Effects of endogenous plasma beta-endorphin levels on ventilatory status of the human newborn in response to the stress of labor and delivery

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Beta-lipotropin and beta-endorphin are released during pregnancy and elevated at delivery in both mother and baby. The purpose of this study was to determine if elevated endorphin levels contributed to respiratory depression in the newborn.

Twenty-one prospective mothers between the ages of 18 and 35 with full-term pregnancies were selected for the study. Fifteen mothers delivered vaginally, while six delivered via cesarean section.

Mixed umbilical cord blood was analyzed for endorphins, pH, and HCO₃. Blood gas analysis was performed on "arterialized" capillary blood obtained from the newborn.

Beta-endorphin levels were compared in five different subgroups. These consisted of:

1. Normal spontaneous vaginal deliveries (NSVD) with artificial rupture of membrane (AROM).
2. NSVD with oxytocin (Pitocin®) induction.
3. NSVD with both AROM and oxytocin.
4. NSVD.
5. Patients who underwent cesarean sections.

There was no significant difference in endorphin levels among the vaginally delivered groups. There was also no difference in beta-endorphin levels in the C-section group in comparison to the vaginally delivered groups.

There was a direct correlation between cord beta-endorphin levels and capillary PCO₂ in the NSVD group and an inverse correlation between cord beta-endorphin levels and cord HCO₃ in the C-section group.

These findings are indicative of respiratory acidosis in the newborn at delivery. In both groups of patients there was no indication that these abnormal levels were high enough to affect the newborns clinically. All infants exhibited Apgar scores of 9-10 at 5 minutes, and there were no signs of respiratory problems from the time of birth to discharge home.

Key words: Beta-endorphin, human newborn, labor and delivery, stress.

Introduction

Current endogenous opioid research indicates that there are more than 20 pharmacologically active peptides in the nervous system. The identification of these peptides is complicated because of their low concentration in nervous tissue. The development of radioimmunoassay and immunohistochemical techniques has helped in defining these substances. In 1964 Li isolated beta-lipotropin, and in 1975 Hughes isolated leu- and met-enkephalin, the first of the endogenous opioid substances found to exhibit opioid agonist properties.

The beta-lipotropin peptide (Figure 1) contains the sequences of enkephalin (62-65) and beta-endorphin (61-91). The term enkephalin is uti-
Figure 1
Amino acid sequence of beta-lipotropin, containing beta-melanocyte stimulating hormone (b-MSH), enkephalin and endorphins

**Beta-melanocyte stimulating hormone**

- Glu-Lys-Lys-Asp-Glu-Pro-Tyr-Lys-Met-Glu-His-Phe-
  40
- Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp-Lys-Arg-
  55

**Beta-endorphin**

- Tyr-Gly-Phe-Met-Thr-Ser-....-Leu-Phe-Lys-Asn-Ala-Ile-Val-
  65

**Enkephalin**

- Lys-Asn-Ala-His-Lys-Lys-Gly-GIn
  85

Adapted from Geiger R. Chemistry of neuropeptide regulation. Advances in Biochemical Psychopharmacology.

lized when referring to the two short-chained pentapeptides—methionine-enkephalin and leucine-enkephalin. Beta-endorphin is the most potent and antinociceptive of the endogenous opioids.1

**Endorphins in gestation and the neonatal period**

Beta-lipotropin and beta-endorphin are released by the pituitary gland during stress. Therefore, it is not surprising that endorphin levels rise during pregnancy and are elevated in both mother and baby at delivery and during the immediate postpartum period.3-11

At delivery the neonate may be exposed to endorphins from three possible sources: the maternal plasma, the placenta, and the fetal pituitary gland.3, 6, 10, 11, 14-16 However, substances with a molecular weight of greater than 600 do not diffuse across the placental barrier, so it is doubtful that beta-lipotropin (molecular weight 1,000) or beta-endorphin (molecular weight 3,500) would be transferred.14

It appears that the fetus is exposed to endorphin either of placental and/or fetal pituitary origin. But it is still unclear if endorphin from these sources is capable of crossing the blood-brain barrier in the newborn and causing respiratory depression.9, 17, 16 This study questions whether there is any correlation between cord endorphin levels and newborn ventilation.

**Population**

Twenty-one prospective mothers between the ages of 18 and 35 with uncomplicated, full-term pregnancies were selected for the study. They had no significant health problems and were taking no medications other than vitamins during their pregnancy. The study was explained to them in detail, and informed consent was obtained. The study was approved by the Clinical Investigation Committee of the Medical College of Pennsylvania.

The population contained 15 mothers who were delivered vaginally and six who were delivered via repeat elective cesarean section with no trial of labor.

