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Title: THE EFFECT OF MORPHINE ON HERPES SIMPLEX VIRUS (HSV)-SPECIFIC CYTOTOXIC T LYMPHOCYTE (CTL) FUNCTION: A POSSIBLE MECHANISM INVOLVED IN HSV RECURRENT INFECTION FOLLOWING EPIDURAL MORPHINE ADMINISTRATION

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Introduction: A significant association exists between the use of epidural morphine and the reactivation of herpes labialis in the obstetric population (1, 2). Coupled with evidence demonstrating that opioids can alter immune function emphasizes the potential importance of morphine in modulating the immune response to HSV infection. The cellular T lymphocyte component of the immune response plays a significant role in the control of latent HSV infection and recrudescent disease. Impaired cell-mediated immunity has been associated with an increased history and severity of recurrent herpetic infections. We have utilized an HSV-specific CTL murine derived cell line and a method to activate HSV-specific cytotoxic T lymphocyte memory cells (CTLm) from the spleens of HSV-primed mice to study the effects of morphine on the activation, proliferation, and cytolytic activity of HSV-specific CTL.

Methods: An HSV-specific, MHC-restricted CTL cell line (RAB-1) was cultured *in vitro* with varying concentrations of morphine (10^{-5} M - 10^{-9} M) in either the absence or presence of naltrexone (10^{-6} M - 10^{-8} M). HSV-induced proliferation of RAB-1 was determined by cellular incorporation of $[^3H]$-thymidine. Cytolytic activity of RAB-1 cells was measured in a standard ^{51}Cr release assay using a syngeneic, HSV-infected mouse embryo fibroblast cell line as the target cell (HSV-infected B6/WT-3). *In vitro* activation of splenic-derived, HSV-specific CTLm was induced by culture with mitomycin C-treated, HSV-infected B6/WT-3 cells.

Results: These studies demonstrate that morphine is able to suppress the proliferation of the HSV-specific CTL (Figure 1). Naltrexone did not block this suppression suggesting that morphine activity is initiated by its binding to a non-classical opiod receptor (data not shown). However, morphine does not suppress the cytolytic activity of RAB-1 cells. In addition, morphine suppresses the activation and/or proliferation of HSV-specific CTLm obtained from the spleens of HSV-primed mice but does not suppress the cytolytic activity of those HSV-specific CTL that have already been activated to the lytic phenotype (Figure 2).

Discussion: The finding of morphine-induced suppression of HSV-specific CTL activation and/or proliferation is important since defense against HSV recurrent infection is highly dependent upon the ability to activate and expand a clonal population of HSV-specific CTL. These results suggest that morphine-induced suppression of the anti-HSV cellular immune response may, in part, be responsible for HSV reactivation and recrudescent disease following epidural morphine administration.

References:

1) Crone, L. A., Conly, J. M., et al. (1988). Recurrent herpes simplex virus labialis and the use of epidural morphine. Anesthesia and Analgesia. 67: 318 - 323.

2) Crone, L. A., Conly, J. M., et al. (1990). Herpes labialis in parturients receiving epidural morphine following cesarean section. Anesthesiology 73: 208 - 213.

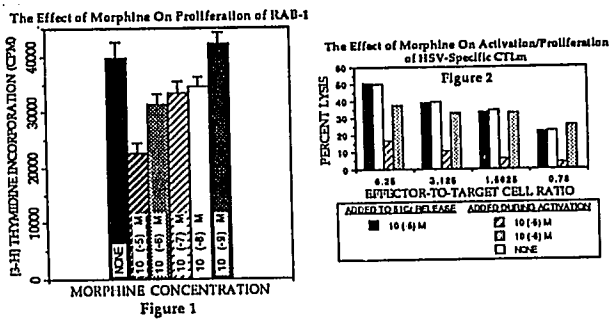

Figure 1

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OPIOID PEPTIDES IN HUMAN PERIPHERAL NERVES.

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The presence of opioid receptors in human peripheral nerves (PN) was recently reported.[1] In addition, May[2] and Viel[3] reported the use of narcotics in peripheral nerve blocks to provide peripheral analgesia. A physiologic role for the opioid receptors on human PN's was suggested by the clinical studies; thus, human PN's were examined for the presence of two opioid ligands - ß endorphin and met-enkephalin.[4]

METHODS: Human sciatic nerves (4) were harvested with Institutional assistance*, frozen in liquid nitrogen, and stored at -70°C. The nerves were heated at 95°C for 15 min, in 1m acetic acid. The tissues were homogenized and centrifuged. The supernatant was lyophilized and stored at -85°C.

ß-Endorphin- Human PN preparations were incubated with 100 μl antiserum in assay buffer for 24 hr at 4°C. Radioiodinated antibody to ß-endorphin was added, the sample incubated, the antibody-bound endorphin was separated, and the samples were centrifuged. The supernatant was counted in a gamma counter.

Met-Enkephalin - Human PN samples were added to bovine antiserum, RIA assay buffer, and tracer with 6,000 cpm (100 μl). The suspensions were vortexed and incubated at 4°C, and bound antigen was separated using 400 μl of 30% polyethylene glycol. The tubes were incubated and centrifuged, and the precipitate was counted in a gamma counter.

RESULTS: All 4 human sciatic nerves contained both ß-endorphin and met-enkephalin.

	ß-Endorphin (pmol/mg protein)	Met-Enkephalin (pmol/mg protein)
1.	0.1400	0.0772
2.	0.1575	0.0906
3.	0.1495	0.0503
4.	0.1358	0.1041
Mean	0.145±0.004	0.081±0.009

DISCUSSION: The presence of opioid peptides ß-endorphin and met-enkephalin on human peripheral nerves suggests a physiologic role for opioid receptors in human peripheral nerves. A wide variety of regional analgesic techniques, including epidural and axillary opioids, may work by exogenous opioids binding to the endogenous peripheral nerve opioid receptors. We suggest that peripheral as well as central nervous system narcotic receptors play a role in the control and modulation of pain. Human peripheral nerves contain endogenous opioid ligands, as well as opioid receptors.

1. Anesthesiology 1989;71(3A).
2. Anesth Analg 1987;66:417-20.
3. Reg Anaesth 1989;14(6):274-8.
4. Life Sci 1983;33(Suppl. I) 519-22.

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