Complete abolition of stereotypic rearing and mGluR5 up-regulation in chronically methamphetamine but not cocaine treated A_{2A} receptor knock-out mice

SR Smith, Zanos P, Yoo JH, Wells LA, Hourani SMO, Kitchen I, Bailey A. University of Surrey, Guildford, UK

Repetitive use of psychostimulants, such as cocaine and methamphetamine (MAP) induce hyperactivity and characteristic repetitive stereotypic-like behaviours which are hypothesised to be a manifestation of a psychotic-like state [1] and in rodent models can manifest as vertical rearing behaviour. A_{2A} receptors ($A_{2A}R$) have been implicated in schizophrenia [2] and in drug addiction [3], however their involvement in repetitive stereotypic-like effects of psychostimulants is unclear. There is also emerging evidence which point towards the existence of key interactions between $A_{2A}R$, mGluR5 and D_2 receptors in the brain and this may influence behavioural and neurochemical effects [4].

To determine if $A_{2A}R$ are involved in these behavioural effects of psychostimulants, male CD-1 wild-type (WT) and adenosine $A_{2A}R$ knock-out (KO) mice (n = 6–8) were treated with either a chronic 'binge' cocaine (3 x15mg/kg/day cocaine, s.c, 14 days) or MAP (1mg/kg/day, i.p., 10 days) administration paradigm and paired with saline controls (4ml/kg). Horizontal and vertical activity was recorded daily via infra-red bream break equipment throughout the duration of the experiment.

Analysis by 3-way ANOVA showed that deletion of the $A_{2A}R$ had no effect on the horizontal locomotor response induced by either cocaine or MAP ($P>0.05$). However, persistent and marked MAP-induced rearing behaviour evident in WT mice over the study duration (28979.3 ± 4626 MAP treated vs. 3919 ± 963.5 beam-breaks in saline-treated) was profoundly reduced in KO animals (11381.2 ± 1935 MAP-treated vs. 6830 ± 2864 beam-breaks in saline-treated) (genotype x treatment interaction, $P<0.01$). No genotype effect was observed in cocaine-treated animals ($P>0.05$). To determine neurochemical changes that might be associated with these effects we carried out D_2 and mGluR5 receptor binding in the brains of these animals using quantitative autoradiography. A marked up-regulation of mGluR5 binding that was observed in forebrain regions of MAP-treated WT mice (nucleus accumbens: core 138.6 ± 7.6, shell 128.1 ± 8.57 MAP-treated; core 103.0 ± 8.8, shell 87.8 ± 6.4 saline-treated), was absent in KO animals (nucleus accumbens: core 100.6 ± 6.3, shell 91.8 ± 11.1 MAP-treated; core 112.7 ± 9.1, shell 101.2 ± 13.4 saline-treated) (genotype x treatment interaction, $P<0.001$). No effect on D_2 or mGluR5 binding was observed in either WT or KO cocaine-treated animals ($P>0.05$).

These results suggest that $A_{2A}R$ are an absolute requirement for the induction of rearing behaviour and mGluR5 up-regulation in response to MAP but not cocaine. These findings have profound implications in the understanding and management of stereotypic behavioural and psychosis-like effects of MAP.

1. Robinson, T.E. and K.C. Berridge, *Brain Res Brain Res Rev*, 1993. **18**(3): p. 247-91.

2. Ferre, S., *Psychopharmacology* (Berl), 1997. **133**(2): p. 107-20.

3. Ferre, S., et al., *Prog Neurobiol*, 2007. **83**(5): p. 332-47.

4. Cabello, N., et al., *J Neurochem, 2009*. **109**(5): p. 1497-507.