

Research Submissions

Cerebrospinal Fluid Sodium Increases in Migraine

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Background.—Pharmaceuticals with calcium- or sodium-channel-blocking activity have proven useful for migraine prophylaxis, and calcium channel, sodium transporter, and sodium channel gene mutations have been found in familial hemiplegic migraine. However, it is not known whether calcium or sodium homeostasis is altered in migraine.

Objective.—To compare levels of sodium, calcium, potassium, and magnesium in cerebrospinal fluid (CSF) and blood plasma between migraineurs and controls.

Methods.—We recruited 20 migraineurs without aura and 11 controls prospectively, and studied migraineurs in sick (MH⁺) and well (MH⁻) states. We collected lumbar CSF and venous blood plasma, quantified elements with ion-selective electrodes or colorimetry, and determined osmolality by depression of freezing point. We compared levels of Na⁺, Ca²⁺, K⁺, and Mg among and also within subjects who were studied in both MH⁺ and MH⁻ states.

Results.—Mean CSF Na⁺ levels were increased by 3 mmol/L in MH⁺ compared with MH⁻ and by 4 mmol/L compared to controls ($P < 0.005$). In 4 subjects who were sampled in both MH⁺ and MH⁻ states, mean CSF Na⁺ concentration increased by 2 mmol/L in the MH⁺ state compared with the MH⁻ state ($P < 0.05$). Simultaneous plasma Na⁺ levels did not differ among the 3 clinical groups, nor did osmolality, total Ca and Ca²⁺, K⁺, and total Mg levels in CSF.

Conclusions.—Compared to both controls and the MH⁻ state, CSF Na⁺ concentration increased in MH⁺ independently from other clinical or pharmacological fluctuations, CSF concentrations of Ca²⁺, Mg, and K⁺, and blood plasma Na⁺ levels. These results implicate a deviation of Na⁺ homeostasis in migraine. The modestly elevated extracellular Na⁺ in MH⁺ may cause the neural changes that underlie clinical features of migraine.

Key words: cerebrospinal fluid, Na⁺, migraine, headache

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The 2 prevailing views of migraine pathophysiology are the neuronal and trigeminovascular theo-

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ries.¹ In the neuronal hypothesis, cortical spreading depression (CSD), a slowing of electroencephalographic activity that propagates across the cortex at 3 to 5 mm/min, has been recorded during migraine aura.² The trigeminovascular hypothesis asserts that an altered modulation of the perivascular nerves of the intracranial vessels sensitizes the nociceptive perivascular fibers projecting to the trigeminal caudate nucleus, which propagates the headache.^{3,4} The current model for migraine is an integration of these 2 theories,⁴ linking the intrinsic brain activity of CSD with trigeminal meningeal afferents.^{5,6} In addition, Moskowitz et al

presented logic to explain the loss/gain of functions found in 2 different familial hemiplegic migraine genes with the migraine phenotype.⁷ However, the basis for hypersensitivity features of migraine—pain, photophobia, phonophobia, osmophobia, nausea, vomiting, and confusion—remains unexplained.

Nonmigraineurs experience the same environmental fluctuations as migraineurs, and it is our hypothesis that all migraineurs have a common biochemistry distinct from nonmigraineurs. It is central to our hypothesis that the migraineurs' common biochemistry decompensates after different types of migraine triggers (including stress, dietary changes, hormonal changes), and has the following attributes: (1) broad distribution and dissemination throughout the brain, (2) capacity for immediate response that can be sustained for hours, (3) influence by many different triggers, and (4) association with many apparently disparate biochemical changes that have been implicated in migraine.

