Characterization of a 5-HT2C antagonist profile of Agomelatine using challenge phMRI in the rat

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PURPOSE Agomelatine (S 20098) is a novel clinically active antidepressant drug. Agomelatine is a potent melatonergic agonist at MT₁ and MT₂ sites and it also acts in vitro as a serotoninergic antagonist of the 5-HT₂C receptors. The antidepressant activity of agomelatine needs the combination of melatonin agonist activity and 5-HT₂C serotoninergic antagonist properties.

In the present study selective 5-HT₂C agonist Ro60-0175 was used to test the robustness of brain activation by 5-HT₂C antagonists (Agomelatine and SB 242084) in vivo using challenge phMRI. The aim of the study was to identify areas in which Ro60-0175-induced activation is modulated by pre-treatment with either agomelatine, or a specific 5HT₂C antagonist (SB 242084). This allowed us to detect the brain regions in which agomelatine modulates serotoninergic activity and to test the hypothesis that this is due to direct interaction with 5-HT₂C receptor subtypes.

METHODS ANIMAL PROTOCOL: Sprague-Dawley male rats (250 ± 40 g, Charles River Laboratories, Inc., Sandwich, UK) were anaesthetized with α-chloralose and introduced into the bore of the 7T magnet. Temperature and respiration rate were monitored.

DRUGS: 5-HT₂C antagonists (1. Agomelatine: 10, 20 and 40 mg/kg (I.R.I.S.); 2. SB 242084: 10 mg/kg) and vehicle (HEC 1%). 5-HT₂C agonist (Ro60-0175: 3 mg/kg) and vehicle (saline + Tween 80).

MR PROTOCOL: Data were obtained on a 7T horizontal-bore magnet (Magnex Scientific Ltd., Abingdon, UK) interfaced to a SMIS console (Surrey Medical Imaging Systems Limited, Surrey, UK) with a transmit-receive surface coil. For functional images, a T₂*-weighted 2D gradient echo sequence was used: TR/TE = 172 ms/15 ms, a matrix 128 x 64 x 4, 11 coronal slices of 1 mm thickness. A total of 72 volumes were acquired. Antagonist or vehicle was injected (i.p.) during acquisition of volume 12, and agonist or vehicle was injected (s.c.) during acquisition of volume 24.

Data were analyzed using the p-block method. Drug and time interactions were analyzed using a three-way ANOVA (agonist x antagonist x time). Any significant differences in the antagonist x agonist interaction indicating an antagonist effect on the Ro60-0175-induced BOLD signal. F-statistical parametric maps were overlaid onto an anatomical template image, with a threshold level of p<0.01 uncorrected. Paxinos and Watson (1998) atlas figures were used to identify the activated brain areas.

RESULTS SB 242084 and agomelatine significantly attenuated the BOLD response to Ro60-0175 in the following brain areas: cortex, midbrain (Fig. 1), hippocampus, thalamic nuclei, pons and cerebellum. Figure 1 shows an example of the BOLD signal changes in the midbrain, the % signal change from pre-infusion baseline is shown as total area under the curve in a single voxel at the position of the crosshairs (b).

In a number of brain regions, the two antagonists have similar effects, with differences in magnitude presumably indicating differing potency. In these brain areas we can conclude that the actions of agomelatine are due to 5HT₂C antagonism.

CONCLUSIONS This study has provided evidence for 5HT₂C antagonist activity of agomelatine in vivo, and has shown a convincing dose response in most of the brain regions in which it is active.

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