# Beta - Endorphin Level Elevation in Human Fetal and Neonatal Pancreas: A Consequence of Intrapartal Stress or the Possible Existence of Pancreatic Islet Cells Autocrine Control?

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**Abstract:** *The presence of neurohormones in the human fetal and neonatal pancreas has not been systematically investigated until now. It has been found that hypoglycemia induced by insulin stimulates beta-endorphin (beta-EP) production, which is also confirmed in stressful situations. Therefore, we investigated beta-EP production and concentrations in human fetal pancreas during gestation and in the immediate neonatal period. Methodology of beta-EP determination was based on its concentrations evaluation in the membranes and cytosol of the pancreas cell substrate using radioimmunoassay. Results indicate that beta-EP production in pancreas exists, with concentrations rising concomitantly with gestational progression and in the stressful intrapartal period. According to our opinion, beta-EPs are incorporated in the endocrine regulation of pregnancy and delivery. (Thai J Obstet Gynaecol 1993;5:19-24.)*

**Key words:** beta-endorphin, pancreas, ectopic hormone secretion, intrapartal stress, antireproductive factor

Beta-endorphin (beta-EP) is a neurohormone (neuropeptide) cleaved from precursor pro-opiomelanocortin (POMC) under the control of corticotropin releasing hormone (CRH). Beta-EP is generated in the central nervous system, hypothalamus and anterior pituitary[1] but it is detected in the ovarian, testicular, thymic and placental tissues as well[2,3].

Developmental patterns of pancreatic opioid peptides, especially beta-EPs and islet hormones studied in experimental conditions indicate their

surge during the first postnatal week[4]. Beta-EP containing cells are in close proximity to insulin containing cells in the endocrine pancreas. It has been confirmed that beta-EP stimulates glucagon release and inhibits somatostatin secretion, effects that can be reversed by naloxone[5,6]. Recent studies indicated that beta-EP infusion caused a significant rise in plasma glucose concentrations preceded by a significant increase in peripheral glucagon levels but no changes occurred in the plasma concentrations of insulin and C peptide[7]. Beta-EPs have morphine-like analgesic properties, behavioral effects and neurotransmitter (neuromodulator) functions, but their role in the perinatal period stays, as yet, unresolved.

The aim of this study was to estimate the production and concentration variations of beta-EPs in the human fetal and neonatal pancreas during the gestation (third trimester) and in the early neonatal period in order to explain their possible function in pregnancy, especially the influence on delivery initiation and on insulin secretion.

## Materials and Methods

This study was performed in the Department of Clinical Pathology, Clinic of Gynaecology and Obstetrics, in collaboration with Institute of Anatomy and Institute for Biomedical Scientific Information, Belgrade the School of Medicine.

We determined the concentrations of beta-EP in human fetal (FPG) and neonatal (NPG) pancreas glands tissue. Samples were obtained at autopsy immediately after spontaneous preterm labour in the eight and a half (n=4), nine (n=4) and nine and a half (n=4) months of gestation as well as at term delivery (n=4). Estimations of beta-EP levels were also performed in placental tissues of the same feto-placental units (n=16).

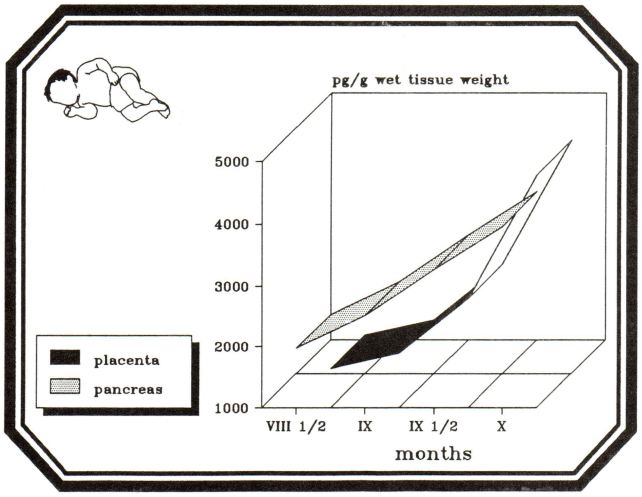
Peripheral blood samples of non-gravid healthy persons (n=10) were taken as controls.

After they were obtained, pancreatic and placental tissue specimens were placed directly into liquid nitrogen and transported to the laboratory. One gram of tissue was cut and, after the microdismembranation process[8], put in 5 ml of homogenization buffer. Beta-EP determination was based on the evaluation of concentrations in both membrane and cytosol of the pancreatic and placental cell substrate by using radioimmunoassay techniques (RIA-Nichols Institute). So results were expressed in picograms of beta-EP in 1 g of wet tissue weight, mean ± SD. Beta-EP concentrations in peripheral blood were determined using RIA Nichols kits.

