The dopamine D1/D3 receptor system mediates anti-nociceptive actions of morphine in the spinal cord

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Dopamine (DA) receptor agonists serve as powerful first-line treatment for restless legs syndrome (RLS), and they modulate spinal reflexes, including nociceptive reflexes, in part via the D3 receptor subtype. We have previously shown that mice lacking the functional D3 receptor (D3KO) exhibit decreased paw withdrawal latencies from painful thermal stimuli. However, altering the DA system in the CNS, including dopamine D1 and D3 receptor systems, reduces the ability of opioids to provide analgesia. Here, we tested if the increased pain sensitivity in D3KO might result from a modified μ-opioid receptor (MOR) function at the spinal cord level. As D1 and D3 receptor subtypes have competing cellular effects and can form heterodimers, we tested if the changes in MOR function may be mediated in D3KO through the functionally intact D1 receptor system.

We found that *in vivo*, a single morphine administration (2 mg/kg) increased withdrawal latencies in WT but not D3KO, and these differential effects were mimicked *in vitro*, where morphine modulated spinal reflex amplitudes (SRAs) in WT but not D3KO. Total MOR protein expression levels were similar between WT and D3KO, but the ratio of phosphorylated MOR (pMOR)/total MOR was higher in D3KO. Blocking D3 receptors in the isolated WT cord precluded morphine's inhibitory effects observed under control conditions. Lastly, we observed an increase in D1 receptor protein expression in the lumbar spinal cord of D3KO.

Our data suggest that the D3 receptor modulates the MOR system in the spinal cord, and that a dysfunction of the D3 receptor can induce a morphine-resistant state. We propose that the D3KO mouse may serve as a model to study the onset of morphine resistance at the spinal cord level, the primary processing site of the nociceptive pathway.