Pharmacological FMRI: measuring opioid effects upon the BOLD response to hypercapnia

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INTRODUCTION

In pharmacological FMRI studies, such as those of pain and analgesia, we aim to interpret drug-induced changes in stimulus-induced BOLD response as neuronal in origin. Unfortunately many centrally acting compounds not only directly alter neuronal activity but can alter the BOLD signal by other means such as changes in cerebral blood flow or vascular tone. Hypercapnia is an elevated arterial partial pressure of carbon dioxide (CO_2). It induces a substantial increase in cerebral blood flow without an increase in oxygen metabolism and hence induces an increase in BOLD signal. Hypercapnia produces a cerebrovascular challenge that has previously been used to map vascular responsiveness using FMRI [1]. We present an investigation of the potential influence of a mu-opioid agonist (remifentanil) on vascular responsiveness. We investigated remifentanil because we are interested in its effects on pain processing [2] and because there is evidence that opioid binding to capillaries may occur [3], potentially altering their responsiveness to CO_2. Whilst opioids induce hypercapnia themselves, we have controlled for this, allowing us to examine the BOLD reactivity to our externally administered CO_2 challenges. The method we present is aimed at understanding the possible vascular influences of opioids that may affect our interpretation of pharmacological FMRI studies and could be extended more generally to human pharmacological FMRI studies.

METHODS

9 healthy volunteers (1 female) took part in the study performed on a Siemens Trio 3T scanner. T2* weighted gradient-echo EPI scanning was performed (TE=30 ms, TR=3000 ms) for 36 minutes (voxel size 3x3x3mm slices). During scanning, phasic hypercapnia was induced by breathing an inspired concentration of 5% CO_2 alternated with air, each for a period of 2 minutes. Remifentanil is a short acting opioid analgesic that is used in anesthesia. Its ultra short context-insensitive half-life (3-4 minutes) allows rapid adjustment of plasma levels when infused using a computer controlled pump pre-programmed with a pharmacokinetic model of the drug (target controlled infusion). A target controlled infusion of remifentanil was delivered during the second half of the scan to a plasma concentration of 1.0 ng/ml. Throughout scanning, the end-tidal partial pressure of oxygen ($P_{ET}O_2$) was maintained at 25 kPa through the manual adjustment of the inspired gas mixture. Fig. 1 shows the recorded end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) in one subject, indicating periods of normocapnia and hypercapnia. The volunteers were asked to adjust their breathing to maintain a target $P_{ET}CO_2$ value that was displayed on a screen ($P_{ET}CO_2$~5kPa during normocapnia and ~6.5kPa during hypercapnia, values determined prior to the experiment by measuring $P_{ET}CO_2$ values at rest and after two minutes of CO_2 challenge). This method provided good $P_{ET}CO_2$ control and mitigated the rise in baseline $P_{ET}CO_2$ from opioid-induced respiratory depression.

The responsiveness of BOLD signal to hypercapnia defined as the BOLD signal change per unit change in $P_{ET}CO_2$, was evaluated over the brain and compared between remifentanil and no remifentanil periods. Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.42, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Voxel-wise statistical analysis was extended to a second (group) level in a mixed effects analysis using (FLAME). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05. Registration to high resolution and/or standard images was carried out using FLIRT.

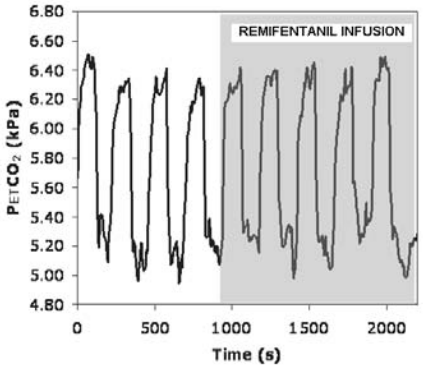
We hypothesized that brain areas previously identified with pain processing would be most likely to have their vascular responsiveness modified by remifentanil [4]. A region of interest analysis was therefore performed to identify drug-induced changes in BOLD response to CO_2 on and off remifentanil in anterior cingulate cortex, insular cortex, thalamus, primary somatosensory and secondary somatosensory cortices.

RESULTS

As previously reported [2] there was a significant global BOLD signal increase in response to hypercapnia. This was generally larger in grey matter than white matter. There was no modulation of this BOLD response to hypercapnia by remifentanil either globally or in the regions of interest examined (2-tailed paired t-tests, *P* threshold for significance 0.05 for the regions of interest). A small focal reduction in BOLD response to hypercapnia was observed in the right inferior temporal lobe.

Using the data from the region of interest analysis, we examined the power of the study. On average there was 80% power to detect an 18.6% drug-induced modulation in the amplitude of the BOLD response to hypercapnia, at significance level of $P<0.05$. For example if normally there was a 2% BOLD signal increase in response to a hypercapnic challenge, we would be able to detect a drug-induced modified BOLD response to hypercapnia of 1.63%.

Fig 1: End-tidal CO_2 for one volunteer



DISCUSSION AND CONCLUSION

The observed modulatory effects of remifentanil upon the BOLD response to a CO_2 challenge were small. We have not demonstrated any effect in regions known to be involved with pain processing. When $P_{ET}CO_2$ was controlled there appeared to be little drug-induced change in vascular reactivity. This result is beneficial for interpreting pharmacological FMRI with opioids, because it means any changes seen in the BOLD response to CO_2 are unlikely to be a drug effect on the cerebral vasculature. We have described a method of examining a drugs effect on cerebrovascular CO_2 reactivity, which we believe is an essential step in pharmacological FMRI studies, especially when investigating drugs that may affect resting $P_{ET}CO_2$ levels through respiratory depression.

REFERENCES

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