β–Endorphin in Multiple Trauma Victims

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ABSTRACT: ***Background:*** In animals and in humans, stress is known to be accompanied by increased β-endorphin secretion. ***Methods:*** Blood samples from 47 patients in a state of stress induced by multiple trauma were assessed for β-endorphin concentration by radioimmunoassays. ***Results:*** We show that there is a clearcut correlation (Spearman's R = 0.72, P = 2.1 x 10^{-6}) between the level of consciousness evaluated with the Glasgow score and levels of circulating β-endorphin. In addition, ß-endorphin levels are higher than normal in patients with Glasgow coma with scores higher than seven, and lower than normal in those with Glasgow coma scores of seven or less. Finally, in the complete absence of stress (shown by the lack of brain activity in six irreversible coma patients), there is a severe drop in the level of circulating β-endorphin. ***Conclusion:*** β-endorphin serum levels correlate with the state of consciousness of multiple trauma patients.

RÉSUMÉ: La ß-endorphine chez les polytraumatisés. ***Objectif:*** L'état de stress, chez l'homme comme chez l'animal, est connu pour être accompagné dune élévation du taux de ß-endorphine circulante. Le but de notre étude a été de rechercher une éventuelle corrélation entre le niveau de vigilance (évalué par le score de Glasgow) de patients en état de stress intense (polytraumatisés) et le taux de ß-endorphine plasmatique. ***Méthodes:*** La concentration en ß-endorphine a été déterminée par radioimmunodosages dans des échantillons de sang veineux de 47 patients polytraumatisés. ***Résultats:*** Il semble exister une corrélation (Spearman's R = 0.72, P = 2.1 x 10^{-6}) entre le score de Glasgow et le taux de ß-endorphine plasmatique. D'autre part il existe un effondrement de la ß-endorphine plasmatique chez certains patients dépourvus d'activité cérébrale. ***Conclusion:*** La ß-endorphine pourrait être un marqueur potentiel de l'état de conscience chez les polytraumatisés.

Can. J. Neurol. Sci. 1995; 22: 160-163

The anti-hypotensive effects of naloxone, a morphine antagonist, in septic shock,[1-3] or hypovolemic shock[4,5] suggested that endorphins are released during shock. This was confirmed by direct assays of β-endorphin.[6,7] Inversely, the administration of β-endorphin led to hypotension.[1] Some authors believe that β-endorphin release is due primarily to stress.[8,9] Thus, stress in rats caused by repeated electric shock to the paws led to increased cerebral levels of β-endorphin.[10,11] Surgical stress in human is associated with increased levels of blood β-endorphin.[12] Other authors believe that opioid release is secondary to pain.[13-15] It is nevertheless difficult to dissociate the two phenomena since pain always causes a stress.

Based on these observations, the dual aim of the present study was to i) determine if there existed abnormalities in blood β-endorphin levels in patients subjected to an intense stress, in the present case multiple trauma patients, and ii) use venous samples from brain dead patients in order to determine if the complete absence of afferent pathways, and thus of stress, was not accompanied by changes in circulating β-endorphin levels.

Patients and Methods

Forty-seven multiple trauma patients (34 men and 13 women), as well as 35 control subjects, were included in this study (see Table 1). The control group was composed of healthy volunteers recruited from the hospital staff. All patients were admitted to the intensive care department of the CHU Nord (University Teaching Hospital North, Marseille, France). Blood samples for assaying β-endorphin were taken 3 to 8 hours after the multiple trauma accident. Patients having received a morphine-based treatment or general anesthetics were excluded from the study. At the moment the sample was drawn from each patient for β-endorphin assay, the following were also determined: heart rate, systolic blood pressure, the Injury Severity Score (ISS, 16), the Simplified Acute Severity Score (SAPS, 17) and the Glasgow score.

In addition, the study also included six patients (4 men and 2 women, 21-34 years old), who at the moment of the study were brain dead (see Table 2) for more than 24 hours and who no longer received treatment other than respiratory assistance.

Sampling method. During the admission workup in the Intensive Care Department, 3 ml of venous blood were drawn over EDTA for assaying β-endorphin. The samples were immediately placed in ice and then centrifuged at 4°C. The supernatants were recovered and frozen (–80°C) before assay.

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RECEIVED FEBRUARY 22, 1994. ACCEPTED IN FINAL FORM NOVEMBER 9, 1994.

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Table 1: Clinical data concerning the multiple trauma patients included in this study (irreversible coma patients are shown in Table 2). At the moment the sample was drawn from each patient for ß-endorphin assay, the following were also determined: heart rate, systolic blood pressure, the Injury Severity Score (ISS), the Simplified Acute Severity Score (SAPS) and the Glasgow score.

