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Monoamines in the Brain Cerebrospinal Fluid of Facial Pain Patients

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The purpose of the study was to assay monoamines in cerebrospinal fluid (CSF) obtained from the trigeminal cistern of 64 patients with intractable facial pain. The CSF was analyzed for homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), end-product markers of activity for the dopamine, serotonin, and norepinephrine systems, respectively. HVA averaged 121 ng/mL in these facial pain patients, compared to 150 to 550 ng/mL in 10 studies of ventricular brain CSF in assorted psychiatric and pain patients. 5-HIAA averaged 29 to ng/mL in our facial pain patients compared to 60 to 120 ng/mL in nine studies of ventricular brain CSF in assorted psychiatric and neurological patients. Trigeminal cistern CSF MHPG averaged 9 ng/mL, similar to the range of 13 studies of lumbar CSF of assorted psychiatric and pain diagnoses. These results indicate that (1) the electrochemical detection method provides a unique way of accurately measuring nanogram concentrations of multiple monoamines in as little as 0.25 mL of CSF; (2) trigeminal cistern and posterior fossa brain CSF monoamine metabolites reflect a different profile of dopaminergic and serotonergic functioning in these facial pain patients from that previously reported with lumbar CSF measurements of other patients; and (3) trigeminal sensory ganglion or brain dopamine and serotonin systems may be concomitantly dysfunctional in intractable facial pain.

The purpose of this work was to measure the concentrations of the three principal metabolites of the dopamine, serotonin, and norepinephrine systems, namely homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), in the trigeminal cistern cerebrospinal fluid (CSF) of facial pain patients. The relatively stagnant 0.5 mL of CSF present in the trigeminal cistern bathes the trigeminal ganglion and is proximate to the brain through the porus trigemini. This 0.4 to 0.8-cc cistern is a blind alley of CSF fed from the posterior cranial fossa. It begins at the porus trigemini posteriorly, through which the trigeminal rootlets pass from the middle fossa into the capacious cerebellopontine angle of the posterior cranial fossa. This pool of CSF is relatively stagnant, as shown by the high content of total protein similar to the thecal sac of lumbar CSF. Intimate proximity of cisternal CSF to the primary afferent cells of the trigeminal ganglion and the brain ought to provide a more accurate estimate of central nervous system (CNS) neurochemistry of those particular sites compared to the lumbar and ventricular CSF reports in the literature.

Previous reports of HVA, 5-HIAA, and MHPG limited to lumbar monoamine CSF measurements have not characterized chronic pain patients.[1–6] Nevertheless, anatomical and neurophysiological studies have implicated serotonin, dopamine, and norepinephrine at limbic, brainstem, and spinal sites central to the modulation of pain.[6–11]

This study compares trigeminal data with published lumbar and ventricular CSF data for normal individuals and neurologic and psychiatric patients, looking for differences in monoamine levels between pain states and other patient diagnoses. These comparisons might provide clues for more specific neurochemical investigation of CNS monoaminergic dysfunction in facial pain.

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Table 1. Diagnostic Criteria Used for Patient Categorization

Diagnosis	*Criteria*
Trigeminal neuralgia	Paroxysmal pain, provokable with low-threshold triggers. Unilateral pain that is confined to the distribution of the trigeminal nerve. No motor or sensory loss can be found.
Atypical facial pain	Facial pain that has been intractable for at least 6 mo, is inconsistent with a medically well-defined diagnosis, and is without objective motor or sensory deficits. This category includes these ICD 9 diagnoses: burning/painful tongue (529.6), trigeminal nerve disorder unspecified (350.9), facial and head pain not otherwise specified (784.0), and atypical facial pain (350.2).
Chronic cluster headache	Recurrent attacks of very severe ocular, frontal, and/or temporal pain. The pain is unilateral and associated with ipsilateral ptosis, miosis, conjunctival injection, lacrimation, and rhinorrhea. Chronicity is defined by the persistence of phenomenologically identical pain beyond the discrete intermittent cluster pattern.
Posttraumatic facial pain	Intractable facial pain caused by facial trauma that lasts longer than 6 mo after the traumatic incident.

