INFLUENCE OF MEDICATION, PAIN AND PROGRESS IN LABOUR ON PLASMA β-ENDORPHIN-LIKE IMMUNOREACTIVITY

T. A. THOMAS, J. E. FLETCHER AND R. G. HILL

SUMMARY

Plasma β-endorphin-like immunoreactivity (β-ELI) was measured at intervals during labour in 42 patients. An increase in β-ELI occurred during labour and increased to a maximum during the second stage. The increase in β-ELI paralleled dilatation of the cervix. A correlation existed between the duration of labour and second stage β-ELI in patients with labours of more than 4 h duration. Analgesic drugs were associated with changes in β-ELI. The patients who received Entonox had greater plasma β-ELI concentrations than those who received pethidine. A significant difference in the second stage β-ELI existed between those who received only Entonox and those who received only pethidine. Induction and augmentation of labour were also associated with differences in β-ELI. Patients in spontaneous labour had significantly lower β-ELI than patients who had either artificial rupture of membranes or Syntocinon augmentation of labour.

Substances with morphine-like properties which occur naturally in the body are referred to as endogenous opioids. Most of these substances are peptides and they have now been found in the brain, pituitary, adrenal, blood, urine and milk (Leong Way, 1980). The opioid which we have studied, β-endorphin, is a large peptide containing 31 amino acids. It is widely believed to be one of the neuromodulatory substances involved in the control of pain perception and there are well described neuronal pathways in which β-endorphin has been identified (Bloom et al., 1978). It has produced analgesia to experimental noxious stimuli when injected into the ventricle of rats (Bradbury et al., 1976) and recently has been injected intrathecally to produce analgesia in intractable pain syndromes (Oyama, Jin et al., 1980) and labour (Oyama, Matsuki et al., 1980).

β-Endorphin is also present within the pituitary (Li and Chung, 1976) and is thought to be released into the circulation during periods of stress (Fraioli et al., 1980).

Pain, stress and marked changes in pituitary secretion occur during labour. A reduction in the appreciation of labour pain during the second stage is said to occur (Selwyn-Crawford, 1972). This is a period in labour when pituitary secretion of hormones is at a maximum (Swaab and Boer, 1979).

Accordingly we have studied the changing plasma β-endorphin-like immunoreactivity (β-ELI) during labour and have attempted to correlate β-ELI with various events and their progress in labour. Preliminary reports of some of these results have been made previously (Fletcher, Hill and Thomas, 1980; Fletcher, Thomas and Hill, 1980).

METHODS

The study was carried out in 42 patients with singleton pregnancies and who were between 17 and 37 yr of age. All of them gave their informed consent for blood samples to be taken and for pain scores to be obtained during labour. All pregnancies were between 38 and 43 weeks gestation, 22 patients were primiparous and 20 were multiparous. Spontaneous onset of labour occurred in 18 patients and in the remaining 24 labour was induced with Prostin pessaries or artificial rupture of the membranes. Cervical dilatation was assessed during routine vaginal examination by the attending midwife. Patients were excluded who, before labour, were receiving therapy likely to interfere with our assays or influence pituitary secretion (e.g. corticosteroids). Patients with endocrine abnormalities (e.g. diabetes) and those receiving anti-hypertensive therapy or sedatives for pre-eclampsia were also excluded. Seven analgesic regimens were identified. These were: no analgesia; pethidine only; Entonox only; pethidine and Entonox; pethidine, Entonox and extradural block; Entonox and extradural. A total of seven patients received pethidine and the remaining 35 received no analgesia, Entonox or an extradural, or both.

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Table I. Blood sampling times

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time of sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pre-labour control</td>
<td>(a) Induced labours approx 12 h before induction</td>
</tr>
<tr>
<td></td>
<td>(b) Spontaneous labours: approx. 36th week of pregnancy</td>
</tr>
<tr>
<td>(2) Early first stage</td>
<td>Dilatation of cervix less than 5 cm</td>
</tr>
<tr>
<td>(3) Late first stage</td>
<td>Dilatation of cervix greater than 5 cm</td>
</tr>
<tr>
<td>(4) Second stage</td>
<td>Within the 30 min preceding delivery</td>
</tr>
<tr>
<td>(5) Post partum</td>
<td>After completion of third stage and within 2 h of delivery</td>
</tr>
<tr>
<td>(6) Cord</td>
<td>From a placental umbilical vessel after completion of third stage</td>
</tr>
</tbody>
</table>

