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Chapter 75

Biochemistry of Blood and Cerebrospinal Fluid in Tension-Type Headaches

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The literature on biochemistry in tension-type headache (TTH) is characterized by the pursuit of a large variety of ideas about pathophysiology, and it may therefore appear somewhat dispersed and confusing. Indeed, in many cases similar studies have been performed that yielded contradictory results, and there may be many reasons for this.

First, many different designations, including chronic daily headache, (chronic) muscle contraction headache, tension headache, and chronic migraine; definitions; and criteria have been used in the past to describe clinically patients suffering from unspecified headaches. This severely hampers straightforward comparison of the results. Only in recent years have most investigators used the 1988 criteria (38). Second, exclusion criteria also vary markedly, the most important being the use of medication at the time of biochemical investigation and the coexistence of migraine or depression. Third, timing of the investigation (during headache or during headache-free periods) also varies and, most confusingly, is not always defined.

Our aim is to present the reader with the available data in a systematic fashion and relate to some of the data with a critical eye. However, because of the assorted pattern of studies and multitude of techniques used, it will not be possible for every substance studied to reach a final conclusion on a pathophysiologic or diagnostic role in TTH.

The subject will be handled in sections on blood chemistry, platelets, immune cells, and cerebrospinal fluid. Data on serotonin in the blood circulation are presented in the platelet section because of the intimate relationship between platelet stores of serotonin and free serotonin in plasma.

BLOOD CHEMISTRY

Magnesium concentrations, which, measured in serum, may reflect brain level and, thereby, level of inhibition of *N*-methyl-*D*-aspartate (NMDA)–type glutamate receptors, were reported to be reduced in patients with TTH in headache-free periods and further lowered during headache in analogy with what was seen in migraine (59). Schoenen et al., on the other hand, found similar magnesium concentrations in chronic TTH and control subjects (60). Lactic and pyruvic acid levels are normal in TTH (55).

Peptides

Several peptides have been studied in TTH, and the endogenous opioid peptides β-endorphin and methionine-enkephalin (met-enkephalin) received much attention for a period. The idea was that headache was a hypoendorphin-syndrome (66). It appears from Table 75-1 that the data are inconsistent with regard to this idea. Furthermore, because circulating endogenous opioid peptides are not vasoactive or have access to the central nervous system, the role of circulating opioid peptides in relation to headache is obscure (4). Plasma neuropeptide Y (NPY) concentrations were normal in patients suffering from episodic TTH (ETTH) and did not differ between headache episodes and pain-free periods (33). Endothelin-1 concentrations in plasma were normal in ETTH and chronic TTH (CTTH) (32).

Neuroendocrine Parameters

Adrenocorticotropic hormone (ACTH) and cortisol were normal in daily chronic headache (24) and CTTH (43). Melatonin is synthesized in the pineal gland from serotonin, but possesses negligible serotoninlike activity. Nocturnal levels are high, whereas diurnal concentrations are low or undetectable. Nocturnal plasma melatonin levels have been found to be reduced in a group of female tension headache patients (16). It was not clear from the patient description whether this group also included depressed patients. The pathophysiologic interpretation of these

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TABLE 75-1 Plasma Levels of Opioid Peptides

Peptide	*n*	*Diagnosis*	*Result*	*Ref.*
β-endorphin	8	DCH	Reduced	(9)
β-endorphin	11	DCH	Reduced	(24)
β-endorphin	47	DCH	Normal	(30)
β-endorphin	41	CTTH	Normal	(7)
β-endorphin	7	ETTH	Reduced	(10)
Met-enkephalin	9	TTH	Elevated	(28)

CTTH = chronic tension-type headache; DCH = daily chronic headache; ETTH = episodic tension-type headache; TTH = tension-type headache.

preliminary findings is not simple, but they were suggested to reflect global sympathetic hypofunction.

Amino Acids

Ferrari et al. (26) studied plasma amino acids in migraine patients and used TTH patients and healthy normal individuals as controls. Whereas the neuroexcitatory amino acids glutamic and aspartic acid were clearly elevated in migraine patients, no abnormalities could be demonstrated in TTH patients. Also, homocysteine levels were normal in a study examining 20 patients with episodic TTH (23).

