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Immunoreactive β-Endorphin in Maternal and Umbilical Cord Plasma

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= Abstract = Immunoreactive β-endorphin was measured in the umbilical arterial and venous plasma of 55 neonates, in venous plasma of 24 women immediately after vaginal delivery and 16 normal nonpregnant women. After birth, β-endorphin concentrations in maternal and umbilical cord plasma were significantly higher than those in normal nonpregnant women. There was no arterio-venous difference in the umbilical cord plasma. Umbilical arterial plasma β-endorphin level was not affected by the mode or route of delivery but umbilical venous plasma β-endorphin level was significantly higher after spontaneous vaginal delivery than at elective cesarean section. Umbilical cord plasma β-endorphin level was significantly elevated in conjunction with fetal distress. No significant correlation was found between maternal and umbilical cord plasma β-endorphin levels.

Key Words: ***Immunoreactive β-endorphin, Mode of delivery, Cord plasma, Fetal distress***

INTRODUCTION

Naturally occurring substances with opiate-like properties, collectively called opioids, have been shown to exist in the pituitary and brain tissue of all vertebrates. Of particular interest to endocrinologists has been the discovery that one of the most potent of these, a 31 aminoacid peptide termed β-endorphin, forms part of a large multifunctional precursor molecule, sometimes termed pro-opiomelanocortin that contains within itself the sequences of adrenocorticotropic hormone, α- and β-melanocyte-stimulating hormone, and β-lipotropin (Mains *et al.* 1977; Roberts and Herbert 1977).

It has been reported in rats and humans that β-endorphin and adrenocorticortropic hormone are released simultaneously from the anterior pituitary into blood in response to stress (Guillemin *et al.* 1977; Höllt *et al.* 1979; Nakao *et al.* 1980). Adrenocorticotropic hormone secretion is well known to rise during labor to reach a maximum level at delivery (Allen *et al.* 1973; Winters *et al.* 1974). The stages of labor and parturition can be regarded as moments of extreme physical stress for both mother and fetus. Therefore several investigators have confirmed activation of the β-endorphin system during labor and delivery (Goland *et al.* 1981; Fletcher *et al.* 1980; Genazzani *et al.* 1981; Csontos *et al.* 1979). However it is not clear whether the mode or route of delivery affects maternal and cord plasma β-endorphin level or not. Peripheral plasma concentrations of β-endorphin were found to elevate in association with hypoxia and acidosis in human adults (Yanagida and Corssen 1981). This study was undertaken in order to determine maternal and cord plasma β-endorphin levels immediately after delivery and to assess the effects of the mode or route of delivery and intrapartum fetal distress upon cord plasma β-endorphin level.

MATERIALS AND METHODS

1. Subjects: Fifty-five term infants were studied; 15 were delivered vaginally after spontaneous labor, 17 by vacuum extraction, 14 by elective cesarean section, and 9 by emergency cesarean section. Table I gives pertinent data on the clinical characteristics of these groups. Seven of the 32 newborn infants who were delivered by vacuum extraction or emergency cesarean section had persistent latent decelerations during labor. One-minute Apgar scores in these infants were less than 6. In

Table 1. Clinical characteristics of study groups (mean±S.E.)

	Spotaneous vaginal delivery (n=15)	Vacuum delivery (n=17)	Elective cesarean section (n=14)	Emergency cesarean section (n=9)
Maternal age(years)	27.93 ± 0.68	28.06 ± 0.53	28.0 ± 1.22	26.78 ± 0.89
Gestational age(weeks)	41.07 ± 0.36	40.59 ± 0.39	39.57 ± 0.41	40.22 ± 0.66
Birth weight(kg)	3.09 ± 0.08	3.21 ± 0.10	3.16 ± 0.16	3.33 ± 0.25
Placental weight(g)	660.67 ± 30.09	650.0 ± 24.77	670.0 ± 24.77	696.67 ± 36.97

other 48 infants without apparent fetal distress one-minute Apgar scores were in the range of 8 to 10. Sixteen nonpregnant volunteers, aged 14-31 year, were also studied for comparison.

2. Collection of samples: Umbilical venous and arterial blood samples were drawn simultaneously from the placenta in utero immediately following cord ligation and section. Simultaneous maternal and umbilical blood samples were obtained in 24 cases after vaginal delivery without apparent fetal distress. The blood samples were taken in chilled polypropylene tubes containing 1 mg/ml EDTA (ethylene diamine tetraacetic acid), centrifuged at 4°C for 10 minutes at 2500 g. The supernatant plasma was stored at -70°C until assay. Samples were thawed only once.

