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SURGICAL STRESS IN HUMANS IS ACOMPANIED BY AN INCREASE IN PLASMA BETA-ENDORPHIN IMMUNOREACTIVITY

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Summary

Surgical stress, but not anesthesia induction, produced a significant increase in plasma beta-endorphin immunoreactivity in eight patients undergoing abdominal surgery. This increase was closely correlated with a parallel increase in plasma cortisol. Post-operative morphine administered for pain relief was associated with a significant reduction in plasma levels of both beta-endorphin and cortisol. These results demonstrate the responsiveness of the endorphin system to acute stress in humans and provide additional evidence linking plasma beta-endorphin to the hypothalamic-pituitary-adrenal axis.

Considerable evidence from animal experimentation supports the hypothesis that the endorphin system plays an important role in the biological response to stress (1-3). Animal and clinical studies in which the periaqueductal gray area is electrically stimulated also support a major role for endorphins in endogenous pain perception and regulation (4-6). We now report that surgical stress, but not anesthetic induction, is associated with significant increases in plasma beta-endorphin immunoreactivity [PBE (ir)], and that levels of PBE (ir) are significantly correlated with levels of plasma cortisol.

Materials and Methods

Anesthetic Technique: Eight patients (six males, two females - age range: 18 - 60), who underwent laparotomies as part of a National Cancer Institute treatment protocol, participated in this study. Their pre-operative assessment was normal except for the existence of testicular or ovarian cancer. Pentobarbital IM was given for premedication. The anesthetic drugs consisted of thiopental and succinylcholine for induction and enflurane, nitrous oxide and muscle relaxant for maintenance. All patients were intubated and had controlled ventilation. They were medication-free prior to anesthesia and no exogenous opiates were administered either before or during surgery. The surgery lasted between 2 and 4 hours. Once recovered from anesthesia (i.e. return of consciousness), between the first and third hour post-awakening, patients were given morphine sulfate IV (dose range: 1.5-3.5 mg per hour) for relief of post-operative pain.

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Blood Collection: Blood samples were collected from each patient prior to and 10-15 minutes after anesthetic induction, 10 minutes after skin incision, at 30 minute intervals during surgery until skin closure and when awake during morphine administration in the Surgical Intensive Care Unit.

Assays: PBE (ir) and plasma cortisol were determined by radioimmunoassay (RIA). Both RIAs used standard rabbit antibodies supplied by New England Nuclear. In human plasma, the beta-endorphin antiserum, raised against human beta-endorphin, shows less less than 5% cross-reactivity with ACTH (M. Cohen, unpublished data), less than 50% cross-reactivity with beta-lipotropin,less than 0.01% with alpha-endorphin and alpha-MSH and less than .004% with met- and leu-enkephalin (New England Nuclear data). Blood samples, collected in polypropylene tubes containing bacitracin (2 mg/ml) to inhibit proteolysis and EGTA anticoagulant (20mM) were placed immediately on ice and spun within 10 minutes at 3000 rev/min for 15 minutes at 4°C. The plasma obtained was frozen at -80°C until being assayed within 3 weeks. Plasma samples from each patient were run on the same assay. Intra-assay variation for plasma cortisol was 6% and for beta-endorphin, 3.5%. Samples were coded and assigned blindly by non-laboratory personnel.

Results

Neither beta-endorphin (ir) nor cortisol were significantly affected by the induction of anesthesia (pre-induction Means ± S.E.M.:20.5 ± 2.9 pmole/liter, 23.7 ± 2.5 µg%, respectively; post-induction Means ± S.E.M.: 26.9 ± 6.4 pmole/liter, 26.1 ± 4.2 µg% respectively). Statistical analysis of the effects of the surgical procedure was performed by ANOVA with repeated measures using the following time points: pre-surgery, mean levels during surgery and when awake during the period of morphine administration. Surgery was associated with robust increases in PBE (ir) ($F=11.2$, $df=2,14$, $P=$ or < 0.0001) and in cortisol ($F=40.2$, $df=2, 14$, $P < 0.001$) (Figure 1).

