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Brain sodium MRI in human epilepsy: Disturbances of ionic homeostasis reflect the organization of pathological regions

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ABSTRACT

In light of technical advancements supporting exploration of MR signals other than ^{1}H, sodium (^{23}Na) has received attention as a marker of ionic homeostasis and cell viability. Here, we evaluate for the first time the possibility that ^{23}Na-MRI is sensitive to pathological processes occurring in human epilepsy. A normative sample of 27 controls was used to normalize regions of interest (ROIs) from 1424 unique brain locales on quantitative ^{23}Na-MRI and high-resolution ^{1}H-MPRAGE images. ROIs were based on intracerebral electrodes in ten patients undergoing epileptic network mapping. The stereo-EEG gold standard was used to define regions as belonging to primarily epileptogenic, secondarily irritative and to non-involved regions. Estimates of total sodium concentration (TSC) on ^{23}Na-MRI and cerebrospinal fluid (CSF) on ^{1}H imaging were extracted for each patient ROI, and normalized against the same region in controls. ROIs with disproportionate CSF contributions ($Z_{CSF} \geq 1.96$) were excluded. TSC levels were found to be elevated in patients relative to controls except in one patient, who suffered non-convulsive seizures during the scan, in whom we found reduced TSC levels. In the remaining patients, an ANOVA ($F_{1100} = 12.37$, $p < 0.0001$) revealed a highly significant effect of clinically-defined zones ($F_{1100} = 11.13$, $p < 0.0001$), with higher normalized TSC in the epileptogenic zone relative to both secondarily irritative ($F_{1100} = 11$, $p = 0.0009$) and non-involved regions ($F_{1100} = 17.8$, $p < 0.0001$). We provide the first non-invasive, in vivo evidence of a chronic TSC elevation alongside Z_{CSF} levels within the normative range, associated with the epileptogenic region even during the interictal period in human epilepsy, and the possibility of reduced TSC levels due to seizure. In line with modified homeostatic mechanisms in epilepsy – including altered mechanisms underlying ionic gating, clearance and exchange – we provide the first indication of ^{23}Na-MRI as an assay of altered sodium concentrations occurring in epilepsy associated with the organization of clinically relevant divisions of pathological cortex.

Introduction

Due in no small part to the flexibility of the magnetic resonance signal - yielding a range of structural, functional and metabolic information - MR imaging has established itself as fundamental to the understanding and treatment of epilepsy (Duncan et al., 2016). It is worth noting, however, that all of the foregoing approaches utilize the proton (^{1}H) to generate signal. While the most abundant, there are other nuclei that can be used to generate an MR signal. In biological tissues, sodium (^{23}Na) yields the strongest MR signal after ^{1}H (Madelin et al., 2014). While previously hindered by limitations in field strength and gradient performance, recent advances in equipment, sequence design and the availability of ≥3 T systems have raised the prospect of ^{23}Na-MRI as an adjunct to ^{1}H-MRI for both biological and clinical research (Thulborn, 2016). ^{23}Na ions are crucial for the maintenance of transmembrane ion concentrations key to normal neural operation

Abbreviations: EZ/IZ1, Epileptogenic/Primary Irritative Zone; IED, Interictal Epileptic Discharge; IZ2, Secondary Irritative Zone;; TSC, Total Sodium Concentration;; VGSC, Voltage-Gated Sodium Channels

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Table 1
Patient clinical demography.

Patient	Age	Sex	Diag.	Dura-tion (yr)	Seizure Freq.	Medication	EZ/IZ1 localisation	MRI findings	Surgery Outcome ILAE@month
01	36	F	Bi. TLE	15	monthly	Cbz; Lev$_2$	Bi. Hipp, Hypothalamus	Hypothalamic Hamartoma	Contraindicated: Bilateral EZ
02	42	F	L.FLE	24	daily	Cbz.; Clon.; Top.	L. OFC, Frontal operculum	Cavity (L. post-traumatic lesion)	Contraindicated: EZ overlaps Broca's Area
03	31	M	L.FLE	14	monthly	Lev.; Lac.	L. SMA, Rolandic cortex	Cavity (horen-cephalic cyst)	ILAE I at 18 months
04	32	M	R.mTLE	19	daily	Oxc.; Clob., BMPs, PER.	R. insula, pre-motor, TPJ	MRI Negative	Contraindicated: Widespread EZ
05	41	F	L.FLE	14	weekly	Cbz.; Clob.; Lam.; Phen.	L. Frontal pole, frontal gyrus	Cavity (Resection)	Awaiting Surgery
06	24	M	L.FLE	22	daily	Oxc.; Lev.; Clob.	L. Frontal, Cingulate & Angular gyri	L. frontal and posterior sequelae	Awaiting Surgery
07	45	F	R.mTLE	32	2–3/yr	Cbz.; Clob.,	R. Hipp.	Cavity (Resection)	Patient elected non-surgical options
08	28	F	Bi. TLE	19	monthly	Clob.; Lam.	Bi. Hipp	MRI Negative	Awaiting Surgery
09	22	F	R.CE	21	weekly	Val.; Clon.; Cbz.;	R. insula, Cingulate & pre-central gyri	R. Front Sequelae	contraindicated: EZ overlaps motor regions
10	21	F	L.FLE	16	Weekly	Val.; Lam.	L. SMA, frontal operculum	L. Front. Thickening	Awaiting Surgery

