EVIDENCE THAT 5-HT$_{2A}$ RECEPTOR FUNCTION IS LINKED TO GENETIC VARIATION IN 5-HT TRANSPORTER EXPRESSION

K.A. Jennings$^1$, M.E. Sprakes$^1$, W.J. Sheward$^2$, A.J. Harmar$^2$ & T. Sharp$^1$  
$^1$University Department of Pharmacology, Mansfield Rd, Oxford OX1 3QT, $^2$Centre for Neuroscience Research, School of Biomedical Sciences, Edinburgh EH8 9JZ

5-HT$_{2A}$ receptors are important in the effects of 5-hydroxytryptamine (5-HT) on neural circuitry and linked to key brain functions and neuropsychiatric disorders. Molecular imaging studies report large inter-subject variability in 5-HT$_{2A}$ receptor levels that may underlie individual differences in brain function and disorder vulnerability (Adams et al., 2004; Bhagwagar et al., 2006). The origin of this variability is unclear but genetic factors are likely. One factor may be expression of the 5-HT transporter (5-HTT) gene as 5-HT$_{2A}$ receptor function and expression are decreased in 5-HTT null mice (Qu et al., 2005). Here we measured 5-HT$_{2A}$ receptor function and expression in transgenic 5-HTT overexpressing mice (Jennings et al., 2006).

5-HT$_{2A}$ receptor function was tested in transgenic and wildtype mice (CBAxC57Bl6J, 3-9 months) by measuring i) regional brain expression of the immediate early gene Arc and ii) head twitches, elicited by the 5-HT$_2$ agonist, DOI (2,5-dimethoxy-4-iodoamphetamine hydrobromide; 2 mg kg$^{-1}$ i.p.). Wildtype mice (male C57Bl6J) were used to test the effect of the 5-HT$_{2A}$ antagonist MDL 100907 (0.3 mg kg$^{-1}$) on DOI responses. For Arc, DOI injected mice were killed by cervical dislocation after 1 h, prior to measuring Arc mRNA using in situ hybridisation (Pei et al, 2004). Head twitches were counted over 15 min immediately after DOI. 5-HT$_{2A}$ receptor binding and mRNA were measured in brain regions (including frontal cortex, hippocampus, striatum) of treatment naïve transgenic and wildtype mice using receptor autoradiography ($^3$H-ketanserin) and in situ hybridisation. Data were analysed using Student’s unpaired t-test or ANOVA with Bonferroni post hoc testing as appropriate.

In wildtype mice, both the increase in regional brain Arc mRNA and head twitches elicited by DOI, were abolished by MDL 100907 (P<0.05). DOI evoked a significantly greater (P<0.05) increase in Arc mRNA in transgenic compared to wildtype mice in several cortical regions (cingulate 178±19 vs 121±10; motor 289±44 vs 170±26; orbital 230±25 vs 134±16 %). DOI also induced a greater increase in head-twitches in transgenic compared to wildtype mice (44±4 vs 27±4 twitches/15 min). The regional distribution of $^3$H-ketanserin binding and 5-HT$_{2A}$ mRNA was similar between transgenic and wildtype mice and levels did not differ between genotype in any region.

In summary, these data show that 5-HTT overexpressing mice exhibit greater 5-HT$_{2A}$ receptor-mediated responses compared to wildtype mice, but these changes were not accompanied by increased 5-HT$_{2A}$ receptor expression. The data support the idea that 5-HTT expression is a genetic determinant of variability in 5-HT$_{2A}$ receptor function but matching changes in 5-HT$_{2A}$ receptor expression were not detected in the model used.


Funded by a MRC studentship (KJ) and EC FP6 Integrated network (LMSH-CT-2004-503474).