How does MDMA (Ecstasy) affect the Endogenous Opioid System?

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The 3,4-methylendioxymetamphetamine (MDMA, Ecstasy) causes complex adaptations at the molecular and cellular levels in the brain. MDMA acts primarily on the serotonin transporter, behaving as a substrate blocking the serotonin reuptake (Capela et al., 2009). Like most drugs of abuse, MDMA also increases the dopamine release in a dose-dependent way in the nucleus accumbens (NA) but also in the striatum, caudate putamen and hippocampus. Several studies suggested the involvement of the endogenous opioid system in the effects of MDMA (Robledo, 2010).

The present study aimed to investigate the effects of MDMA on the opioid system using two different experimental models. *In vitro* studies investigated the effects of MDMA on the opioid receptor gene expression. To this purpose, human neuroblastoma SH-SY5Y cells that constitutively express opioid receptors were used. Cells were exposed to 0.3, 0.6 and 1.2 mM MDMA for 24 h. Data showed a decrease of NOP and MOP gene expression following 0.3 and 0.6 mM MDMA exposure, and an increase following the exposure to the higher dose. MDMA induced no changes of KOP and DOP gene expression. The pretreatment with the NOP receptor antagonist, J113397 reversed the effect of the lower doses of MDMA the on the NOP gene expression, whereas it further increased the NOP upregulation induced by 1.2 mM MDMA cell exposure. The J113397 pretreatment also reversed the MOP gene expression alterations at the higher doses of MDMA exposure. The pretreatment with the MOP receptor antagonist Naloxone reversed the effect on MOP gene expression and also reversed the NOP gene expression changes induced by the two higher doses of MDMA. The present *in vitro* data demonstrated that MDMA cell exposure induces a significant alteration on NOP and MOP gene expression sparing the KOP and DOP ones; these findings suggest that the opioid receptors are differently affected by this drug of abuse. Moreover, data from NOP and MOP antagonist pretreatments indicate a possible functional interaction between these two receptors in the cellular mechanisms underlying MDMA effects.

For *in vivo* studies we performed acute (single injection, 8 mg/kg) or chronic (two injections a day for 7 days; 8 mg/kg) i.p. administrations of MDMA in the Male Sprague-Dawley rats. Animals were assessed for the locomotor activity. The opioid precursor prodynorphin and pronociceptin gene expressions were measured in the NA by the real-time PCR technique. Data showed an increase of mRNA prodynorphin levels after chronic MDMA treatments. In contrast, both acute and chronic MDMA treatments induced no changes of pronociceptin gene expression. Recent experimental observations suggested that epigenetic mechanisms may contribute to the modification of gene expression and therefore to long-lasting plasticity-related changes due to substances of abuse. To this purpose, the MDMA effects on the epigenetic modifications at the promoter regions of prodynorphin and pronociceptin genes have been investigated using Chromatin Immuno Precipitation technique. The following histone modifications have been studied: H3K4me3 and H3K9Ac (activating markers), H3K27me3 and H3K9me2 (repressive markers). Specific histone modification changes at the promoter regions of dynorphin and nociceptin genes have been observed following both acute and chronic treatments.

The increase of prodynorphin gene expression in the Na here reported is in agreement with analogous data observed following the cocaine exposure. Furthermore, epigenetic data contribute to clarify the mechanisms upstream of the above mentioned gene expression modifications. In conclusion, the *in vivo* data demonstrate selective MDMA-triggered changes of the endogenous opioid system in the NA, confirming the central role of this brain area in the processes underlying the addiction and defining opioid-related alterations.

Capela J.P. et al. (2009). *Mol. Neurobiol*. 39, 210-271.
Robledo P. (2010). *Current Drug Targets.* 11, 429-439.