Monoamines

Shimomura et al. (62) found that plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), which seem to reflect central noradrenergic metabolism, predict the clinical response of TTH patients to tizanide hydrochloride. Those patients who showed the best clinical response after 4 weeks of treatment had the highest pretreatment MHPG plasma levels and presumably the highest central noradrenergic activity. Several methodologic reservations, however, apply to this interesting observation, most importantly the way the clinical response was measured (undefined criteria, open uncontrolled evaluation), how clinical outcome groups were formed and related to the MHGP levels (open or blinded), and lack of clinical information on the patients (use of medication, diet, and depression). Furthermore, those patients who improved most also had by far the shortest duration of the illness, suggesting that other factors were involved. Nevertheless, this approach is most promising and should be confirmed in a prospective, placebo-controlled, double-blind design.

Dopamine β-hydroxylase catalyzes the conversion of dopamine to norepinephrine, and serum levels of this enzyme were found to be reduced in 10 patients with TTH compared with control subjects (31). The same reduction was also seen in migraine patients. Gallai et al. (31) consider serum activity of dopamine β-hydroxylase a useful indicator of sympathetic activity, considering the instability of serum norepinephrine concentrations. Suggesting a reduced noradrenergic tonus in TTH (and migraine), this study should be reproduced on larger groups of patients and the status of headache at the time of sampling made clear.

Castillo et al. measured plasma concentrations of epinephrine, norepinephrine, and dopamine under standardized conditions in 30 patients with ETTH in headache phase. Pain and depression were rated on separate scales. Plasma concentrations of all three catecholamines were lower than in control persons, supporting the idea of reduced sympathetic activity in TTH (15). There was no association between depression scores and catecholamine concentrations. Reduced plasma norepinephrine concentrations also were found in 15 patients with muscle contraction headache (69).

Urinary excretion of 5-hydroxytryptamine (5-HT), noradrenaline, adrenaline, and dopamine and their acidic metabolites have been studied in female, chronic daily headache patients (28). Preliminary data suggested that in these patients the 24-hour excretion of dopamine was reduced and the circadian rhythmicity of the excretion of the metabolites was disturbed. Thus, the normally existing difference between diurnal and nocturnal excretion (diurnal > nocturnal) was absent in the headache patients. Chronic daily headache patients were similar to migraine patients in this respect. More studies are needed.

Martignoni et al. (47) found that baseline β-endorphin plasma levels and the β-endorphin plasma response to clonidine were significantly lower in patients with combined migraine without aura and tension headache than in healthy controls. This was interpreted as evidence for failure of central noradrenergic activity. It is not clear whether similar results could be obtained in patients with pure tension headache without associated migraine.

Immunologic Changes

Link and colleagues (45) have investigated several immunologic parameters in cerebrospinal fluid (CSF) and plasma of patients with chronic headache (of unspecified and undefined type). However, in these studies the headache patients were used as controls for patients with multiple sclerosis, and no healthy, normal controls were included. Accordingly, no qualitative conclusions regarding these observations can be drawn.

Nagasawa et al. (51) found slightly higher serum levels of complement C3 and C4 in patients with muscle contraction headache compared with normal individuals. However, the patient group was a mean of 10 years older than the control group, and both C3 and C4 levels increased with age. Accordingly, the conclusion of Nasagawa et al. that inflammatory aspects are involved in muscle contraction headache is interesting but should be confirmed in a study with a matched control group.

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Diaz-Mitoma et al. (20) reported that significantly more patients with so-called new daily persistent headaches had evidence of active Epstein-Barr infection (84% versus 25% in controls). It is unknown how frequent this headache syndrome is and how it relates to TTH. We are unaware of similar studies conducted with TTH patients.

Interleukin-2 is a cytokine activating T-lymphocytes. Shimomura et al. found reduced serum levels of interleukin-2 in 46 patients with TTH and similarly reduced levels in migraine (61).

