THERAPEUTICAL IMPLICATIONS OF INTRAMEMBRANE RECEPTOR/RECEPTOR INTERACTIONS AMONG DOPAMINE RECEPTORS

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Over the last decade, numerous studies have demonstrated that G-protein coupled receptors (GPCRs) can form homo- and heterodimers. Their significance for drug discovery and characterisation is exemplified by findings that receptor heterodimerization can markedly change drug affinities and efficacies in a ligand-dependent fashion (Angers *et al*, 2002; Agnati *et al*, 2003; Maggio *et al*, *2005*). Dopaminergic receptors have attracted particular interest inasmuch as heterodimerization has been shown for members of both the D_1/D_5 and $D_2/D_3/D_4$ receptor families which couple positively and negatively, respectively, to adenylyl cyclase (AC). Thus, heterodimers can be formed by: adenosine A_1 and D_1 receptors, adenosine A_2 and D_2 or D_3 receptors and somatostatin SST_5 and D_2 receptors. In addition, amongst dopaminergic receptors themselves, D_1 and D_2 heterodimers D_1 and D_3 heterodimers and D_2 and D_3 heterodimers have all been described. The existence of D_2/D_3 heterodimers is of particular interest since D_2 and D_3 receptors share a high degree of sequence homology and show similar ligand binding profiles and coupling patterns to cellular signals. Nonetheless, D_3 receptors couple less "robustly" to G-proteins than D_2 receptors and several selective antagonists differentiating D_3 and D_2 receptors have been described. We will present evidences that heterodimerization between dopamine D_2 and D_3 receptors changes substantially the pharmacology of dopaminergic drugs.