Interaction between 6-chloro PB and CCPA on [^{35}S]GTPγS binding in rat striatum

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Substantial evidence suggests that adenosine and dopamine receptors antagonise each other at different levels in the CNS (Franco *et al*, 2000). This study investigates possible interactions between A_1 and D_1 receptors at the level of [^{35}S] GTPγS binding in rat striatum, a region known to co-express both receptors.

G-protein stimulation was measured by incubating rat striatal membranes with drugs and [^{35}S] GTPγS, as previously described (Roberts *et al*, 2004), with minor modifications. The A_1 agonist CCPA stimulated [^{35}S] GTPγS binding with an EC_{50} of 15 nM and an E_{MAX} of 63% increase over basal. The effects of CCPA were significantly reduced by the A_1 antagonist DPCPX ($p<0.01$, 1-way ANOVA). The D_1 agonist, 6-chloro PB (6-Cl PB), and partial agonist, SKF38393, also stimulated [^{35}S] GTPγS. Their EC_{50} and E_{MAX} values were: 6-Cl PB: 300 nM and 90%; SKF38393: 598 nM and 63%. However, despite the fact that these agonists behaved in a manner consistent with their relative intrinsic activities at D_1 receptors, their effects on [^{35}S] GTPγS binding were not blocked by the D_1 antagonist SCH23390. To investigate possible interactions between A_1 and D_1 receptors, the responses to CCPA and 6-Cl PB were examined in the presence of antagonists and agonists for the other receptor. SCH23390 did not alter the response to CCPA and DPCPX did not alter the response to 6-Cl PB. The combination of 1 nM - 100 μM 6-Cl PB with 1 μM CCPA resulted in a parallel upward shift of the 6-Cl PB concentration-effect curve, consistent with a strictly additive effect. However, combining 1 nM - 100 μM CCPA with 1 μM 6-Cl PB resulted in a non-parallel upward shift of the CCPA concentration effect curve. Analysis of the data by 2-way ANOVA revealed a significant interaction ($p<0.001$) between treatment and concentration, such that low concentrations (1-10 nM) of CCPA had a greater than expected effect in the presence of the D_1 agonist.

These data indicate that the D_1 agonist 6-Cl PB stimulates the binding of [^{35}S] GTPγS in rat striatal membranes via an A_1- and D_1-independent target. When this target is co-activated with A_1 receptors the stimulation of G-proteins is greater than additive.

Franco R *et al*. (2000) *Neuropsychopharmacology* 23, S50-S59.
Roberts DJ *et al*. (2004) *Mol Pharmacol* 66, 1573-1579.