The importance of connections between the immune and nervous systems is becoming increasingly clear, not the least in the field of pain. In a series of experiments, Christoph Stein et al. have provided evidence that β-endorphin may be synthesized in immunocytes and, following stimulation by inflammatory mediators such as corticotropin-releasing hormone and interleukin-1, released into inflamed tissue. Here, β-endorphin may bind to opioid receptors on nociceptive fibers and reduce nociception (14). Three independent groups have measured decreased β-endorphin concentrations in peripheral blood mononuclear cells in patients with episodic TTH during a headache-free period (10,44,48). Although the results are premature in the sense that β-endorphin was not characterized on the molecular level, these data are interesting in the light of development within the field. However, speculations about β-endorphin concentrations in peripheral blood mononuclear cells reflecting central nervous system concentrations of the same substance (44) have no support in scientific data (3).

SEROTONIN (5-HT) METABOLISM AND PLATELET FUNCTION

Many groups have investigated platelet function and platelet-related biochemical factors in relation to TTH, but with often contradictory results. The data are discussed as follows. Relevant data on serotonin are summarized in Table 75-2.

General Methodologic Considerations

Most importantly, when investigating blood levels of 5-HT, it is necessary to discriminate between the two distinct compartments of 5-HT in blood: the 5-HT in platelets with concentrations in the micromolar range and representing a pharmacologically inactive, slow-turnover, reserve pool;

TABLE 75-2 Serotonin Metabolism and Platelet Function in Tension Headache

Variable	*CDH*	*N*	*CMCH-P⁺*	*N*	*CMCHP⁻*	*N*	*THE-P⁺*	*N*	*THE-P⁻*	*N*	*CTTH-P⁺*	*N*	*Ref.*
5-HT Platelets	↔	9											(29)
Platelets	↓	95											(1)
Platelets			↓	23									(58)
Platelets					↔	14							(65)
Platelets									↑	28			(19)
Platelets							↑	30					(42)
Platelets											↓	31	(52)
Platelets											↓	13	(64)
Platelets											↔	40	(12)
Platelets							↑	13	↔	13			(39)
Plasma											↔	9	(29)
Plasma											↔	40	(12)
Plasma									↑	28			(19)
Plasma					↑	23							(68)
Serum							↔	10					(57)
5-HIAA													
Platelets									↑	28			(19)
Plasma									↑	28			(19)
Plasma	↔	9											(29)
Serum							↔	7					(57)
Urine											↔	39	(12)
5-Hydroxytryptophan													
Plasma	↔	9											(29)
5-HT uptake platelets											↓	21	(37)
5-HT uptake platelets									↑	20			(65)

CDH, chronic daily headache; CMCH, chronic muscle contraction headache; CTTH, chronic tension-type headache; P⁺, during pain; P⁻, during pain-free period; THE, tension headache episodic type; ↑, increased level; ↔, normal level; ↓, decreased level.

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and the 5-HT in (platelet-free) plasma with concentrations in the nanomolar range, which shows rapid turnover and is pharmacologically potentially active (2,56). Several researchers have incorrectly used the designation "plasma 5-HT" while indicating the 5-HT concentration in platelet-rich plasma and thus of platelets. In this chapter we reserve the designation "plasma 5-HT" for measurements made in platelet-poor or platelet-free plasma.

Other factors may explain inconsistency between studies. Mean ages of the study populations vary between 29 and 46. Mean duration of illness was between 9 and 12 years. The female:male ratio was at least 3:1, except in the studies of Anthony and Lance (1) and Nakano (52), which included more males than females. Freedom from medication was not required in the study of Hannah et al. (37). Patients were free from medication for at least 3 days in the study of Rolf et al. (58) and at least 7 days in the other studies. The use of a diet and coexistence of depression varied by study or are not reported.

Platelet 5-HT

Four groups have found significantly reduced levels of platelet 5-HT in TTH (1,52,58,64), whereas three studies reported normal levels (12,28,65) and two studies increased levels (19,42). The study of Anthony and Lance (1) differs by substantially lower absolute levels of platelet 5-HT in the control and patient groups, compared with those measured by other investigators. It was not stated whether their patients were on a particular diet or were also suffering from depression. The Shukla et al. (65) and D'Andrea et al. (19) studies investigated TTH patients during headache-free periods.

