Title: μ-, δ- AND κ-RECEPTOR AGONISTS PRESERVE THE ADRENAL MEDULLARY RESPONSE EVOKED BY SEVERE HEMORRHAGE: STUDIES ON ADRENAL CATECHOLAMINE AND MET-ENKEPHALIN SECRETION IN CATS

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Introduction: Opioids reduce the secretory adrenal medullary response to painful stimulation. This effect may be mediated, apart from brain and spinal cord, by direct actions on opioid receptor systems located on adrenal chromaffin cells and splanchnic nerve endings (1,2). In the present study, staged hemorrhage was induced to evaluate the concurrent adrenal release of norepinephrine (N), epinephrine (E), dopamine (D) and met-enkephalin (M). To evaluate possible modulatory effects of specific opiate receptor agonists on the sympatho-adrenal medullary system, μ- (sufentanil), δ/μ- (metkephamid) and κ- (U50488H) receptor preferring agonists were administered in cats prior to induction of hemorrhage.

Methods: In four groups of cats (n = 5 in each group) experiments following the same time course were carried out under 1 MAC of halothane anesthesia. In Group I (control) baseline samples (S1) from the adrenal vein (AD) were taken for N, E, D and M 1 hour after surgical preparation. A bolus of 0.9% NaCl i.v. (2 ml over 1 min) was then administered and sample S2 taken. Sample S3 was taken after hemorrhage of 25% of total blood volume (BV), and sample S4 after further hemorrhage of 50% of total BV. In Group II (μ-agonist) a bolus of sufentanil (25 μg/kg i.v.) followed by a continuous sufentanil infusion was administered prior to S2. Group III (δ/μ-agonist) received a bolus of metkephamid (3 mg/kg i.v.) and Group IV (κ-agonist) a bolus of U50488H (3.5 mg/kg i.v.) prior to S2. Assays for catecholamines (CA) were performed by high performance liquid chromatography with electrochemical detection, for M by a C-terminal selective radioimmunoassay after Sep-pak separation. Statistical analysis was carried out after logarithmic transformation of values by ANOVA one-way and repeated measures followed by the Duncan multiple range test.

Results: Experimental results are summarized in Figure 1. Under baseline conditions measurable levels of all hormones were observed in the AD. In the saline group, 25% hemorrhage resulted in a significant decline in BP (Δ -60 mm Hg from baseline) and no change in adrenal secretion. 50% hemorrhage evoked no significant further fall in BP (Δ -75 mm Hg from baseline) but led to prominent increases in AD levels of N (70-fold), D (30-fold), E (16-fold) and M (5-fold) as compared to baseline. During the pre-hemorrhage baseline state, administration of sufentanil evoked a significant 6- to 20-fold rise in AD CA and M levels, whereas the administration of metkephamid and U50488H produced no change in adrenal secretion and a decrease in BP. Under 25% and 50% hemorrhage there was no difference in AD hormone levels in the μ-, δ- and κ-agonist groups compared to the saline group.

Discussion: While systemic opioids block the sympathetic response to noxious somatic stimuli, the present observations emphasize the lack of a suppressive effect of μ-, δ- and κ-receptor agonists at high, systemically active concentrations on the adrenal secretory response evoked by hypovolemia. These results, though surprising, are in accordance with observations during opioid anesthesia for cardiac surgery. During cardiopulmonary bypass, even excessively high doses of opioids do not suppress the adrenal catecholamine secretion (3). We thus conclude that opioids are not involved in the regulation of the adrenal medullary secretion evoked by baroreceptor reflexes, and that the systems involved in mediating these cardiovascular reflexes differ pharmacologically from those systems mediating the autonomic response evoked by pain.

References:

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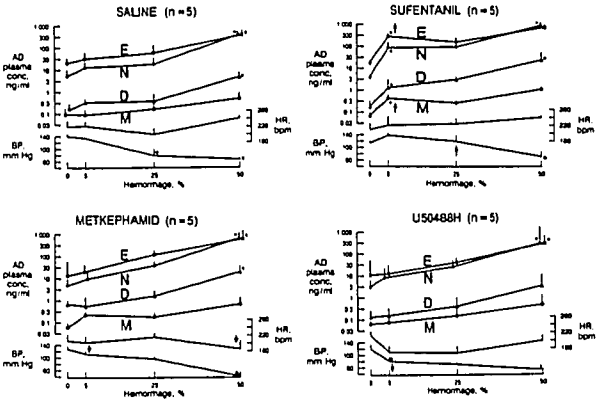

Figure 1: Summary of experimental results in four groups of cats treated with: saline, sufentanil, metkephamid and U50488H prior to induction of hemorrhage. Adrenal vein plasma levels (geometric mean ± geometric SE) are presented for norepinephrine (N), epinephrine (E), dopamine (D) and met-enkephalin (M) at baseline (0), after drug administration (5) corresponding to 5% hemorrhage due to sample volume, and after 25% (25) and 50% (50) hemorrhage. (*P<0.05 within group comparison; 5 versus 0, 25 and 50 versus 5; ↑↓ P<0.05 comparison to saline group; ↑ >saline, ↓ <saline).

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