Neuropathic and chronic pain stimuli downregulate central μ-opioid and dopaminergic transmission

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Clinical studies have demonstrated that when morphine is used to control pain in cancer patients, psychological dependence is not a major concern. The present study was undertaken to ascertain the modulation of psychological dependence on morphine under a chronic pain-like state in rodents. Although the μ-opioid receptor agonist morphine and DAMGO induced a dose-dependent rewarding effect, the morphine-induced rewarding effect was significantly suppressed under inflammatory pain-like state. In vivo microdialysis studies clearly showed that the morphine-induced increase in the extracellular levels of DA and its metabolites, DOPAC and HVA, in the nucleus accumbens (N.Acc.) was significantly decreased in rats that had been pretreated with formalin. This effect was reversed by the microinjection of a specific dynorphin A antibody into the N.Acc. These findings suggest that the inflammatory pain-like state may have caused a sustained activation of the κ-opioidergic system within the N.Acc., resulting in suppression of the morphine-induced rewarding. We also found that sciatic nerve ligation suppressed a DAMGO-induced reward and reduced both the increase in the level of extracellular DA by morphine in the N.Acc. and [35S]GTPγS binding to membranes of the ventral tegmental area (VTA) induced by DAMGO. These effects were eliminated in mice that lacked the β-endorphin gene. Furthermore, intra-VTA injection of a specific antibody to β-endorphin reversed the suppression of the DAMGO-induced rewarding effect by sciatic nerve ligation in rats. These results provide molecular evidence that nerve injury results in the continuous release of endogenous β-endorphin to cause the dysfunction of μ-opioid receptors in the VTA.