To test the effect of the type of delivery on the cord endorphin level, patients with normal spontaneous vaginal deliveries (NSVD) were further subdivided into four groups:

1. NSVD with artificial rupture of membrane (AROM).
2. NSVD.
3. NSVD with oxytocin induction and/or augmentation.
4. NSVD with AROM and oxytocin induction.
5. All C-section patients (Table I).

Data were also collected on complications at the time of delivery, such as the presence of nuchal cord, meconium staining, neonatal bradycardia, or the use of forceps.

<table>
<thead>
<tr>
<th>Table I</th>
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<tr>
<td><strong>Beta-endorphin levels in patient subgroups</strong></td>
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<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects in group</th>
<th>Mean cord beta-endorphin pg/mL</th>
<th>Standard error</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>118.31</td>
<td>19.89</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>139.40</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>138.10</td>
<td>28.22</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>123.00</td>
<td>10.44</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>148.50</td>
<td>30.84</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>118.20</td>
<td>7.06</td>
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1. Includes all C-section patients
2. Patient with initial twin pregnancy deleted

**Methods**

Upon delivery, two prechilled ethylenediaminetetraacetic acid (EDTA) vacutainers were filled with mixed umbilical cord blood and placed on ice until centrifugation. An additional 1-mL sample of mixed cord blood was drawn in a heparinized
syringe and placed on ice for analysis of pH and HCO₃.

Apgar scores were performed by the investigator at 1 and 5 minutes of age.

The iced EDTA tubes were transported to the laboratory and spun down at 22,000 rpm in a refrigerated centrifuge at 4°C. The supernatant plasma was drawn off, placed in polypropylene tubes and stored at −70°C until assay.

At approximately 30-60 minutes after birth, the newborns were admitted to the nursery. The infants' right arms and hands were placed in a warm wrap for 5 minutes to optimize "arterialization" of the capillary bed. A finger stick capillary blood gas was drawn and analyzed using a Corning 178 Blood Gas Machine.

Capillary blood gases were analyzed by the staff of the institution's pulmonary laboratory. Radioimmunoassay for endorphins was performed by the investigator using a kit from the Immuno Nuclear Corporation of Stillwater, Minnesota. All procedures were conducted with strict adherence to the protocol provided by the corporation. Data were analyzed in the following manner: For comparison of more than two groups, ANOVA was used. If only two groups were compared, a student's t-test was used. Pearson's product-moment correlations were calculated rather than multiple regression analysis, because of the small size of the population (Table II).

Results
The hypothesis that patients with assisted NSVD (Groups 1, 3, and 4) would have a higher endorphin level than NSVD (Group 2) was not borne out. There was no significant difference in endorphin levels found among these groups.

The effect of complications at delivery, such as presence of nuchal cord, meconium staining, neonatal bradycardia, or use of forceps, was examined. There was no significant difference found among complicated and normal spontaneous vaginal deliveries (Table III).

Patients delivered by C-sections had the highest endorphin levels (148.5 pg/mL), which was puzzling since the literature suggests that there is no difference between vaginal delivery of C-section on endorphin levels. However, the study's results found that one subject in the C-section group had a very high endorphin level (300 pg/mL) compared to the rest. In reviewing her history it was found that her pregnancy had started as a twin gestation. One fetus was lost at approximately 6 weeks, and the pregnancy continued uneventfully. Whether this would precipitate release of more endorphin is unknown, but it certainly should be considered. Analysis of data was repeated with the beta-endorphin levels of this patient deleted (Table I). This reduced the mean endorphin levels in the C-section group considerably so that there was no significant difference between NSVD and C-sections for endorphin levels in cord blood.

The gestational age ranged from 37 to 42 weeks for NSVD and 37 to 41 weeks for C-sections. There was no significant difference found between these two groups.

Finally, the study looked at types of anesthesia during C-section, comparing patients who received epidural versus general anesthesia. Again, no significant difference between these two groups was found (Table IV).