In summary, these studies are seemingly conflicting but in fact are not comparable. The very large study of Anthony and Lance (1) suggests reduced platelet 5-HT in chronic daily headache patients, but this may be restricted to male patients only. Remarkably, Glover et al. (35) also found reduced activity of platelet monoamine oxidase (MAO) in male TTH patients only. Thus, the data of Anthony and Lance should be reanalyzed separately for males and females and should be confirmed by others, taking into account potential sex (and age) differences. It is hard to conclude from so different data, but if only studies using the International Headache Society (IHS) criteria for TTH and with patient materials cleaned of concomitant disorders are included, a picture of normal or reduced platelet 5-HT appears (12,28,64).

Platelet 5-HT Uptake

Shukla et al. (65) found evidence for increased uptake of 5-HT in platelets of TTH patients. However, Hannah et al. (37) found that the 5-HT uptake sites in platelets of TTH patients have reduced affinity for 5-HT, independent of coexisting depression, age, or sex. Binding of serotonin reuptake–inhibiting drugs to platelets may reflect the number of 5-HT tranporters and thereby the uptake ability. The number of imipramine binding sites were reduced (46), but studied by paroxetine binding, the number of 5-HT transporters were estimated to be normal (13).

5-HT Binding to Lymphocytes and Monocytes

Giacovazzo et al. (34) found that lymphocytes and monocytes of TTH patients show a complete loss of high-affinity binding sites for 5-HT during the headache but a normal *in vitro* 5-HT binding curve during headache-free periods. No information, however, was given regarding whether the patient and control groups were age matched. In addition, compared with the control group, the patient group contained proportionally more females, who were also using medication. Accordingly, no firm conclusions can be drawn on the validity of these findings.

Platelet Enzymes

No differences have been found for phenolsulphotransferase (PST)-P or -M isoenzyme activity in TTH patients (28), but platelet MAO activity has been found to be reduced during headache in female patients (28) and during headache-free periods in males only (35). Superoxide dismutase activity was normal in TTH and migraine without aura as opposed to reduced activity in migraine without aura (63).

5-HT and 5-HT Precursors and Metabolites in Plasma and Serum

Plasma levels of 5-HT, its precursor 5-hydroxytryptophan (5-HTP), and the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) were found to be normal by Ferrari et al. (28) in female TTH patients during headache. Bendtsen et al. also found normal plasma 5-HT and urine 5-HIAA levels during pain (12), whereas two other studies showed increased levels in headache-free periods (19,68). Finally, a study on ETTH showed normal plasma 5-HT levels in headache-free periods and increased levels during headache (39).

Ribeiro et al. (57) found normal serum levels of 5-HT and 5-HIAA during headache in TTH patients who were on a phenylethylamine- and tyramine-restricted diet. Serum concentrations are difficult to relate to plasma and platelet levels because during the process of serum preparation, blood is coagulated and platelets are activated, causing release of platelet 5-HT. Indeed, their control values for serum 5-HT were about 50 times higher than values generally considered normal for plasma 5-HT.

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Methionine-Enkephalin

Methionine-enkephalin is colocalized with 5-HT in the dense granules of platelets (21) and seems to possess neutralizing activity with respect to the endothelial damaging effects of 5-HT (36). Platelet met-enkephalin levels have been found to be normal in TTH patients, but plasma met-enkephalin levels proved to be markedly increased compared with both normal individuals and migraine patients, during as well as outside of attacks (27). Thus, determination of plasma and platelet met-enkephalin levels may prove to be a useful marker to distinguish between TTH and migraine without aura. This should be confirmed in a larger study, especially because in the study of Ferrari et al. (27) patient and control groups were not age matched.

Release of Platelet Methionine-Enkephalin and 5-HT

Plasma collected from migraine patients during an attack has been shown to release met-enkephalin *in vitro* from platelets collected from the same migraine patients during attack-free periods (Fig. 75-1). No such release could be measured from platelets from TTH patients or healthy control persons (28). This suggests another biochemical difference between migraine and TTH patients. No release of platelet 5-HT was observed by Ferrari et al. (28), either when platelets from migraine patients were used or when platelets from TTH patients or healthy controls were incubated.

