LONG-TERM INTRATHECAL MORPHINE IN PATIENTS WITH CHRONIC NON-CANCER PAIN UP-REGULATES MU OPIOD RECEPTOR GENE EXPRESSION IN LYMPHOCYTES

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Morphine is frequently used as palliative therapy in order to control pain in several diseases, and is the most commonly used medication for intrathecal pump delivery system. Studies completed in humans and animals have shown that opioids have profound effects on the immune system. Wybran et al (1) demonstrated for the first time the presence of opioid receptors in the peripheral blood lymphocyte; several other studies reported that peripherally administered opioid agonists can modulate the immune system through a direct action on the immune cells. Neurochemical changes in the central nervous system can also lead to opioid-mediated alterations of the immune system via autonomic nervous system (ANS) and neuroendocrine system. Morphine, but not N-Methylmorphine (a form of morphine which does not penetrate the blood-brain barrier) is able to produce suppression of natural killer cell activity on the spleen. On these basis, central opioid system seems to be involved in the modulation of immune system. Bupivacaine is often used in combination with morphine in order to dimish the progression of the intrathecal morphine doses. In this study we evaluated mu-opiod receptor mRNA expression in periferal lymphocytes of patients with chronic non-cancer pain and intrathecally treated with morphine and morphine/bupivacaine for 3-5 years. Briefly, lymphocytes were isolated from blood of control and treated patients using a commercial preparation. mRNAs from lymphocytes were retrotranscribed and amplified employing a semiquantitative RT-PCR method using a ribosomial protein (L19) as internal control. Costant intrathecal administration of morphine produces an increase of mu-opioid receptor mRNA levels in a dose dependent manner. Low doses (0.25-0.5 mg/day) increase the expression by only 14% vs controls, while at higher doses (1.5-4 mg/day) the increase is approx. 57% vs controls. Higher mRNA levels are observed in the morphine (1.25-3.75 mg/day)/bupivacaine (0.2-0.4 mg/day) patient group (195% vs controls). Elevation of mu-opioid receptor mRNA expression was confirmed in a second set of experiments performed 12 months later. Several studies have shown that cytokines may mediate morphine-induced up-regulation of mu-opioid receptors in immune cells. Moreover, immune cells containing and releasing opioid peptides can accumulate in chronically inflamed tissue and may activate an autocrine/paracrine immune response acting on mu-opioid receptos expressed on lymphocytes.

1)Wybran J, Appelboom t, Famaey JP, Govaerts A. J Immunol. 1979 Sep;123(3):1068-70.