Beta-endorphin levels in infant apnea syndrome: a preliminary communication

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Endorphins (β-endorphin and metenkephalin) are naturally occurring, endogenous peptides with opioid properties and potencies more than ten times that of morphine.[1,2] Release of endorphins results in neurotransmitter and neuroendocrine effects in the central nervous system. During stress, endorphins produce analgesia, which can be blocked by naloxone.[3] Endorphins can also induce important cardiovascular effects, including hypotension, bradycardia, and peripheral vasodilation.[4-6] The respiratory effects of endorphins include bradypnea, apnea, and hypoventilation.[7,8]

We have previously reported abnormal serum and cerebrospinal fluid (CSF) β-endorphin levels in children with the obesity-hypoventilation or Pickwickian syndrome and improvement in ventilatory status with a narcotic antagonist (intravenous naloxone therapy).[9,10] Others have suggested a possible role for endorphins in the sudden infant death syndrome (SIDS)[11] and recent reports have implicated enkephalin in transient apnea and respiratory depression in preterm rabbits.[12] Narcotic antagonist therapy with naloxone has been used to decrease the duration of primary apnea in neonatal asphyxia.[13]

The infant apnea syndrome (IAS) is the new name for near-miss SIDS. The IAS characterizes

infants between 42 weeks gestational age and 12 months chronological age who experience clinically significant apneas of greater than 10 seconds' duration, some of whom may require tactile stimulation or rarely even cardiopulmonary resuscitation to abort the apneic episode. Because of controversy as to whether the pathophysiology of the apneas in infants previously identified as near-miss SIDS is the same as in those who die of SIDS, and whether the two entities represent a continuum, we prefer to use IAS rather than near-miss SIDS until the association can be proved.

Polygraphic sleep monitoring studies have delineated a number of abnormalities in infants with IAS including prolonged sleep apneas,[14, 15] frequent short apneas,[16] excessive periodic breathing,[17] hypoventilation and carbon dioxide retention during sleep[18, 19] and a depressed ventilatory response and possibly depressed cardiac response to hypercarbia and hypoxia during sleep.[20, 21]

The possibility of endorphins playing a role in the apneas and abnormal polygraphic sleep findings of IAS is an interesting hypothesis and we believe this to be the first paper to report on levels of β-endorphins in the CSF and serum of IAS babies.

Materials and methods

Six infants (five boys and one girl) had been referred to the Cleveland Clinic for evaluation of clinically significant apneas, detected by parents or medical personnel and documented at the referring hospital before transfer to the Cleveland Clinic. The infants ranged from 4 weeks to 3 months of age. In addition to a thorough history and physical examination each infant had a chest radiograph, ECG, EEG, complete blood count, and blood glucose, electrolytes, calcium and phosphorus levels were ascertained. Because of the age of the infants and the known association of apneas with sepsis, a septic work-up, including blood cultures, urine culture and lumbar puncture, was performed. Some of the infants were given antibiotics because of their clinical condition pending results of cultures. Small samples of CSF and serum were frozen for β-endorphin assays from the specimens obtained for the septic work-up. Only one infant had a positive culture, a urine with greater than 100,000 *Escherichia coli*. Each infant also had a barium swallow to rule out gastroesophageal reflux, and a few of the infants also underwent CT scan of the brain or echocardiography to further evaluate the neurologic or cardiovascular system. None of the medical evaluations revealed a cause for the apneas. Each infant also underwent polysomnography (polygraphic sleep recording), and continuous apnea and bradycardia monitoring in the hospital.

Beta-endorphins in serum and CSF were assayed by a specific, homologous radioimmunoassay for human β-endorphin.[22] Blood samples were obtained by venipuncture, centrifuged and the serum was separated. Serum and CSF were frozen until assays were run (*Table*). Each infant had been documented by apnea alarms to have apneas of greater than 20 seconds' duration frequently associated with bradycardias when monitored in the hospital. The only possible medical cause of apnea was the positive urine culture greater than 100,000 *E. coli* of Patient 6.

Five of the six infants had polysomnographic studies. Apneas were defined as cessation of ventilation for greater than 10 seconds and respiratory pauses as cessation of breathing for 3 to 10

Table. Beta-endorphin levels in six infants with IAS

Patient	Age	CSF β-endorphins (pg/ml)	Serum β-endorphins (pg/ml)	Polysomnogram	
				Apneas/hr*	Resp. pauses/hr†
1	2 mo	52	8	0	0
2	4 wk	52	44	1	21
3	3 mo	66	28	0	2
4	2 mo	54	34	2	20
5	6 wk	47	65	...	...
6	2 mo	66	...	2	17
Controls					
1	4 wk	10	...	...	...
2	2 mo	1	...	...	...

Normal CSF β-endorphin levels <15 pg/ml. Normal serum β-endorphin levels 100–300 pg/ml.
* Apnea = cessation of breathing for more than 10 sec.
† Respiratory pause = cessation of breathing for 3–10 sec.

seconds. Despite documented apneas during hospitalization of greater than 20 seconds in each of the infants, two patients had normal sleep studies with no apneas and only rare respiratory pauses during the study period. Three of the infants had abnormal sleep studies with documented central apneas and multiple respiratory pauses. One polysomnogram was unsuccessful because of equipment malfunction and the patient never returned for a repeat study.

