Research Article

Mu, Delta and Kappa Opioid Receptor Involvement in the Hypothermic Response to Caffeine and Theophylline

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Summary. *This study describes the effect of the methylxanthines, caffeine and theophylline, on core body temperature (T_b) of unrestrained mice at normal ambient temperature. Acute administration (IP) of caffeine and theophylline produced a dose-dependent hypothermia; caffeine induced hypothermia was of a greater magnitude and longer time-course than theophylline. The hypothermic response was attenuated (50%) by naloxone HCl, a peripheral and central non-selective opioid antagonist, showing that methylxanthine-induced hypothermia is partly mediated by opioid receptors. In part the hypothermic response appeared to be naloxone-insensitive (50%) indicating that other mechanisms may mediate this effect. Only theophylline-treated mice exhibited an attenuation by 25% of this response when pretreated with naloxone methiodide which only acts peripherally, indicating that part of the opioid receptor mediation of theophylline-induced hypothermia is dependent on a peripheral mechanism. No attenuation occurred when theophylline- and caffeine-treated mice were pretreated with low-dose naloxone HCl, a Mu- selective antagonist while naltrindole HCl, a Delta-selective antagonist produced a mild attenuation. The greater attenuation produced by nor-binaltorphimine, a Kappa-selective antagonist, would suggest that the Kappa receptors are mainly responsible for the opioid receptor mediation of both caffeine- and theophylline-induced hypothermia. The acute effects of caffeine and theophylline on thermoregulation are not unlike those of morphine and endogenous opioids. The pharmacological, clinical and biological significance of the thermoregulatory effects of caffeine and theophylline are discussed.*

Keywords: *caffeine, theophylline, naloxone, naltrindole, nor-binaltorphimine, body temperature, mouse*

Drugs exerting their effects through the opioid system have profound effects on body temperature. The particular effect seen is dependent on species, ambient temperature, degree of restraint imposed on the subject and route of drug administration (Adler et al, 1988).

Moderate to high doses of caffeine (>30mg/kg) have been reported to induce dose-related reductions in core body temperature in rats and mice (Durcan et al, 1991) kept at ambient temperatures in the standard range. Doses of caffeine in the range from 37.5mg - 300mg/70kg in stimulant drug abusers have also been reported to cause up to 4°C drop in skin temperature (Rush et al, 1995).

There are a number of reports of methylxanthines exerting their effects through interactions with opioid receptors, although the majority of studies have used caffeine. High doses of caffeine and other methylxanthines have been reported to potentiate the antinocioceptive actions of opioid receptor agonists such as morphine (Misra et al, 1985; Sweeny et al, 1991; Nicholson et al, 1991). Narcotic administration particularly of morphine sulphate and fentanyl can be safely carried out in the preterm infant when using intravenous caffeine simultaneously to offset the risk of apnea (Mainous, 1995).

It has been reported that naloxone hydrochloride (a non-selective opioid antagonist) attenuates the hypothermic action of caffeine (Durcan et al, 1992). The attenuation of the hypothermic effect should apply to other methylxanthines provided that the dose of naloxone used does not have an intrinsic hypothermic effect. Further studies are thus needed to fully define the role, precise mechanisms and the extent of interaction.

At present there are no studies on the involvement of the main opioid receptor types (i.e., *mu, delta* or *kappa*) in the hypothermic effect caused by methylxanthines. Discrimination between the individual involvement of each opioid receptor type would enable the determination of the exact molecular target of methylxanthines as well as to determine the involvement of central and/or peripheral effects.

In this series of experiments reported here we examined whether the hypothermic effects of caffeine and theophylline are opioid-dependent, receptor type specific and peripheral or central in origin with respect to the opioid system.

Materials and methods

Subjects

Twenty male albino mice (inbred), 8 weeks old, weighing 24g - 34g at the start of the experiment were used. They were singly housed on a 12:12 hr light:dark cycle with food and water available *ad libitum* except during testing. The mice were handled daily to reduce stress trauma to a minimum.

Temperature studies were carried out in the animal house