Fluctuations in Ca^{2+} and/or Na^{+} ion concentrations would be consistent with these criteria. The concentrations of Ca^{2+} or Na^{+} may be altered by many perturbations, ranging from changes in specific ion channels or membrane composition to ion transport machinery, all of which are subject to their own extensive physiologic regulation. Uncompensated changes at any level might alter ion balances across cell membranes. Evidence for Ca^{2+} or Na^{+} alteration is supported by the findings that mutations in the slow calcium channel gene (*CACNA1A*),^{8,9} the $\text{Na}^{+}, \text{K}^{+}$ -ATPase transporter gene (*ATPIA2*),^{10,11} or the voltage-gated sodium channel gene (*SCN1A*)¹² underlie cases of the rare familial hemiplegic migraine. Similar mutations have not been found in the more common forms of migraine,¹³ although the *SCN1A* gene has not yet been evaluated. Further evidence supporting a disturbance of these ions in migraine is that drugs blocking Ca^{2+} or Na^{+} channels are among the best agents currently employed to reduce the frequency of migraine.¹⁴⁻¹⁹ However, no direct measures of brain or cerebrospinal fluid (CSF) Ca^{2+} or Na^{+} have been reported for migraine.

To further test the hypothesis that there is a core disturbance of either calcium or sodium ion homeostasis in migraine, we measured their levels in CSF.

METHODS

Population Source.—We advertised in local newspapers and gave presentations on this research in the community to recruit potential migraineurs and controls. Children were excluded because of the invasiveness of CSF collection. The Huntington Hospital Internal Review Board (FWA 2338) approved our protocol and consent forms.

Diagnosis.—We recorded lifetime histories of all participants' troublesome headaches. Two of the authors, who are neurologists with headache expertise, diagnosed each headache type using the International Headache Classification²⁰ and reached consensus for the diagnosis with a validated, structured interview and computerized classification.²¹ Because there is evidence that migraine with aura is different from other migraine types, to reduce clinical heterogeneity we selected only those classified with "migraine without aura" as the primary headache problem. Those with additional primary headache disorders of migraine or tension-type that were less frequent were not excluded. Migraineurs self-reported their headache frequency, severity, and duration by structured interview and, to further restrict clinical heterogeneity, we included only those with a minimum of 1 attack per year and a maximum frequency of 10 days per month.

We recruited volunteer controls (C) who stated that they did not suffer from troublesome headaches and then administered a different structured interview (designed to elicit responses to 15 potential headache situations and available from the authors by request) to rate and record their headache histories. Controls were accepted for the study only if their answers to the headache interview did not meet IHS criteria for headache of any type, they revealed no headache propensity (defined as no more than mild [<4 of 10 severity] for any specific headache provocation), and they had no family history of migraine. After this assessment, 4 of the initial applicants were excluded because of previously undiagnosed migraine ($n = 3$) or sinus headache ($n = 1$); on the basis of the number of applicants screened, this is consistent with estimated prevalence rates for undiagnosed migraine.²²

Additional Clinical Criteria.—For both migraineurs and controls, all maintenance therapy was unchanged for >30 days prior to sampling; sleep, diet

(including alcohol/caffeine), and stress levels were unchanged and catastrophic events had not been experienced within the 24 hours prior to lumbar puncture (LP). Subjects were excluded if rescue medications for headache were taken within 24 hours prior to sampling or if LP could not be performed because of fever, bleeding disorder, coumadin treatment, pregnancy, or other acute medical conditions. Migraineurs sampled in MH^- were defined as having no headache (0 of 10) for >24 hours at LP. Migraineurs in MH^+ were defined according to the following criteria: severity at time of LP of >5 on a scale of 0 to 10 (headache duration was noted); IHS diagnostic classification of 1.1.1 of the headache state(s) at the time of study; clinician differentiated between a 1.1.1 attack and other types, when relevant, and the headache was spontaneous and typical for each person; all prescription and over-the-counter medications as well as supplements recorded for 30 days before sampling; and all maintenance and rescue therapy unchanged for >30 days prior to LP.

Cerebrospinal Fluid Collection.—To minimize diurnal fluctuations, we collected CSF between 1 PM and 6 PM in the lateral or sitting position using a 20/22-gauge Quincke-type needle between the L3/4 or L2/3 positions. We drip collected the CSF in 3 consecutive 6- to 7-mL fractions, centrifuged each at $3000 \times g$ for 5 minutes to pellet cells, and stored 1-mL aliquots of the CSF supernatant at -80°C until thawed for assay, after taking an aliquot of $10\ \mu\text{L}$ for total protein assay.