METHODS

Patient Selection

Sixty-four patients with intractable facial pain for greater than 6 mo who were about to be treated with retrogasserian rhizotomy were evaluated. Diagnoses included trigeminal neuralgia (46), atypical facial pain (3), cluster headache (7), and posttraumatic trigeminal pain (8). Diagnostic criteria are described in Table 1. Patients were not anesthetized or medicated except for one dose of intravenous methohexital given just prior to placement of the rhizotomy electrode. Patients were awake and cooperative.

CSF Acquisition

Correct placement of the electrode through the foramen ovale and into the retrogasserian rootlets was performed under fluoroscopic control. Once the electrode was correctly positioned, the stylet in the electrode was withdrawn, and CSF surrounding the trigeminal ganglion allowed to flow from the trigeminal cistern. The first 0.5 mL of CSF was collected in a glass tube, immediately frozen on dry ice, and then refrigerated at −70° C.

Measurement of CSF Monoamines

The biochemical system used for analysis consisted of a liquid chromatography separation column and a 16-sensor coulometric electrochemical detector (ESA Co., Bedford, MA).[12] These coulometric electrodes (sensors) were used in series following the chromatographic separation to provide a very selective, sensitive system to measure coeluting neuromodulators. The principle of electrochemical detection is that an electrical potential will oxidize or reduce compounds, resulting in an electrical current. The current resulting from these reactions is proportional to the quantity of the electroactive compounds eluting from the chromatographic column. The system yields a three-dimensional map of the compounds present. The three dimensions, or axes, are (1) elution time (ET), (2) electrical potential (from the redox reaction), and (3) charge (coulombs) proportional to the concentration. Actual measurement of the compounds of interest is made by the display of the characteristic ratios of the dominant to the leading and following sensors. These characteristic ratios are compared to standards with preset confidence intervals for assuring the identity of a peak prior to calculating its value.

The graphite sensors were modified by polymer impregnation to provide operating capabilities from 600 mV to 1100 mV. Data acquisition was performed over a concentration range from 100 fg to 10 μg. The resolution and sensitivity limits of the system for any sample depend on the interplay of analyte interaction potential, interfering substances, and selectable instrumental variables. In practice, the number of specific analytes resolved was between 300 and 700 compounds. The typical procedure used in the preliminary work was to subtract a blank (synthetic) CSF reading from the sample uncorrected raw display. The corrected data were then automatically reduced to a listing of peak height and location for each channel using operator-selected variables of digital filters, gates, and threshold values, and then edited using manual data reduction on a touchscreen.

Quality Control Specifications

Sample Acquisition. Sampling tubes and Teflon sampling needles were tested as a system using blank

CSF and blank CSF spiked with known quantities of monoamines for loss and contamination. Six separate needles and tubes were tested. No loss or contamination from the sampling equipment could be detected.

Sample Contamination. Iron analyses were performed on 25-μL aliquots of the CSF to test for extent of hemolysis and possible effects on the serotonin system. The analyses always showed less than 0.01% hemolysis, which even at the maximum 0.01% would have had a negligible effect on monoamine measurement.

Sample Storage. Samples frozen for some time could have been oxidized, as reflected in a low ascorbate concentration and doubtful stability of the other analytes. Any samples with very low ascorbate would have been eliminated from the analysis, except that none were found. To check for the effect of freeze-thaw on sample stability, some CSF was taken through 10 repetitive freeze-thaw cycles. Within a precision of 3%, no degradation of the patterns were observed for either known or unknown compounds.

Sensitivity. High sensitivity was obtained by incrementing oxidation potentials of 16 in-series electrodes from 0 to 900 mV. Extended studies of 100 or more samples have been demonstrated to be accurate to between 4% and 12% in concentration and 1% to 4% in retention time, depending on the compound.

