The relationship between local dopamine changes and phMRI response to acute cocaine challenge in the rat revealed by concurrent in situ microdialysis

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Introduction

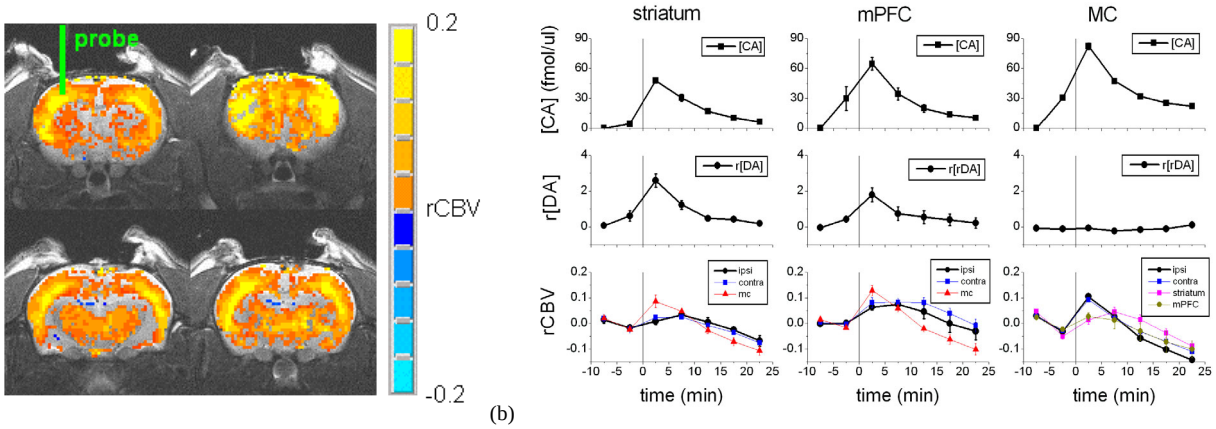
Cocaine (CA) has been widely used in phMRI studies in the rat, where it produces a widespread central response involving the cortex, pre-frontal cortex (PFC), and thalamus, with a weaker response in the striatum (Fig. 1(a)). Interestingly, intravenous administration of cocaine results in temporal phMRI profiles that vary with anatomical location[1]. Although often used as a probe of the dopamine (DA) system, the mechanism of action of cocaine is complex and also involves the serotonin and noradrenaline systems. While parallel temporal profiles of phMRI signal changes and DA concentration in the rat striatum following amphetamine and CFT challenge have been noted[2], the precise relationship between the haemodynamic response to acute intravenous cocaine challenge and neurotransmitter modulation remains to be fully elucidated. Open questions include the extent to which the inter-animal variability in the amplitude of the phMRI response is determined by variability in the [DA] increase following cocaine injection, and whether the different time courses are driven by different [DA] temporal profiles. Here, we report on simultaneous changes in [CA], [DA] and regional Cerebral Blood Volume (rCBV) in response to i.v. cocaine challenge in the rat with concurrent microdialysis samples obtained *in situ* during the phMRI experiment. A Mass-Spectrometry assay was developed in order to increase the time resolution of the microdialysis sampling to 5-minute intervals, enabling better delineation of the [DA] and [CA] time courses.

Methods

Male Sprague-Dawley rats were surgically prepared in three groups, with non-magnetic microdialysis probe guide cannulae (Microbiotech, Sweden) implanted into either the dorsal striatum (n=8), medial PFC (mPFC, n=7) or motor cortex (MC, n=8). Animals were singly housed with free access to food and water for 6-8 days. The MRI experiments were performed under halothane anaesthesia (maintenance level 0.8%), artificial ventilation and paralysation. Ventilation parameters were adjusted to keep the arterial blood gases values within physiological range. The MRI acquisition was performed using a Bruker Avance Biospec 4.7T wide-bore MR system (Bruker, Ettlingen, Germany), a volume transmit coil and curved quadrature surface receive coil with a central opening allowing the microdialysis probe to remain *in situ* during the MR acquisition. The time series experiment used the RARE sequence[4]: matrix 128x128; FOV 40mm; TH=2mm; 8 contiguous coronal slices; TE_{eff}=110ms; TR=2700ms; δt=10s, N_t=256. A 2.67 ml/kg dose of blood pool contrast agent (Endorem, Guerbet, France) was administered i.v. following 5 reference image frames to sensitise the acquisition to changes in CBV[5]. 15 minutes later, an i.v. bolus of 0.5mg/kg cocaine was injected. In the mPFC and striatum groups, rCBV time courses were extracted from 3x3 ROIs centred on the probe tip and contralaterally, as well as from the MC. In the MC group, time courses were extracted from ROIs in the MC ipsi- and contralaterally, as well as in the striatum and mPFC. For each rat microdialysis samples were obtained at a time resolution of 5 minutes, starting 50 minutes prior to the cocaine injection, which was timed to coincide with the beginning of a new microdialysis sample. CA and DA concentrations were determined concurrently in the same assay. [DA] changes were normalised to mean baseline value and re-expressed as fractional changes (r[DA]).

Results

Mean baseline [DA] levels were 0.53 fmol/ul (striatum), 0.30 fmol/ul (mPFC) and 2.24 fmol/ul (MC). The anatomical dependence of the phMRI time courses was consistent with that reported[1] and obtained in-house previously. In the striatum and mPFC groups, [CA] and [DA] peaked during the first 5-minute period post-injection, then rapidly decreased (Fig. 1(b)). This represents a faster dynamic than the local rCBV response profiles, which were broader and whose peak response was delayed by some minutes relative to that of [DA]. Surprisingly, in the motor cortex group, the microdialysis revealed no change in [DA] following CA injection, despite a strong local [CA] and robust rCBV response. No correlation between the amplitudes of individual rCBV and [DA] responses was found.



(a) (b)

Figure 1: *(a) Group response map from MC cohort (anterior 4 slices). (b) Changes in [CA], r[DA] and rCBV (rebinned to 5-minute time points) following CA challenge. All time courses are shown as mean±SEM across animals. Values are shown in the middle of their corresponding 5-minute window. The negative trend in rCBV curves is due to contrast agent washout.*

Discussion

The rCBV time courses in the striatum and mPFC are significantly delayed and of broader temporal profile than changes in [DA], implying that [DA] alone is not directly driving the haemodynamic response. Moreover, in the motor cortex, where strong and robust rCBV changes are observed, the microdialysis revealed absolutely no change in [DA] locally, despite local [CA] changes. These findings imply that the rCBV response in the motor cortex does not reflect local dopamine changes. Other neurotransmitter systems, or projections from other structures, may be driving the response in this region.

References

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