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REVIEW ARTICLE

Opioids and the control of respiration

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Respiratory depression limits the use of opioid analgesia. Although well described clinically, the specific mechanisms of opioid action on respiratory control centres in the brain have, until recently, been less well understood. This article reviews the mechanisms of opioid-induced respiratory depression, from the cellular to the systems level, to highlight gaps in our current understanding, and to suggest avenues for further research. The ultimate aim of combating opioid-induced respiratory depression would benefit patients in pain and potentially reduce deaths from opioid overdose. By integrating recent findings from animal studies with those from human volunteer and clinical studies, further avenues for investigation are proposed, which may eventually lead to safer opioid analgesia.

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With potentially fatal consequences, opioid-induced respiratory depression is a major limiting factor for the provision of effective analgesia. Opioid drugs, such as morphine, are a mainstay for pain relief for patients around the world. They are used in a wide variety of clinical situations, for example, after surgery and in control of pain due to cancer. The incidence of postoperative opioid-induced respiratory depression in the UK has been estimated to be approximately 1%.[21] Although progression to death is very rare, the numbers of patients treated with opioids mean that respiratory depression remains an important clinical problem. Unfortunately, medical fear of respiratory depression means that pain is often undertreated and patients experience unnecessary suffering. In addition to humanitarian concerns,[18 149] inadequate postoperative analgesia has been related to postoperative pulmonary complications.[72] Therefore, it is of paramount importance to achieve sufficient analgesia with minimal side-effects, and although this usually involves a combination of therapeutic approaches,[148] opioids remain the backbone of therapy. In drug addicts, respiratory depression is the major cause of death.[147]

Over the past 15 yr, there has been considerable progress in the understanding of respiratory control, mainly through the use of rodent models.[36 37] These have helped to explain previous findings from human studies and have started to generate translational opportunities that could be tested in human volunteer and clinical studies. Furthermore, with the advent of methods of imaging brain activity [e.g. functional magnetic resonance imaging (FMRI) and positron emission tomography (PET)], *in vivo* studies of opioid effects on breathing in humans are now possible. This article reviews the mechanisms of opioid-induced respiratory depression, from the cellular to the systems level, to highlight gaps in our current understanding, and to suggest avenues for further research. The ultimate aim of combating opioid-induced respiratory depression would benefit patients in pain, and potentially reduce deaths from opioid overdose.

Opioid receptors

Opioid receptors are members of the family of more than a 1000 G-protein coupled receptors (GPCRs).[3] GPCRs consist of seven trans-membrane subunits. Stimulation by agonists activates the G-proteins tethered to the inner surface of the cell membrane and initiates an intracellular signalling cascade that mediates the actions of many hormones and neurotransmitters. In the case of opioid receptors,[139] ligand binding activates inhibitory intracellular pathways that lead to the closing of voltage sensitive calcium channels, stimulation of potassium efflux, and reduction of cyclic adenosine monophosphate (cAMP) production. These intracellular changes lead to reduced neuronal excitability.

Current consensus describes four classes of opioid receptor: the MOP (μ), KOP (κ), DOP (δ), and the nociceptin/orphanin FQ peptide receptor (NOP).[87] The endogenous ligands for these receptors include the endorphins (MOP), enkephalins (DOP and MOP), the

dynorphins (KOP), and nociceptin/orphanin FQ (NOP). The endogenous opioid system mediates many physiological effects, including pain, respiratory control, stress responses, appetite, and thermoregulation.

In addition to their major presence on pain neurones in the central nervous system, opioid receptors are present in multiple non-respiratory sites around the body, but these are outside the scope of this review. With regard to respiration, opioid receptors are abundant in respiratory control centres[140] that include the brainstem,[2] but also include higher centres such as the insula, thalamus, and anterior cingulate cortex.[7 9 83] Opioid receptors are also located in the carotid bodies[75 146] and in the vagi.[76] Mechanosensory receptors located in the epithelial, submucosal, and muscular layers of the airways[61 153] relay mechanical and sensory information from the lungs and express opioid receptors.[154]

Brainstem mechanisms of respiration

The fundamental drive to respiration is generated in the brainstem[36 74] and is modulated by inputs that include conscious inputs from the cortex,[56 83] central (brainstem), and peripheral (carotid and aortic bodies) chemoreceptors[19 116] that sense changes in the chemical constituents of blood.

Respiratory rhythm generation

The original work by Lumsden,[74] performed in decerebrate cats, confirmed that the brainstem is essential for respiration, by demonstrating that transections at different levels of the pons and the medulla produce varying effects upon the respiratory rhythm. Subsequent studies have proposed a network that is responsible for controlling breathing that is located in the medulla and pons.