Peak Purity. In every sample, the sample peak of each monoamine of interest was compared to a known standard. This was essential where complex samples containing various drug metabolites could interfere with some peaks. It was found that acetaminophen made the measurement of 3-methoxytyrosine inaccurate. Coeluting metabolites potentially contaminated other peaks. For example, 4-hydroxyphenylacetic acid (4-HPAC) co-elute with 5-HIAA. In our 16-channel system, these two could be separated, enabling specific measurement of the two compounds.

Ratio Accuracy. A 31-compound synthetic CSF with concentrations approximating those found in the patient samples was used for calibration. For the electrochemical detector, the ratio accuracy was required to be within ±20% to be considered accurate when the system was on the fully automatic mode.

RESULTS

Out of the roughly 400 peaks that could be distinguished by the electrochemical detector, the three reported here are HVA, 5-HIAA, and MHPG. Mean trigeminal cistern concentrations of these metabolites for patients with atypical facial pain, trigeminal neuralgia, cluster headache, and posttraumatic facial pain are shown in Table 2. These mean concentrations suggest that atypical facial pain patients have lower levels of 5-HIAA, HVA, and MHPG than the three other diagnoses. The highest titers of 5-HIAA and HVA were found in posttraumatic facial pain. Trigeminal neuralgia and cluster headache had almost the same metabolite concentrations. Overall, HVA averaged 121 ng/mL for all the facial pain patients, compared to 150 to 550 ng/mL in 10 studies of ventricular brain CSF in assorted psychiatric and pain patients and the much lower concentrations in lumbar CSF (Figure 1).[1,3,13–25] 5-HIAA averaged 29 ng/mL in our facial pain patients, similar to that found in lumbar CSF, but less than the 60 to 120 ng/mL in nine studies of ventricular brain CSF in assorted psychiatric and neurological patients (Figure 2).[1,3,13–26] MHPG averaged 9 ng/mL, with a similar range as 13 studies of lumbar CSF of normal controls and assorted psychiatric and pain diagnoses (Figure 3).[1,19–22,27–30] The latter comparison with lumbar CSF was by default because no study of ventricular MHPG could be found.

Comparison of trigeminal neuralgia with the other three facial pain diagnoses using Wilcoxon scores (rank sums) and analysis of variance yielded no statistically significant differences between pain diagnoses for HVA, 5-HIAA, and MHPG. The small sample sizes of the nontrigeminal diagnoses led us to this grouped diagnostic analysis to avoid a type 1 statistical error. Simple inspection of the differences in monoamine levels between the four facial pain diagnoses shows relatively little variation in comparison to the far greater differences between ventricular studies and the facial pain diagnoses shown in Figures 1 and 2 for HVA and 5-HIAA, respectively. MHPG remains a matter of conjecture, because lumbar but no ventricular CSF data in the literature were available for comparison. Knowing the similar concentrations of our trigeminal CSF and the lumbar CSF MHPG, plus the usual lumbar-cisternal gradient of approximately three, one might hypothesize low concentrations of brain MHPG in facial pain, albeit without proof.

DISCUSSION

The trigeminal cistern concentrations of HVA and 5-HIAA measured in this study are 25% to 50% the values reported in ventricular CSF. These trigeminal samples have similar HVA, 5-HIAA, and MHPG concentrations to those reported in lumbar CSF, strikingly low considering there is a two-to-three fold gradient between lumbar and posterior fossa CSF for 5-HIAA and MHPG. The question is how to interpret these low monoamine values?

Table 2. Monoamine Metabolite Concentrations in Trigeminal Cistern of Facial Pain Patients[a]

	n	*5-HIAA (ng/mL)*[b]	*HVA (ng/mL)*	*MHPG (ng/mL)*
Atypical facial pain	3	14.1 ± 3.2	94.0 ± 24.6	7.6 ± 3.4
Trigeminal neuralgia	46	28.9 ± 16.4	130.4 ± 31.5	9.5 ± 2.5
Headache	7	28.0 ± 11.2	120.5 ± 37.5	10.4 ± 4.5
Posttraumatic facial pain	8	44.2 ± 16.3	141.8 ± 29.7	9.0 ± 3.0