Furthermore, analysis of data using Pearson's product-moment correlation coefficients revealed

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<th>Table II</th>
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<td>Cord endorphin level pg/mL</td>
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<tr>
<td>Type of delivery</td>
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<td>Prenatal history</td>
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<tr>
<td>Medications used for normal spontaneous vaginal deliveries (NSVD), i.e., analgesics, pudendal block, naloxone, epidural and general anesthesia</td>
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<tr>
<td>Problems at delivery</td>
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<tr>
<td><strong>Cord endorphin level pg/mL</strong></td>
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<tr>
<td>Length of labor in minutes</td>
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<td>Apgar 1 (1 minute)</td>
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<td>Apgar 5 (5 minutes)</td>
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<tr>
<td>Resuscitative measures at birth</td>
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<tr>
<td>Cord pH</td>
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<tr>
<td>Cord HCO₃</td>
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<tr>
<td>Capillary pH</td>
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<td>Capillary PO₂</td>
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<td>Capillary HCO₃</td>
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<td>Capillary beta-endorphin</td>
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<td>Capillary O₂ saturation</td>
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<td><strong>ANOVA Student's t-test</strong></td>
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<td><strong>Pearson product-moment correlations</strong></td>
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<th>Table III</th>
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<td><strong>Effect of complications during normal spontaneous vaginal deliveries (NSVD) on beta-endorphin levels</strong></td>
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<tr>
<td><strong>Group</strong></td>
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<tr>
<td>NSVD no complications</td>
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<tr>
<td>NSVD with complications</td>
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Table IV
Comparison of beta-endorphin levels between epidural and general anesthesia for cesarean sections

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects in group</th>
<th>Mean cord beta-endorphin (pg/mL)</th>
<th>Standard error (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section epidural</td>
<td>3</td>
<td>185.00</td>
<td>57.58</td>
</tr>
<tr>
<td>Cesarean section general</td>
<td>3</td>
<td>112.00</td>
<td>10.40</td>
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</table>

two significant findings. In the NSVD group, there was a direct correlation between cord beta-endorphins and capillary PCO₂ ($P < .05$) (Figure 2). In the C-section group, there was an inverse correlation between cord beta-endorphin levels and cord HCO₃⁻ ($P < .025$) (Figure 3).

Discussion

Beta-endorphin levels were not significantly different among patients undergoing various types of delivery, experiencing complicated versus uncomplicated labor, and those receiving general versus epidural anesthesia for cesarean section. These results support current findings in the literature.

Bridgens found no relationship between beta-endorphin in cord blood and other variables, including use of oxytocin, opioids, length of labor, or rupture of membranes. However, he did find that infants born to mothers receiving no anesthesia had a higher beta-endorphin level than those born to mothers receiving anesthesia.

A study by Moss and associates showed no correlation among cord endorphin levels and Apgar scores or gestational age. Shaaban and colleagues found no correlation among umbilical vein beta-endorphin concentration and the presence or absence of labor, and mothers who received opioids versus those who did not, and the mode of delivery. Steinbrook et al also showed no correlation between Apgar scores and maternal or umbilical beta-endorphin levels. Wardlaw and associates found no significant differences in cord endorphin concentration in relation to mode of delivery, presence or absence of opioid administration, length of labor, or rupture of membranes.

This study found an inverse correlation between cord beta-endorphin levels and cord HCO₃⁻ in the C-section group and a direct correlation between cord beta-endorphin levels and capillary PCO₂ in the newborn. These findings are indicative of respiratory acidosis in the newborn at delivery.

These results are certainly consistent with patients with high circulating levels of opioids. Bridgens wrote that there is a degree of hypoxia and acidosis associated with even a normal delivery, and so it is not unexpected that the study found an inverse relationship between cord beta-endorphin levels and cord HCO₃⁻. What is surprising is that this study found this correlation only in the C-section group. There is no explanation for it other than the small size of the population and unknown intervening variables.

The literature supports a relationship between beta-endorphins and fetal acidosis. Most
sources concur that, during gestation, beta-endorphin levels reach a peak at delivery.\textsuperscript{2,9,11–13} The highest cord levels of beta-endorphins are found when the fetus is hypoxic.\textsuperscript{13,15,19,22}

It is clinically important to note that all neonates in this study compensated well, as evidenced by good Apgar scores (6-9 at 1 minute and 9-10 at 5 minutes) and lack of respiratory problems from birth to discharge.

The direct correlation between cord beta-endorphin and newborn capillary $\text{PCO}_2$ is consistent with hypoventilation and may indicate central opioid ventilatory depression. However, clinical evidence of such depression was not seen, even in the presence of high cord beta-endorphin levels.

Chernick emphasizes that endorphins seem to play a role in ventilation in pathological situations.\textsuperscript{22} Shaaban and colleagues confirm that cord levels of endorphin were significantly elevated with fetal distress, as evidenced by prolonged bradycardia, late and prolonged variable fetal heart rate deceleration, and fetal acidosis.\textsuperscript{13}

The significance of the findings in this study is seriously tempered by the small sample size, but they do confirm the results of Puolakka et al.\textsuperscript{23} They found that in full-term healthy babies the possible depressive effect of beta-endorphin on respiration is of minor significance, but in asphyxiated newborns it may depress respiration still further.

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