Abnormally high CSF β-endorphin levels were found in all six infants. The normal CSF β-endorphin level is less than 15 pg/ml from published reports[22] (19 adults undergoing diagnostic lumbar puncture), although age and sex-matched controls were not obtained in this study because of ethical restrictions. The CSF β-endorphin levels exceeded 45 pg/ml in all cases, more than three times the normal adult level. Serum β-endorphin levels were low in all six infants. Normal serum β-endorphin levels are higher than plasma levels and should be at least 100–300 pg/ml and probably 200–300 pg/ml. Cord plasma levels are normally 250 ± 54 pg/ml (n = 6) and normal plasma levels are 115 ± 9 for adult males (n = 27) and 112 ± 5 for adult females (n = 25).[22] It is also known that normal serum levels as measured in this study are twice as high as plasma levels.[22] However, normal levels for infants in our age range have not been established. There is a diurnal variation in β-endorphin levels and all samples in this series were drawn in the morning, which is when the lowest level normally occurs.

Discussion

We have demonstrated abnormally high β-endorphin levels in the CSF of infants with apneas, and abnormally low serum levels of β-endorphins in these same infants. Endorphin levels are known to increase with stress[23] and because of their potent opiate effects they can produce significant cardiopulmonary perturbations.[23] Endorphins can depress ventilation with a reduction in tidal volume, respiratory rate, and minute ventilation with subsequent hypoxia and hypercarbia.[7,8] Endorphins and enkephalins have also been implicated in neonatal apneas[12] and have been shown to cause transient apneas in preterm rabbits.[11] Endorphins can also cause

bradycardia.[4] These same problems of apneas, respiratory depression during sleep and bradycardias are a prominent part of the IAS. The demonstration of increased endorphin levels in the CSF of IAS babies suggests that the β-endorphins may be responsible for the apneas and bradycardias of the syndrome. An alternative interpretation might be that the β-endorphins increase in response to the stress of the apneas and bradycardias that may be caused by some other abnormality, such as brainstem immaturity. Even if the increased β-endorphins are a secondary rather than primary factor, their increased concentration may nevertheless be harmful because of their known potential for cardiopulmonary depression. If the increased endorphin levels were a response to the stress of an apnea, their increased concentration might prevent the infant from spontaneously aborting the apnea and result in a fatal outcome, namely, SIDS.

Even if SIDS victims were demonstrated to have increased β-endorphin levels in the CSF, it would still not answer the question of whether increased CSF β-endorphin levels are a primary abnormality in SIDS and IAS, or secondary to the stress of the apneas.

One might approach this dilemma by assessing the clinical response of apneas and β-endorphin levels to a trial of a narcotic antagonist. If the apneas decrease or disappear in response to a narcotic antagonist such as naloxone or naltrexone, and the levels of CSF β-endorphins decrease, it would be good presumptive evidence that endorphins, if not primarily responsible, at least contribute to the occurrence of apneas. It would also be of value to follow CSF endorphin levels over a period of time, since SIDS has its peak incidence between 2 and 4 months of age, a rapid decrease after 7 months of age, and is rarely seen after 12 months.[24] If CSF endorphin levels were found to parallel this chronologic data, it would also strengthen the role of endorphins in SIDS and IAS. Another way to test the hypothesis of the possible role of endorphins in IAS would be to assess the response of IAS babies versus normal controls to injections of endorphins and enkephalins. If endorphins are responsible for the apneas then one would expect to see apneas in IAS babies at lower doses of endorphins and more severe apneas in these patients. The ethical restrictions to such a study, however, are immense.

Further evidence for a possible role of endorphins in the pathogenesis of SIDS and IAS is the known increased incidence of SIDS among infants of opiate-addicted and methadone-maintained mothers.[25, 26] The incidence of SIDS in infants of drug-dependent mothers appears to be five to six times greater than that of SIDS in the general population. The incidence of SIDS is 2–3 deaths per 1000 live births (0.25%),[24] whereas in infants of mothers maintained on methadone it is 1.4%.[26] Opiate addiction with overdose and withdrawal or chronic maintenance with methadone in the mother could potentially alter the normal production and distribution of endorphins in the infant with a resultant increase in endorphins leading to apneas, respiratory depression, and possibly death.

The reason for the low serum levels of β-endorphins is unclear. They may reflect a maldistribution of endorphins compared to the normal due either to a barrier to passage from CSF to blood or an increased peripheral metabolism in response to elevated CNS levels. Alternatively, peripheral synthesis of β-endorphins may be impaired. Further

studies in normal controls and IAS babies will be necessary to delineate the normal levels in infants and the significance of these findings.

If further studies confirm these preliminary findings of abnormally high CSF β-endorphin levels in IAS, it will open up the potential for therapy of these infants. Previously, we could only monitor them for apneas and bradycardias during sleep and instruct parents in infant cardiopulmonary resuscitation to avert a catastrophe. If β-endorphins prove to be responsible for the apneas and bradycardias in these infants, the potential for successful therapy with narcotic antagonists will be high, assuming the risks of therapy do not outweigh the benefits.

We hypothesize that the increased CSF levels of endorphins may be responsible for the apneas of the IAS and SIDS, either by chronically elevated levels preventing an appropriate stress response, causing depressed hypoxic and hypercarbic respiratory drives, or already high CSF endorphin levels elevate in response to stress, reaching a critical threshold that results in apneas.

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