The pre-Bötzinger complex is a small area in the ventrolateral medulla that can generate a 'respiratory' rhythm, in isolation, *in vitro*.[115 129 130] Although present in rats, this area has not yet been identified in humans. Initially thought to be the pacemaker or 'kernel' for respiratory rhythm, the pre-Bötzinger complex has been shown by emerging evidence to form a coupled oscillator with the nearby retro-trapezoid and parafacial respiratory group (RTN/pFRG).[58 100] The pre-Bötzinger complex and RTN/pFRG do not act in isolation in the intact animal. The rhythm generating centres in the medulla are strongly modulated by influences from the pons[131] that include the Kölliker-Fuse nucleus, the parabrachial complex, and the locus coeruleus. The approximate locations of these nuclei in humans are illustrated in Figure 1.

The most opioid sensitive aspect of respiration is rhythm generation, and changes in the respiratory pattern are observed at lower opioid doses than change in tidal volume.[64] Higher opioid doses cause reduction in tidal volume probably due to decreased tonic inputs from opioid sensitive chemoreceptors, which *in vivo* are partly compensated by increases in Pa_{CO_2}. The work described below suggests mechanisms of how opioids cause an irregular respiratory pattern[15 74] that is commonly seen in patients given opioids.[54]

In the ventrolateral medulla, the pre-Bötzinger complex is active during inspiration and is inhibited by opioids, whereas the RTN/pFRG is active during expiration and importantly is insensitive to opioids.[58] Exploitation of this differential sensitivity to opioids has revealed important insights into mechanisms of opioid-induced respiratory depression.[86] When the MOP agonist DAMGO [D-Ala(2), NMePhe(4), Gly-ol(5) enkephalin] was applied to a rat brainstem slice preparation containing only the pre-Bötzinger complex, the respiratory rhythm slowed gradually. However, when DAMGO was applied to a preparation containing both the RTN/pFRG and the pre-Bötzinger complex, the rhythm also slowed, but with a remarkable change in pattern; the increased inspiratory periods resulted from skipped inspirations and the breathing rhythm became irregular. These skipped breaths represented intermittent attenuation of the output from the pre-Bötzinger complex, during which subthreshold action potentials were recorded. This respiratory pattern was named 'quantal', due to the fact that the rhythm of action potentials in the pre-Bötzinger complex remained regular, but action potentials were not transmitted further, similar in nature to Mobitz type-II second-degree heart block. Similar effects on the respiratory pattern were observed in intact rats given fentanyl. This work provides evidence of redundancy in the respiratory rhythm-generating centres in the brainstem, because when the pre-Bötzinger complex is depressed, rhythm generation is taken over by the RTN/pFRG.

Although the pre-Bötzinger complex is clearly important for opioid effects on respiratory rhythm, there is evidence that opioid actions in the Kölliker-Fuse and parabrachial nuclei of the pons also contribute towards irregular respiration.[67] These nuclei have reciprocal connections with the ventral respiratory group of the medulla,[59] and modelling studies suggest these areas have important regulating influences on the output from the pre-Bötzinger complex.[121] The Kölliker-Fuse nucleus is thought to control the transition from inspiration to expiration, as lesions and pharmacological manipulation of this nucleus prolongs the duration of inspiration.[31 32]

Understanding receptor systems that modulate respiratory control may lead to novel therapies for opioid-induced respiratory depression. For example, the 4a subtype of the serotonin receptor ($5HT_{4a}$) is expressed on respiratory but not pain neurones. In the pre-Bötzinger complex, $5HT_{4a}$ activates cAMP via the same intracellular pathway that is inhibited by the MOP receptor.[57] BIMU8, an agonist at the $5HT_{4a}$ receptor,[109] antagonizes opioid-induced respiratory depression but does not affect analgesia (Fig. 2).[79] Similar findings have been observed in cats treated with D_1-receptor agonists,[66] and postulated to be due to enhancement of the hypercapnic ventilatory response