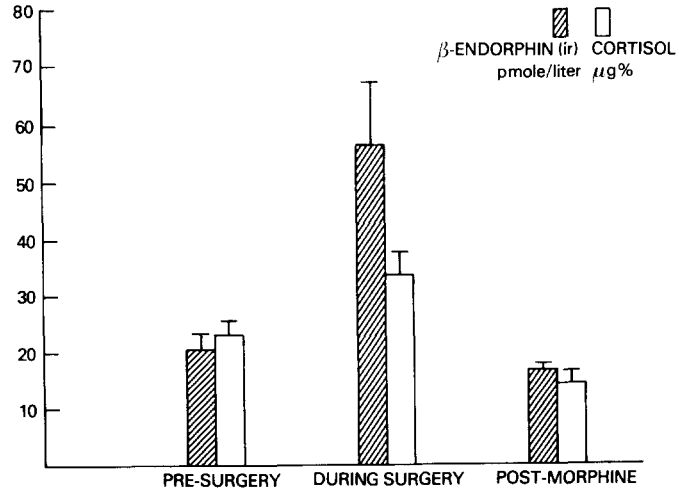

FIG.1

Mean ± SEM of plasma cortisol and beta-endorphin (ir) obtained before, during, and after abdominal surgery. Presurgical samples were taken after pentobarbital pre-medication and before anesthetic induction. Surgical values are the means of all values obtained during surgery. Post-morphine values represent samples taken during morphine administration for postoperative relief.

Levels of cortisol and beta-endorphin (ir) across these time periods were significantly related ($r=0.61$, $P < 0.01$) (Figure 2).

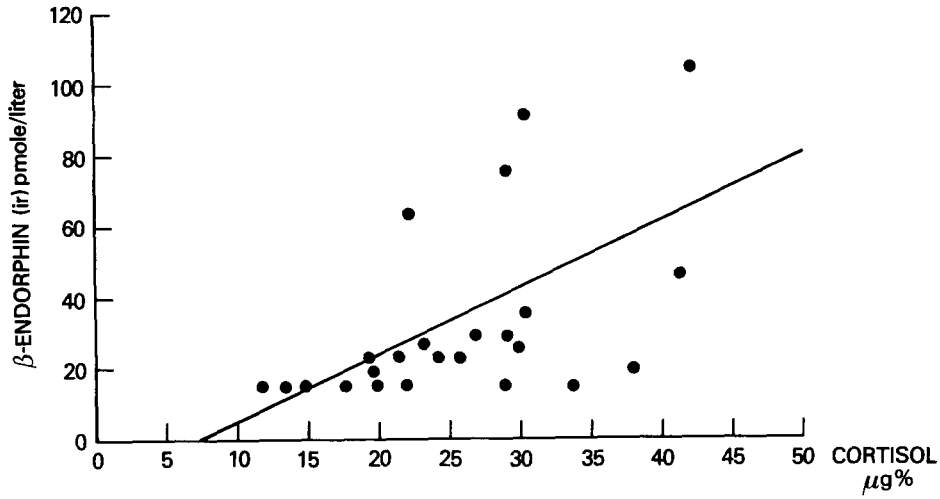

FIG.2

Correlation between beta-endorphin (ir) and plasma cortisol plasma levels obtained before, during and after surgery.

In six of the eight patients, additional plasma samples were collected following awakening from anesthesia but prior to morphine administration. In these individuals, pre-morphine levels of PBE (ir) and cortisol were comparable to those found during surgery. Mean ± SEM pre-morphine values were, for PBE (ir): 56.9 ± 11.5 pmole/liter during surgery and 74.9 ± 29 pmole/liter after awakening; for cortisol: 33.5 ± 3.5 μg% before and 44.2 ± 4.1μg% after awakening. Morphine administration was associated with significant reductions in each: Mean values during morphine administration were, for PBE(ir): 16.6 ± 0.8 pmole/liter and for cortisol; 14.1 ± 2.3 μg% (Mean ± SEM, $P < .001$ for cortisol: $P < 0.05$ for PBE (ir): paired t-test, two tailed, in comparison to pre-morphine levels).

