REGULATION OF DYNORPHIN GENE EXPRESSION BY K-OPIOID AGONIST TREATMENT

D'Addario C., 2° anno di corso del Dottorato in Farmacologia e Tossicologia, XVI ciclo. Durata del dottorato in anni: 4. Sede di servizio: Dipartimento di Farmacologia, Università degli Studi di Bologna, Via Irnerio 48, 40126 Bologna.

It is known that k-opioid agonists are able to contrast behavioral effects of cocaine. In fact, U-69593, a selective k-opioid receptor agonist, decreases acute locomotor effects associated with cocaine and cocaine sensitization, as well as it blocks enhancement of cocaine-induced place conditioning and reduces cocaine self-administration in rats. Conversely, when cocaine is administered chronically, k-opioid receptors are increased in some cerebral areas, such as nucleus accumbens, while k-opioid receptor mRNA is decreased in others. Our previous data show that dynorphin mRNA levels are significantly increased in striatum and decreased in hypothalamus following intracerebroventricular administration of cocaine, suggesting that cocaine and dynorphin interact differently depending on the brain region. In order to determine whether there are changes in dynorphin that may play a role in the alteration of cocaine-related behaviors by k-opioid agonists, the effects of k-opioid receptor agonist treatment on prodynorphin mRNA expression in the rat brain were examined. In this study, prodynorphin mRNA expression was examined 3 days following a 5-day treatment with U-69593 (0.32 mg/kg, s.c.). This treatment produces a marked decrease in the locomotor activating effects of cocaine and alters a numbers of dopaminergic markers. In addition, a second group of rats was treated with U-69593 (0.32 mg/kg, s.c.) for 5 days and prodynorphin mRNA levels were examined 17 days later (on day 22). The results show that 3 days after a 5-day treatment with U-69593, prodynorphin mRNA expression is significantly decreased in the striatum ($66.6 \pm 8.5\%$, $p<0.05$ vs control, Newman-Keuls test), frontal cortex ($63.5 \pm 6.7\%$, $p<0.05$ vs control), and hippocampus ($64.7 \pm 5.4\%$, $p<0.05$ vs control) and increased in the hypothalamus ($226 \pm 44\%$, $p<0.05$ vs control). On day 22, prodynorphin mRNA levels remained sustained in the hypothalamus ($351.4 \pm 76.5\%$, $p<0.05$ vs control) in the rats that were pretreated with U-69593, compared to vehicle. In the striatum ($160.4 \pm 9.4\%$, $p<0.05$ vs control) and the frontal cortex ($210.6 \pm 18.4\%$, $p<0.05$ vs control), however, there was a reversal of effects with significant increases in prodynorphin mRNA.
It is of interest that prodynorphin mRNA levels continue to change long after the treatment with U-69593 has ended. In addition, the direction and pattern of the changes varies across brain regions. In the hypothalamus, for example, prodynorphin mRNA is elevated 3 days after treatment with U-69593 and continues to increase by day 22. In contrast, the initial decreases in prodynorphin mRNA in the striatum and frontal cortex are reversed at the later time point. It is possible that these increases are compensatory response to the earlier decreases. All together, these data suggest that the different brain regions are differentially affected both by U-69593 and by altered dynorphin and that kappa agonists have long-term effects on prodynorphin gene expression.