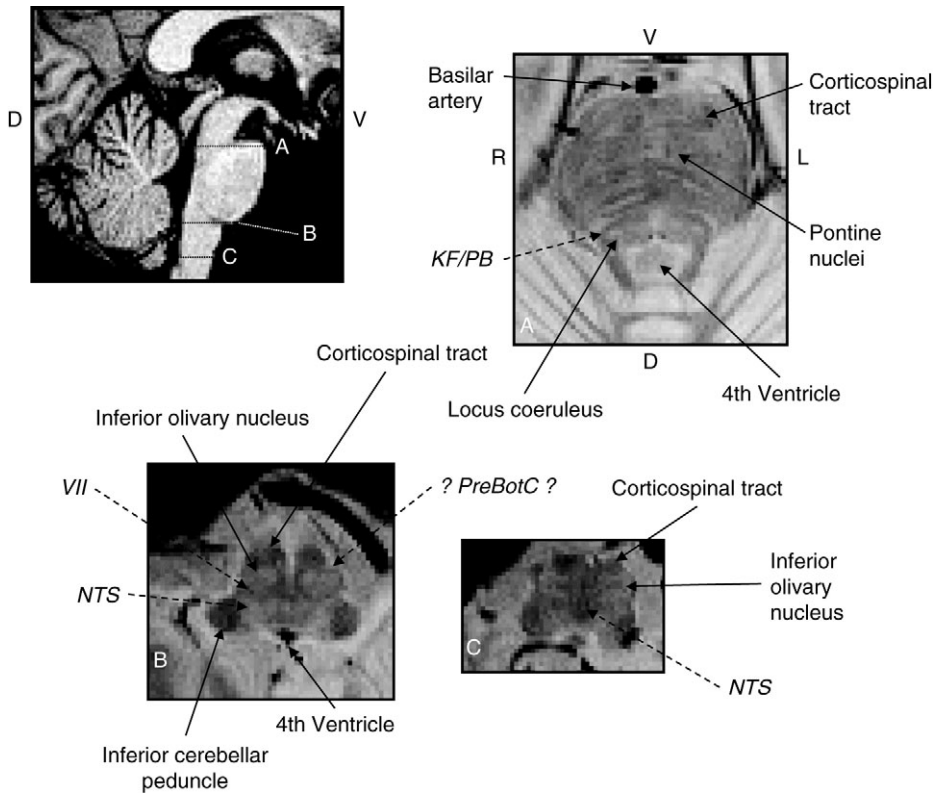

Fig 1 MRI scan of human brainstem showing approximate locations of nuclei that mediate the control of respiration. The top left (saggital) scan shows the position of the slices A (superior pons), B (superior medulla), and C (inferior medulla). The nuclei in italics cannot be identified from the scans, and localization was performed by referring to a histological atlas.[33] All nuclei illustrated are bilateral, but only labelled on one side for clarity. *KF/PB*, Kölliker-Fuse and parabrachial nuclei; *VII*, facial nucleus; *NTS*, nucleus tractus solitarius; *PreBotC*, pre-Bötzinger complex (not identified yet in humans). Orientation: A, B, and C have the same orientation, although only labelled on A: D, dorsal; V, ventral; R, right; L, left.

(HCVR).[65] Currently, these findings have not been successfully translated into humans, possibly due to untoward side-effect profiles.[34] The development of a highly specific antagonist of opioid-induced respiratory effects has still not been attained.

Chemoreceptors

Central chemoreceptors

Central chemoreceptors provide tonic drive to the respiratory motor output by sensing changes in pH. Although classically three separate chemoreceptive areas were described in the ventral medulla,[73 90 91 126] it is now known that multiple chemosensing areas exist in the lower brain, located mostly in the brainstem.

Chemoreceptive areas that modulate respiration include the nucleus tractus solitarius (NTS), midline medullary raphe, pre-Bötzinger complex, and the RTN/pFRG in the medulla,[37] the locus coeruleus[101] in the pons, and the fastigial nucleus in the cerebellum.[80] To date, it has been impossible to separate pattern generation from chemosensing in the pre-Bötzinger complex and the RTN/pFRG[37] as these areas perform both functions.

Although the literature relating to direct effects of opioids on specific chemoreceptive areas is somewhat limited, early studies demonstrated that localized application of opioids to different parts of the brainstem[135] had differential depressant effects on respiration. More recently, MOP agonists were shown to affect chemoreception in the midline medullary raphe[155] and the NTS.[110]

Peripheral chemoreceptors

The type I glomus cells in the carotid body are the body's main sensors for hypoxia.[63] Nearly 98% of the glomus cells exhibit enkephalin immunoreactivity.[143] Enkephalin inhibits carotid body activity, whereas naloxone augments activity and the hypoxic ventilatory response (HVR).[85 108] In cats, morphine has a much weaker effect on carotid body activity than enkephalin,[85] and this may account for the lack of effect of morphine on the HVR[10] seen in this species. In humans, however, depression of the HVR by morphine is well reported.[4 125 145] Glomus cells also sense CO_2, and synergistic interactions between hypoxia and hypercapnia can be present.[62 63] Impulses from the carotid body travel in the glossopharyngeal nerve to the NTS in the dorsal medulla and modulate respiration via direct connections between the NTS and the RTN.[132] In humans, the carotid bodies are essential for mediating the HVR, which is abolished with bilateral carotid body resection.[27]