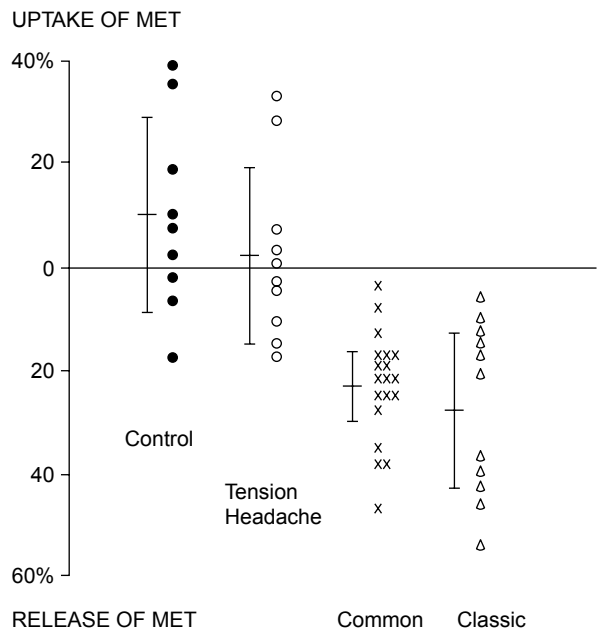

FIGURE 75-1. Change in platelet met-enkephalin content induced by incubation with plasma collected during migraine attacks. Each symbol indicates, per individual, the proportional increase (uptake) or decrease (release) of platelet met-enkephalin content induced by incubation with migraine-attack plasma compared with the met-enkephalin content of the platelets that were only resuspended in water. Vertical lines represent 99% confidence intervals and group means.

Other Platelet Constituents

Gamma-aminobutyric acid (GABA) concentrations in platelets from 27 TTH patients were higher than in 21 healthy control persons (40). Glycine, glutamate, and aspartate concentrations, on the other hand, were normal (18). Substance P concentrations in platelets from patients with TTH during pain were similar to migraine patients and higher than in healthy control persons (52). Ionized magnesium was reduced in platelets from 20 patients with TTH, whereas concentrations of cyclic adenosine monophosphate (AMP) and cyclic guanylic acid (GMP) were normal (50).

Conclusions From Platelet Studies

Because the fundamental idea in studying platelet biochemistry in TTH is the concept of platelets being a model of serotonergic neurons, the work of obtaining consistent data between groups of researchers should at this time be redirected toward efforts to validate this concept further.

CEREBROSPINAL FLUID

Quantitative analysis of the biochemical constituents of CSF are performed on the assumption that CSF concentrations reflect brain or spinal cord tissue concentrations, and perhaps synaptic activity, because CSF is in constant exchange with extracellular fluid of the central nervous system (CNS). Evidence in support of this assumption is available for monoamines (72) and neuropeptides (11). However, some common issues related to biochemical measurements in CSF have to be addressed to validate the results:

1. Most substances of interest exist in both CNS and blood and can be regarded as markers of CNS activity only if the blood–CSF barrier is relatively complete for a given substance and patient group. The evidence to date suggests that CSF monoamines and neuropeptides originate mainly in the CNS and do not leak in from the circulation in patients without CNS lesions (11,73). Exceptions are prolactin, gonadotropins, and cortisol (74).
2. It may be difficult to identify which CNS regions contribute to the CSF pool of a given substance. It is likely that superficial regions located close to the subarachnoidal space and near the sampling site contribute

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more than deeper regions at the opposite end of the neuraxis. Methionine-enkephalin and dynorphin are examples of neuropeptides that are abundant in, and can be released from, the spinal cord (49). CSF obtained by lumbar puncture may therefore be suitable to evaluate processes in the spinal cord, although both peptides are also abundant supraspinally. β-Endorphin, on the other hand, is almost entirely supraspinally located (67), and the relevance of lumbar sampling of CSF thus relies on the positive correlation found between central and lumbar CSF β-endorphin concentrations (8).

3. If effects of age, sex, menstrual phase, and diurnal variation on CSF peptide levels are not ruled out, materials and sampling procedures have to be standardized accordingly.
4. Centrally acting drugs may influence neuropeptide production, processing, and secretion. Such drugs should be avoided for weeks before CSF sampling.
5. Neuropeptides such as opioid peptides and tachykinins are processed from precursors in one or more steps, and the products may be further derivatized (54). As a result, radioimmunoassays will rarely be specific for a single neuropeptide. For example, some antisera recognize several β-endorphin–related peptides in CSF (5). Because derivatization usually changes the biologic activity of a peptide, ideally it should be examined if the degree of derivatization differs between groups investigated.

