Response to Donepezil Challenge in Rat Brain by rCBV-based phMRI

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Introduction

Pharmacological MRI (phMRI) is a usefull tool to study the response of the brain to pharmacological stimulation. A variety of drugs has already been studied and characterized by this method [1-5]. Here we use rCBV-based phMRI to study the rCBV response to the application of donepezil, an acetylcholinesterase inhibitor (AChEI) used to treat the symptoms of mild cognitive impairment (MCI) in Alzheimer's disease. The results are compared to responses of the reference compounds nicotine and the vasodilator acetazolamid (ACZ).

Animal Handling and Methods

MRI data were acquired on a Biospec 47/40 scanner (Bruker BioSpin, Ettlingen, Germany) at 4.7 Tesla. Male wistar rats (250-280g) were anaesthetized through continuous inhalation of 1.5-1.7% isoflurane (in 70:30 N_2O:O_2). Following a pilot scan and a high resolution anatomical reference scan phMRI was performed using a RARE protocol (TE_{eff}/TR 94.5/5000 ms; FOV 2.8 x 2.8 cm²; 24 slices, thickness 0.75 mm, RARE factor 16; matrix 192x96, 1 image/min, 80-100 images in total). Sensitization to rCBV was achieved after a baseline period of 15 images by intravenous administration of the blood-pool agent Endorem (Guerbet) at a dose of 25 mg iron oxide/kg. Following a 25 minutes precontrast period after Endorem administration animals received an intravenous bolus of either of the following drugs: Donepezilhydrochloride 0.2 or 0.5 mg/kg, nicotine (free base) 0.14 mg/kg, ACZ 66 mg/kg, saline (control). Drugs were dissolved in saline, application volume was 2 ml/kg.
Image data were mainly analysed using the AFNI program collection [7]. Analysis steps of phMRI data consisted of motion correction, pixelwise trend correction [6] and remapping to yield a ΔrCBV image series. Anatomical data were aligned and normalized to a reference data set, on which a set of regions-of-interest (ROIs) was defined. Subsequently ΔrCBV image data underwent the same geometrical transformation as the anatomical data to match the template. Time-course data were generated as an average of pixel values over each respective ROI. Quantification of peak response was done by averaging over a period of 5 minutes around the time point of the highest initial response.

Results

Fig. 1 shows the time course of the ΔrCBV response after challenge with Donepezil and ACZ extracted in a cortical ROI (drug application time = 0). Response to donepezil shows clear dose dependence with a pronounced peak response within the first 10 minutes after application followed by a longer response of lower amplitude. Challenge with ACZ shows an acute response with a similar intensity as one obtained for the high-dose donepezil stimulation but with a larger time constant.
In **fig. 2** peak response data for a set of ROIs are shown for the respective challenge. Dose-response relation for stimulation with donepezil are most dominant in cortical regions. Stimulation with nicotine also gives strong responses in cortical areas, while the ACZ challenge shows among the highest responses in all regions. The saline control group showed no significant responses in any analysed ROI.

Fig. 1

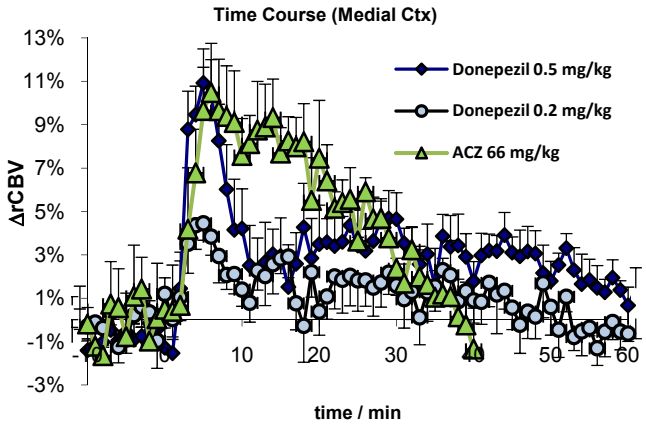
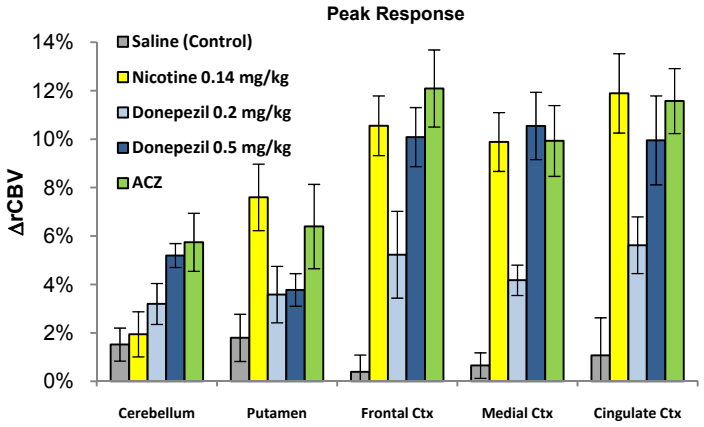


Fig. 2



Conclusion

Dose-response relation for pharmacological stimulation with donepezil was revealed by ROI-based analysis of rCBV time course data. Peak response data are in good agreement with literature data obtained for stimulation with the AChEI rivastigmine [4] with the latter exhibiting a longer lasting response of a plateau type. Comparison to ACZ challenge, which is considered to be a test for the cerebral vascular reserve, suggests that rCBV responses at high dose of donepezil and nicotine are near the maximum level for the species under investigation.

References

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