Blood Collection.—Blood was collected at the time of LP in potassium EDTA tubes by venipuncture from the antecubital fossa, and plasma was separated by centrifugation ($5000 \times g$ for 3 minutes), aliquoted and stored at -80°C until thawed for assay. An aliquot of $10\ \mu\text{L}$ was taken for total protein assay (see below), and urea and creatinine were measured using a chemical autoanalyzer.

Protein Assay.—Concentrations of protein in CSF were determined using a micro titer plate-based Coomassie protein assay using human serum albumin (Sigma), 0 to $100\ \mu\text{g}/\text{mL}$, as a standard. Briefly, $5\ \mu\text{L}$ of diluted CSF ($10\times$ and $100\times$) was added to a 96-well microtiter plate in triplicate. Coomassie dye (BioRad, Hercules, CA) was diluted ($5\times$) and $200\ \mu\text{L}$ was added to each well. After 5 minutes, the OD at 595 nm was obtained using a microplate reader (Molecular Devices,

Sunnyvale, CA), and protein concentrations in each sample were computed using Softmax software from Molecular Devices.

Measurement of Ion and Element Concentrations.—Ions were all measured, without knowledge of the diagnosis, from $300\ \mu\text{L}$ of fluid that came from the first CSF fraction and from $300\ \mu\text{L}$ of blood plasma. Na^+ and K^+ levels were determined using a Roche/Hitachi Modular analyzer. The ion-selective electrode module employed electrodes of the liquid-liquid junction type that are based on neutral carriers. Imprecision studies conducted according to NCCLS guidelines yielded a within-run CV of 0.2% for both Na^+ and K^+ . Ca^{2+} was measured on a Bayer/Chiron 634 analyzer using an electrode based on an ion exchanger, with a typical within-run precision CV of 1%. Total Ca and Mg levels were determined on the Roche/Hitachi Modular analyzer by colorimetric endpoint methods: *o*-cresolphthalein binds with total Ca with a within-run precision CV of 0.9%; xylydyl blue binds with total Mg with a within-run precision CV of 1.2%. Osmolality was determined by depression of freezing point (Model 3300 osmometer; Advanced Instruments, Inc., Norwood, MA).

Statistical Analysis.—Comparison of prescription drug usage between migraineurs and controls was done using the Mann-Whitney test. Comparisons of Na^+ , K^+ , Ca^{2+} , and total Ca and Mg concentrations among all 3 clinical groups (MH^+ , MH^- , and C) were done using analysis of variance (ANOVA). Dunn's method was used for pairwise comparisons. Comparison within subjects of Na^+ during MH^+ and MH^- states was done using repeated measures ANOVA. All tests were 2-sided with 0.05 significance levels.

RESULTS

Clinical.—We assessed 20 migraineurs with the IHS diagnosis of 1.1.1 (migraine without aura²⁰) and 11 non-headache-suffering controls. Of the 20 migraineurs, 10 were sampled in MH^- , 6 were sampled in MH^+ , and 4 were sampled in both MH^+ and MH^- . While some of the migraineurs had additional primary headache conditions in their lifetime histories, migraine without aura (1.1.1) was the dominant headache for all included in the study.

Table 1.—Cation-Impacting Prescription Medication Usage in Migraineurs and Controls

Drug	Number of Migraineurs n = 20	Number of Controls n = 11
Hydrochlorothiazide	1	1
Gabapentin	1	1
Verapamil	1	0
Topiramate	5	0
Valproate	1	0
No medication	3	5
Mean (SD)* number of drugs* taken per subject*	4.8 (4.4)	1.5 (1.7)

* $P < 0.05$ by Mann-Whitney.

Increased prescription drug usage was reported by migraineurs, mainly for antimigraine treatments, and these included drugs known to act on ion channels (topiramate, gabapentin, valproate, verapamil). Mean per-subject usage (number of drugs taken) of all reported prescription drugs and identification of those known to have effects on cations are itemized in Table 1. Migraineurs made no change in their prescription drug usage between their MH⁺ and MH⁻ samplings. The 4 migraineurs sampled in both MH⁺ and MH⁻ had no change in medication throughout the study: 2 were not taking any medication, a third was taking topiramate, and the fourth was taking valproate, but neither of the latter 2 made any change in therapy for 3 months prior to or during the study.

