[Difference in tolerance to anti-hyperalgesic effect and its molecular mechanisms between chronic treatment with morphine, fentanyl and oxycodone in a chronic pain-like state].


Abstract
In the present study, we demonstrated that repeated treatment with fentanyl, but not morphine or oxycodone, causes a rapid desensitization to its ability to block the hyperalgesia associated with the attenuation of mu-opioid receptor resensitization in mice in a chronic pain-like state. In contrast, no such effect was noted in beta-endorphin knockout mice under the chronic pain-like conditions. On the assumption that beta-endorphin might be released within the spinal cord under pain-like conditions, we further examined whether beta-endorphin could be responsible for a desensitization and resensitization of fentanyl under the chronic pain. In cultured cells, unlike morphine, fentanyl and oxycodone induced a robust mu-opioid receptor internalization and, in turn, its resensitization. In the presence of beta-endorphin, the internalized mu-opioid receptor induced by fentanyl, but not oxycodone, remained within the cytosolic component even after washing out. The findings suggest that beta-endorphin could attenuate the resensitization of mu-opioid receptors. This phenomenon may explain the high degree of tolerance to fentanyl that develops with hyperalgesia caused by a chronic pain-like state.

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