3. Radioimmunoassay: Immunoreactive β-endorphin was determined without extraction using a β-endorphin radioimmunoassay kit purchased from New England Nuclear (Boston, Mass). We modified the procedure as follows. Samples and standard of 100 μl were incubated at 4°C for 24 hours with 30 μl antiserum containing antibodies against 0.002 μCi/30 μl [^{125}I] human β-endorphin. After incubation, unbound [^{125}I] human β-endorphin and human β-endorphin were separated from human β-endorphin bound to antibody by centrifugation with 100 μl charcoal. [^{125}I] activity in the supernatants was counted in Packard autogamma counter. Standards and samples were counted in duplicate. The β-endorphin antiserum used in this study crossreacts to the extent of 50% with β-lipotropin but not with (<0.01%) α-endorphin, leucine enkephalin, methionine enkephalin, or α-melanocyte stimulating hormone. Current assay sensitivity is 1 pg/0.01 ml. The intraassay coefficient of variation was 11%.

RESULTS

1. Plasma immunoreactive β-endorphin concentrations in normal nonpregnant women and parturients immediately after vaginal delivery (Fig. 1): The mean (± S.E) β-endorphin level of the plasma of 16 nonpregnant women was 63.69 ± 5.63 pg/ml. Mean plasma β-endorphin concentrations were significantly higher in parturients immediately after vaginal deliveries than in the nonpregnant state ($P<0.001$). No significant difference in mean plasma β-endorphin levels relating to the mode of delivery was observed. Mean (± S.E.) concentrations were 167.62 ± 221.4 pg/ml for normal spontaneous vaginal deliveries, and

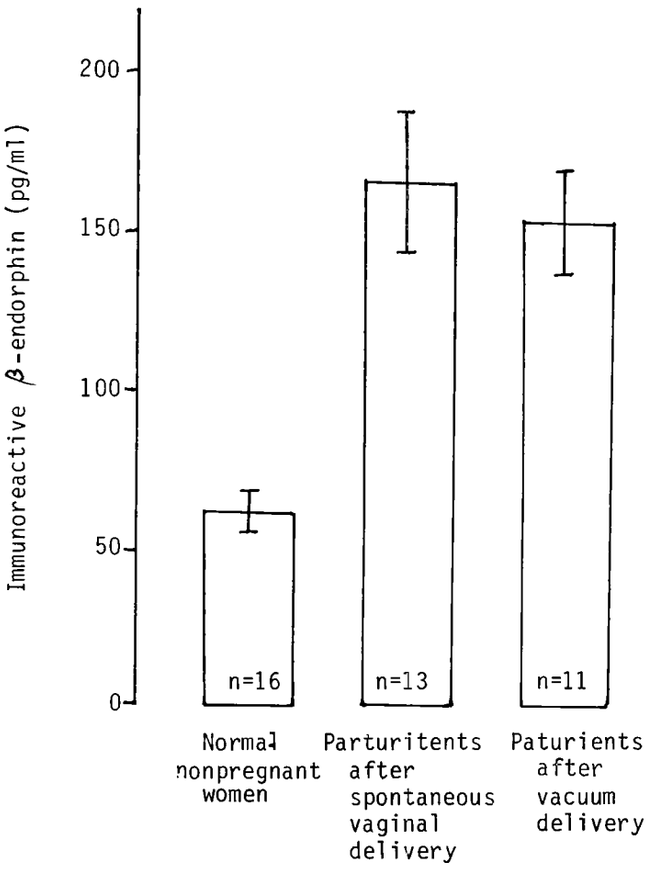

Fig. 1. Plasma immunoreactive β-endorphin levels in nonpregant women and parturients after spontaneous vaginal delivery and vacuum delivery. Bars represent means ± S.E.

Table 2. Cord plasma immunoreactive β-endorphin levels in newborns delivered by various routes and modes without and with apparent fetal distress (mean ± S.E.)

Delivery route and mode	Fetal distress	No.	β-endorphin level (pg/ml)	
			Umbilical artery	Umbilical vein
Spontaneous vaginal delivery	−	15	125.53 ± 23.86[1)]	141.93 ± 13.42[4)]
Vacuum delivery	−	13	107.17 ± 13.24	118.46 ± 18.16
Elective cesarean section	−	14	91.21 − 11.59	97.50 ± 7.73[5)]
Emergency cesarean section	−	6	115.17 ± 14.63	109.33 ± 12.80
Vacuum delivery and emergency cesarean section	−	19	110.11 ± 17.58[2)]	115.58 ± 56.18[6)]
Vaccum delivery and emergency cesarean section	+	7	181.43 ± 12.69[3)]	197.14 ± 14.72[7)]

1), 3): $P<0.01$ 2), 3): $p<0.001$ 4), 5): $p<0.01$
4), 7): $p<0.05$ 6), 7): $p<0.005$

154.0 ± 19.37 pg/ml for vacuum deliveries.