The obtained data were analyzed by Student t and $x^2$ tests.

## Results

Immunoreactive beta-EP in the human pancreas was found to increase




| Beta - Endorphins | Month of Gestation | | | |
|---|---|---|---|---|
| Wet tissue weight (pg/g, mean +/- SD) | VIII 1/2 | IX | IX 1/2 | X |
| Pancreas | 1980 +/- 186 | 2520 +/- 223 | 3276 +/- 648 | 3960 +/- 637 |
| Placenta | 1086 +/- 212 | 1336 +/- 288 | 2243 +/- 548 | 4234 +/- 848 |

**Fig. 1** Concentrations of beta-EP in human fetal and neonatal pancreas and placenta.

Immunoreactive beta-EP levels in peripheral blood of non-pregnant women were 45 ± 8 pg/ml.

in pancreatic and placental cellular substrates with the progression of gestation. The highest beta-EP levels were observed in term pancreatic and placental tissue specimens (3960 ± 637 pg/g and 4234 ± 840 pg/g, respectively) (Fig. 1).

## Discussion

The pancreas develops from two buds growing from the fetal endoderm, the dorsal evagination budding first followed by the ventral one. The system of budding and evagination forms interlobular ducts and ductules and the intralobular ductules from which the acini develop[9]. It is also confirmed that ductules form the islets of Langerhans[10]. According to the opinion of most authors, islet cells are derived

from the neural crest as a part of the dispersed endocrine system or amino precursor uptake and decarboxylation (APUD) system[11,12]. Nevertheless, some studies indicate that islets develop in embryos even after removal of the neural crest[13]. Immunoreactive insulin and glucagon are demonstrable in pancreatic tissue from the 90th day of gestation onwards. At the beginning of the 6th month of gestation, lymphocytes are stated to be numerous in the interlobular connective tissue, but decrease during the 10th month[14]. It has been proved that lymphocytes have hormone receptors and that they can produce large amounts of beta-EP[15,16]. The pancreas is found to be a very important source of many hormones and opioid peptides during fetal and neonatal life[4].

In pregnancy, and particularly during labour, which represents an extremely stressful situation, maternal and fetal production of blood beta-EP is increased[17], which our study confirmed. There is a putative bidirectional network carrying information between the endocrine and reproductive systems[18]. The pancreas is incorporated in the hypothalamic-pituitary-gonadal axis and production (secretion) of opioid peptides during the gestational period is likely to be increased[19]. Results of this investigation indicate that opioid peptides beta-EPs are components of the intrapancreatic regulatory system, that means beta-EP of pancreatic origin may function as ultrashort loop or autocrine regulator of pancreatic islet cells, because their concentration rises during gestation, throughout the intrapartal period and in early neonatal life.

While hypophyseal and gonadal hormones feedback information to the pancreatic islet cells exists, providing a modulatory system for regulation of pancreatic cell maturation and peptides production, the pancreas and its peptides secretion can exert a modulation of gonadotropin secretion via a direct action at the hypothalamic LHRH level[18].

Neurohormone beta-EP appears to have a significant physiological role as a regulator of pain perception, by increasing the threshold of this perception and as an endocrine factor in human reproduction. Beta-EP stimulates secretion of prolactin (PRL), growth hormone (GH) and vasopressin (AVP), and inhibits production of oxytocin (OT), dopamine, follicular stimulating (FSH) and luteinizing (LH) hormones, resulting in depression of copulative effects, that is, it exerts anti-reproductive influence both in female and male reproductive tract[6]. It is worth noting that pancreatic islet cells were found to produce several neurohormones, including beta-EP[4], which show antagonistic effects. This interaction has already drawn attention of investigators in the field of neuroendocrinology. It has been found that beta-EP protects the reproductive system from both the excessive secretion and effects of pituitary trophic hormones. The mechanism of opioid

peptide action is via opioid receptors and can be antagonized by competitive binding antagonist naloxone. Naloxone and its possible relationship to fetal endorphin levels and fetal distress have been studied by Goodlin[5].

The results obtained in this study could suggest that the identified increased beta-EP production in both membrane and cell substrate cytosol from fetal and neonatal pancreas are most probably caused by intrapartal stress. As an alternative hypothesis we propose that beta-EP of the pancreatic origin represents an anti-reproductive factor, throughout intrauterine fetal and early neonatal lives. There is no doubt that beta-EP of pancreatic origin influences intrapancreatic hormones and other opioid peptides synthesis, that means beta-EP may function as ultrashort loop or autocrine regulator of pancreatic islet cells.

Endocrinology of pancreatic cells requires further research in order to obtain a definitive exact insight in human reproduction.

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