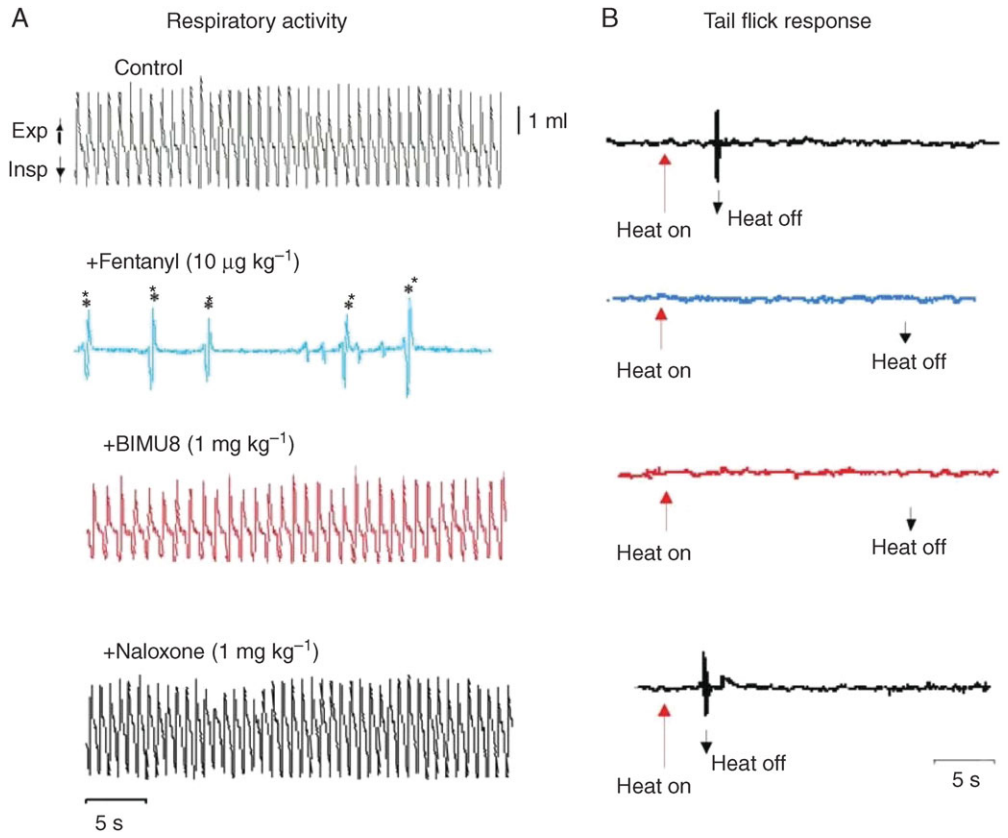

Fig 2 (A) Respiratory airflow in an anesthetized, spontaneously breathing rat. Administration of fentanyl (blue) caused profound respiratory depression. Administration of BIMU8 (red) restored stable breathing as did naloxone. Asterisks indicate artificial ventilation during fentanyl treatment necessary to rescue the animal. Exp, expiration; Insp, inspiration. (B) Tail flick response to noxious stimulation. During control conditions this was normal (black), but was abolished with fentanyl (blue), remained abolished with coadministration of fentanyl and BMIU8 (red) (despite respiration returning towards normal levels), but was reversed with naloxone. Figure reproduced with permission from AAAS (Manzke and colleagues).[79]

Measuring opioid effects on breathing in humans

In humans, opioids cause respiration to slow and become irregular,[15 69] leading to hypercapnia and hypoxia. Although single measurements of Pa_{CO_2} are unhelpful in predicting impending respiratory depression[52] (Fig. 3), the techniques described below have helped interpret opioid-induced changes in respiratory control in humans from a mechanistic point of view.

Modelling has successfully explained pharmacodynamic and pharmacokinetic interactions between CO_2 and opioids on breathing.[14] With a gradual increase in opioid levels, for example, with a constant rate infusion, progressive respiratory depression causes gradual hypercapnia that contributes to the maintenance of respiration (Fig. 3). On the other hand, a fast rise in opioid receptor occupancy resulting from an i.v. bolus would lead to apnoea until the Pa_{CO_2} rises to its steady-state value. This explains why drugs with slower receptor binding (e.g. morphine) may be safer than those that bind more quickly (e.g. alfentanil and remifentanil), despite equianalgesic effects.

Although reduced ventilatory frequency and pattern is well described with opioids,[15 38 54 74] currently no human studies have fully investigated the subtle effects of opioids on respiratory rhythm. 'Quantal' breathing[86] has not been investigated. Modelling approaches have been used to examine the interaction between respiratory variability and chemoreflex responsiveness,[92 137] but have not as yet been used to investigate drug effects on breathing. Using such approaches, it could be possible to simultaneously identify drug effects on chemoreception and pattern generation, in human volunteers and patients.