Abbreviations: Bi, Bilateral; CBZ, Carbamazepine; CE, Central Epilepsy; Clob, Clobazam; Clon, Clonazepam; d, day; Diag., Diagnosis; F, Female; FLE, Frontal Lobe Epilepsy; Hipp, Hippocampus; Lac, Lacosamide; Lam, Lamotrigine; L, Left; Lev, Levetiracetam; mo, month; M, Male; m, mesial; OFC; Orbito-frontal Cortex; Oxc.; Oxcarbazepine; PER, Perampanel; Phen., Phenobarbital; R, Right; SMA, Supplematary Motor Area; TLE, Temporal Lobe Epilepsy; Top., Topiramate; TPF; Temporal-parietal Junction; Val., Valproate; yr, year. ILAE outcome: I: Completely seizure free, no aura; II: Only auras, no other seizures; III: One or two seizure days per years, ± auras; IV: Four seizure days per year to 50% reduction of baseline seizure days, ± auras; V: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days, ± auras; VI: More than 100% increase of baseline seizure days, ± auras.

(Oliva et al., 2012). This is energetically expensive, as concentrations are maintained against their electrochemical gradients, such that any deficiency of cellular energy production is likely to induce ion imbalances (Madelin and Regatte, 2013). To date, the biological and clinical significance of a potential non-invasive assay of in vivo ionic homeostasis and cell viability has led to the exploration of mechanisms that impact sodium levels as detected by ^{23}Na-MRI in a range of pathologies, including stroke (Tsang et al., 2011), brain tumors (Ouwerkerk et al., 2003), multiple sclerosis (MS) (Maarouf et al., 2014; Petracca et al., 2016; Zaaraoui et al., 2012) as well as Alzheimer's (Mellon et al., 2009), Huntington's disease (Reetz et al., 2012) and even whole body applications (Malzacher et al., 2016; Trattnig et al., 2012).

Given that sodium homeostasis is a major mediator of neuronal excitability, it is reasonable to ask whether ^{23}Na-MRI might be able to detect disturbances in conditions characterized by pathological paroxysms of hyper-excitability, such as epilepsy (Badawy et al., 2009a). Processes in epilepsy that might impact ^{23}Na-MRI signal range from contraction of the extracellular space under transmembrane osmotic pressures in areas undergoing pathological electrical activity (Antonio et al., 2016; Dietzel et al., 1982; Lux et al., 1986), in addition to ongoing modifications to the expression and function of sodium channels (Mantegazza et al., 2010), mitochondrial dysfunction (Folbergrová and Kunz, 2012) and cell loss and gliosis (Badawy et al., 2009a, 2009b). However, as in vivo ^{23}Na-MRI has yet to be performed in human epilepsy, the extent to which alterations in such processes might translate to modified signals at the level of ^{23}Na-MRI is unclear. Only a single study has looked at in vivo ^{23}Na-MRI changes in Sprague Dawley rats with kainate-induced tonic-clonic seizures (Wang et al., 1996). In pyriform cortex and the amygdala, diffusion and T_2-weighted images showed signal decreases 5 h post-ictally, which intensified at 24 h and had returned to control levels 7 days post-ictally. Sodium concentrations were significantly elevated at 24 h and remained elevated at 7 days, which the authors attributed to energy deficiency and failure leading to cell swelling and eventually cell death. These results are particularly intriguing, as they suggest homeostatic aberrations are discernable to ^{23}Na-MRI even during interictal periods, making its acquisition alongside other imaging modalities more convenient and obviating the need to acquire data immediately after a seizure.

Thus, there appears to be good reason to hypothesize that ^{23}Na-MRI may be modified, probably in terms of elevated ^{23}Na signal levels, in human epilepsy. However, epilepsy is a complicated disorder and necessitates several methodological caveats. Firstly, all things being equal, ^{23}Na-MRI should be a sensitive assay of intracellular concentrations (Nielles-Vallespin et al., 2007), but problems can arise when confounding changes occur in parallel: increased contributions from extracellular sources such as CSF due to atrophy or surgical/traumatic loss of tissue being one example. Secondly, not all cortices participating in epileptiform activity are subject to the same pathological processes: at the very least various systems of classification distinguish between epileptogenic and primary irritative zones (EZ/IZ1) on the one hand and those secondarily irritative regions (IZ2) to which seizure may propagate and may generate their own intrinsic interictal spikes (Bartolomei et al., 2016; Chauvel, 2001; Palmini, 2006).

Here we propose to use Stereo-EEG (SEEG) to define regions of interest where we can both classify cortices in terms of clinically-relevant divisions using the intracerebral electroencephalography gold-standard, and quantify not only sodium concentrations but also contributions from CSF in both patients and a normative control sample. Thus, we will evaluate for the first time the possibility that ^{23}Na-MRI is sensitive to pathological processes occurring in human epilepsy; how these changes might be impacted by potential confounds; and their relationship with epileptological divisions and phenomena in epileptic networks.