

Date : April 17, 1980

Title : ROLE OF ENDORPHIN TO CONTROL CANCER PAIN IN MAN FOLLOWING PITUITARY ADENOLYSIS. - AN EXPERIMENTAL STUDY OF BETA-ENDORPHIN ACTIVITY IN HYPOPHYSECTOMIZED RATS.

Authors : H. Yanagida, M.D. and G. Corssen, M.D.

Affiliation : Yokohama Teishin Hospital, Yokohama, Japan
and
Maricopa County General Hospital, Phoenix, Arizona 85254

Introduction. Overproduction of beta-endorphin has been suggested as one of the mechanisms possibly involved in the prompt relief of intractable pain experienced by patients suffering from advanced cancer following hypophysectomy. In the present study this theory was tested by studying the effect of hypophysectomy on cerebral beta-endorphin levels in rats.

Methods. Thirty-two intact and 52 hypophysectomized male, Sprague Dawley rats served as subjects. Ablation of the hypophyseal gland was accomplished surgically by the oropharyngeal-sphenoidal approach. The animals withstood the procedure without complications. They were sacrificed employing the Toshiba microwave oven. The brain was removed and various regions of the brain were dissected, frozen with dry ice, weighed and homogenized in a 0.2 M HCL solution. After thawing the supernatant and centrifugation, a clear supernatant evolved which then was subjected to radioimmunoassay.

A conjugate was prepared by coupling camel beta-endorphin to bovine serum albumin employing the glutaraldehyde method. Rabbits were immunized by intradermal injection of 500 μ g of this beta-endorphin conjugate combined with 5 mg of complete Freund's adjuvant at multiple sites of the back of the animal. After two booster injections of 0.5 mg of conjugate 25 per cent of the rabbits showed significant immunoreactivity.

Iodination of [¹²⁵I] somatostatin was accomplished as described by Ogawa et al¹ and [¹²⁵I]-labelled-beta-endorphin was prepared by the lactoperoxidase method.

The diluent of the reagents consisted of 0.1 ml of 0.14 M sodium phosphate buffer to which 25 mM EDTA and 0.5 per cent bovine serum albumin at a pH of 7.4 was added. Each assay tube contained 0.1 ml of the buffer used for binding assays, 0.1 ml of anti-beta-endorphin rabbit serum, 0.1 ml of beta-endorphin standard, or samples, and 0.1 ml of [¹²⁵I]-labelled-beta-endorphin. 0.1 ml of 4 per cent sheep anti-rabbit serum were then added. After centrifugation of the substrate, the drawn off fluid was subjected to counting of radioactivity employing an automatic gamma-counter.

Results. Beta-endorphin levels in the whole brain of all hypophysectomized rats markedly decreased within 50 days after the operation. A similar reduction of beta-endorphin levels was observed in the midbrain and hypothalamic homogenates. Concentrations of beta-endorphin in the thalamus, sub-thalamus, and in the hippocampus were essentially unaffected.

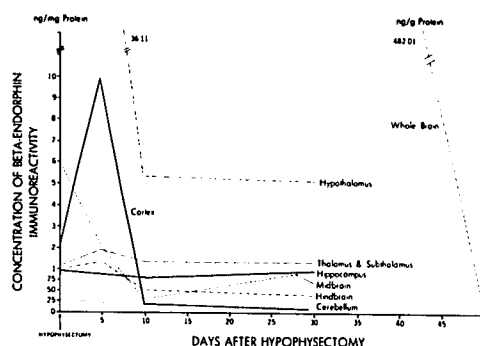
Beta-endorphin levels increased in the cortex within 5 days after hypophysectomy and then declined during the following 10 to 30 days, eventually falling behind the control levels.

The changes in beta-endorphin immunoreactivity as recorded in various regional brain areas and in whole brain are summarized in the graphic illustration (Figure).

Discussion. That hypophyseal ablation affected beta-endorphin activity differently in various brain regions was a surprising finding and may explain why in the past assaying blood serum or spinal fluid samples of hypophysectomized patients as to endorphin activity has not yielded reproducible values from which to draw conclusions.

An immediate and sustained decline of beta-endorphin levels was found in the whole brain and in certain separate brain regions, including the midbrain, hind brain, cerebellum and the hypothalamus while beta-endorphin concentrations were unaffected in thalamic, sub-thalamic, and hippocampal regions.

Most interesting, is the observation that in the cortex beta-endorphin levels increased during the first 5 days following hypophysectomy and declined thereafter. This finding seems to be in accord with our recent observations made in primates² in which the narcotic antagonist naloxone reversed the hypophysectomy-induced changes in tooth pulp-evoked potentials recorded from the cortex but failed to affect the potential changes recorded from the thalamic region and from the mid-brain reticular formation. The immediate, but transient, elevation of beta-endorphin concentrations in the cortex may also lend support to the assumption that an increase in cortical endorphin may be a factor responsible for the immediate relief of pain observed with alcohol-induced pituitary adenolysis in man.



References.

1. Ogawa N, Thompson T, Friesen HG, Martin JB, Brazeau P: Properties of soluble somatostatin-binding protein. *Biochem Biophys Acta* 251: 363-369, 1971.
2. Yanagida H, Corssen G et al: Alcohol-induced pituitary adenolysis: how does it control intractable cancer pain? - An experimental study using tooth pulp-evoked potentials in rhesus monkeys. *Anesth Analg* 58:279-287, 1979