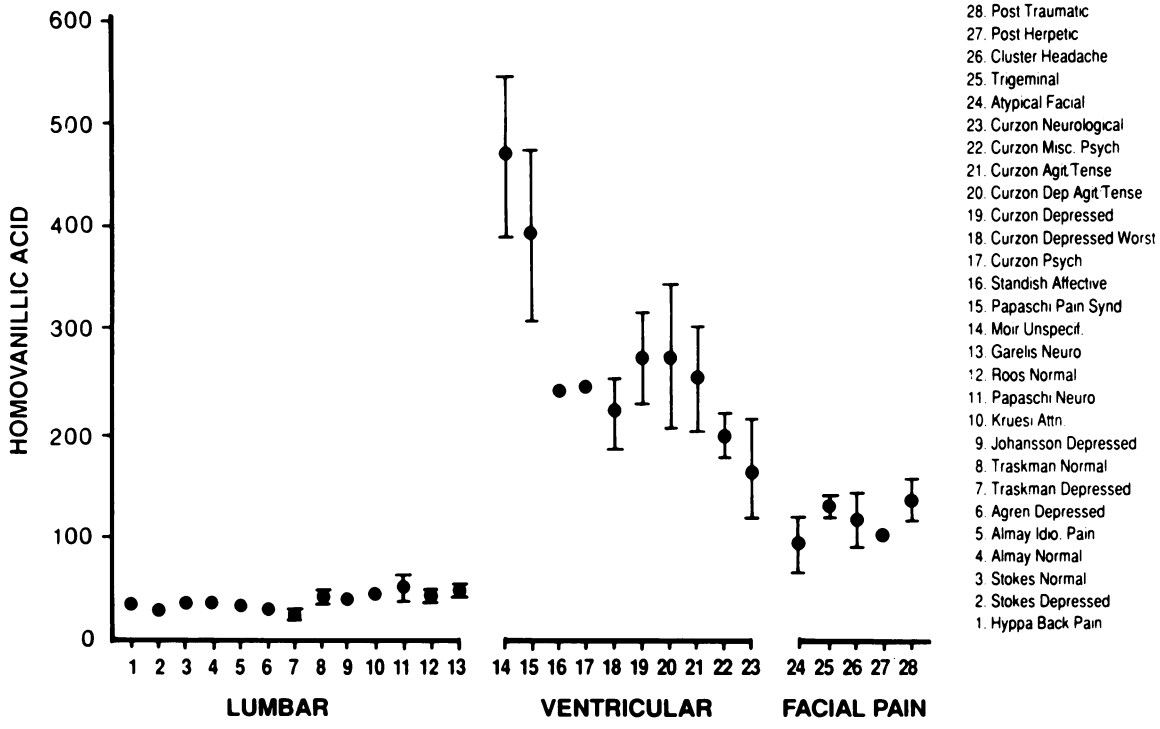
[a] Values are given as the mean ± SD.
[b] 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Evaluation of the low 5-HIAA and HVA CSF concentrations must consider the special methods used in arriving at these measurements and their scientific face validity with respect to what is known about monoamines and pain.

The special methodological detail used in this study addressed five problems in the earlier literature: sampling site, number of samples, comparison with other studies, comparison of diagnoses, and accuracy of the assay.

The sampling site of CSF in intimate proximity to the primary sensory afferent cells and the brain provides a closer estimate of the neurochemistry of those particular central sites than does measurement of lumbar CSF. We have avoided extrapolating meaning from lumbar CSF data where concentration gradients, spinal cord metabolism (amine production in the cord, active transport, and differential diffusion), and physical differences between patients, (height, weight, sex) all contribute to variations in CSF measurements that make applicability to brain functioning problematic.[28,31,32] CNS CSF monoamines are indicative of brain amines in that lateral ventricle CSF amines correlate with surrounding tissue amine concentrations.[24,33,34] Furthermore, drugs or illnesses that alter brain tissue amine turnover alter CNS CSF amine turnover in tandem. Hence, these trigeminal CSF amines are likely to reflect CNS tissue metabolism. The origin of the monoamines measured here could be from the cavernous sinus, mesolimbic system, autonomic nervous system,

Figure 1. Interstudy comparison of homovanillic acid concentrations (ng/mL) in lumbar, ventricular, and trigeminal cisternal cerebrospinal fluid. Brackets indicate the 95% confidence limits of the mean. The source for each value is indicated on the right.



