

Title: Receptor Mediation of Opiate Effects on Temperature

Authors: C. Rosow, M.D., J. Miller, B.S., and J. Cochin, M.D., Ph.D.

Affiliation: Department of Pharmacology, Division of Medical Sciences, Boston University, and the Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

**Introduction.** The acute administration of morphine produces complex effects on body temperature which are mediated by a direct action on the anterior preoptic hypothalamus (1). In several species including mice the effect appears to be production of a poikilothermic state (2) which can be modified by pretreatment with opiate antagonists. Temperature change after morphine is of particular interest since it is an easily measured effect on a CNS site which is relatively well-defined (compared to other opiate agonist effects like analgesia). This study was designed to determine whether morphine and other pure opiate agonists affect body temperature by interacting with a receptor population similar to that mediating analgesia.

**Methods.** Male CD-1 mice were restrained, and rectal temperatures were measured with indwelling thermistor probes. Tests were run at 20, 25, and 30°C. ambient. After a two hour equilibration period the animals were given subcutaneous injections of water or drug solution. Temperatures were recorded immediately prior to injection and at 30 minute intervals for 150 minutes. Responses were measured as mean change from control, and significance was determined by analysis of variance and Dunnett's test (3). The agonists tested were morphine-SO<sub>4</sub> (2.5, 10, 40, and 160 mg/kg), levorphanol tartrate (1, 10, and 30 mg/kg), and hydromorphone-HCL (1, 5, 20, and 40 mg/kg). Dextrorphan, the analgesically inactive stereoisomer of levorphanol was tested at doses of 1, 10, 30, and 60 mg/kg. Antagonist blockade was tested by injecting naloxone-HCL (2.5 mg/kg) immediately before and 60 minutes after a single injection of 30 mg/kg morphine. To assess the effects of chronic opiate administration one group of mice was given morphine (40 mg/kg b.i.d. x seven weeks) and a second group was given levorphanol (30 mg/kg b.i.d. x two weeks). The temperature responses to these maintenance doses were measured at weekly intervals. A third group of animals was treated for two weeks with morphine and tested with levorphanol.

**Results.** At an ambient temperature of 20° low doses of morphine, levorphanol, and hydromorphone produced small increases in temperature. Higher doses produced dose-related hypothermia. At 25° the hypothermia was attenuated, and most of the responses became biphasic, i.e. hypothermia was followed by hyperthermia. At 30° these drugs produced only dose-related increases in temperature. Dextrorphan produced no significant change in

temperature at 20°, and a barely significant rise in temperature at 30° which was not dose-related. Naloxone blocked both morphine hypothermia and hyperthermia. Chronic administration of either morphine or levorphanol attenuated the hypothermic responses and augmented the hyperthermic responses. Chronic administration of morphine attenuated the hypothermic response to levorphanol and augmented the hyperthermic response.

**Discussion.** These results suggest that opiate agonists share the ability to impair thermoregulation in mice rather than producing hypo- or hyperthermia per se. The effects are the same for the three analgesically active compounds, and the doses which produce comparable temperature changes correlate well with the relative analgesic potencies. Stereoisomers like dextrorphan, dextromethorphan, and 1-propoxyphene lack analgesic effect but may still interact with certain types of opiate receptors (e.g. those involved in cough suppression). Dextrorphan produces minimal changes in body temperature even after a dose of 60 mg/kg (this dose of levorphanol is lethal in mice). Both the hypothermia and the hyperthermia are effectively antagonized by naloxone, and this would suggest that the two effects are mediated by a common receptor mechanism. However, only the hypothermia is diminished by the development of opiate tolerance or cross-tolerance. Hypothermia may represent a depressant opiate effect (like analgesia) to which tolerance develops rapidly. Hyperthermia may be an excitatory effect (like miosis or G.I. spasm) to which tolerance develops only slowly, if at all. Temperature changes produced by opiate agonists are true opiate effects mediated by typical opiate receptors.

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#### References.

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