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Opioid suppression of conditioned anticipatory brain responses to breathlessness

Anja Hayen[a,b,*], Vishvarani Wanigasekera[a,c], Olivia K. Faull[a], Stewart F. Campbell[c], Payashi S. Garry[a], Simon J.M. Raby[c], Josephine Robertson[a], Ruth Webster[c], Richard G. Wise[d], Mari Herigstad[a,e], Kyle T.S. Pattinson[a,c,**]

[a] Nuffield Department of Clinical Neurosciences (NDCN), University of Oxford, Oxford, UK
[b] Department of Psychology, University of Reading, Reading, UK
[c] Nuffield Department of Anaesthetics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[d] Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, UK
[e] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

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ABSTRACT

Opioid painkillers are a promising treatment for chronic breathlessness, but are associated with potentially fatal side effects. In the treatment of breathlessness, their mechanisms of action are unclear. A better understanding might help to identify safer alternatives. Learned associations between previously neutral stimuli (e.g. stairs) and repeated breathlessness induce an anticipatory threat response that may worsen breathlessness, contributing to the downward spiral of decline seen in clinical populations. As opioids are known to influence associative learning, we hypothesized that they may interfere with the brain processes underlying a conditioned anticipatory response to breathlessness in relevant brain areas, including the amygdala and the hippocampus.

Healthy volunteers viewed visual cues (neutral stimuli) immediately before induction of experimental breathlessness with inspiratory resistive loading. Thus, an association was formed between the cue and breathlessness. Subsequently, this paradigm was repeated in two identical neuroimaging sessions with intravenous infusions of either low-dose remifentanil (0.7 ng/ml target-controlled infusion) or saline (randomised).

During saline infusion, breathlessness anticipation activated the right anterior insula and the adjacent operculum. Breathlessness was associated with activity in a network including the insula, operculum, dorsolateral prefrontal cortex, anterior cingulate cortex and the primary sensory and motor cortices.

Remifentanil reduced breathlessness unpleasantness but not breathlessness intensity. Remifentanil depressed anticipatory activity in the amygdala and the hippocampus that correlated with reductions in breathlessness unpleasantness. During breathlessness, remifentanil decreased activity in the anterior insula, anterior cingulate cortex and sensory motor cortices. Remifentanil-induced reduction in breathlessness unpleasantness was associated with increased activity in the rostral anterior cingulate cortex and nucleus accumbens, components of the endogenous opioid system known to decrease the perception of aversive stimuli.

These findings suggest that in addition to effects on brainstem respiratory control, opioids palliate breathlessness through an interplay of altered associative learning mechanisms. These mechanisms provide potential targets for novel ways to develop and assess treatments for chronic breathlessness.

Introduction

Breathlessness debilitates millions of people with cardiorespiratory disease, terminal cancer and neuromuscular disorders. Chronic breathlessness often correlates poorly with objective measures of disease severity (Hayen et al., 2013; Herigstad et al., 2011; Lansing et al., 2009). This poor correlation between breathlessness and disease markers might be explained by interindividual variability in brain processing of respiratory sensations, hence the justification for neuroimaging studies. Breathlessness is considered a multidimensional symptom, including sensory components of 'work of breathing', affective and emotional components of breathlessness sensations

* Corresponding author at: Department of Psychology, University of Reading, Earley Gate, Whiteknights, Reading RG6 7BE, UK.
** Corresponding author at: Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK.
E-mail addresses: a.hayen@reading.ac.uk (A. Hayen), kyle.pattinson@nda.ox.ac.uk (K.T.S. Pattinson).

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(Hayen et al., 2013; Lansing et al., 2009) compounded by the various psychological processes associated with an individual's suffering (Hayen et al., 2013; Oxley and Macnaughton, 2016).

There has been growing interest in the use of low-dose opioids for the treatment of chronic breathlessness (Ekstrom et al., 2015; Rocker et al., 2013). The neural mechanisms of opioid-driven breathlessness relief are largely unknown (Peiffer, 2011). Opioids depress respiration by acting upon brainstem respiratory centres (Pattinson, 2008) and also act in higher brain centres involved in respiratory control (Pattinson et al., 2009). Importantly, in experimental settings low-dose opioids have been shown to differentially act on the “unpleasantness" (a component of the affective dimension) compared to the "intensity" (a component of the sensory dimension) of aversive stimuli (Price et al., 1985).

Over repeated episodes of breathlessness, associations are formed between previously neutral stimuli, e.g. a flight of stairs (conditioned stimulus [CS]) and breathlessness (unconditioned stimulus [US] (De Peuter et al., 2004)). This has two important outcomes: firstly, learnt breathlessness anticipation may increase breathlessness itself (De Peuter et al., 2005), reinforcing the CS-US pairing, and secondly, the feared activity is avoided, fuelling a downward spiral of activity avoidance, physical deconditioning and worsening breathlessness.