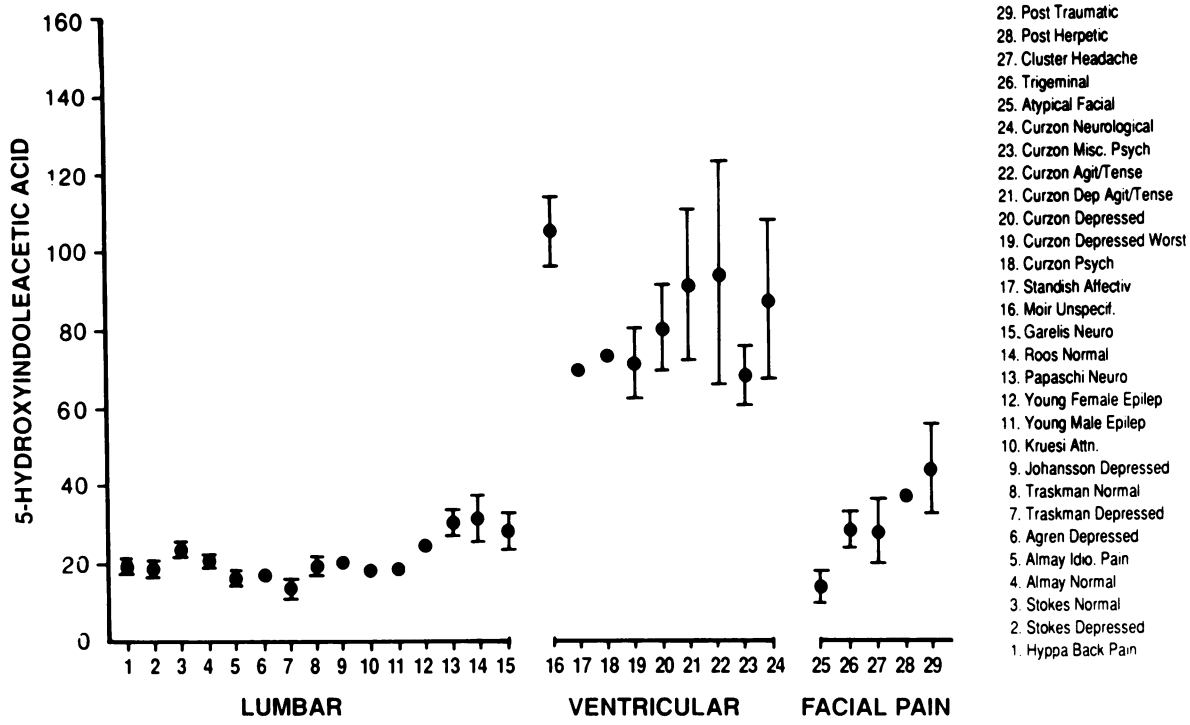
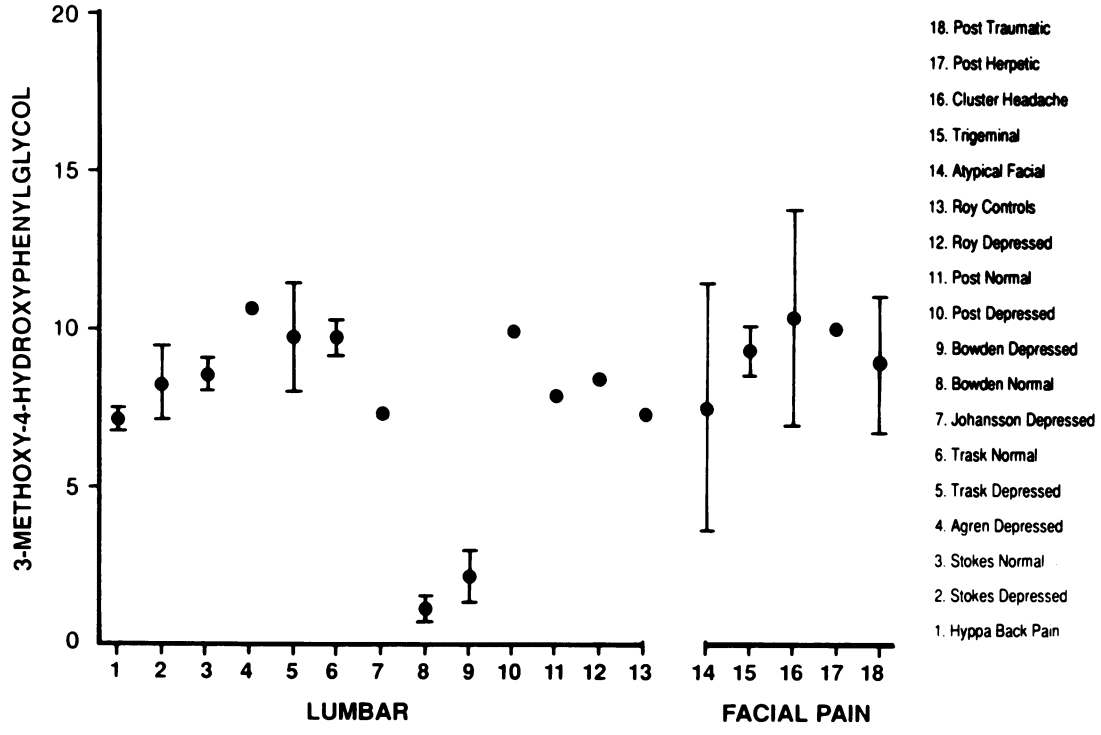