Five-millilitre blood samples were taken from an antecubital vein at the times indicated in table I. Five maternal samples and one cord blood sample were taken and placed in lithium heparin tubes. They were spun in a refrigerated centrifuge within 15 min of being taken and the supernatant plasma was stored at — 20°C. Peptides were extracted from plasma and assayed using the method described by Csontos and others (1979), which was modified to deal with 2-ml sample volumes. The samples were mixed with silicic acid (100 mg) which adsorbed the peptides and the resulting silicic acid-peptide complex was washed twice with distilled water (2 × 2 ml). Peptides were then desorbed from silicic acid with a hydrochloric acid 0.1 mol litre⁻¹: acetone (80:20 v/v) mixture 3 ml and the solvent mixture evaporated with nitrogen. The residue was dissolved in radioimmunoassay buffer 0.5 ml and the extract was stored at — 20°C. Assay was performed using the New England Nuclear Radioimmunoassay Kit (¹²⁵I) for β-endorphin so our results are recorded as β-endorphin-like immunoreactivity (β-ELI). The extraction system we have used is not specific for β-endorphin. It also concentrates similar molecules such as β-lipotropin (β-LPH) and the antibody in the NEN assay kit cross-reacts 50% with β-LPH. It has been variously estimated that 69–94% of total circulatory β-ELI is attributable to β-LPH, the remainder being β-endorphin (Bertagna et al., 1981). As only 50% β-LPH is likely to be detected in the NEN assay system, this would suggest between 12 and 47% of the concentrations we estimate are attributable to β-endorphin alone, an estimate confirmed by other workers (Genazzini, Facchinetti and Parrini, 1981).

![Graph](https://academic.oup.com/bja/article-abstract/54/4/401/264500/0)
P-endorphin in labour

Control Early first Late first Second Post Cord samples stage stage stage partum samples

Sample time

FIG 2 Plasma β-endorphin-like immunoreactivity concentration at each sampling interval during labour, mean values and SEM. □ Patients who did not receive pethidine; ● patients who did receive pethidine.

Pain scores were obtained immediately before or after each blood sample. Patients used a linear analogue pain scale to assess the severity of their pain at that time. The left-hand end of the line represented no pain (0%) and the right-hand end the worst pain imaginable (100%). The use of the scale was explained to patients when the control sample was taken.

RESULTS

β-ELI and progress in labour

Considerable variations in plasma β-ELI occurred, both within and between patients during labour.

An increase in assayed plasma concentrations of β-ELI was detected as labour progressed in all patients (fig. 1), which was more clearly seen when mean β-ELI was estimated for each sampling time (fig. 2).

β-ELI was also recorded in relation to the stage of labour as judged by cervical dilatation. A significant increase in β-ELI occurred as the cervix dilated except in patients who received pethidine (fig. 3).

The latter group had uniformly small values of β-ELI throughout early labour. The pethidine group are identified separately in figures 1–3 because of the possibility of feedback by this opiate on β-endorphin release from the pituitary.

Duration of labour, as judged by the attending midwife, in patients who did not receive pethidine, was plotted against β-ELI recorded in the second stage of labour to give some idea of the response time and capacity for the secretion of β-endorphin during labour. A correlation (r=0.81) exists between the plasma β-ELI in second stage and the duration of labour in patients with labours in excess of 4 h duration (fig. 4). Not all patients follow a linear relationship. Two patients (fig. 4) had long labours, but showed only a small increase in β-ELI. Both of these patients were exceptionally anxious. One of them was receiving a diuretic (bendrofluazide), a nasal decongestant (Dimotapp LA) containing two sympathomimetics and an antihistamine. The other patient was so apprehensive that she was difficult to examine vaginally and was stated to have a low pain threshold before labour began.
**FIG 3.** Mean plasma β-endorphin-like immunoreactivity and ACTH concentrations related to cervical dilatation, during the first stage of labour. ACTH results from Kauppila, Tuimala and Haapalahu (1974). ††Significantly different groups (Mann-Whitney U test $P<0.05$)

We have therefore excluded these two patients from the calculations in figure 4. The six patients with labours of less than 4 h duration showed a very rapid increase in β-ELI and five of them achieved high plasma concentrations in the second stage.

**β-ELI and pain in labour**

No correlation existed between β-ELI and pain scores at any stage of labour. Patients did, however, seem to have one of three types of β-ELI response patterns. The first response pattern showed a small increase (less than 2.5 times above control). The second response pattern showed a rather greater increase (2.5–4.5 times control) and the third response pattern showed the greatest change (more than 4.5 times control). No significant difference was detectable between the pain scores of the groups. An increase in pain scores occurred as labour progressed (table II).

