Detection of exposure related cortical responses by amphetamine using PCASL and pharmacokinetic/pharmacodynamic dose modeling

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Introduction: Arterial Spin Labeling technique (ASL) has become an important tool to provide repetitive and quantitative brain perfusion measurements. ASL techniques have great potential for longitudinal studies since it is non-invasive with excellent test-retest repeatability [1,2,3,4]. It is therefore well suited for pharmaceutical MRI (phMRI) studies to investigate how drugs change the cerebral perfusion status and further, neuronal activity [5,6]. Particularly pseudo-continuous arterial spin labeling (PCASL) can provide high SNR efficiency and whole brain coverage without the need of special hardware which also makes it well suited for clinical practice. Many CNS drugs have a dose dependent effect on neuronal activity in specific neuronal populations [7]. In this study PCASL has been used to study the central effects of dextro(d)-amphetamine by measuring the dynamical changes of regional cerebral blood flow (rCBF) after drug administration. The CBF response has also been related to the independent amphetamine pharmacokinetics (PK) measurements from blood samples.

Materials and Method: Twelve healthy normal male volunteers participated in the study. All MRI measurements were performed using a 3T Magnetom Trio (Siemens, Erlangen Germany) equipped with a 32 channel receive only head coil. At the first visit a screening of the subjects was performed including a health examination within 30 days prior to the study date. The subjects were asked to be fasting from midnight before the study. Before the MRI scanning the subjects had a cannula inserted into the forearm for collection of blood samples. The experiment was based on a double blinded design, six of the subjects were randomly selected to receive a single oral dose of 20 mg d-amphetamine and six of them were given placebo. Before the dose MRI baseline measurements were done including anatomical T1-weighted MPRAGE, resting-state BOLD and PCASL scans. After the dose PCASL measurements were repeated 9 times during a 10 hours period (15 min, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs and 10 hrs). The acquisition parameters for the PCASL sequence were TE/TR = 18/3330ms, FOV = 230×230, bandwidth = 2790Hz/pixel, matrix = 64×64, 18 slices of 6 mm thickness, 150 acquisitions with a total time of 8:26 min. Vital signs (pulse rate, respiratory rate and blood pressure) and blood samples were collected in connection to the MRI acquisitions. Intake of standardized meals was done at certain time points.
The post-processing of PCASL data was performed off-line using shell scripts calling C-programs from the AFNI package. The main steps included: 1) motion correction by 3D rigid-body image registration; 2) creation of brain mask; 3) voxel-wise computation according to previously established equation [8]; 4) brain normalization to align individual CBF data to brain atlas template by using affine transformation and mutual information as cost function; 5) voxel-wise statistical analysis of the CBF data by computing the cross correlation coefficient between the CBF time course and plasma concentration from PK measurements; 6) statistical significance at $p<0.05$ was assessed by threshold of cross-correlation coefficient and cluster size.

Results: The analysis of whole brain mean grey matter CBF showed significant reduction of CBF ($p<0.05$) at 3 hrs, 4 hrs and 6 hrs after 20 mg of d-amphetamine compared to placebo. Voxel-based analysis showed a significant overall difference between placebo and d-amphetamine that was most clear in the regions of basal ganglia, frontal and insular cortex. This basic anatomical pattern is also seen at individual time points. Individual data of the total CBF in grey matter and individual plasma concentrations of d-amphetamine was analyzed using nonlinear mixed effects modeling as implemented in NONMEM version 6.2.0. Modeling of PK and pharmacodynamic (PD) was sequential, first a PK model was fit to d-amphetamine plasma concentrations and individual PK parameters derived using a Bayesian method in NONMEM. Subsequently a PK/PD model was fit to the CBF data using the dose of d-amphetamine and individual PK parameters as input to the model. PK data was described by a 1-compartment model with transit compartment absorption. Total CBF in grey matter was described by an indirect response model with PK of d-amphetamine having an inhibitory function on production of response. A linear model was used to describe the drug effect. Baseline of CBF was estimated to 51.2 ml/100g/min. The half-life of the turn-over of response was short, approximately 54 minutes. The decrease in CBF at the reference concentration of 30 ng/ml was estimated to be approximately 15%. All voxels where CBF showed a significant correlation with the plasma concentration according to the PK/PD model used are shown in figure 1. In figure 2 the plasma concentration of d-amphetamine is plotted to the CBF values for voxel clusters with a significant relationship between plasma exposure and CBF.