Discussion:

Our finding that induction of general anesthesia did not significantly alter the levels of plasma cortisol is consistent with previous reports using the same anesthetic technique (7). To our knowledge, there has been no previous report of the effects of general anesthesia on PBE (ir). Initial studies suggesting the reversal of general anesthesia by naloxone in rats and humans raised speculation regarding a possible endorphin mediation of anesthetic effects. These findings, however, have not been consistently replicated (8-13). Our data do not support an involvement of the endorphin system - as reflected by PBE (ir) - during induction of general anesthesia. They do not exclude, however, a possible role for brain endorphins, whose contents have been shown to vary independently from pituitary beta-endorphin contents (14). It is also possible that circulating plasma endogenous opioids other than beta-endorphin may be related to anesthetic effects.

Our observation of increased levels of PBE (ir) during surgery suggests an activation of the endorphin system. Increases in PBE (ir) have been found in animals subjected to a variety of painful stresses (1-3) and in incidental cases in man (15). These are consistent with the known phenomenon of stress-induced analgesia (16). While it has been shown that intraventricular or intrathecal administration of beta-endorphin produces profound and long-lasting analgesia (17-20), intravenous beta-endorphin in humans shows only a mild analgesic effect (19,21). Beta-endorphin-rich CNS sites such as hypothalamus have been shown by neurophysiological monitoring to be activated by noxious stimuli in anesthetized animals (22). The increased PBE (ir) observed in our study may originate from the pituitary as well as from other peripheral sources such as pancreas (23). A relationship between CNS and pituitary beta-endorphin,supported by the high levels of beta-endorphin found in the hypophyseal portal blood (24), raising the possibility that circulating beta-endorphin reflects CNS activation.

The activation of the hypothalamic-pituitary-adrenal (HPA) axis during surgery has been previously shown (25-28). The correlated activation of the endorphin system found in our study during surgical stress is further evidence linking beta-endorphin to the HPA axis. It is known that: 1) ACTH and beta-endorphin are present in the same cells in the anterior and intermediate lobes of the pituitary (29,30); 2) ACTH and beta-endorphin share the same precursor prohormone peptide (31); 3) Concomitant inhibition or stimulation of ACTH and beta-endorphin release has been shown to occur after stress, after administration of metyrapone and in various experimental and physiological or pathological conditions (32-38). Our data suggest a relationship between the HPA axis and beta-endorphin in man under conditions of acute surgical stress.

We observed that surgically stimulated elevations of beta-endorphin (ir) and cortisol persisted into the post-surgery awake period and were significantly diminished following opiate administration. This is consistent with the reported inhibitory effect of opiates on cortisol secretion in man (39-43), although the nature of the regulation is unknown. An inhibitory effect of opiates on plasma beta-endorphin (ir) has to our knowledge not previously been reported. This effect may be an indirect result of the reduced pain perception produced by the saturation of opiate receptors by clinically effective doses of morphine or may indicate a direct opiate-endorphin feedback mechanism.

The use of parenteral opiates to supplement general anesthesia is a recent and increasingly utilized clinical approach. The use of opiates during surgery has been shown to dampen catecholamine release which is associated with potentially dangerous cardiovascular responses (44) as well as to diminish HPA activity without adverse clinical effect (39-41).

In conclusion, the significance of our results is two-fold. They provide further clinical evidence for the responsiveness of the endorphin system to stress and add additional support for a physiological association of beta-endorphin and the HPA axis. Further investigations focusing on the endorphin system during opiate-supplemented general anesthesia and on the relationship between endorphin response and post-operative pain and behavior are needed. Such studies may provide additional heuristic and clinical information on the role of the endorphin system in man.

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