Effect of the Novel Anti-Depressant Agomelatine determined by pharmacological MRI in the rat.

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Introduction

Agomelatine (*Valdoxan®*) is a novel, clinically effective antidepressant that behaves as an agonist at melatonin (MT_1 and MT_2) sites and, at higher concentrations, as an antagonist at 5-HT_{2C} receptors[1,2]. We have previously shown how pharmacological-challenge fMRI (phMRI) can be used to image 5-HT_{2C} activity and antagonism in rats[3]. Based on this previous study, here we analyse the direct effects of 3 doses of agomelatine with antidepressant properties in animal models on Blood Oxygenation Level Dependent (BOLD) signal in several rat brain areas.

Methods

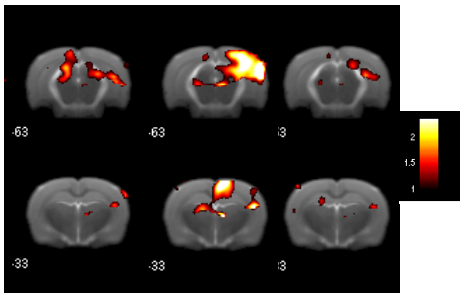
Sprague-Dawley male rats were anaesthetized with α-chloralose (n=6 rats per group). Data were obtained on a 7T magnet using a T_2*-weighted 2D gradient echo sequence (TR/TE = 172 ms/15ms, matrix 128 x 64, 4 averages, 11 coronal 1mm thick slices). A total of 24 volumes were acquired. Agomelatine at doses of 10, 20, 40 mg/kg or vehicle (hydroxyethylcellulose 1%) was injected (i.p.) during acquisition of volume 12. Data were analyzed using the p-block method[3,4] in which time-binned data post-infusion were compared to pre-infusion. Second level analysis compared agomelatine infusion to vehicle using ANOVA. Images were realigned, normalized and interpreted using a rat brain stereotaxic template provided with permission by Schwarz[5].

Results

We detected significant effects of agomelatine on BOLD signal in a number of brain areas, including motor, sensory and cingulate cortex, and thalamic and limbic areas including hippocampus and caudate. Both positive and negative BOLD responses were seen with approximately equivalent numbers of voxels activated or deactivated at a threshold of p(unc)<0.01. There was a striking dose-dependence, with much more activity detected at 20 mg/kg compared to either 10 or 40 mg/kg. This is demonstrated in Fig.1 in which significant positive effects of agomelatine are shown. There is marked cortical and thalamic activation detected at 20 mg/kg which is either attenuated or absent at the other doses. The number of significantly activated voxels in the brain was higher at 20 mg/kg compared to the other doses :

Voxels / dose (mg/kg)	**10**	**20**	**40**
# +ve BOLD	66	344	55
# -ve BOLD	162	221	64

More brain areas showed significant activation at 20 mg/kg compared to the other doses (16 compared to 5 or 6 regions) and the *Z*-score and BOLD effect size were uniformly larger in commonly activated areas at the intermediate dose.
Fig.2 displays % BOLD signal change in one brain area – the right visual cortex. These results exemplify the 'inverted U' shape of the dose response to agomelatine.



A10-Veh A20-Veh A40-Veh

Fig.1 Example images showing significant BOLD signal increase (false-colour) following agomelatine (A) administration at 3 doses, overlaid onto anatomical images of the rat brain.

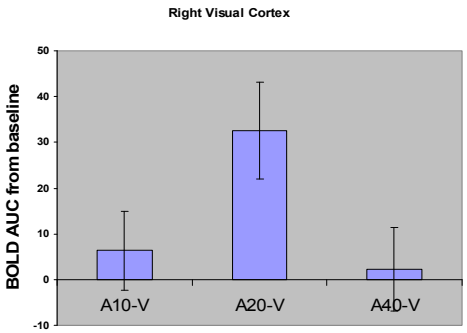


Fig.2 % change in BOLD signal following agomelatine administration at 3 doses relative to vehicle infusion. Mean and standard deviation are shown for a region of interest in right visual cortex.

Conclusion

These data demonstrate that agomelatine can induce significant changes in brain activity leading to both increases and decreases in regional BOLD signal. These data do not indicate whether the effects are mediated via melatonin or 5HT_{2C} receptors, but it is likely that both receptors are involved, possibly in different brain regions.

References

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