Cerebrospinal Fluid.— *Proteins, Osmolality, and Metabolites in Cerebrospinal Fluid.*—Our initial studies examined protein concentrations in CSF to determine whether any changes could be due to blood-brain compartment disruption. Protein concentrations in controls (26.8 ± 13.5 mg/dL, $n = 11$) did not differ significantly from concentrations in MH⁺ (28.7 ± 6.7 mg/dL, $n = 6$) or MH⁻ (29.5 ± 9.7 mg/dL, $n = 10$). Thus, there is no evidence of plasma leakage or contamination of the CSF in these sample groups. CSF osmolality did not differ among controls (283 ± 20 mOs/kg), MH⁺ (275 ± 23 mOs/kg), and MH⁻ (272 ± 25 mOs/kg), consistent with no fluid shift between the CSF, blood, and brain tissue compartments. There

Table 2.—Mean (\pm SD) CSF and Plasma Na⁺ Levels from Migraine States (MH⁺ and MH⁻) and Controls (C)

Clinical State	**CSF Na ⁺ (mmol/L)	Plasma Na ⁺ (mmol/L)
MH ⁺ (n = 6)	149 \pm 2	136 \pm 5
MH ⁻ (n = 10)	146 \pm 2	135 \pm 2
C (n = 11)	145 \pm 4	135 \pm 2

** $P < 0.005$ by ANOVA.

were no differences in blood plasma urea or creatinine concentrations among the C, MH⁺, and MH⁻ (data not shown), consistent with no change in renal function, nutritional status, or hydration.

Sodium Concentrations.—The most general and direct determinants of ion channel and pump activities are the concentrations of their substrates, the ions themselves. CSF Na⁺ levels differed significantly by clinical group (Table 2). Pairwise comparison revealed that the differences were between the MH⁺ and both the MH⁻ and control groups.

We then analyzed a subgroup of 4 migraineurs in both MH⁺ and MH⁻. Two were on no therapy, and 2 were taking a stable maintenance dose of drugs that influence sodium (topiramate or valproate). Repeated measures comparison of their MH⁺ and MH⁻ CSF Na⁺ levels revealed they had higher Na⁺ in MH⁺ than in MH⁻ (Table 3), supporting the result from the total study population.

To determine if the CSF changes were a reflection of systemic levels, we measured blood plasma concentrations. There were no differences in the Na⁺ from blood plasma (obtained at the same time that the CSF

Table 3.—Mean (\pm SD) CSF Na⁺ Levels in Paired Samples from Migraineurs in MH⁺ and MH⁻ States (n = 4)

Clinical State	*CSF Na ⁺ (mmol/L)
MH ⁺	148 \pm 2
MH ⁻	146 \pm 1

* $P < 0.05$ by repeated measures.

Table 4.—Means (\pm SD) of Other CSF Cation Concentrations in Migraine States (MH⁺ and MH⁻) and Controls (C)

Clinical State	CSF K ⁺ (mmol/L)	Total CSF Ca (mg/dL)	Ionized CSF Ca ²⁺ (mmol/L)	Total CSF Mg (mg/dL)
MH ⁺ (n = 6)	2.8 \pm 0.1	4.45 \pm 0.34	0.58 \pm 0.08	2.64 \pm 0.18
MH ⁻ (n = 10)	2.8 \pm 0.1	4.54 \pm 0.44	0.62 \pm 0.12	2.58 \pm 0.04
C (n = 11)	2.7 \pm 0.2	4.36 \pm 0.28	0.60 \pm 0.08	2.59 \pm 0.06

There were no significant differences among the 3 clinical groups.

was collected) among the MH⁺, MH⁻, and control groups (Table 2).

Potassium Concentrations.—To determine whether changes were specific for sodium, we measured the monovalent ion, K⁺, in CSF. K⁺ was similar in the MH⁺, MH⁻, and control groups (Table 4).