The closed nature of the chemoreflex loop means that changes in breathing will affect Pa_{O_2} and Pa_{CO_2}, and vice versa. As breathing is also modulated by many factors other than chemoreflexes, opening the chemoreflex loop by delivering hypoxic and hypercapnic challenges allows straightforward estimation of chemoreflex gain.[23 52] Specialized experimental protocols and equipment[97 105 125] allow dissection of the peripheral and central components of the respiratory chemoreflex feedback loop. Opioids profoundly depress the HVR and HCVR[145] through depression of central and peripheral chemoreception, described above. The degree of respiratory depression varies between drugs, but there are currently no opioids available that are devoid of respiratory side-effects.

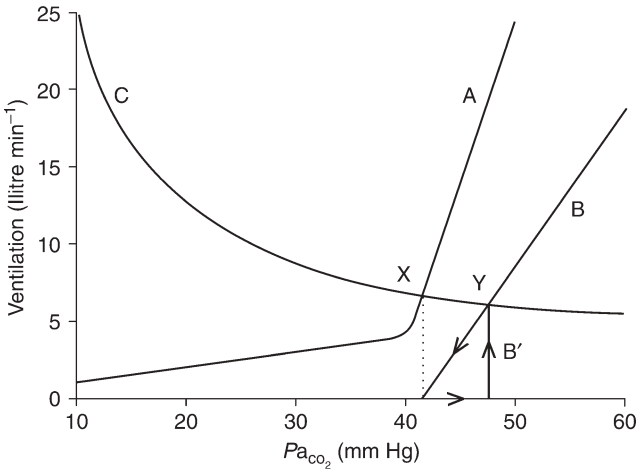

Fig 3 This diagram demonstrates how opiates can induce apnoea at the same Pa_{CO_2} as before opioid administration (dotted line) and also demonstrates that significant reductions in the HCVR only cause small changes in steady-state Pa_{CO_2}. Curve A represents the normal ventilatory response to CO_2 in an awake individual, demonstrating that ventilation is maintained at very low Pa_{CO_2} levels and that apnoea does not occur. Line B represents a 50% depression of the HCVR caused by opioid administration. A notable difference between curve A and line B is that in B apnoea can occur. Note also that in this case Pa_{CO_2} must rise to steady-state values (i.e. along the *x*-axis) for breathing to recommence (line B'). Curve C represents the CO_2 excretion hyperbola and demonstrates how changes in ventilation affect Pa_{CO_2}. Point X represents the awake state and point Y represents opioid-depressed breathing. Despite a 50% depression of the HCVR, the CO_2 changes only relatively modestly, illustrating the limited utility of single measurements of CO_2 in assessing respiratory depression. Figure reproduced with permission from Gross.[52]

Although the HVR is mediated by the peripheral chemoreceptors (which express opioid receptors),[143] Bailey and colleagues[6] demonstrated, in healthy human volunteers, that morphine is likely to exert its depressant effect on the HVR by direct action in the brainstem. They compared HVR between a group that received intrathecal morphine with a group that received an approximately equianalgesic dose of i.v. morphine. In the intrathecal morphine group, they observed a substantial reduction in the HVR, despite extremely low plasma levels. The authors concluded that opioids depress the HVR through central mechanisms, but did not propose a mechanism or site of action. As more recent evidence suggests that MOP agonists inhibit activity in the dorsolateral and medial parts of the NTS,[110] an area which contains chemoreceptive neurones[104] and is the location of the afferent inputs from the carotid body,[44] we can hypothesize that opioids affect the peripheral chemoreflex pathway by interrupting it where impulses synapse in the brainstem.

Factors that modulate opioid-induced respiratory depression

The interpretation of animal and human volunteer studies in the clinical context is complicated by a number of factors. These include interspecies differences[54] and by the fact that drug interactions, sleep, pain, genetic differences, and the stress response may also have important contributions to the ultimate respiratory output.[122 123]

Drug interactions

Many drugs used in anaesthesia act to enhance opioid effects on respiratory depression. Propofol,[98] sevoflurane,[25] and midazolam[53] are respiratory depressants, through agonist effects on GABA and antagonist effects on NMDA receptors,[45 55] and have additive or synergistic effects on respiration when combined with opioids. Although the respiratory depressant effects of ethanol[88] and benzodiazepines are mild, the concurrent use of these drugs with opioids is usually present in drug addicts suffering fatal opioid overdose.[147] Similarly, in the postoperative period, the opioid-mediated depression of breathing may be further exacerbated by residual effects of anaesthetic agents and sedative premedication.