In this context of conditioned learning, opioids have shown profound effects on association learning and memory formation to aversive experiences (Sandkühler and Lee, 2013; Fanselow 1998; McNally 2004). Two of the key structures involved in these processes are the amygdala and hippocampus (Phelps, 2004). As these structures are rich in opioid receptors (Favaroni Mendes 2008; McGaraughty and Heinricher, 2002), we hypothesised that opioid effects on association learning with regards to breathlessness are mediated, at least in part, by the amygdala and hippocampus.

Therefore, the effect of opioids on breathlessness most likely stems from multiple actions within the central nervous system. A better understanding of these brain mechanisms could be used to develop alternative therapies with fewer safety concerns than opioids (Pattinson, 2015; Ray et al., 2016; Robertson et al., 2016; Vozoris et al., 2016). In the present study we used functional neuroimaging to identify the neural correlates of the conditioned response to breathlessness and their modulation by the mu-opioid receptor agonist remifentanil. We tested the hypothesis that in addition to direct effects on respiration, remifentanil would also act on neural mechanisms associated with conditioned learning in the amygdala and hippocampus.

Methods

This double-blind, randomized, placebo-controlled mechanistic study investigated the neural correlates of the opioid remifentanil upon the anticipation and perception of breathlessness. An aversive delay-conditioning session was followed by two FMRI sessions (remifentanil or saline placebo, counterbalanced across participants). The sessions were performed on three consecutive days at the same time each day.

Data acquisition

Participants

Data from 19 healthy participants (10 females, age 24 (±7 SD) years) was analysed in this study. Written informed consent was obtained in accordance with the Oxfordshire Research Ethics Committee. Although 29 participants originally participated, 10 were excluded for the following reasons: 2 participants exhibited vasovagal syncope during cannulation; 1 participant did not comply with study instructions; 4 participants did not learn the association between visual cues and respiratory stimuli; 3 participants were excluded because of technical difficulties with the MRI equipment. Participants were right-handed non-smokers and had no history of neurological (including painful conditions), pulmonary or cardiovascular disease, were free from acute respiratory infections and were currently not receiving any medication. Participants fasted solids for 6 h and liquids for 2 h before every session.

Initial session

The Center for Epidemiologic Studies Depression Scale (CES-D; (Radloff, 1977)) was used to identify (and exclude) participants with clinical depression. The trait scale of the Spielberger State-Trait Anxiety Inventory (STAI; (Spielberger, 2010)) was used to characterize general participant anxiety.

Breathlessness stimulus

The breathlessness stimulus used in this study was intermittent resistive inspiratory loading for 30–60 s administered via the MRI compatible breathing system illustrated in Supplementary Fig. 1. Manually operated hydraulic valves diverted inspiratory flow via one of three routes that either did not restrict breathing, or provided a mild or strong resistive load. Expiration was unrestricted via a one-way valve (Hans Rudolph, Shawnee, Kansas, USA).

In an externally cued delay conditioning paradigm (Fig. 1), participants learned associations between three visual cues (conditioned stimuli, (CS), either a white square, star or triangle shape presented on a black background) and resistive inspiratory loading that was intermittently applied to induce three different respiratory sensations (unconditioned stimuli, (US), either breathlessness (strong inspiratory load, approximately −12 cm H_2O), a mild inspiratory load (approximately −3 cm H_2O) or no inspiratory load). The pairing between the visual cue (CS) and respiratory load (US) was maintained constant for each participant during all 3 experimental sessions, but was counterbalanced between participants. Four repeats of each of the mild load and strong load (breathlessness) and eight repeats of the unloaded condition were performed. Immediately after each inspiratory load,

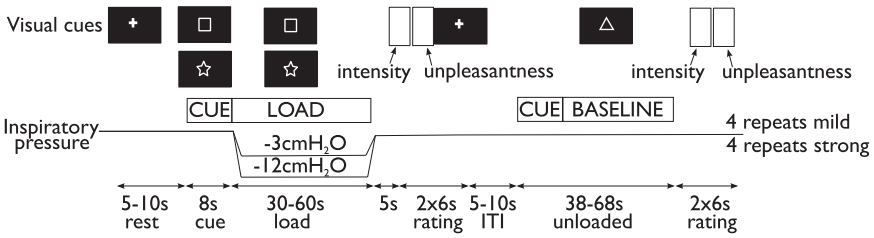

Fig. 1. Schematic illustration of experimental session and aversive conditioning paradigm. Prior to the application of each inspiratory load, the fixation cross on the screen changed to one of three shapes, a triangle, a square and a star to signal the imminent application of a stimulus (mild inspiratory load, strong inspiratory load) for eight seconds (anticipation period). The shape remained on the screen during the application of the stimulus (stimulus period) for 30–60 s and changed back to the fixation cross when the stimulus ceased. The shapes were counterbalanced across participants. Each inspiratory load was followed by an unloaded period of between 30 and 60 s that was indicated by a third visual cue. The use of relatively long breathlessness stimuli was chosen to maximize the emotional responses associated with anticipation of breathlessness. Participants rated their respiratory intensity and unpleasantness after each stimulus. Visual stimuli were generated and presented in white on a black background using the Cogent toolbox (www.vislab.ucl.ac.uk/Cogent/) for MatLab (MathWorks Inc., Natick, MA, USA).