Characterization of D_2 antagonist sulpiride effects on cerebral hemodynamics in a conscious rabbit with fMRI

H. Zhang[1], T. Ji[1], R. Leslie[2], P. D. Hockings[3], D. Templeton[2], A. M. Wyrwicz[4]

[1]Center for Basic MR Research, ENH Research Institute, Evanston, IL, United States, [2]Neurology CEDD, GlaxoSmithKline, The Frythe, Welwyn, United Kingdom, [3]MRI group, RIRP CEDD, GlaxoSmithKline, The Frythe, Welwyn, United Kingdom, [4]Center for Basic MR Research,ENH Research Institute, Neuroscience Institute, Northwestern University, Evanston, IL, United States

Introduction

The substituted benzamide sulpiride is used to treat negative symptoms of schizophrenia at low doses, and florid positive symptoms at high doses. In the first case, sulpiride blocks presynaptic dopamine D_2/D_3 receptors, antagonizing dopamine negative feedback mechanisms, thus enhancing dopaminergic transmission; at higher doses it binds to postsynaptic receptors and reduces dopaminergic transmission(1). Given the long half-life of the drug in plasma, acute sulpiride administration should result in a longlasting alteration of dopamine function which may mediate glutamatergic and GABAergic neuronal function. We examined the spatial distribution of sulpiride-induced BOLD changes in conscious rabbit brain using sequential T_2*-weighted single shot EPI (ssEPI). Presented are drug-induced cerebral activation maps and the corresponding BOLD signal profiles for low and high doses of sulpiride.

Methods

All animal experiments were carried out under IACUC approved protocols. Dutch-belted female rabbits (2-2.5 kg) were used in this study. Stereotaxic implantation of restraining headbolts was accomplished under general anesthesia, then after recovery, rabbits were habituated to the restraining setup before MRI experiments were performed. 2 mg/kg or 20 mg/kg sulpiride doses were introduced by bolus injection (over ~2 min) via an ear vein catheter to a conscious, behaving rabbit.

MRI measurements were performed on a 4.7 T GE-OMEGA CSI system using a circular surface coil (40 mm I.D. and 53 mm O.D.). Head positioning in the magnet was adjusted using imaging profiles from multi-slice high-resolution images. BOLD signal response to the drug was followed over time using a multislice GRE ssEPI sequence with FOV 52.5 mm, TR 2 s, effective TE 29 ms, 4 scans, and 2 ms sinc-shaped pulses. Sixteen 2 mm thick slices in the coronal plane were acquired with 0.94 x 0.94 mm^2 in-plane resolution and 1 min temporal resolution. 20 sequential images were collected prior to the injection of sulpiride followed by 310 sequential EPI images, all acquired continously.

Imaging data were analyzed on a Sun Sparc2 workstation using software written in-house in IDL (Research Systems, Inc.). Activation maps were generated and color-coded based on the type of BOLD response. They were overlaid on anatomical images with 0.23 x 0.23 mm^2 in-plane resolution.

Results and discussion

The temporal patterns of BOLD signal changes for selected pixels are shown in Fig. 1 for the two doses studied. The brain regions selected included cerebral cortex (prefrontal, parietal, temporal, and visual), hippocampus, striatum and habenula. For the 2 mg/kg dose, negative BOLD responses that were slow in onset were observed in all cortical regions examined, with maximum signal changes of 15-30% occurring ~ 150 min after sulpiride administration. Only positive BOLD responses were observed in sub-cortical structures, again starting ~ 150 min after the drug injection, with maximum amplitudes of 20%. A different pattern was seen with the 20 mg/kg dose. With the exception of prefrontal cortex, only positive BOLD responses were detected in both cortical and sub-cortical loci immediately following injection of sulpiride, with maximum signal changes of 20 %. Prefrontal cortex showed negative responses with a slow onset, similar to those seen at the lower dose of sulpiride.

Color-coded activation maps for the 2 mg/kg dose of sulpiride are shown in Fig. 2, with blue representing negative, and red positive hemodynamic responses. The six brain images span the prefrontal cortex to the mid brain.

Decreases in BOLD signal observed in the prefrontal cortex are consistent with decreases in spontaneous activity of prefrontal cortical neurons observed after iontophoretic application of dopamine(2). The positive BOLD responses observed in the striatum are consistent with increased striatal neuronal activity under similar conditions(3).

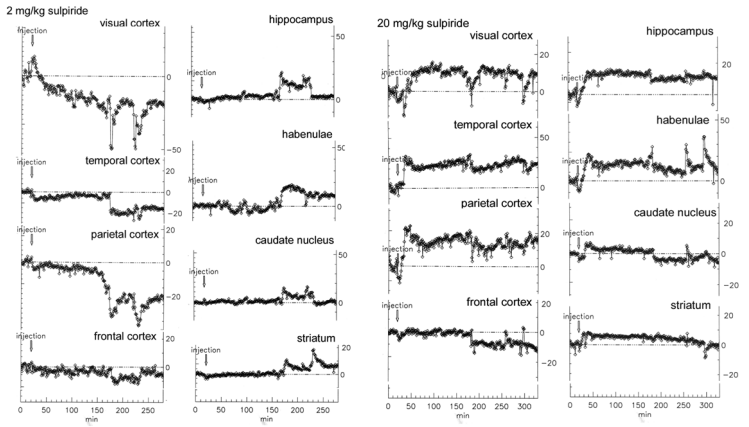

Fig. 1 Temporal patterns of BOLD responses to 2 mg/kg and 20mg/kg doses of i.v. sulpiride in conscious rabbit brain in selected anatomical regions.

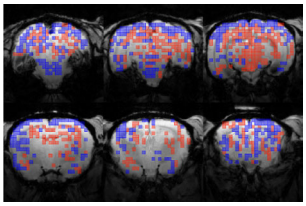

Fig.2 Color-coded activation maps for 2 mg/kg of sulpiride administered i.v to a conscious rabbit. Blue represents negative and red positive responses.

Conclusions

We have applied the fMRI technique to explore dose-dependent effects of the D_2/D_3 receptor antagonist sulpiride on brain hemodynamic responses in conscious rabbits. The results suggest that different temporal patterns of BOLD response occur in the brain depending upon drug dose and anatomical location. These data suggest that this approach in a conscious animal model can be used to evaluate the action of potential therapeutic agents in the CNS. (*This work was supported by GlaxoSmithKline*).

References

(1) G. Giovanni, M. Vincenzo, V. Matteo, E. Esposito, *J. Pharmaco. Exp. Therapeu.*, 287:51-57(1998).

(2) S. Pirot, R. Godbout, J. Mantz, J.P. Tassin, J. Glowinski. Neuroscience, 49:57-865(1992).

(3) K. Takada, T. Murai, T. Kanayama, N. Koshikawa, Br. J. Anaesth., 70:181-185(1993).