Sleep

Altered chemoreception during sleep has a profound effect upon respiration,[70 94–96] and may be a mechanistic factor in sleep disordered breathing that is seen in obstructive sleep apnoea, Ondine's curse, and multiple systems' atrophy.

The medial pontine reticular formation plays a role in the control of rapid eye movement (REM) sleep.[77] Direct application of morphine to this area (in cats) disturbs sleep and increases the frequency of central apnoeas.[60] In humans, opioids disrupt sleep by increasing the amount of sleep stage 2 (light sleep) and decreasing stages 4 (deep sleep) and REM sleep.[127 138]

Despite the above evidence, there are few studies of the effects of opioids on breathing during sleep in humans. In a study of 12 healthy humans,[117] hydromorphone increased the frequency of central apnoeas during sleep. The only other comparable study was limited by small sample size (seven subjects).[127] More studies have been conducted in opioid addicts, but this study population often is receiving other depressive medications (benzodiazepines and ethanol) that limit interpretation of these studies. The largest study, performed in 50 stable drug addicts on methadone therapy[142] demonstrated a substantially increased incidence of central apnoea during sleep compared with normal controls. The effects of opioids on breathing during sleep are not fully understood, and further studies could help elucidate the magnitude of this potential problem.

Pain

Pain stimulates respiration.[12 122] Substance P and NK-1 receptors mediate nociception and respiration, and therefore it is not surprising that there is such a close link

between pain and breathing. Indeed, in several brainstem sites, nociceptive and chemoreceptive functions converge; these include the ventral medulla,[4] the parabrachial complex,[59] and the NTS,[13] areas that all express opioid receptors.[140 141]

It is hypothesized that pain increases tonic input to the respiratory centres,[122] rather than enhancing chemoreflex sensitivity. Pain does not affect the slope of the HVR and HCVR. The only human laboratory study that has specifically examined the interaction between pain, opioids, and the HCVR[12] demonstrated that pain reversed the respiratory depression induced by morphine, again without affecting the slope of the HCVR. It is unfortunate that this study did not examine changes in baseline ventilation or $P_{E'CO_2}$, which would make it more applicable to the clinical context. The reversal of opioid-induced respiratory depression by pain can lead to potentially disastrous consequences when alternative analgesic techniques are introduced and highlights the balance between pain and breathing in clinical situations. This is particularly important, in clinical situations where a patient has received opioids, remains in pain (but still breathing), with subsequent neuraxial block causing severe respiratory depression.[84]

Genetics

Studies in knockout mice

Genetic studies in knockout mice have given some insight into the mechanisms of action of opioids. Knockout mice lacking the MOP receptor display no analgesia[81] or respiratory depression[119] with morphine, reinforcing clinical observations that analgesic and respiratory effects of opioids are strongly linked. β-Arrestins regulate receptor signal transduction[68] on GPCRs. β-arrestin2 knockout mice derive more analgesia from morphine[11] than wild-type mice, yet have strongly attenuated respiratory depression.[113] The mechanism for this differential effect is unclear. Hypotheses proposed include the following: first, β-arrestin may mediate cellular signalling independently of GPCRs; secondly, β-arrestin may have an effect on other receptor systems, for example, by enhancing the activity of serotonin receptors in respiratory neurones of the pre-Bötzinger complex;[79] finally, there may be differential effects of the altered β-arrestin upon MOP receptor subtypes, but their existence is debated.[39]

Human studies

In humans, interindividual variability in response to opioids may be explained by genetic factors that include sex differences, polymorphisms affecting MOP receptor activity, bioavailability, and metabolism of opioids. In most cases, respiratory and analgesic effects change in parallel, and only one study suggests a potential genetic basis for differential respiratory and analgesic effects.

Sex differences

There is an increasing interest in the investigation of sex differences in pain and in the response to analgesics.[51] Initial studies suggested that women derive greater analgesia from opioids than do men,[47 48 125] whereas more recent studies found no differences.[40 41 118] Two of these negative studies[40 41] studied a considerably larger sample than previously. Only three, relatively small studies have specifically examined sex differences in opioid-induced respiratory depression[24 107 125] and each observed a greater respiratory depressant effect in women than in men. In one of these studies,[124] the separate components of the peripheral and central chemoreflex loops were examined. As the strongest effect on respiration was found in the HVR and in the fast (peripheral) component of the HCVR, the authors hypothesized that these sex differences in the behaviour of the peripheral chemoreflex loop are related to sex steroids. The phase of menstrual cycle was not controlled in these studies. Given the recent contradictory findings in the analgesic response to opioids, there may be benefit in studying a larger group of subjects.

