THE K-OPIOID RECEPTOR AGONIST U-69593 PREVENTS COCAINE-INDUCED DARPP-32 PHOSPHORYLATION AT THR34 IN THE RAT BRAIN

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DARPP-32 (dopamine- and cAMP-regulated phosphoprotein) is a potent endogenous inhibitor of protein phosphatase-1, which plays an important role in dopaminergic transmission. A large body of evidence supports the key role of DARPP-32-dependent signalling in mediating the actions of multiple drugs of abuse, including cocaine, which, when acutely administered, increases the Thr34 phosphorylation of DARPP-32 in the striatal and cortical areas. The purpose of our study was to investigate the alterations occurring in DARPP-32 activation after a single injection of cocaine, and the effects evoked by a pretreatment with the selective kappa-opioid agonist U-69593 in selected rat brain areas. Results showed that a single injection of cocaine induces a significant increase in DARPP-32 phosphorylation at Thr34 in the hippocampus (156.7±15.5% of control, $t = 3.346$, $P<0.01$), caudate putamen (178.4±35.0% of control, $t = 4.789$, $P<0.05$) and prefrontal cortex (236.3±44.7% of control, $t = 3.935$, $P<0.01$). In addition, pretreatment with the kappa opioid receptor agonist U-69593 prevented cocaine effects in all the investigated areas. No changes were observed in total DARPP-32 levels following all the treatments in the rat brain areas explored. These U-69593 actions appear to be consistent with the ability of kappa opioid agonists to attenuate many behavioural effects of cocaine, and our findings support the hypothesis that this class of drugs might act as functional antagonists of cocaine.