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Biased Agonism of Mu-Opioid Receptor Ligands in T Lymphocytes is Involved in the Induction of Interleukin-4

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Opioids are irreplaceable for the treatment of severe pain. However, immunomodulatory side effects influence opioid therapies. Often these are negative, immunosuppressive side effects. On the other hand, antiinflammatory side effects of opioids, for example the opioid-mediated induction of interleukin-4, may be beneficial in certain disorders. Among the three specific opioid receptors termed mu, delta and kappa, mu opioid receptors are of utmost importance, because they mediate the effects of almost all clinically used opioids. Here we report that treatment of primary human T lymphocytes and cells of the human T cell line Jurkat with the mu opioid receptor ligands fentanyl, methadone, loperamide and beta-endorphin resulted in significant ($p < 0.01$; $n = 8$), strong, 55 ± 7 to 64 ± 10 -fold induction rates of interleukin-4 mRNA, as assessed by quantitative RT-PCR (values are compared to unstimulated controls by students t test). In contrast, the mu opioid receptor ligands morphine and buprenorphine produced significantly induced ($p < 0.05$; $n = 8$), but markedly lower levels of interleukin-4 mRNA (7.5 ± 2 and 9 ± 3 -fold). Comparable effects were observed at the interleukin-4 protein level, as demonstrated by using a human cytokine antibody array. Within the signaling cascade responsible for the opioid-mediated induction of interleukin-4 we observed strong phosphorylation of p38 mitogen-activated protein kinase in Western blots, significant ($p < 0.05$; $n > 5$), 1.6 ± 0.1 to 2.3 ± 0.3 -fold activation of phospholipase D2 (values are compared to unstimulated controls by students t test) and, by using confocal microscopy, a marked internalization of mu opioid receptors after treatment of the T cells with fentanyl, methadone, loperamide and beta-endorphin. In contrast, morphine and buprenorphine showed significantly weaker or no activation of these enzymes and induced very little or no internalization of mu opioid receptors. These findings demonstrate for the first time agonist biased mu opioid receptor signaling in T cells on a molecular level. In contrast, another well-known effect of opioids in T lymphocytes, namely the inhibition of the transcription of interleukin-2 from activated T cells, was not significantly different among the various opioids. This indicated that certain mu opioid receptor-mediated, immunomodulatory effects are dependent on the ligand that is used. Understanding biased agonism of mu opioid receptor ligands in immune effector cells will offer the possibility to select opioids for a therapy with more favorable and/or less detrimental side effects in the future.