CROSSTALK

Rebuttal from Gaspard Montandon and Richard Horner

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We agree with Lalley *et al.* (2014) that various brainstem sites may contribute to opioid-induced respiratory depression. Our focus here, however, is on respiratory *rate* depression by systemically administered drugs acting on μ-opioid receptors.

Of all the potential neural sites where systemically administered μ-opioids *could* act, Lalley *et al.* suggest that the parabrachial/Kölliker–Fuse complex may be critically mediating respiratory rate depression. First, if pontine nuclei were responsible for rate suppression, then depression should not be observed in the absence of the pons. Still, respiratory slowing occurs in preparations where transections are performed caudal to the pons (Takita *et al.* 1997; Gray *et al.* 1999). Also, the blocking of μ-opioid receptors alone in pontine regions has a stimulatory effect on respiratory rate that can be misinterpreted as a reversal of opioid-induced respiratory depression (Phillips *et al.* 2012; Prkic *et al.* 2012).

Using microdialysis tools to locally manipulate cells, we showed that the preBötC is highly sensitive to μ-opioid receptor agonists and mediates respiratory rate depression by systematically administered μ-opioids (Montandon *et al.* 2011). One caveat raised when using local drug application is that drug concentration in tissue is unknown as diffusion depends on the molecule, concentration and route of perfusion. To circumvent these issues, we designed strategies to assess how effective drug perfusion is. First, we simulated drug diffusion *ex situ* and found that after 2 h of perfusion less than 18% of the delivered concentration was present beside the probe membrane and 5% was found at a 1 mm distance (Grace *et al.* 2014), which invalidates the notion that drugs diffuse beyond the preBötC and affect other respiratory nuclei. Secondly, perfusion close to the preBötC was more potent in causing rate depression or its reversal than perfusion further away (Montandon *et al.* 2011). Also, if the μ-opioid receptor antagonist naloxone was affecting other nuclei, it should also block the impact of systemic μ-opioids on genioglossus muscle activity since the hypoglossal premotor/motor neurons are close to the preBötC. It did not, however, and we previously revealed separate medullary sites for hypoglossal motor suppression (Hajiha *et al.* 2009; Montandon *et al.* 2011).

In conclusion, we *dispute the belief* that the preBötC plays an indirect role in opioid-induced respiratory rate depression. Other sites may indeed mediate other components of respiratory depression, such as reduced respiratory drive transmission and upper airway dysfunction, but based on the evidence discussed (Montandon *et al.* 2011), we restate that the preBötC plays a critical role in mediating opioid-induced respiratory *rate* depression.

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Additional information

Competing interests

None declared.

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