PATIENTS								CONTROLS	
Age/Sex	**Heart Rate**	**Blood Press**	**SAPS**	**ISS**	**Glasgow score**	**Cranial injury**	**β-endorphin plasma level**	**β-endorphin plasma level**	**Age/Sex**
22/M	52	100	16	54	5	Yes	7	7	25/M
42/M	45	220	22	34	6	Yes	10	12	21/M
78/M	105	150	21	34	13	Yes	25	7	33/F
25/M	70	140	8	25	15	No	11	4	25/M
25/M	125	110	9	34	8	Yes	7	14	24/F
22/M	104	170	13	26	3	Yes	7	10	27/M
59/M	111	140	10	38	6	Yes	6	13	28/M
27/M	132	100	15	41	15	No	16	6	31/M
39/F	135	85	11	25	4	Yes	6	5	19/F
42/M	45	220	22	34	15	Yes	25	5	36/M
25/M	120	110	25	8	15	No	13	5	42/M
43/F	140	150	10	38	7	Yes	13	6	33/M
23/M	120	110	15	41	15	No	8	11	50/F
40/F	160	90	11	25	15	No	15	6	31/M
45/M	120	110	11	34	15	No	23	5	24/F/M
27/M	142	180	14	17	15	No	20	9	25/F
22/M	73	120	9	41	6	Yes	6	13	28/M
29/M	150	60	14	34	4	Yes	3	9	29/F
22/F	104	170	13	26	3	Yes	17	10	36/M
25/M	110	120	12	25	12	Yes	20	5	35/M
22/F	120	110	15	41	5	Yes	5	10	24/M
22/M	104	170	13	26	3	Yes	5	20	27/M
25/M	110	125	9	34	7	No	5	6	54/M
27/M	132	100	15	41	7	Yes	5	18	34/M
35/M	140	160	12	34	15	No	30	5	35/F
23/M	120	140	10	38	7	Yes	11	22	37/F
24/F	150	170	15	41	14	Yes	29	22	26/F
25/M	100	160	13	26	12	No	7	16	27/F
29/M	142	180	14	17	15	Yes	25	16	31/F
70/F	76	120	9	41	6	Yes	9	13	33/F
24/F	150	60	14	34	4	Yes	6	5	34/F
25/M	130	120	14	26	12	No	14	12	49/M
27/F	160	100	11	25	15	No	9	16	31/F
28/M	140	80	14	38	4	Yes	5	12	33/M
29/F	100	140	12	26	12	Yes	21	15	33/F
30/M	160	80	14	34	3	Yes	5		
24/M	140	60	16	32	4	No	5		
25/M	150	170	15	41	8	Yes	13		
26/M	135	85	11	25	4	Yes	5		
22/F	110	140	10	38	6	Yes	6		
21/M	110	120	11	25	14	Yes	26		
20/F	110	120	12	25	12	No	13		
19/M	132	100	15	41	12	Yes	8		
27/M	120	100	17	41	6	Yes	6		
35/M	110	120	10	25	12	No	20		
29/F	150	110	10	22	7	Yes	12		
31/M	130	114	10	22	6	Yes	10		
Mean age 30	119	123	13.2	31	9.1		12.1	10.5	31.7
SD 12	28	38	3.6	8.6	4.5		7.5	5.2	7.7

https://doi.org/10.1017/S0317167100040245 Published online by Cambridge University Press

Table 2: Clinical data on six brain dead patients included in the study. The criteria adopted for diagnosing irreversible coma were: Complete abolition of spontaneous breathing; abolition of all activity in the region of cranial nerves; absence of all electroencephalographic electrical activity in the course of two 10 minute evaluations at maximal amplitude, practiced 24 hours apart; absence of any toxic or drug product; absence of hypothermia. The Glasgow score as well as the ß-endorphin levels are also shown.

Age/Sex	EEG Activity	Glasgow Coma Scale	β-endorphin blood level
21/M	no	3	< 5
23/M	no	3	< 5
24/M	no	3	< 5
31/F	no	3	< 5
34/F	no	3	< 5
22/M	no	3	6

Radioimmunoassay. β-endorphin concentrations were determined by radioimmunoassay (RIA) in human sera after extraction with the silicic acid absorption method. RIA were performed using the β-endorphin ^{125}I-RIA kit (NEN Research Products, Les Ulis, France), as previously described.[18,19] Sensitivity was defined by ED_{50} = 3pg/ml. Assays were run in duplicate.

Cross-reactions. Cross-reactivity with β-LPH was 50% on a molar basis. Other opioid peptides (met-enkephalin, leu-enkephalin, dynorphin 1-8, dynorphin 1-17) did not interfere with the assay.