Polymorphisms affecting MOP receptor activity and opioid bioavailability

In humans, the *118A>G* polymorphism of the MOP receptor causes structural changes that affect opioid sensitivity.[20] Two small studies of respiratory effects of this polymorphism suggest differential effects on respiration and analgesia.[99 120] The *ABCB1* gene encodes for bioavailability by regulating uptake of drug passage across the blood–brain barrier[20] and one study suggests that this polymorphism is associated with differences in the respiratory depressant effect of fentanyl.[102]

Polymorphisms affecting opioid metabolism

Polymorphisms of the cytochrome P450 enzymes (*CYP2D6*) have strong effects on the metabolism of codeine and tramadol. People with no functional *CYP2D6* alleles are considered to be 'poor metabolizers' and constitute about 7–10% of the White (or Caucasian) population. People with gene duplications are classified as ultrarapid metabolizers[28] and constitute 1–7% of Whites, and more than 25% of Ethiopians.[46] As tramadol and codeine are both prodrugs that require metabolism to their active metabolite (*O*-desmethyl-tramadol in the case of tramadol and morphine in the case of codeine), enhanced respiratory and analgesic effects may be seen in ultrarapid metabolizers,[46] with reduced effects in poor metabolizers.[30 128] An ultra-rapid metabolizer mother was given codeine for pain after childbirth, the high concentrations of morphine and morphine-6-glucuronide in her breast milk[78] led to the death of her baby from respiratory depression.

Atypical opioids

Many studies in humans have compared the respiratory effects of different opioids, including comparisons of drugs with differing potencies, durations of action, partial agonists, and opioids with effects on other receptor systems. Two drugs of particular interest are tramadol and buprenorphine which appear to have differential analgesic and respiratory effects.

Tramadol

This is a synthetic analogue of codeine and a weak MOP opioid receptor agonist.[54] A proportion of its analgesic effects is mediated by inhibition of norepinephrine and serotonin uptake in the central nervous system.[114] Although tramadol depresses the HCVR,[97] the effect on the HVR is less pronounced.[144] Human studies suggest tramadol causes less respiratory depression than meperidine[89 134] or oxycodone[133] at approximately equianalgesic doses. Only one of these studies[89] was performed in conscious humans, where subjective pain assessment was possible. Unfortunately, the other two studies[133 134] are limited by the fact that they were performed in premedicated, anaesthetized patients and that equianalgesia between the two study drugs was not demonstrated. Tramadol-induced respiratory depression has been reported in patients with renal failure.[8] The utility of tramadol is limited by its weak to moderate analgesic effect and is contraindicated in epilepsy and renal failure.[93] Furthermore, tramadol is subject to pharmacogenetic differences in metabolism[111] as described above.

Buprenorphine

This is a partial agonist at the MOP receptor, which may cause less respiratory depression than conventional opioids at equianalgesic doses. Human laboratory studies suggest a ceiling effect in depression of the HCVR, but not in its analgesic effects.[26 150–152] Although serious respiratory depression has been reported in accidental buprenorphine overdose,[16 49] reports suggest that buprenorphine is associated with fewer fatalities than methadone[5 50] when used in the treatment of heroin addicts. It is unclear what specific cellular mechanisms account for the beneficial respiratory profile of buprenorphine.

Cortical effects on breathing

In contrast to the study of brainstem mechanisms where rodent models are used, behavioural and subjective respiratory control mechanisms are ideally suited to being studied in humans, subjects who are able to communicate subjective feelings, and comply with specific tasks. Early studies established the existence of a 'wakefulness drive to breathe'[42] and established the importance of chemoreflexes in maintaining respiration during sleep[29] and anaesthesia,[43] when the 'wakefulness drive to breathe' is absent.

More recently FMRI has identified, in humans, a network of cortical areas responsible for volitional control of breathing and mediating dyspnoea. Studies of dyspnoea consistently identify the anterior insula, the anterior cingulate, thalamus, and amygdala as brain areas that mediate this unpleasant sensation.[7 17 35 71 103 106] These areas also mediate pain[136] and demonstrate high opiate binding.[9] As opiates improve dyspnoea,[1 22 112] it is therefore likely that opioid action in these areas has a role in respiratory depression by reducing the sensory feedback and 'urge to breathe'. Such sensations are ideally suited to FMRI experimental paradigms.