Divalent Cation Concentrations.—To further define the specificity of the changes, we determined the concentrations of the 2 divalent cations, Mg²⁺ and Ca²⁺. There were no differences in total calcium, ionized calcium, or total magnesium between the MH⁺, MH⁻, and C groups, as shown in Table 4.

Together, these data suggest that the Na⁺ changes are specific and not associated with changes in these other common mono- or divalent ions.

COMMENTS

Cations are important in brain functions and implicated in the pathophysiology of several diseases, including migraine. Definitive proof of the importance of cations is in hemiplegic migraine, where mutations of cation-related genes are known.⁸⁻¹² In these studies, we examined CSF cations to test our hypothesis that a single biochemistry typifies all migraine episodes. Our data suggest that changes in CSF Na⁺ concentration are specific and selective for migraineurs without aura. This Na⁺ change may unify neural mechanisms that underlie the clinical features of migraine.

While we are unaware of previous studies of CSF Na⁺ measurements in migraine to compare with our results, Campbell et al²³ reported elevated sodium blood levels in migraine (as distinct from our measurements that revealed no change in plasma sodium), accompanied by a decrease in protein that they at-

tributed to overhydration. Differences between our results and theirs cannot be ignored, but may be attributed to the methods of measuring sodium (they used an indirect gravimetric method based on pyroantimonate, now abandoned as less accurate) and the variations from circadian rhythm fluctuations,^{24,25} which had not been identified at the time of their study and which they did not address. The only other literature on this subject is from Brainard, who reported salt loading as a trigger for migraine.²⁶ He correlated this phenomenon with elevated plasma angiotensin and aldosterone levels²⁷ but did not measure sodium. These appear to constitute the total literature on sodium and migraine, despite the recent interest in ion transport genetics and the established success of sodium-channel-blocking drugs for migraine prophylaxis. (see Addendum)

The absence of significant CSF changes of total Ca and Mg, ionized Ca²⁺, and K⁺ highlights the singular finding of this observed Na⁺ increase in CSF. The lack of change in osmolality suggests there is no fluid shift. We do not know why the Na⁺ concentration alters in the absence of detectable change in these other cations, especially when they influence each other so much. There is 1 study (an abstract only) of CSF Mg that reported lower Mg in migraine compared with controls.²⁸ However, no levels were mentioned to allow comparison with our results, the methodology used was different (atomic absorption spectrometry), and their controls were not well described. Further research is required to explore these complex relationships.

The difference in CSF Na⁺ between MH⁺ and MH⁻ suggests that this is an ictus-specific change of migraine. That these findings appear to persist in the 4 migraine participants who were analyzed in both states

restricts the interpretation more emphatically to their ictal event and removes the possibility that their drug treatment was responsible since these subjects acted as their own controls and had no change in medication or other clinical state between samplings. Study of sodium homeostasis in other diagnoses will be required to explore further clinical specificity.

The lack of Na^+ change in the blood plasma of all clinical groups strongly suggests that this CSF increase is not due to a peripheral/dietary origin but is generated from the brain. Furthermore, there was no evidence that our participants had peripheral dehydration (based on blood urea and creatinine) that could increase CSF Na^+ . CSF Na^+ equilibrates in less than 2 hours between blood and CSF,^{29,30} and the brain/extracellular fluid/CSF equilibrates much more rapidly, especially in mobile subjects.³¹⁻³³ Thus, we can confidently assume that the observed change in CSF Na^+ reflects a similar level in brain extracellular fluid.

The major confounding variable in this study is the greater prevalence of prescription drug usage in the migraine population. While a concern, it is unlikely to be the cause of any CSF cation changes for a number of reasons. Three of the 8 participants were taking different medications that would not be expected to have the same effect on cations as topiramate has. Second, the majority of migraineurs (12/20) were not taking any daily medication that has a known impact on cations. They were prescribed a variety of antihypertensives, antidepressants, analgesics, hypnotics, hormone replacement therapy and antiallergy medications, different in overall quantity from the controls but not dissimilar in class. This variety makes it unlikely that there would be any consistent drug effect leading to our CSF Na^+ finding. Furthermore, the main CSF Na^+ change found in this study is between MH^+ and MH^- when both groups are taking the same cation-impacting drugs, in stable regimens. Finally, we found the CSF Na^+ was still altered in paired samples of the subset of 4 migraineurs who served as their own controls when sampled in both MH^+ and MH^- , independent of drugs.

