INFLUENCE OF COCAINE ON A2A AND D2 RECEPTORS: IN VIVO AND IN VITRO STUDIES

[1]Genedani Susanna, [1]Agnati Luigi F., [1]Filaferro Monica, [1]Carone Chiara, [2]Guidolin Diego, [3]Roberts David C.S., [4]Marcellino Daniel, [4]Fuxe Kjell

[1]Department of Biomedical Sciences, University of Modena and Reggio Emilia and [2]Department of Anatomy and Human Physiology[2], University of Padova, Italy;[3]Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA; [4]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Cocaine actions on A2A and D2 receptors (A2AR, D2R) have been studied in a vivo model of cocaine abuse and in a vitro model. In vivo studies: Effects of extended cocaine self-administration and its withdrawal (Marcellino et al., Brain Res. in press) have been studied on A2A and D2 receptor binding characteristics and expression in the nucleus accumbens and the anterior and posterior dorsal striatum of the rat. Biochemical binding techniques have been used with the D2-like receptor antagonist [3H]-raclopride and the A2AR antagonist [3H]-ZM241385 and immunoblots to study their expression. A substantial and significant increase in functional A2AR, but not in D2R, was observed in the nucleus accumbens immediately following 10 days of cocaine self-administration which returned to normal levels after 7 days of drug withdrawal. In contrast, in the posterior dorsal striatum significant reductions in A2A expression were observed immediately after cocaine self-administration. In cocaine withdrawal group, significant increases in the density and Kd value of D2-like antagonist binding sites were observed in the nucleus accumbens in the absence of changes in D2 expression, suggesting an up-regulation of D3 receptors. A2AR increases in the nucleus accumbens induced by cocaine may represent a compensatory up regulation to counteract cocaine induced increases in D2 and D3 signalling which is in line with its disappearance in the 7-day withdrawal group displaying increased reinforcing efficacy of cocaine. In vitro studies: Effects of cocaine on A2AR and D2R has been studied in CHO cells stably cotransfected with the two receptors. A2AR and D2R were visualised by means of immunocytochemistry. The effects of quinpirole (50μM) on A2AR and D2R densities and colocalization were evaluated at different time intervals after cocaine exposure. The exposure of cells to cocaine for 3 or 8 hours had no influence on A2AR and D2R densities but decreased the ability of D2R stimulation to internalise A2A^D2 receptor complexes. The observed cocaine effect on A2A/D2 heteromers trafficking might be explained by a direct interaction of cocaine with receptor(s) and/or adapter proteins and/or their lipid environment to maintain receptor complexes at the membrane level after quinpirole-induced D2 activation. Thus, cocaine addiction may in part be caused by a failure of internalization of D2R and a disruption of some A2A/D2 heteromers. Overall, the present data indicate that cocaine influences A2A/D2 heteromers both “in vivo” and “in vitro” and suggest that the pharmacological modulation of A2A transmission might be considered in treatment of cocaine addiction.