

ROLE OF CREB IN THE PRODYNORPHIN GENE EXPRESSION REGULATION BY MDMA

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Drug exposure causes complex adaptations at the molecular and cellular levels in the brain, including the reward circuitry (*Nestler, 2001*). An example of this plasticity is the activation of the transcription factor cAMP response element (CRE)-binding protein (CREB) in several regions following exposure to different drugs of abuse. Once phosphorylated, CREB can interact with CREB-binding protein and this complex binds to the CRE sequence located in the promoter region of genes such as prodynorphin.

We studied the effects of single and repeated injections of the serotonergic neurotoxin 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on the phosphorylated cAMP-response element binding protein (CREB) and on the gene expression of the opioid precursor prodynorphin in the rat brain.

Acute (8 mg/kg, intraperitoneally) and chronic (8 mg/kg, intraperitoneally, twice a day for 7 days) MDMA markedly raised, two hours later, CREB phosphorylation at SER 133 and prodynorphin mRNA levels in the Brain Stem, area rich in neurons containing serotonin.

Moreover, in the Ventral Tegmental Area, prominent in brain reward circuitry, acute MDMA induced a significant decrease in phospho-CREB, consistent with the down-regulation in prodynorphin mRNA already reported (*Di Benedetto et al., 2006*).

No changes in the phosphorylation of CREB at SER 133 have been observed in the other brain regions studied: Nucleus Accumbens, Prefrontal Cortex, Caudate Putamen.

These findings suggest the role of CREB in mediating the effects of drugs of abuse, such as 3,4-methylenedioxy-N-methylamphetamine, in some rat's brain regions. The phosphorylated CREB may in turn induce the up-regulation of the dynorphinergic system confirming the importance of the opioidergic mechanisms activated by addictive drugs.

References: Di Benedetto M, D'Addario C, Candeletti S, Romualdi P. Chronic and acute effects of 3,4-methylenedioxy-N-methylamphetamine ('Ecstasy') administration on the dynorphinergic system in the rat brain. *Neuroscience*. 2006; **137**: 187-196.

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