related kinase B (TrkB). Binding of BDNF to TrkB results in the facilitation of enhanced glutamatergic neurotransmission in the phrenic motor pathway. Although an exogenous stimulus, AIH induces endogenous mechanisms of spinal motor plasticity, evidenced by an increase in phrenic burst amplitude due to enhanced respiratory drive transmission to phrenic motor neurons (Fuller & Mitchell, 2017). Few studies have examined the effects of acute morphine administration on mechanisms of respiratory neuroplasticity such as pLTF. This is surprising given that endogenous mechanisms of plasticity within the respiratory control system may have a key role in alleviating opioid-induced disruption and destabilisation of breathing.

Opioids are known to induce inflammation (Tadjalli et al. 2021a), which can compromise respiratory neuroplasticity, namely pLTF (Huxtable et al. 2015). Toll-like receptor 4 (TLR4) is a pattern recognition receptor in the innate immune system. Interestingly, a single dose of systemic lipopolysaccharide (LPS), a potent TLR4 agonist, inhibited pLTF in rats (Tadjalli et al. 2021b). These data suggest that activation of TLR4 signalling blocks phrenic motor plasticity. Microglia are important cells that mediate immune defence in the spinal cord and brain. p38 MAPK is a regulator of inflammatory signalling, and its activation in spinal phrenic motor neurons and adjacent microglia has previously been shown to undermine pLTF (Huxtable et al. 2015). Opioids are known to have off-target effects via their action on TLR4, where they bind to the TLR4-myeloid differentiation protein-2 complex, promoting the production of inflammatory cytokines (Tadjalli et al. 2021a). The effects of therapeutic opioid use on cervical spinal inflammatory signalling and the implications this may have for phrenic motor plasticity is unclear.

In their recent publication in The Journal of Physiology, Tadjalli and colleagues (2021a) sought to address three distinct experimental questions: (i) Does acute systemic morphine administration block pLTF? (ii) Does systemic (+)-naloxone pre-treatment preserve pLTF following morphine delivery? And (iii) does morphine increase phosphorylated p38 MAPK levels in the ventral horn of the cervical spinal cord?

The authors reported that a single low dose of morphine had no effect on baseline phrenic nerve activity in urethane anaesthetised, vagotomised, paralysed, and mechanically ventilated male Sprague Dawley rats. While vehicle-treated rats exposed to moderate AIH produced profound increases in phrenic burst amplitude, rats pre-treated with morphine showed no potentiation in phrenic nerve activity, i.e. did not display pLTF. This is a significant finding in that pLTF was absent over 4 h post-morphine injection, when serum levels of morphine were below those capable of impairing breathing. Given that morphine can modulate TLR4 signalling and since TLR4-mediated inflammatory signalling can block pLTF (Tadjalli et al. 2021b), the authors reasoned that morphine may act via TLR4 to inhibit pLTF. To test this, the authors administered (+)-naloxone subcutaneously in rats prior to morphine. (+)-Naloxone is a novel TLR4 inhibitor and an enantiomer of (−)-naloxone, a drug commonly used to treat opioid-induced respiratory depression. Indeed, (+)-naloxone attenuated morphine-induced blockade of pLTF, revealing a long-latent off-target effect of morphine, which blocks this form of respiratory neuroplasticity (Tadjalli et al. 2021a).

Furthermore, morphine administration blunted the phrenic nerve response...
to maximum chemo-stimulation with hypoxic-hypercapnia, suggesting that acute morphine blunts respiratory chemosensitivity in rats. Moreover, morphine administration has previously been shown to increase the propensity for apnoea in mice (Varga et al. 2020). These data are of physiological relevance given that chemoreflex control of breathing is an important safeguard mechanism that negates blood gas disruption during periods of unstable breathing, such as apnoea. Of note, TLR4 inhibition restored the phrenic response to maximal chemoreflex activation, indicating a potential therapeutic target in the treatment of opioid-induced respiratory depression.

A novel observation of the current study is that morphine increased activation of p38 MAPK in microglia but not neurons, located in the ventral horn of the C3–C5 spinal cord (containing the phrenic motor nucleus); this was blocked by systemic TLR4 inhibition. While phosphorylation of p38 MAPK is well characterised as a downstream mediator of TLR4 signalling, it is an interesting observation that expression of this enzyme, as determined by optical density immunofluorescence, was upregulated in microglia only and not putative phrenic motor neurons. The authors therefore speculate that the microglia may be acting as a key mediator of morphine-induced spinal inflammation and subsequent blockade of pLTF, thus revealing novel insights into how neuro-glial interactions can act to modulate respiratory motor plasticity following an acute systemic dose of morphine in rats. This study by Tadjalli et al. (2021a) offers many areas of further investigation to determine if these novel findings are of translational value. For patients undergoing surgery that require a therapeutic dose of morphine for pain relief, administration of a TLR4 inhibitor may have benefits for breathing, maintaining respiratory chemoreflex mechanisms. Furthermore, administering AIH with a TLR4 inhibitor following acute morphine administration may further stabilise breathing by promoting endogenous mechanisms of plasticity, which may act to limit respiratory instability. Nevertheless, TLR4 inhibition with (+)-naloxone may have implications for immune function, particularly in chronic disease, thus warranting further study. These data also have implications for individuals with compromised respiratory and motor function, such as in spinal cord injury, who experience comorbid pain and are prescribed opioids. Therapeutic AIH, a novel therapy which has shown great promise at alleviating deficits in respiratory and somatic motor function in pre-clinical and clinical trials (Fuller & Mitchell, 2017), may have limited benefits in this patient cohort. Notably, rats metabolise morphine in a manner that is different to humans, adding another layer of complexity to the translational potential of this study. Collectively, these results should be interpreted with caution as phrenic burst amplitude is a measure of phrenic nerve activity and not of ventilation per se. Future studies should include assessments of breathing using whole-body plethysmography and direct assessment of respiratory flow and electromyogram activity, during baseline and chemically-activated breathing in rats following acute morphine administration. AIH-induced pLTF is one model of respiratory plasticity and may not be the only mechanism of plasticity altered by morphine, thus warranting further investigation. As such, a broad assessment of the effects of opioids on respiratory sensory- and motor-plasticity are greatly needed. It would be interesting to examine if opioid-induced long-latent effects on plasticity are also observed in cranial motor pathways involved in the maintenance of upper airway patency and in spinal pathways which innervate accessory muscles of breathing.

In conclusion, Tadjalli et al. (2021a) have made a significant contribution to understanding the effects of acute morphine delivery on respiratory plasticity. This study highlights significant long-latent off-target effects of morphine, which have the potential to modulate inflammatory signalling, inhibit endogenous mechanisms of respiratory plasticity, and alter respiratory chemoreflexes. The TLR4-mediated effects of morphine on spinal phrenic motor plasticity reveal a potential therapeutic target for the treatment of opioid-induced impairment of breathing.

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Additional information

Competing interests
The authors declare that they have no competing interests.

Author contributions
Both authors have approved the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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