ALTERED EXPRESSION OF METABOTROPIC GLUTAMATE RECEPTORS IN THE NUCLEUS ACCUMBENS DURING OPIATE DEPENDENCE AND WITHDRAWAL IN THE RAT

Modafferi Antonella M.E[1]., Diana Marco[2], Scaccianoce Sergio[1]

[1]Dept. of Human Physiology and Pharmacology - University of Rome La Sapienza;
[2] Dept. of Drug Sciences - University of Sassari

Multiple lines of research have demonstrated that the nucleus accumbens (NA) plays a crucial role in the mechanisms of drug addiction. Metabotropic glutamate (mGlu) receptors form a family of eight subtypes, subdivided into three groups. Group-I includes mGlu1 and -5 receptors; group-II includes mGlu2 and -3 receptors and group-III includes mGlu4, -6, -7 and -8 receptors. Emerging evidence indicates that mGlu receptors: i) regulate many behavioral actions of addictive drugs; ii) are involved in the synaptic adaptations that occur in response to chronic drug exposure, and iii) contribute to the aversive behavioral syndrome observed during withdrawal (1). Therefore, the aim of the present study was to evaluate the expression of mGlu1, –2/3, –4 and –5 receptors in NA and in the caudate putamen (Cpu) after acute (10 mg/kg), chronic (14 days) morphine treatment (from 10 to 140 mg/kg twice a day at escalating doses) as well as after 1, 3, 7 and 14 days of spontaneous withdrawal in the adult male Sprague Dawley rats. Western blot analysis was used to evaluate receptor density. mGlu1 and mGlu5 receptor expression in the CPu and in the NA was not affected by any of the experimental manipulation. On the contrary, mGlu2/3 receptors expression in the NA, but not in the CPu, was significantly increased at day 1, 3 and 14 of morphine withdrawal ($p<0.05$; $p<0.01$, Dunnett test). Regarding the effects on mGlu2/3 presynaptic receptors, which are on the afferent axon terminals in the NA, our results are consistent with the demonstration that during morphine withdrawal long-term depression is blocked (2). Thus the increase observed in the density of these receptors could take part, directly or as a compensative adaptation, to this phenomenon. Regarding mGlu4 receptors, it has been shown that activation of these receptors is protective against excitotoxic neuronal death and there is evidence for an opioid induced neurotoxicity (3). On the basis of our results, it could be proposed that the reduced availability of mGlu4 receptors observed after acute or chronic morphine treatment, is an etiological determinants of opioid induced neurotoxicity. Overall, these results implicate mGlu receptors subtypes in the long term consequences of opiate dependence.

This study was supported by MIUR (PRIN 2004).

1. Kenny P.J. and Markou A. (2004) Trends Pharmacol Sci. 25: 265-272.
2. Robbe D., Bockaert J. and Manzoni O.J. (2002) Eur J Neurosci. 16: 2231-2235.
3. Daeninck P.J. and Bruera E. (1999) Acta Anaesthesiol Scand. 43: 924-938.