Figure 2. Interstudy comparison of 5-hydroxyindoleacetic acid concentrations (ng/mL) in lumbar, ventricular, and trigeminal cisternal cerebrospinal fluid. Brackets indicate the 95% confidence limits of the mean. The source for each value is indicated on the right.

Figure 3. Interstudy comparison of 3-methoxy-4-hydroxyphenylglycol concentrations (ng/mL) in lumbar and trigeminal cisternal cerebrospinal fluid. Brackets indicate the 95% confidence limits of the mean. The source for each value is indicated on the right.



temporal lobe, posterior fossa, or trigeminal ganglion, as they are all nearby and could flow into the trigeminal cistern CSF.

The numbers of patients in most lumbar CSF studies are small, accuracy of the measurements are not stated, standard deviations are large, and methods of dealing with outlying results are not specified. A couple of extreme values can alter a mean and standard deviation considerably, making the generally small differences between groups imprecise. Our relatively large sample of 64 patients, accurate measurements, and inclusion of all data (no discarded outliers) add credence to the numbers in this study.

The meaning of particular chemical measurements, (with their standard errors) requires numerous comparison with other diagnoses before their value can be established. What is significantly high or low? The tactic of interstudy comparison helps interpretation of the range of values found in this study with others in the literature.

The comparison of four different facial pain diagnoses strengthens our ability to identify variations in monoamine levels attributable to trigeminal pain in general or specific diagnoses.

The ESA neurochemical detector method is not only comprehensive and sensitive, but enables the separation of coeluting compounds, notably 4-HPAC and 5-HIAA. Many assay systems do not have this sensitivity and erroneously report the combined level as 5-HIAA.

