Highly-selective dopamine D3 receptor antagonist potentiates phMRI response to acute amphetamine challenge in the rat brain

A. J. Schwarz[1], A. Gozzi[1], T. Reese[1], S. Bertani[2], V. Crestan[2], J. J. Hagan[3], C. A. Heidbreder[4], A. Bifone[1]

[1]Neuroimaging, GlaxoSmithKline Psychiatry Centre of Excellence for Drug Discovery, Verona, Italy, [2]Laboratory Animal Sciences, GlaxoSmithKline, Verona, Italy, [3]Biology, GlaxoSmithKline Psychiatry Centre of Excellence for Drug Discovery, Verona, Italy, [4]Neurochemistry and Drug Dependence, GlaxoSmithKline Psychiatry Centre of Excellence for Drug Discovery, Verona, Italy

Introduction

The D_2 family of dopamine receptors (D_2, D_3 and D_4) is currently of therapeutic interest, being implicated in schizophrenia and being the primary site of action of most antipsychotic drugs. The highest concentrations of the D_3 subtype present a focal distribution in limbic brain areas known to be associated with cognitive and emotional functions, including the nucleus accumbens shell, the islands of Calleja and the ventral palladum, with lower densities in the striatum and elsewhere [1]. The precise biological role of the D_3 receptor, however, remains to be fully elucidated. The selective D_3 antagonist SB-277011-A shows high affinity and 100-fold selectivity for D_3 over D_2 receptors and other ion channels [2]. Most *in vivo* D_3 receptor studies to date have focused on behavioural or point-sampled neurochemical readouts; however an indication of the effects of selective D_3 antagonism *in vivo* throughout the brain would help elucidate the mechanisms of action.

Methods

17 male Sprague-Dawley rats (250-350g) were scanned under halothane anaesthesia (maintenance level 0.8%) and artificial ventilation. MRI 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 256 time points using the RARE sequence [3]: matrix 128x128; FOV 40mm; slice thickness 2mm; 8 contiguous coronal slices; TE_{eff}=110ms; TR=2700ms; δt=10s. 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. Subsequently, either SB-277011-A (20mg/kg; n=8) or vehicle alone (beta-hydroxypropyl-cyclodextrin; n=9) was administered i.p., and then 30 minutes later a 1mg/kg i.v. amphetamine challenge was delivered. Inter-subject co-registration and pixel-wise group comparisons were performed using AFNI. Time courses were examined from 3x3 pixel regions of Interest (ROIs) in areas previously studied using neurochemical methods (accumbens, cingulate, striatum), as well as areas identified *a postiori* by the image-based analysis.

Results

The response to the amphetamine challenge was *increased* in the SB-277011-A group compared with controls. The distribution of the increased response is indicated in the thresholded group comparison map in Figure 1(a). The regions affected include the nucleus accumbens, and ventral palladium/islands of Calleja – key D_3-rich structures. However, there was also an increase in the caudate putamen, in midline ventral and lateral thalamic areas, in a region encompassing to the caudate linear nucleus of the Raphe, lateral regions encompassing the perirhinal and entorhinal cortex, and in the anterior cingulate and retrosplenial cortices. The nucleus accumbens (Figure 1(b)), caudate putamen, cingulate cortex, and the centromedial thalamic nucleus represent regions of normally weak response that are greatly potentiated by SB-277011-A.

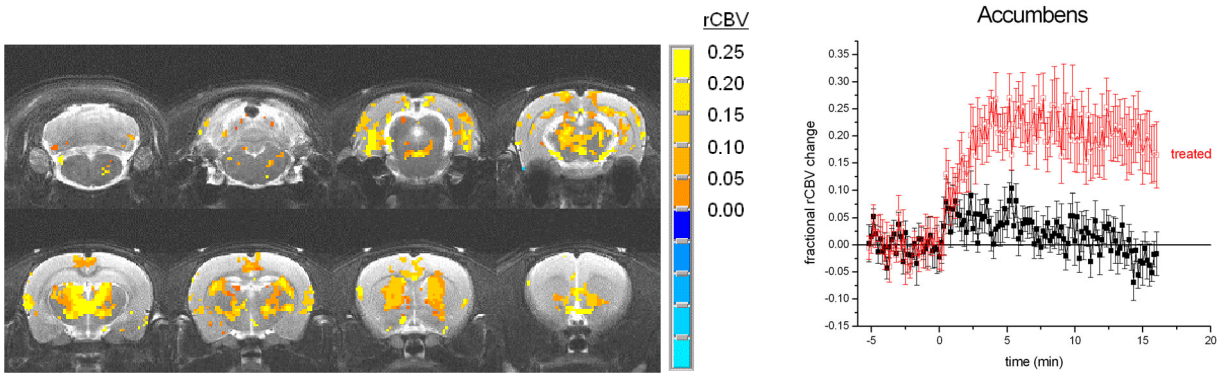

Figure 1: (a) Group comparison between SB-277011-A and control groups, 1-11 minute post-challenge vs 4-minute baseline, p_u<0.01. Red/yellow indicate an increased response in the SB-277011-A group. (b) Group time courses (mean±SEM) from the accumbens ROI.

Discussion

PhMRI response to amphetamine challenge in the rat, as measured by rCBV changes, was increased by acute pre-treatment with SB-277011-A in a regionally specific manner, but regions of activation extended beyond the distribution of the highest concentrations of the D_3 receptor. This is in contrast to the attenuation in rCBV response that occurs in the case of pre-treatment with D_1 antagonists [4]. An increased dopaminergic response following D_3 blockade is consistent with the DA D_3 receptor mediating an inhibitory action on extracellular DA concentration, either via autoreceptors regulating DA synthesis pre-synaptically [5], or mediating an inhibitory action in a homeostatic balance with excitatory actions of D_1 and D_2 receptors, analogously to what has been observed in behavioural studies [6].

References

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