![Diagram](https://academic.oup.com/bja/article-abstract/54/4/401/264500)
patients we have studied and this finding has been reported by other workers (Akil et al., 1979; Cson- tos et al., 1979). The change may be a response to stress, may be specifically related to pain perception or may have a totally different role. The correlation between plasma concentrations of pituitary–adrenal axis hormones and cervical dilata-
tion (Kauppila, Tuimala and Haapalahti, 1974) may be indicative of a stress response. β-ELI may play a role in this response and our results indicate that the increase in plasma β-ELI parallels that of plasma ACTH previously measured in experiments on stressed animals (Guillemin et al., 1977).

Because of the opioid nature of β-endorphin it

![Graph showing relationship between plasma β-ELI and duration of labour](https://academic.oup.com/bja/article-abstract/54/4/401/264500)

**FIG 4** Relationship between plasma β-ELI in second stage and duration of labour in patients who did not receive pethidme. □Patients with labour less than 4 h duration; ■ patients with labours of greater than 4 h duration; ○ patients included in regression line calculations; ● patients excluded from regression line calculations for reasons given in the text. Slope of regression line 0.053 ± 0.026; r = 0.81; P < 0.001.

**TABLE III.** Number of patients and mean β-ELI concentrations in each analgesic regimen group

*"Total" does not reflect the total number of patients in the study, as a complete set of blood samples was not obtained from all patients.

<table>
<thead>
<tr>
<th>Analgesics received before blood sampling</th>
<th>Early first stage</th>
<th>Late first stage</th>
<th>Second stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Mean plasma β-ELI (fmol ml⁻¹)</td>
<td>Number of patients</td>
</tr>
<tr>
<td>None</td>
<td>22</td>
<td>9.2</td>
<td>6</td>
</tr>
<tr>
<td>Pethidine only</td>
<td>2</td>
<td>10.6</td>
<td>3</td>
</tr>
<tr>
<td>Entonox only</td>
<td>7</td>
<td>12.1</td>
<td>11</td>
</tr>
<tr>
<td>Extralural only</td>
<td>2</td>
<td>12.6</td>
<td>6</td>
</tr>
<tr>
<td>Pethidine + Entonox</td>
<td>3</td>
<td>8.5</td>
<td>3</td>
</tr>
<tr>
<td>Pethidine, Entonox + extralural</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Entonox + extralural</td>
<td>1</td>
<td>37.8</td>
<td>7</td>
</tr>
<tr>
<td>Total*</td>
<td>37</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>
might be expected that a correlation would exist between $\beta$-ELI and pain scores, but we have found no significant relationship linking them.

We have found a relationship between $\beta$-ELI and different methods of analgesia. In the patients studied, Entonox was associated with a greater increase in $\beta$-ELI than other forms of analgesia. It has been shown that nitrous oxide analgesia is antagonized by naloxone (Gillman, Kok and Lichtigfeld, 1980) and our results indicate that administration of nitrous oxide during labour is accompanied by $\beta$-endorphin release into the bloodstream. Large concentrations of plasma $\beta$-endorphin following the administration of Entonox may be an indication of the mechanism of analgesic action of nitrous oxide.

Pethidine and extradural blocks were both as-

<table>
<thead>
<tr>
<th>Induction agents received before blood sampling</th>
<th>Early first stage</th>
<th>Late first stage</th>
<th>Second stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Mean plasma $\beta$-ELI (fmol ml$^{-1}$)</td>
<td>Number of patients</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>14.1</td>
<td>5</td>
</tr>
<tr>
<td>ARM</td>
<td>2</td>
<td>12.6</td>
<td>2</td>
</tr>
<tr>
<td>Syntocinon</td>
<td>3</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Prostin</td>
<td>1</td>
<td>13.5</td>
<td>1</td>
</tr>
<tr>
<td>Prostin + Syntocinon</td>
<td>9</td>
<td>10.2</td>
<td>2</td>
</tr>
<tr>
<td>ARM + Syntocinon</td>
<td>2</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td>Prostin + ARM + Syntocinon</td>
<td>5</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
<td><strong>30</strong></td>
<td><strong>24</strong></td>
</tr>
</tbody>
</table>
associated with lower levels of β-ELI in our patients. It is tempting to suggest that the low activity measured following administration of pethidine indicate a negative-feedback effect of this opiate on pituitary secretion of β-endorphin. The low levels that we have found after extradural analgesia with bupivacaine cannot be accounted for by the same hypothesis. It has been postulated that neurogenic blockade by extradural local anaesthetic agents interrupts the pathways responsible for mediating the afferent limb of the endocrine metabolic reflex during surgery (Hagen, Brandt and Kehlet, 1980). We believe that the removal of the pain appreciation and stress of labour reflected by lower plasma cortisol concentrations (Maltau, Eielsen and Stokke, 1979) and small acid–base changes (Pearson and Davies, 1974), may be the reason for the low β-ELI values found in patients receiving extradurals. The absence of stress responses from higher centres in the central nervous system would complement a neurogenic block of afferent pathways in stress response reflexes.