2. Immunoreactive β-endorphin concentration in umbilical cord plasma: In 24 cases from which simultaneous maternal and umbilical cord blood samples were obtained immediately after vaginal delivery, the mean (± S.E.) β-endorphin level in maternal vein (161.38 ± 14.67 pg/ml) was significantly higher ($P<0.05$) than that in umbilical artery (126.21±9.57 pg/ml) but not in umbilical vein (136.67±12.57 pg/ml). Table 2 shows cord plasma β-endorphin levels in newborns delivered by various routes or modes without and with apparrent fetal distress. Mean β-endorphin levels in umbilical venous and arterial plasma were significantly higher than levels in normal nonpregnant women ($p<0.05$). There was no significant difference in the mean β-endorphin levels between the umbilical artery and umbilical vein, irrespective of the mode or route of delivery. No significant differences in the mean β-endorphin levels in umbilical artery relating to the mode or route of delivery were found. Similarly, the mean umbilical venous β-endorphin level in newborn infants after normal spontaneous vaginal delivery didn't differ from that in infants delivered by vacuum extraction or emergency cesarean section but was significantly higher than that in infants born by elective cesarean section ($P<0.01$). The mean umbilical venous and arterial β-endorphin levels found after fetal distress were significantly higher than those measured in the absence of fetal distress ($p<0.001$). There were no significant sex differences in the mean umbilical venous and arterial levels.

3. Relationships of cord plasma immunoreactive β-endorphin level with maternal plasma level, fetal weight and placental weight: As shown in Fig. 2, there was a significant correlation between umbilical arterial (x) and umbilical venous (y) β-endorphin levels ($y= 0.746 x + 37.65$, $r= 0.66$, $p<0.05$, $n=55$) but no correlation was found between maternal and cord plasma β-endorphin levels. There were no significant relationships of cord plasma β-endorphin level with

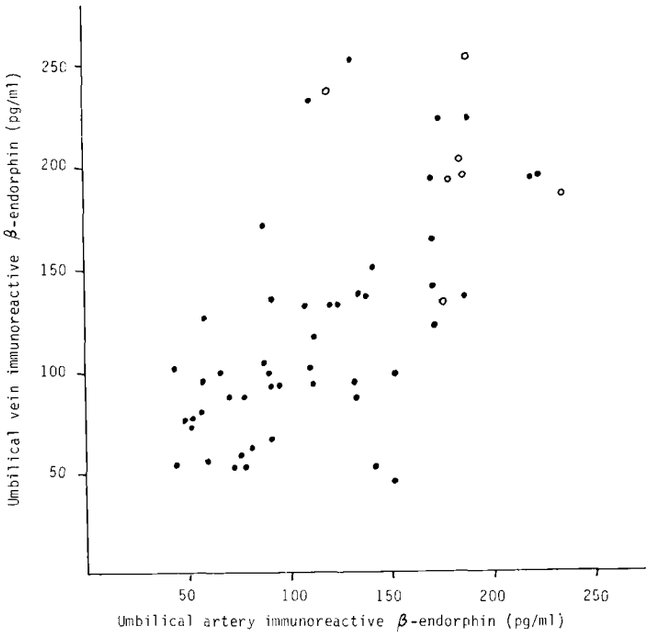

Fig. 2. Correlation of umbilical arterial (x) and venous (y) immunoreactive β-endorphin concentrations measured simultaneously in newborn infants without (dots) and with (circles) apparent intrapartum fetal distress. The regression line equation $y=0.746 x+37.65$ ($r=0.66$, $p<0.05$, $n=55$)

fetal weight and placental weight.

DISCUSSION

The mean of the venous plasma β-endorphin levels reported in this paper for 16 normal nonpregnant women are higher than those of Wardlaw *et al.* (1979) and Furuhashi *et al.* (1982), lower than those of Wilkes *et al.* (1980) and Moss *et al.* (1982) and generally agrees with those obtained by Kimball *et al.* (1981) and Goebelsmann *et al.* (1984). Some of these differences may be due to differences in methodology, particularly those caused by variations in antibody specificity.

We have found that postpartum maternal plasma β-endorphin levels are significantly higher than concentrations in nonpregnant state as previously reported by several other investigators (Csontos *et al.* 1979; Genazzani *et al.* 1981; Fletcher *et al.* 1980; Wilkes *et al.* 1980; Kimball *et al.* 1981; Goland *et al.* 1981). Recently tissue concentrations of β-endorphin in the rat brain has been shown to undergo alterations associated with pregnancy and parturition (Wardlaw and Frantz 1983).

The physiological significance of elevated maternal β-endorphin level is conjectural at this time. It may reflect the extreme stress of the birth process. The analgesic properties of β-endorphin are well known (Loh *et al.* 1976). Thus an increase in β-endorphin level may help to render the mother less sensitive to the pain of labor and parturition. It is also possible that it mediates the mother's postpartum gratification and tends to program maternal and infant affect and behavior toward each other.