The scientific face validity of low 5-HIAA and HVA is consistent with the antinociceptive effects of serotonin and dopamine for the descending inhibitory system, opioid analgesia, behavioral analgesia, and stimulation-produced analgesia from the limbic system to the dorsal horn. The finding that 5-HIAA, the principal metabolite of serotonin, might be low in intractable pain is quite consistent with serotonin's inhibition of pain. Morphine analgesia without the participation of serotonin is diminished by 80%. Tolerance and decreased efficiency of stimulation-produced analgesia are marked without serotonin. The descending inhibitory system requires serotonin from the raphe, down the dorsolateral funiculus into the dorsal horn. Quantitative reports of operational criteria for low serotonergic activity in lumbar CSF have been reviewed by van Praag,[35] predicated on the search for a low 5-HIAA subtype of depression. Studies of Goodwin et al,[36] Van Praag,[35] and Asburg et al[37] define low 5-HIAA as in the 70 to 90 ng/mL range, and high as 160 to 170 ng/mL. Traskman and coworkers reported CSF 5-HIAA of 5 to 15 ng/mL in a group of nine individuals who died of violent or drug suicide attempts.[21] This range is at the extreme of the low lumbar 5-HIAA concentrations shown in Figure 2. These values are also at the low end of the range we found in the trigeminal cistern of facial pain patients, although the effect of a gradient from the trigeminal cistern to the posterior fossa mitigates the power of such comparisons. Future reports will describe the gradients of monoamines; however, we believe that such gradients do not change the general findings presented here. Our mean 5-HIAA of 29 ng/mL is strikingly lower than ventricular values and even most lumbar values in the literature.

The finding that HVA was low in trigeminal cistern/posterior fossa CSF is consistent with the knowledge that dopamine has important inhibitory functions for pain in the brain. The ventral tegmentum has a rich dopaminergic projection to the striatum that is inhibitory in nature. Most studies, usually involving spinally mediated pain, have not found dopamine to be of interest, perhaps because the spinal cord has little dopamine in it (except for the deeper lamina 10 area). Pain sensitivity has been negatively correlated with HVA and 5-HIAA.[5,38] Depression has also been associated with low HVA, not surprising given the association of dopamine and serotonin with 5-HT_2 receptors.[39] Without exception, the evidence is consistent that low dopaminergic activity can be associated with pain. Lechin et al[40] have demonstrated the value of pimozide, a dopaminergic agent in the treatment of trigeminal neuralgia. Additional evidence for the behavioral importance of dopamine are data showing that dopamine in the mesolimbic (ventral tegmental) area is crucial for motivation and the ability to behave flexibly. The negativism and lack of response to many treatments often seen in chronic pain patients might be analogous to those inflexible, amotivational states correlated with low dopamine. The physiological meaning of low levels of HVA and 5-HIAA might reflect hypometabolism if monoamine release were decreased. Conversely, the rate of synthesis could be normal and catabolism increased, with a resultant lowering of CSF monoamines. We cannot resolve this question with this study.

Norepinephrine has contradictory effects on pain at different levels of the neuroaxis. There are inhibitory effects on pain at the spinal cord level and in the pons near the locus coeruleus where stimulation produces behavioral analgesia. There are also excitatory effects above the locus coeruleus and peripherally on the primary afferent neurons. Neuropsychiatrists see norepinephrine as having a relatively nonspecific role in setting a tone of activity or response bias to changes in input consistent with its diffuse distribution in the neuropil throughout the nervous system.[41] Post and associates[28] reviewed CSF data on MHPG in which normal values are clustered around 10 ng/mL. Neurologic and depressed patients are clustered slightly above 200 ng/mL. The manic patients extend into the 400 ng/mL range. This range is not very different from the values we found in the facial pain diagnoses, making any distinction on the basis of MHPG impossible.

CONCLUSION

The results of this study indicate that in intractable facial pain there are low levels of CSF HVA and 5-HIAA, which impute dysfunction of central dopamine and serotonin systems. Monoamine profiles in trigeminal cistern CSF reflect a distinct alteration of dopaminergic and serotonergic functioning in these facial pain patients, different from the studies previously reported with lumbar CSF measurements. Future research might use the electrochemical detection method to measure accurately very small concentrations of multiple neuromodulators in as little as 0.25 mL CSF. In this way codysfunction of several CNS neuromodulators, both monoamines and peptides, might be studied, and treatment algorithms designed.

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