Opioid-induced changes in cerebral blood flow in the human brain during controlled breathing

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Introduction
Studies using positron emission tomography have demonstrated opioid induced alterations in regional cerebral blood flow (rCBF). These have included increases in cortical areas such as the cingulate, orbitofrontal and medial prefrontal cortex [1], and subcortical regions including brainstem (pons) [2], as well as decreases in frontal, cerebellar and temporal areas [3,4]. Recently, non-invasive MRI arterial spin labelling (ASL) methods have demonstrated their utility in quantifying opioid-related changes in rCBF [4], with opioid-induced CBF increases reported in thalamus and other areas [5]. The location of opioid-induced CBF increases is broadly consistent with the pattern of μ-opioid binding in the human brain [6]. Most previous studies of CBF have not fully accounted for confounding effects of opioid-induced respiratory depression which can increase rCBF as a result of the rise in arterial partial pressure of CO2 [4]. However, we recently employed control strategies during opioid administration to map BOLD signal reactivity following opioid administration [7], to identify networks engaged in the control of breathing [8] and their modulation by opioid administration [9].

The present study examines the effect of remifentanil, a potent μ-opioid agent, on CBF while volunteers to control their breathing to suppress the respiratory depressive effects of the drug. We hypothesize that remifentanil increases CBF in areas of have high opioid binding (e.g. thalamus) and, by virtue of the sustained breathing task, in areas engaged in the control of breathing [8,9].

Methods
13 healthy volunteers (5 female; mean age 26.5; range 21-35) underwent single-shot pulsed ASL perfusion measurements before and during intravenous infusion of remifentanil, each scan lasting for 5 mins. Remifentanil was delivered by target controlled infusion pump to achieve a steady-state plasma concentration of 1.5 ng/ml. During ASL measurements volunteers controlled their rate and depth of breathing [7]. Following training, they were asked to maintain their end-tidal CO2 at a target value displayed on a screen alongside their current value. This procedure mitigated the rise in arterial CO2 normally caused by opioid-induced respiratory depression. The target end-tidal CO2 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 using pulsed ASL QUIPSIII [10] with GE-EPI readout. 16 slices (7 mm thick, 1mm gap) provided whole brain coverage with a 64x64 matrix (3.75mm in-plane resolution, TR/TE=2200/19.8ms, single inversion time with T1/T2=700/1350ms, 136 volumes). A 1x1x1mm T1 weighted structural scan was acquired for image registration.

The perfusion timeseries were motion-corrected (MCFLIRT [11]) and CBF maps computed using in-house software. Following affine registration of EPI data (FLIRT [11]) to the Montreal Neurological Institute template, mean grey matter flow was computed. A voxel-wise paired group analysis was performed comparing the drug infusion period with that preceding it (FEAT, [11]), incorporating individual scan-mean end-tidal CO2 as a regressor of no interest to account for residual differences in arterial CO2. Results are quoted as mean ± standard deviation.

Results
Group mean grey matter perfusion was 32.5±5.7 ml/100g/min preceding remifentanil infusion and 33.4±8.6 ml/100g/min during infusion (p>0.2 1-tailed t-test). Before infusion, group mean end-tidal CO2 was 38.5±3.3 mmHg, increasing slightly to 39.6±3.3 mmHg (p<0.01 1-tailed t-test). Remifentanil induced a significant increase in CBF bilaterally in the ventral anterior/lateral nuclei of the thalamus and in the nuclei reticularis of the brainstem. Significant CBF decreases were found bilaterally in the putamen/globus pallidum. Mean CBF in positive flow-responding regions (Fig 2) rose from 33.4±7.8 to 42.2±10.5 ml/100g/min (up 26%) and mean rCBF in negative flow-responding regions fell from 30.1±5.8 to 25.5±8.0 ml/100g/min (down 15%).

Discussion
These data demonstrate the sensitivity of pulsed ASL to opioid administration. Localised changes in rCBF were observed after controlling end-tidal CO2. Flow increases in thalamus and brainstem are consistent with strong opioid binding potential in these regions. However, the putamen, also a region of strong opioid binding [6], showed a significant decrease in CBF. This is consistent with our previous opioid study (end-tidal CO2 uncontrolled) in which the putamen exhibited only a small increase in CBF. Increased CBF in VAVL thalamus, subthalamic nuclei and pons is consistent with our previous studies of breathing control [7,8] identifying these regions as more active during volitional and spontaneous changes in breathing. The observed CBF changes are potentially linked to the greater conscious control of breathing required during opioid administration.

The small average rise in end-tidal CO2 (~1mmHg) in this experiment would be expected to cause an approximately uniform (in grey matter) 3% increase in global CBF [12], close to our observed increase. The global influence of CO2 is unlikely to explain the larger, regionally dependent flow changes. Furthermore, we have accounted for changes in end-tidal CO2, in our comparison by assuming that rCBF changes are proportional to changes in end-tidal CO2 [12]. Our results demonstrate that the effects of μ-opioid administration on CBF are not uniform across the brain. These regional effects on CBF must be accounted for when considering the role of drugs in modulating stimulus-induced brain activity [9].

References

Acknowledgements: UK Medical Research Council