Temporal dynamics of brain tissue pO2, blood flow and blood volume in phMRI of cocaine

L. Ceolin[1], A. J. Schwarz[1], A. Giarola[2], T. Reese[1], A. Gozzi[1], A. Bifone[1]

[1]Department of Neuroimaging, Psychiatry CEDD, GlaxoSmithKline, Verona, Verona, Italy, [2]Department of Safety Assessment, GlaxoSmithKline, Verona, Verona

Introduction:

Functional MRI methods have been applied to map the central haemodynamic response to acute cocaine challenge as a surrogate for drug-induced changes in brain activity [1,2]. However, the complex effects of cocaine on neuronal activity, brain metabolism and vascular response are not fully understood. Here, we examine the temporal correlation between the partial pressure of tissue oxygen (pO2), cerebral blood flow (Laser Doppler Flow, LDF) and blood volume (CBV) in the rat brain in an acute cocaine challenge protocol. PO2 reflects the balance between oxygen consumption and supply from vasculature, and is sensitive to local changes in oxygen metabolic rate. Optical methods were applied to concurrently measure pO2 and LDF in two cohorts, probing the motor cortex and dorsal striatum respectively. CBV changes were measured in a third group of animals using functional MRI methods but identical animal preparation, and were compared with tissue pO2 and LDF time courses to investigate the interplay of haemodynamic parameters during response to cocaine challenge.

Methods:

All experiments were carried out in accordance with Italian regulations governing animal welfare and protection and internal ethical review.

pO2 and CBF measurements: Male Sprague-Dawley rats (250-350 g) were anaesthetised with halothane (3% induction, 1.5 % for surgery) in O_2/N_2 1:2, tracheotomised and mechanically ventilated under infusion of the neuromuscular blocker D- tubocurarine (0.25 mg/kg bolus i.v. + 0.25 mg/kg hr). The femoral artery was cannulated with a polyethylene catheter to monitor arterial blood pressure and blood gas levels. Subsequently, the animals were placed in a stereotaxic frame and implanted with a combined fluorescence-quenching/Laser-Doppler-Flow (LDF) probe (Oxylite, Optronix) either in the motor cortex (M1, n=11; stereotactic coordinates from dura mater AP +2.2 mm, ML +2.8 mm, DV -2.5 mm) or in the dorsal striatum (dStr, n=12; AP +1.0 mm, ML +2.5 mm, DV -4.1 mm). After surgery, the anaesthesia was decreased to 1% halothane for maintenance. After a 2h stabilisation period, animals were challenged with cocaine (0.5 mg/ 1.4 ml/ kg i.v.) or its vehicle (saline) infused over ~ 30 sec. PO2 and LDF were measured prior to and for 30 min following cocaine injection.

CBV measurements: MRI experiments were performed on 12 male Sprague-Dawley rats, prepared and challenged with cocaine or vehicle as described above. The data were acquired using a Bruker Biospec 4.7T system, a 72mm birdcage resonator for RF transmit and a quadrature surface receive coil (Bruker, Ettlingen, Germany). The time series experiment comprised 90 time points using the RARE sequence: matrix 128x128; FOV 40mm; slice thickness 2mm; 8 contiguous coronal slices; RARE factor 32; TE_{eff}=110ms; TR=2700ms; δt=40s. A 2.67 ml/kg dose of Endorem blood pool contrast agent (Guerbet, France) was administered i.v. following 5 reference image frames, to sensitise the acquisition to changes in CBV. Time-courses were extracted from 3x3 ROIs centred in the M1 and dStr for comparison with the bench measurements above.

Results and discussion:

In the motor cortex, pO2, LDF and CBV all increased rapidly and peaked approximately 4 minutes after cocaine challenge (Fig. 1(a)). The pO2 and LDF temporal profiles were positively correlated (mean intra-animal cross-correlation ρ=0.66) and returned to baseline within 15-20 min from injection, while the CBV response was more sustained and approached baseline values more slowly. In the dorsal striatum, all three parameters followed again similar time courses - increasing rapidly following injection to a plateau (Fig. 1(b)). Inter-animal variability in the tails of the CBV and LDF time courses is reflected in the larger inter-animal error bars at the later time points, consistent with our previous observations [2]. We also note that peripheral changes in mean blood pressure (MBP), co-acquired with the pO2 and LDF data, show minimal changes and do not correlate with the central measures. An increase in tissue oxygen level is thought to be needed to sustain increased oxygen consumption rates in the mitochondria, and has been previously associated with activation of the rat somatosensory cortex in response to fore-paw electrical stimulation [3]. Our data are consistent with this picture and extend the evidence to pharmacologically induced activity, showing elevation of tissue oxygen levels in brain regions where cocaine induces an increase in glucose metabolism [4]. Interestingly, pO2 time-course vary with anatomical location, and is temporally tightly coupled with LDF in both brain regions.

[1] Marota et al., Neuroimage **11**, 13 (2000). [2] Schwarz et al., Neuroimage **23**, 296 (2004). [3] Ances et al., Neurosci. Lett. **306**, 106 (2001) [4] Thomas et al., J. Pharmacol. Exp. Ther. **278**, 347 (1996).

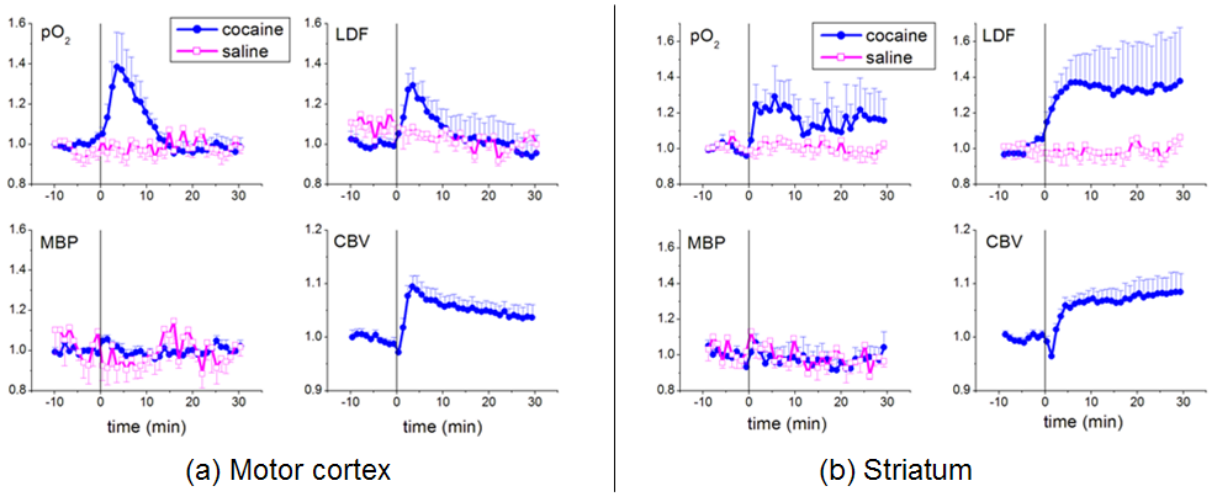

Figure 1: Group time courses of pO2, LDF and MBP from the two anatomical regions. The CBV curves shown for comparison are from ref. [2].