With these precautions in mind, CSF examinations may be a valuable tool for the study of nociceptive and antinociceptive mechanisms in headache.

Neuropeptides

Opioid Peptides

Endogenous opioid peptides are derived from three distinctive gene products—the precursor molecules pro-opiomelanocortin, proenkephalin A, and proenkephalin B—and are commonly classified as the endorphins, the enkephalins, and the dynorphins, respectively (49). Several forms of derivatization of the peptides with or without preservation of the biologic activity exist within each opioid family. β-Endorphin may be C-terminally truncated or *N*-acetylated and loses its opioid activity in the latter case.

β-Endorphin

Lumbar CSF from eight patients suffering from migraine with interparoxysmal headache for 1 to 10 years revealed a mean β-endorphin concentration that was only 20% of the mean of the control subjects. All individual concentrations were below the defined normal range (53). Similar levels of β-endorphin were found in patients with migraine without aura, whereas patients with symptomatic headaches (posttraumatic and postischemic) had normal CSF β-endorphin levels (53). On the other hand, a study including 47 patients with CTTH according to the criteria of the IHS showed almost identical CSF β-endorphin levels in the patient group and the control group (7). In contrast to the former study, patients with migraine attacks more than once per month were excluded. Nineteen of the patients included had migraine attacks 1 to 12 days per year. Although migraine was not associated with low β-endorphin concentrations in our study (7), it may be that the low concentrations found by Nappi et al. (53) are related more to migraine than to tension headache. On the other hand, an inverse relationship between chronic pain factors and CSF β-endorphin also has been reported in patients with low back pain (17). Demographic characteristics of the patients and control group were matched in both studies, and both radioimmunoassays applied distinguish between β-endorphin and β-lipotropin. Patients with fibromyalgia, a disorder with many similarities to chronic tension-type headache, have a normal β-endorphin level in CSF (70).

N-Acetylated β-Endorphin

CSF concentrations of *N*-acetylated β-endorphin (Ac-β-EP) in 15 patients with migraine and associated CTTH were significantly higher than in 22 controls ($p < 0.01$) (25). β-endorphin concentrations in the same samples, however, were lower in the headache group ($p > 0.05$) (Fig. 75-2). As a consequence, the β-endorphin:Ac-β-EP ratio was much lower in patients than in controls (25) (see Fig. 75-2). In

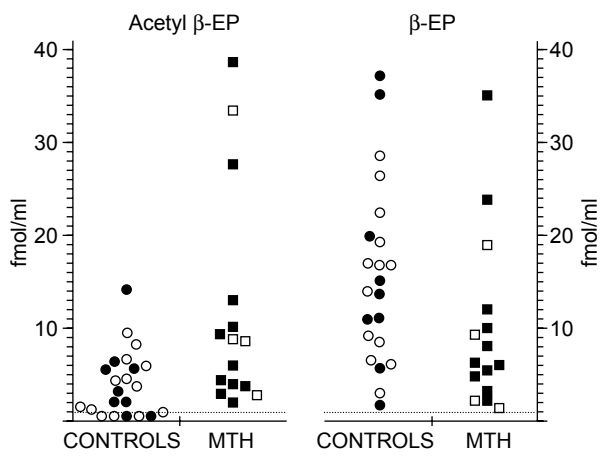

FIGURE 75-2. Individual CSF concentrations of β-endorphin and Ac-β-EP in control subjects (*circles*) and patients with migraine with tension-type headache (MTH) (*squares*). The concentration of peptides in each sample was calculated by adding the peak values to the values for the two adjacent fractions. Open symbols refer to males; solid symbols refer to females.

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this study, there was also a negative relationship between CSF β-endorphin and a headache pain index.