There are few studies about the effect of the mode or route of delivery on maternal and cord plasma β-endorphin level. It has been reported that maternal plasma β-endorphin level is significantly higher after vaginal delivery than following elective cesarean section (Kimball *et al.* 1981; Facchinett *et al.* 1983). In the present study there were no significant differences in mean maternal β-endorphin levels relating to the mode of delivery as shown in Fig. 1. Wardlaw *et al.* (1979) and Shaaban *et al.* (1982) found no significant differences between umbilical venous plasma β-endorphin levels of newborn infants delivered vaginally, by elective cesarean section, and by emergency cesarean section. However in the present study umbilical venous β-endorphin level was significantly higher after spontaneous vaginal delivery than following elective cesarean section. This finding is partially in accordance with that of Räisänen and Laatikainen (1985) who reported that both umbilical venous and arterial plasma β-endorphin levels are significantly higher after spontaneous labor than at elective cesarean section. Puolakka *et al.* (1982) also demonstrated that umbilical plasma β-endorphin level after vacuum extraction is significantly higher than that after vaginal birth.

Our data indicate that intrapartum fetal distress as evidenced by prolonged late decelerations is associated with significant elevations in umbilical venous and arterial β-endorphin concentrations. This finding is in agreement with the results of Shaaban *et al.* (1982) and Goebelsmann *et al.* (1984). Recent studies have established an inverse relationship between arterial plasma β-endorphin immunoreactivity and arterial pO_2 and pH(Wardlaw *et al.* 1979; Yanagida and Corssen 1981). Our finding, with these observations seems to lend support to the hypothesis, according to which fetal hypoxia and acidosis may provoke the release of β-endorphin which in turn affect fetal heart fate patterns. Actually, by administering naloxone, a potent narcotic antagonist, to a mother whose fetus was severely depresed, normal beat-to-beat- variability was restored while severe fetal acidosis remained essentially unchanged (Goodlin 1981). In experimental animal response to hypoxia increases with gestational maturation and older fetus has higher concentrations of plasma β-endorphin immunoactivity with hypoxia than younger fetus (Stark *et al.* 1982). Elevated concentrations of amniotic fluid β-endorphin immunoactivity have been found in pregnancies complicated by fetal distress (Gautray *et al.* 1977) or premature labor and intrauterine growth retardation (Divers *et al.* 1982).

The physiologic role of β- endorphin in the fetoplacental unit and the newborn infant remains incompletely understood although one may assume that β-endorphin modulates the central regulation of hypoxia-induced changes in fetal heart rate patterns. It is conceivable that one of the roles of β-endorphin is to reduce the level of pain the fetus must endure during labor. Since opiates are known to depress the respiratory center, the increased β-endorphin secretion may not be only beneficial. In full-term healthy babies, the possible depressive effect of β-endorphin on respiration is very likely of minor significance but in asphyxiated newborns high endorphin levels may depress respiration still further.

Potential sources of the elevated levels of β-en-

dorphin circulating in the fetus constitute the fetal pituitary, the maternal plasma, and the placenta. β-endorphin was detected in human placental tissue (Nakai *et al.* 1987; Fraioli and Genazzani; 1980) and Liotta *et al.* (1982) demonstrated that cultured human placental cells produce β-endorphin. Facchinetti *et al.* (1982) reported that newborn infants are able to produce β-endorphin at least during the first hours of life. In the present study there was no significant correlation between simultaneous maternal and cord plasma β-endorphin concentrations. These results suggest that fetal β-endorphin may not originate from maternal plasma but from the placenta as well as fetus.

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= 국문초록 =

모체 및 제대혈장 β-endorphin에 관한 연구

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김정구 · 이진용 · 장윤석

분만직후 모체 및 제대혈장 β-endorphin 치의 변화 분만방식 및 태아곤란증이 제대혈장 β-endorphin 치 미치는 영향을 알아보고자 신생아 55명의 제대동맥 및 정맥혈장, 분만직후의 산욕부 24명과 정상 비임부 16명의 혈장에서 β-endrophin를 측정하여 다음과 같은 결과를 얻었다.

1. 분만직후의 산욕부 및 제대혈장 β-endorphin 치는 정상비임부의 것보다 유의하게 높았다.
2. 제대정맥과 동맥혈장 β-endorphin 치의 사이에 유의한 차이가 없었다.
3. 분만방식은 제대동맥혈장 β-endorphin 치에 유의한 영향을 주지않았으나 자연질식분만을 한 신생아제대정맥혈장 β-endorphin 치는 선택적 제왕절개술식 분만을 한 신생아의 것보다 유의하게 높았다.
4. 태아곤란증을 가진 신생아 제대혈장 β-endorphin 치는 정상 신생아의 것보다 유의하게 높았다.
5. 제대혈장 β-endorphin 치는 모체혈장의 것과 유의한 상관관계가 없었다.