Differential effects of opioid analgesics on functional connectivity of cortical-subcortical networks in humans

R. G. Wise[1], A. Jolly[2], K. Murphy[1], C. J. Evans[1], and J. E. Hall[2]
[1]CUBRIC, School of Psychology, Cardiff University, Cardiff, S. Glamorgan, United Kingdom, [2]Department of Anaesthetics and Intensive Care Medicine, School of Medicine, Cardiff University, Cardiff, S. Glamorgan, United Kingdom

Introduction

The human opioid system consists of cortical-subcortical networks including the anterior cingulate cortex (ACC), insular cortex, putamen, thalamus, and the brainstem [1,2]. Remifentanil that binds to mu-opioid receptors is a potent modulator of this system. We have previously demonstrated that the functional correlates of its analgesic effects measured with BOLD FMRI [3] co-localise with opioid-induced cerebral blood flow (CBF) *increases* in the ACC, insula, thalamus and brainstem, and with CBF *decreases* in the basal ganglia [4].

Here we tested the effect of remifentanil on functional connectivity in BOLD-weighted FMRI performed in the same sessions as CBF measurements reported in Wise et al 2010 [4]. Functional studies have demonstrated a covariation between the insula and ACC and brainstem activity in the context of pain [5] and opioid administration [2]. Here we hypothesized an opioid-induced increase in functional connectivity between these brain regions, reflecting their role in pain control. As previous evidence suggests an effect of remifentanil on basal ganglia activity [4], which is consistent with the drug effect on muscle tone [6], we also investigated drug-related changes in functional connectivity of deep grey matter structures.

Methods

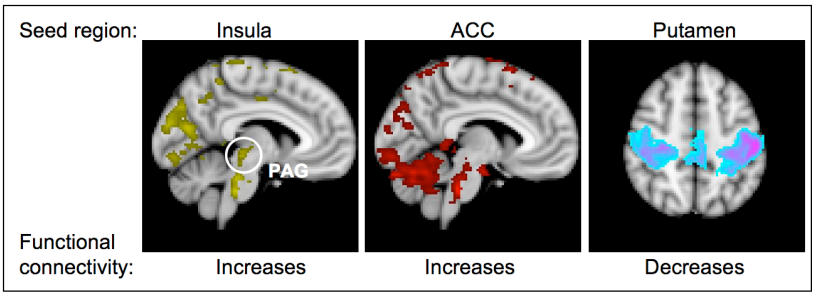
14 healthy volunteers (6 female; age 21-35 years) underwent T2* weighted (BOLD) FMRI scanning before, during and after intravenous infusion of remifentanil during a single imaging session. Comparisons presented here are only those between the period before and during drug administration. Remifentanil was delivered by target controlled infusion pump to achieve a steady-state plasma concentration of 1.5 ng/ml. During scanning volunteers controlled their rate and depth of breathing [7]. They were trained to maintain at a target value their end-tidal CO_2 displayed on a screen. This procedure mitigated the rise in arterial CO_2 normally caused by opioid-induced respiratory depression. The target end-tidal CO_2 was set to 1-2mmHg below the volunteer's resting value to ensure compliance with the task both before and during the remifentanil infusion.

Imaging was performed on a 3T GE HDx system with GE-EPI readout with whole-brain coverage (TR=3s, TE=35ms, 3.2x3.2x3.2mm voxels). A 1x1x1mm T1 weighted structural scan was acquired for image registration. Baseline CBF scans and BOLD FMRI scans during sensory stimulation were also recorded but are not reported here. 140 volumes of resting (besides the breathing task) BOLD data were acquired. The breathing task was performed continuously before and during drug administration and should therefore present a minimal confound in our comparisons.

BOLD timeseries were motion corrected (MCFLIRT [8]), highpass filtered (cut-off 120s) and smoothed with a Gaussian kernel of 5mm. Nonlinear registration to the MNI template was performed. Regional mean timeseries were extracted from the following regions of interest for each volunteer before and during drug administration: ACC, bilateral insula and putamen. Regions were defined by the Harvard-Oxford cortical and sub-cortical atlases within FSL. Seed region timeseries were used in GLM analyses (FEAT) as the main regressor of interest. End-tidal CO_2 was also included as a nuisance regressor. A second level paired GLM analysis was performed to identify group mean drug-induced differences (during-before infusion) in functional connectivity involving the specified regions (threshold Z >2.3 with cluster corrected p<0.05).

Results

Before and during infusion group mean end-tidal CO_2 were 38.5±3.3 mmHg and 38.3±6.7 mmHg respectively (*NS*). The administration of remifentanil predominantly increased functional connectivity of the insula and ACC to other brain regions. The ACC showed increased connectivity to lateral occipital cortex, thalamus, cerebellum and pre-motor cortex. Insula showed increased connectivity to occipital cortex, thalamus and premotor cortex. Both the insula and ACC showed increased connectivity with the pons. However, the insula additionally showed an increased connectivity to the periaqueductal grey (PAG).



To test changes in functional connectivity of deep grey matter structures we seeded from the putamen, which has previously shown drug-related reduction in CBF [4]. We found a reduction in functional connectivity between the putamen and primary sensorimotor cortical and auditory cortices.

Discussion

Our results suggest that the effects of the opioid are dissociated into enhancement and reduction of FMRI-derived functional connectivity when seeding in different opioid-modulated areas.

We observed an increase of connectivity between ACC/insular cortical areas and the brainstem. In particular, the insula covaried with the PAG more strongly during opioid administration, suggesting an enhancement of the pain-control system for modulating spinal cord activity.

Interestingly, we found a reduction of functional connectivity between the putamen, whose perfusion [4] is decreased by opioid administration, and sensorimotor areas. Changes in the strength of functional connectivity of these regions may be mediated by drug-related interference on the excitatory-inhibitory balance within the basal ganglia circuits [9] and may represent the functional correlate of the opioid effect on muscle tone [6].

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