CSF Na^+ levels are known to be carefully regulated,³⁴⁻³⁶ and the 3 mmol/L Na^+ increase that we observed in MH^+ reflects a migraine process that is still tightly regulated, as distinct from a systemic hyper-

natremic crisis. Increased extracellular Na^+ has been shown to affect the inactivating peptide on voltage-gated sodium channels, directly displacing it from the extracellular orifice of the channel.³⁷ While the resting membrane potential is mainly derived from the K^+ gradient across the membrane (unchanged in the CSF in our study), an increased extracellular Na^+ in MH^+ will slightly reduce the resting membrane potential, decreasing the threshold for action potentials. Moreover, increases in extracellular Na^+ of <10 mmol/L have been reported to reduce the threshold for repetitive neuronal firing by increasing Na^+ conductance,³⁸ increasing pH-induced nociceptor discharge,³⁹ and altering coincidence detection in medial superior olivary neurons.⁴⁰ These effects in humans would contribute to a substantial neural disturbance.

Such neural disturbances from elevated extracellular Na^+ are directly consistent with the main clinical features of migraine: pain, photophobia, phonophobia, osmophobia, nausea, vomiting, and confusion. While not statistically significant, the mean Na^+ level in MH^- is just 1 mmol/L above the level of our control group. This may represent a predisposition for the migraineur such that additional provocation transitions them more easily to MH^+ .

CONCLUSIONS

There is a significant increase of CSF Na^+ during migraine attacks not associated with changes in total calcium, total magnesium, and ionized calcium or potassium; with other clinical or pharmacological causes; or with a change in plasma Na^+ . At present, we cannot measure Na^+ levels in brain, and the origin of the elevated CSF Na^+ is unclear. However, CSF rapidly equilibrates with brain extracellular Na^+ and mildly elevated extracellular Na^+ has biophysical consequences, many of which are estimated to render neurons more susceptible to excitation and functional disruption. These effects may underlie many of the clinical symptoms of migraine.

The observed elevation of CSF Na^+ appears to meet the requirements for our central hypothesis of a common biochemistry for migraineurs. Sodium ion and sodium regulatory mechanisms are present throughout the brain, subject to tight physiologic

regulation and influenced by many different factors. Any deviation in Na^+ is expected to have a wide and considerable impact on brain functions. The modest degree of alteration observed in this homeostasis is consistent with migraine, as distinct from major changes that would be unviable.

Ictus-specific sodium changes observed in this study may not only provide a possible explanation for migraine symptoms, but may establish a connection between these features and the current models of migraine pathophysiology. However, these are the first data on CSF Na^+ , and much study is required both for replication and to investigate the kinetics, the source location, the clinical specificity, the effect of treatments, and the mechanism behind this change in migraine Na^+ homeostasis.

ADDENDUM

After our manuscript was accepted for publication, we discovered descriptions of CSF sodium in migraine in 2 references: (1) Barrie M, Jowett A. A pharmacological investigation of cerebro-spinal fluid from patients with migraine. *Brain*. 1967; 90:785–94 reported measuring sodium and potassium by flame photometry in CSF from 20 patients during migraine attacks and 1 between attacks, with 10 control patients whose CSF was obtained for “routine investigations” with “various diagnoses, but excluding inflammatory brain diseases and head injury.” They reported that the Na^+ and K^+ levels were “all within the normal range.” While these findings are an important reference, we do not think this conflicts with our results as they did not compare the levels of well with sick migraineurs, levels were not reported, migraineurs were varied in description, their controls had various ill-defined neurological conditions, and their assay method was different. (2) Kerppola W. über die entstehung und eiweisbehandlung der migräne. *Monatschr. F. Psychiat. u. Neurol*. 1926; li:83-92 reported normal NaCl levels in 5 migraineurs in the headache state. They did not compare these with the headache-free state or controls.

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