The suggestion that different pain levels are responsible for the association between β-ELI and methods of analgesia is not supported by our results as we found no correlation between pain scores and β-ELI in any group of patients nor any correlation of pain scores and method of analgesia. The greatest pain scores were commonly recorded by patients in the second stage of labour and this result contradicts the claim that second stage is the least painful part of a woman's labour. Peripheral events do have an effect on central processes, however. The influence of ARM on circulating β-ELI is an example of this link as ARM inevitably results in vaginal and cervical stimulation. The cervix is richly innervated with pain receptors and is arguably the origin of much of the pain in labour, so early stimulus of this site may result in earlier and greater increases in β-ELI. Vaginal distension has been shown in rats to produce analgesia which is reduced by naloxone (Hill and Ayliffe, 1981) and we suggest that a direct cause-and-effect relationship exists between ARM and an increase in plasma β-ELI produced as part of an endogenous analgesic system.

Before further investigation of the role of plasma endogenous opioids in pregnancy and labour is possible, more information must be obtained as to the absolute identity of these circulatory β-endorphin-like peptides. In order to overcome the problem of non-specificity of the antiserum and in an attempt to improve sensitivity, work is currently in progress both to develop a better radioimmunoassay and to fractionate plasma extracts using high-performance liquid chromatography. It is hoped that these methods will aid our identification of the opioid peptides and their role in pregnancy and labour.

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l'antinoceptive action de la stimulation vaginale dans le rat.


INFLUENCE DE LA THERAPEUTIQUE, DE LA DOULEUR ET DE L’AVANCEMENT DU TRAVAIL SUR L’IMMUNOREACTIVITE DE TYPE BETA-ENDORPHINE DU PLASMA

RESUME

L’immunoreactivité plasmatique de type -endorphine (-ELI) a été mesurée à intervalles réguliers au cours du travail chez 42 patientes. Une augmentation de -ELI apparaissait au cours du travail et augmentait pour atteindre un maximum pendant la deuxième phase. L’élévation de -ELI était parallèle à la dilatation du col. Il existait une corrélation entre la durée du travail et la -ELI au cours de la deuxième phase chez les patientes dont le travail dura plus de 4 h. L’administration d’analgésiques correspondait à des modifications de -ELI. La -ELI plasmatique des patientes qui recevaient de l’Entonox était significativement plus importante que celle des patientes qui recevaient de la pethidine. Il existait une différence significative dans la -ELI de la deuxième phase chez les patientes qui ne recevaient que de l’Entonox par rapport à celles qui ne recevaient que de la pethidine. Le déclenchement et l’accélération du travail s’accompagnaient aussi de différences de -ELI. Les patientes avec un travail spontané avaient des -ELI significativement plus basses que celles dont le travail était accéléré par la rupture artificielle des membranes ou le Syntocinon.

DER EINFLUSS VON MEDIKAMENTATION, SCHMERZ UND WEHENTATIGKEIT AUF DIE PLASMA-ß-ENDORPHINÄHNLICHE IMMUNOREAKTIVITÄT

ZUSAMMENFASSUNG


INFLUENCIA DE LA MEDICACION, DEL DOLOR Y DEL PROGRESO DEL PARTO ANALIZADA EN FUNCION DE LA INMUNOREACTIVIDAD DEL TIPO BETA-ENDORFIN DEL PLASMA

SUMARIO

Se midió la inmunoreactividad de tipo -endorfina del plasma (-ITE) a diversos intervalos del parto en 42 pacientes. Durante el parto se produjo un incremento de la -ITE, alcanzando este incremento su punto álgido durante la segunda fase. El incremento de la -ITE fue paralelo a la dilatación del cervix. En aquellas pacientes cuyo parto duró más de 4 horas, tuvo lugar una correlación entre la duración de dicho parto y la -ITE de la segunda fase. Las drogas analgésicas vinieron asociadas con cambios en la -ITE. Las pacientes que recibieron Entonox presentaron mayores concentraciones de -ITE en el plasma que aquellas que recibieron pethidina. Hubo una diferencia significativa en la -ITE de la segunda fase entre aquellas pacientes que recibieron Entonox solamente y aquellas otros que recibieron tanto pethidina. La inducción y el incremento de la intensidad del parto vinieron también asociadas con diferencias en la -ITE. Las pacientes cuyo parto fue expontáneo presentaron una -ITE significativamente inferior que las pacientes a los que se les practico la ruptura artificiel de las membranas o la aceleración del proceso de parto mediante Syntocinon.