Methionine-Enkephalin

CSF from 48 patients of the same group with CTTH examined for β-endorphin by Bach et al. (7) revealed a higher mean level of met-enkephalin immunoreactivity (41). Studies on patients suffering from other types of pain have shown that patients with neurogenic pain syndromes had higher met-enkephalin levels than controls, whereas patients with idiopathic pain syndromes had normal levels (71). Increased CSF levels of met-enkephalin-Arg^6-Phe^7 were found in patients with fibromyalgia, although the control samples were not concurrently obtained (70).

Dynorphin

Dynorphin immunoreactivity was lower in 38 patients from the group with CTTH described above than in 10 healthy controls (6). Patients with idiopathic pain syndromes revealed lower CSF dynorphin levels than controls (71), whereas fibromyalgia patients had higher levels than a nonconcurrent control group (70).

Other Neuropeptides

Calcitonin gene-related peptide (CGRP) is present in C-fiber afferents colocalized with substance P and is depleted from the trigeminal nucleus after electrical stimulation. Thus, CSF CGRP levels may reflect the level of activity in C-fiber afferents. Cholecystokinin may on the spinal level act as an analgesic in high doses, but act as an inhibitor of opioid-induced antinociception in lower doses. Somatostatin is thought to exert an inhibitory effect on nociceptive afferents. We determined CSF concentrations of these three neuropeptides in patients with CTTH and found normal levels (6).

Other Substances

CSF levels of prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were detectable in 20 patients with CTTH but were undetectable in control persons (22). CSF cortisol was lower in the headache patients than in controls (22). However, these differences seem to reflect similar differences in serum (22), which agrees with the view that CSF levels of all these substances correlate with serum or plasma levels (74). Thus, the significance of these findings is unclear.

Conclusions

Analysis of neuropeptides in CSF from patients with CTTH clearly indicates changes in the CNS that may be either adaptive or pathophysiologic (Table 75-3). The finding of a decreased CSF β-endorphin:Ac-β-EP ratio in patients with migraine and TTH is particularly intriguing, indicating the existence of a disease due to biologic inactivation of β-endorphin (25). However, another study, using a radioimmunoassay that does not detect Ac-β-EP to a significant degree, failed to find decreased β-endorphin levels in a patient group who were similar except that they were suffering from fewer migraine attacks (7). Future studies will be needed to show if such an inactivation of β-endorphin occurs in other idiopathic pain syndromes. The finding of decreased dynorphin levels might likewise indicate opioid hypoactivity. Increased CSF met-enkephalin levels in patients with CTTH may be the result of an increased input from the nociceptive afferents, followed by increased activity in descending or segmental antinociceptive systems mediated by met-enkephalin. Alternatively, met-enkephalin release is increased compensatorily to insufficiency of other central pain-inhibitory systems acting presynaptically on the primary afferent. The findings outlined here do not easily fit into a simple pathophysiologic model for CTTH but provide evidence of disturbances in the endogenous opioid system.

TABLE 75-3 CSF Findings in Chronic Tension-Type Headache

Substance	*Level in CSF*	*Reference*
Opioid peptides		
β-endorphin	Decreased	(53)
β-endorphin	Normal	(7)
N-acetylated β-endorphin	Increased	(25)
Met-enkephalin	Increased	(41)
Dynorphin	Decreased	(6)
Calcitonin	Normal	(6) gene-related peptide
Cholecystokinin	Normal	(6)
Somatostatin	Normal	(6)
Hormones		
FSH	Normal	(22)
LH	Normal	(22)
Prolactin	Normal	(22)
Cortisol	Normal	(22)

CSF = cerebrospinal fluid; FSH = follicle-stimulating hormone; LH = leutinizing hormone.

COMPARISON WITH MIGRAINE

Distinguishing between migraine without aura and TTH is not always easy to do on purely clinical grounds. Ferrari and co-workers studied biochemical differences between these two entities (see Chapter 31). Their data show that patients with tension headache and patients with migraine differ biochemically. In addition to these data,

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Anthony and Lance (1) showed in a large study that platelet 5-HT levels are markedly reduced in TTH patients compared with both controls and migraine patients (but see above for comments), but Shukla et al. (65) found the opposite. The reviewed studies of neuropeptides in plasma or CSF do not consistently point at parameters that distinguish TTH and migraine. Although some studies reveal biochemical differences that might be of relevance for diagnostic purposes, much more work is needed to validate these options.

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P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
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