Title: THE EFFECT OF MEPERIDINE AND NALOXONE ON COLD-INDUCED SHIVERING

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Post anesthetic shivering is attenuated by I.V. meperidine[1] but not by equianalgesic doses of morphine and fentanyl,[2] implying that the anti-shivering effects of meperidine are not related to its opioid activity. The purposes of this study were: 1) to document meperidine's effects on cold-induced (non-anesthetic related) shivering and 2) to note the effect of naloxone on the anti-shivering effect of meperidine.

Method: Informed consent was obtained and the study met the standards of the Human Subjects Review Board. Oxygen consumption (VO_2), CO_2 production (VCO_2), ventilation (V_E), rectal temperature ($T°_R$), EKG and EMG were measured continuously in 5 male subjects. After 20 minutes of resting data, cooling was effected by circulation of 4°C water through cooling blankets and with iced bags of saline on axillae, groins, legs, and neck. After shivering was established, meperidine 0.4 mg/kg or placebo was administered I.V. in random order with shivering established between each injection. In a second part, I.V. meperidine (0.4 mg/kg) was repeated. Three minutes later, I.V. naloxone (40 mcg/kg) was administered.

Results: Surface cooling induced shivering indicated by EMG activity and over 300% increase in VO_2, VCO_2, and V_E. Meperidine significantly reduced EMG and metabolic evidence of shivering (table 1). After meperidine, shivering returned spontaneously after 12.5 ± 2.7 minutes. I.V. naloxone administered 3 minutes after the second dose of meperidine caused abrupt return of shivering within 1.5 ± 0.4 minutes, compared to 9.5 ± 2.7 minutes with placebo injection ($p<0.05$), see (fig.1).

Conclusion: 1) Meperidine stops cold-induced shivering in the absence of anesthetic. 2) Naloxone reverses the anti-shivering effects of meperidine, implying that this activity of meperidine is related to its opioid activity.

TABLE 1

	VO_2 (ml · kg^{-1} · min^{-1})	VCO_2 (ml · kg^{-1} · min^{-1})	V_E (ml · kg^{-1} · min^{-1})
CONTROL	2.81 ± 0.22	2.43 ± 0.10	102 ± 6.43
SHIVERING	9.77 ± 1.00	8.98 ± 1.74	395 ± 80.64
4 MIN. POST PLACEBO	9.35 ± 1.02	8.92 ± 0.68	336 ± 34.69
4 MIN. POST MEPRIDINE	4.06 ± 0.53	2.34 ± 0.34	109 ± 25.25

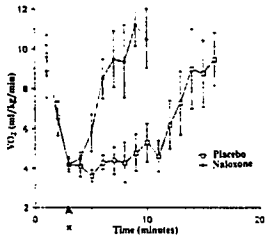

Fig. 1

Meperidine I.V. at Time = 0 min.

Naloxone or Placebo at Time = 3 min. (X)

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Adrenal Neuropeptide Concentrations in Endotoxic Shock

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Introduction: The autonomic nervous system and the endocrine system are well known to have critical roles in the pathophysiology of endotoxic shock. We have shown that selected endogenous neuropeptides (NP) increase in plasma concentration after endotoxin administration. To determine the role of the adrenal in this response, we studied adrenal NP tissue levels in endotoxic shock.

Methods: Pathogen-free castrated male pigs (*Sus Scrofa*) were divided into an experimental (n=7) and control (n=3) group. The experimental group received 0.3 mg/kg *E. Coli* endotoxin intravenously. After a 4 hr monitoring period, the pigs were killed; bilateral adrenal glands were harvested and divided into medulla (MED) and cortex (CTX). These tissues were extracted and assayed for vasoactive intestinal peptide (VIP) and neuropeptide-Y (NPY) via RIA as described by Yaksh, *et al* (1).

A paired Student's t-test was used to evaluate the significance of differences between control and endotoxin-shocked adrenal NP levels.

Results: The experimental group had a 54% drop in blood pressure (MAP) at 60 min ($p\leq.001$) and the MAP remained depressed for 4 hours. In the control animals, VIP was 92 ± 30 ng/g (mean ± SEM) in the MED compared to 18 ± 4 ng/g in the CTX ($p=.05$). NPY was 7.5 ± 0.7 and 3.7 ± 0.4 ng/g in the MED and CTX, respectively ($p=.002$). Experimental animals' VIP levels remained constant, compared to controls, in both the MED (61 ± 15 ng/g, $p\geq.05$) and the CTX (18 ± 4 ng/g, $p\geq.05$). Conversely, NPY remained constant in MED (11.5 ± 2.0 ng/g, $p\geq.05$) but increased in the CTX (7.1 ± 0.4 ng/g, $p=.001$).

Discussion: In the present study, we found that the adrenal MED NP concentrations remain unchanged whereas adrenal CTX concentrations of NPY increase after endotoxin administration, likely secondary to increased production. We speculate that the increased levels of NPY in the adrenal gland indicate a possible role for NPY in the pathogenesis of sepsis.

References:

1. Yaksh TL, Michener SR, et al; Survey of Distribution of Substance-P, Vasoactive Intestinal Polypeptide, Cholecystokinin, Neurotensin, Met-Enkephalin, Bombesin and PHI in the Spinal Cord of Cat, Dog, Sloth and Monkey, *Peptides*, 9: 357-372, 1988.