Region specific up-regulation of metabotropic mGlu5 receptors in brains of A2A receptor knockout mice following chronic morphine administration and naloxone-precipitated morphine-withdrawal

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There is a substantial amount of evidence showing that mGlu5 receptors (mGluR5) play an important role in opioid addiction. Chronic morphine treatment and long term withdrawal from such treatment up-regulates mGluR5 binding in brains of mice (Bailey et al., 2009). Functional interactions between mGluR5 and A2A adenosine receptors have been implicated in the striatum and hippocampus (Tebano et al., 2005, Nishi et al., 2003) and are hypothesised to play an important role in opioid addiction and withdrawal.

To further investigate mGluR5-A2A receptor interactions, we carried out quantitative autoradiographic mapping of the mGlu5 receptor labelled with [3H]MPEP in brains naïve male CD-1 wild-type (WT) and adenosine A2A receptor knockout (KO) mice. To assess the interaction in opioid addiction, WT and KO mice were treated with a chronic “intermittent” saline or escalating dose morphine paradigm (2x20 mg/kg/day on days 1 and 2, 2x40 mg/kg/day on days 3 and 4, 2x80 mg/kg/day on days 5 and 6 and 2x100 mg/kg/day on days 7 and 8 at 8 h intervals; i.p.) and killed 3 hour post final injection. To investigate naloxone precipitated withdrawal, a parallel group of mice were treated with the same chronic morphine administration paradigm, following which naloxone (1mg/kg i.p.) was administered 2 hours after the last injection to precipitate withdrawal. Mice were killed 30 minutes following naloxone administration.

A significant effect of genotype (P<0.01) and region (P<0.001) was observed in naïve WT and KO brains (2-way ANOVA), and a significant down-regulation of mGluR5 binding in the nucleus accumbens (Acb) core in KO animals (P<0.01, LSD Post-Hoc test). Chronic morphine treatment caused a significant KO-specific down-regulation of mGluR5 binding in the Acb (P<0.05, LSD Post-Hoc test) and KO-specific up-regulation of mGluR5 binding in the thalamus and hypothalamus (P<0.05, LSD Post-Hoc test). This trend was observed in KO mice following naloxone-precipitated withdrawal, and a significant KO-specific up-regulation of mGluR5 was observed in the hippocampus (P<0.01, LSD Post Hoc test). Additionally, there was WT-specific up-regulation of mGluR5 receptors in Acb core following naloxone precipitated withdrawal.

This data is consistent with the hypoglumatamergic striatal profile of naïve KO mice (Dassesse et al., 2001) and provides evidence for a role of A2A in region-specific direct and indirect regulation of mGluR5 binding in the presence of morphine. Given the key roles of mGluR5 and hippocampal plasticity in inhibitory learning, dysregulation of the A2A-mGluR5 interaction may contribute toward the development of aversive learning during withdrawal. This data provides direct evidence for an mGluR5-A2A receptor interaction in vivo, which may have implications for the development of opioid tolerance and addiction.

BAILEY, A., VIEGAS, V., MARTIGNONI, E. & KITCHEN, I. 2009. Withdrawal from chronic morphine, but not cocaine induce marked upregulation of mGluR5 binding in the mouse brain. pA2online.org, 7.