Other FMRI studies of conscious respiratory control include one of motor aspects of respiration using a voluntary hyperventilation paradigm[83] and identified activity in cortical and subcortical areas relating to motor control, but not the nociceptive areas identified in the dyspnoea studies. Another FMRI study used a breath holding paradigm[82] (Fig. 4) to identify a bilateral network of cortical and subcortical structures associated with response inhibition (the motor act of breath holding) and its sensory feedback, identifying some of the areas identified with dyspnoea. Currently, there are no imaging studies of opioids and respiration in humans, such studies could dissociate opioid-sensitive and insensitive parts of the respiratory control network.

Conclusions and directions for future research

Opioids depress respiration by a number of mechanisms and neuronal sites of action. It is therefore not surprising that there has been such difficulty in combating opioid-induced respiratory depression. Some of the specific target sites of opioid action on respiratory centres have been elucidated only recently. The differential effects on rhythm generation and chemoreception suggest that there are many potential therapeutic targets with differing neuronal functions. For example, BIMU8, a compound that reverses opioid-induced respiratory depression without affecting analgesia through stimulating 5HT4a receptors in the pre-Bötzinger complex,[79] suggests one particular avenue for further research.

Both hypoxic and hypercapnic responses are strongly affected by opioids and appear to be strongly mediated in the brainstem. The role of carotid bodies remains unclear, although opioid receptors are expressed here, and they mediate hypoxic and hypercapnic responses; there appears to be a strong case for their transmission being blocked where they input to the NTS in the brainstem. Enhancing carotid body output may overcome some of these central effects.

The effects of opioids on the cortical (as opposed to brainstem) aspects of respiration have received less

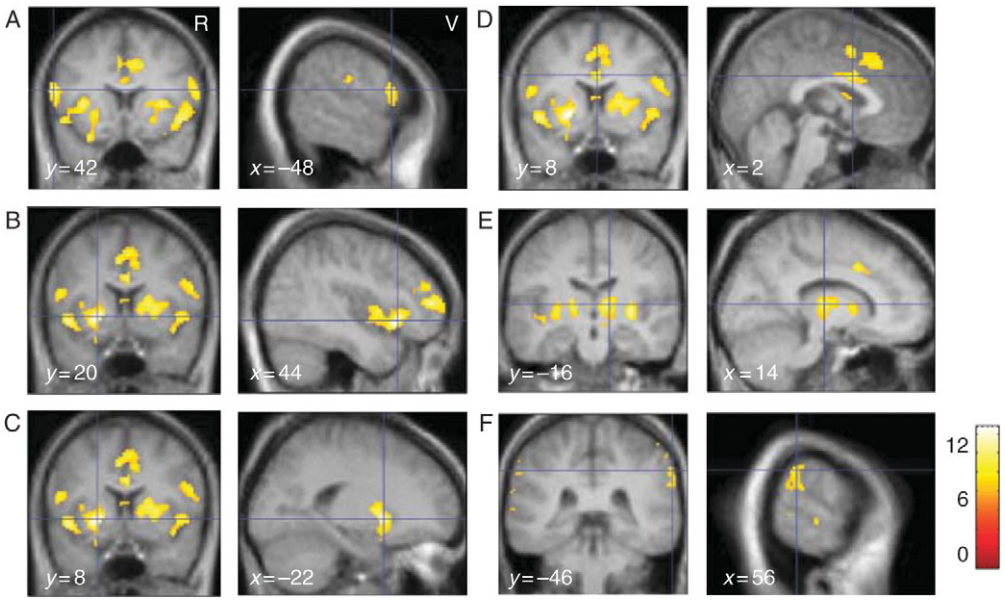

Fig 4 Areas in the brain that are active in response to breath hold. Of these areas the insula, anterior cingulated, and dorsolateral pre-frontal cortex (DLPFC) express high MOP-receptor binding, and are therefore potential brain regions that may contribute to opioid-induced respiratory depression. In these images, a colour-coded statistical map of significant activity (in eight healthy volunteers) is superimposed onto a group mean structural brain scan. The cross hairs are centred on each signal maxima. (Key: a, DLPFC; b, insula; c, putamen; d, cingulate; e, ventrolateral thalamus; f, supramarginal gyrus). V, ventral; R, right. The colour scale indicates the *T*-score or statistical significance. *x* (saggital) and *y* (coronal) are co-ordinates in mm from the intracommisurial plane. Figure reproduced with permission from McKay and colleagues.[82]

attention. Animal models are less suited to such investigations, but in humans, FMRI and PET may provide answers or targets for translation back to animal models. With regard to clinical investigations, there are few studies directly comparing analgesic and respiratory effects in controlled conditions (i.e. without confounds of anaesthesia and potency) and especially the interaction between opioids, pain, arousal states, and other sedative drugs has not yet been fully explored. This review of the control of respiration and opioid effects on breathing may provide avenues for further research in humans and in animal models.

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