Stasistical analysis. The Mann-Whitney test was used to compare the results. The six patients in irreversible coma were excluded from this statistical analysis.

Results

There was no significant difference in β-endorphin concentrations between multiple trauma patients and controls (Mann-Whitney test, S = 777, p = 0.26, see Table 1). In addition, there was no significant difference between the victims of head injuries (N = 32 cases) and those without head injury (N = 15, Mann-Whitney test: S = 176, p = 0.068). There was nevertheless a correlation between the Glasgow score and β-endorphin levels assayed in multiple trauma patients (Spearman's R = 0.72, p = 2.1 x 10^{-6}, see Figure). Furthermore, if we consider patients whose Glasgow score was higher than 7 (N = 21), the mean β-endorphin level in these patients was 16.5 with a significant increase (Mann-Whitney test: S = 187, p = 6 x 10^{-4}) in comparison to controls (mean = 10.5). If we consider those patients in whom the Glasgow score was less than or equal to 7 (N = 26), the mean β-endorphin level was 8.6, thus significantly reduced (S = 346, p = 0.035) in comparison to controls. There is no correlation between β-endorphin plasma levels and others injury scales (SAPS / β-endorphin: Spearman's R = 0.38 p > .05; ISS / β-endorphin: R = 0.42 p > .05).

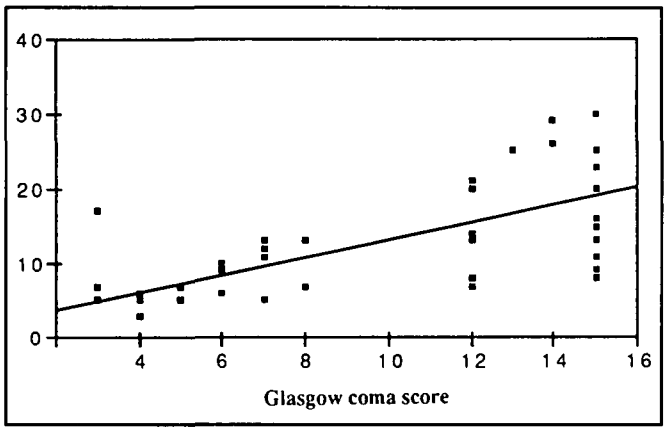

Figure: *β-endorphin plasma level as a function of Glasgow coma scale, evaluated in 47 patients with multiple trauma.*

In the six brain dead patients, it was noted that β-endorphin levels were very low (see Table 2). With the exception of these patients, there were no other deaths.

Discussion

Endogenous opioids are involved in a large and varied number of physiological processes, including gastrointestinal motor function, feeding behavior, epilepsy or some mental disorders (see 20 for review). The majority of research on this subject, however, has involved the participation of these neuropeptides in pain and stress.

Correlations between the Glasgow score and cerebral blood flow in adults,[21] and between the ISS and the level of plasma β-endorphin in children, have been reported.[22] Our study clearly shows that there is a correlation between the level of venous β-endorphin and the Glasgow score. This is logical, since β-endorphin is one of the stress hormones,[8,9] and so the patient is all the more in a state of stress since he is conscious of his state and his afferent pathways are intact. Inversely, we have shown that when the patient is brain dead, and thus in a state of total absence of stress, β-endorphin levels are very low. In adults, an increase in the β-endorphin level in trauma patients[23] have been reported.

Studies about β-endorphin plasma levels in head injury patients are controversial,[24,25] but in our study, it appears that the presence of head injuries does not change the β-endorphin level. The variations of β-endorphin levels are thus not related to contusions of the CNS.

Plasma β-endorphin arises primarily from the pituitary stem.[26] Small quantities of β-endorphin, however, are secreted by the adrenal medulla, the thyroid gland, the pancreas or the stomach,[27,28] but quantities secreted peripherally are negligible.

Our study confirms that β-endorphin secretion depends on stress, since in brain dead patients, and who are thus in the absence of stress, β-endorphin levels were very low. We have also shown that there is a correlation between the level of secretion of this neural peptide and the state of conciousness. Thus, β-endorphin could be a conciousness marker in trauma patients. Since the radioimmunoassay of β-endorphin is not an emergency laboratory test, it is noted that the determination of the plasma levels of this neuropeptide is not yet a useful tool in medical practice. Additional work is required to evaluate the potential predictive value of determining plasma endorphin levels.

Acknowledgement

The authors thank B Dijoux for typing the manuscript.

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https://doi.org/10.1017/S0317167100040245 Published online by Cambridge University Press

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