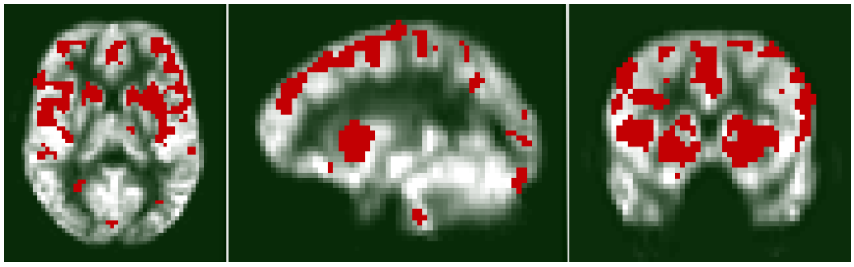

Figure 1. Non-linear regression showing voxels with significant relation between d-amphetamine exposure and CBF changes ($p<0.05$, cluster size threshold 35).

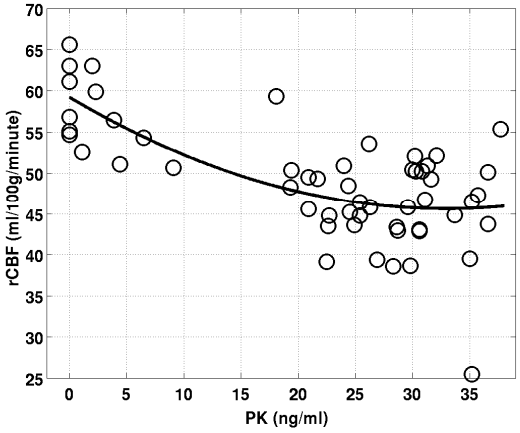

Figure 2. Individual CBF values extracted from voxel clusters with significant relationship between plasma exposure and CBF using 2nd order polynomial regression, plotted *vs.* plasma concentration.

Discussion: Expected changes were also seen in blood pressure and pulse rate for those subjects who received d-amphetamine. Compared to the placebo group a 20% change in the global CBF was observed in grey matter for the subjects that received d-amphetamine. The most significant reduction of cerebral blood flow was shown in the basal ganglia and frontal and insular cortex using voxel based analysis. A relation between d-amphetamine exposure and CBF response could be found using PK/PD modeling. The model predicted a 15% decrease in the mean CBF at a plasma concentration of 30 ng/ml for the whole brain grey matter. In this study we have shown that perfusion measurements by PCASL technique can be sufficiently robust to differentiate the neurological response between the groups receiving a placebo and a real d-amphetamine dose. Quantitative and repetitive CBF measurements are not only useful for clinical diagnosis, but also very important for monitoring treatment response in longitudinal studies and clinical trials.

References: [1] T-Q. Li et al MRI 18(5):503-512 (2000), [2]T-Q. Li et al. NeuroImage 12:442-451 (2000), [3]T-Q. Li et al. JMRI 12(5):757-762 (2000), [4] SL. Talagala et al. Proc ISMRM p.1916 Toronto (2008), [5] TQ. Li et al. Proc ISMRM p.1753 Stockholm (2010), [6] Y. Chen et al. Proc ISMRM p.720 Stockholm (2010), [7] J. Ren et al. Synapse 63(9):764-772 (2009), [8] Ze Wang et al. MRI 26(2):261-269 (2008)