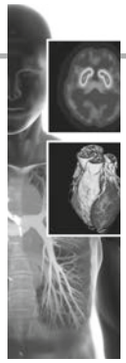

What can sodium MRI reveal about sodium accumulation in the brain: implications for multiple sclerosis

"*...brain sodium MRI is an emerging tool that enables depiction of cerebral sodium accumulation related to neuronal injury as evidenced in multiple sclerosis.*"

KEYWORDS: brain ■ disability ■ multiple sclerosis ■ neuronal injury ■ sodium MRI

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Multiple sclerosis: needs for biomarkers of neuronal injury

Multiple sclerosis (MS) is a chronic disease of the CNS, representing the leading cause of neurological disability in young adults. Focal inflammatory and demyelinating lesions disseminated in the cerebral white matter have been considered for several decades to be the main feature of MS. However, recent histological studies have also demonstrated the presence of diffuse and progressive damage in cerebral white and gray matter, leading to neuronal injury [1–3]. While neuronal injury is known to occur progressively from the onset of MS and is thought to be a significant cause of increasing clinical disability, the mechanisms underlying neuronal injury are still poorly understood. Furthermore, the conventional MRI metrics lack the specificity required to depict this pathological process, so noninvasive and *in vivo* biomarkers of neuronal injury are needed.

Recently, several experimental studies have highlighted the potential key role of sodium accumulation leading to the pathogenesis of neuronal injury [4–7]. It appears that occurrence of demyelination is followed by upregulation and redistribution of sodium channels along the entire demyelinated axolemna [4,8,9]. The increased number of sodium channels enhances the amount of energy required from the Na^+/K^+ ATPase. Concomitantly, soluble mediators of inflammation disturb the functional integrity of mitochondria, resulting in decreased ATP production [5,10]. All of these mechanisms driven by mitochondrial energy failure result in axonal sodium accumulation, which leads to reversed activity of the Na^+/Ca^{2+} exchanger and axonal calcium import. This calcium overload stimulates a variety of toxic calcium-dependent enzymes, causing structural and functional axonal injury [6,10].

Brain sodium MRI: a unique noninvasive tool to depict accumulation of sodium in MS

Sodium (^{23}Na) MRI appears to be the unique noninvasive way to detect and quantify *in vivo* the sodium concentration in the brain based on the magnetic properties of the ^{23}Na nucleus [11–13]. In the human brain, sodium is distributed in two compartments; the intracellular and the extracellular compartments. The concentration gradient between the two compartments is kept constant through the effect of the sodium–potassium pump. The total sodium concentration measured by sodium MRI is the average sodium concentration between the two compartments. Sodium MRI is a promising diagnostic tool since pathological processes can alter this ion gradient. This technique has already been used to investigate strokes and brain tumors [14]. However, sodium MRI remains a challenging technique due to several limitations. A major problem of sodium MRI is related to the very short transverse relaxation time (T_2) of ^{23}Na (<2 ms) that requires the use of imaging sequences with very short echo times (<200 µs), generally not provided by the manufacturers to detect the MR signal. The second major limitation of sodium MRI is related to its very low *in vivo* sensitivity, 20,000-times lower, compared with proton and leading to poor signal-to-noise ratio [15].

To date, only two studies have been performed in MS that examine the total sodium concentration accumulation in lesions and normal appearing brain tissue [16,17]. Both studies demonstrated significant accumulation of total sodium concentration inside white matter lesions, normal appearing white matter and gray matter compartments. In patients with early stage relapsing–remitting MS, Zaaraoui *et al.* found that sodium MRI revealed abnormally high concentrations of sodium in specific brain

Future Medicine part of fsg

regions, including the brainstem, cerebellum and temporal pole. In the advanced-stage relapsing–remitting MS patients, abnormally high sodium accumulation was widespread throughout the whole brain, including in normal-appearing brain tissue. Another striking point of this study was that the amount of sodium accumulation in gray matter associated with the motor system was directly correlated with the degree of patient disability [17].

The abnormal sodium accumulation in macroscopic white matter lesions may be related to increases in sodium concentration inside the extracellular and/or intracellular compartments. The increase of sodium concentration in the extracellular compartment, if present, would probably be related to edema as encountered in acute lesions or loss of tissues in chronic lesions. On the other hand, the increase in sodium concentration in the intracellular compartment may be explained by demyelination or gliosis processes. In the normal-appearing brain tissues, the diffuse sodium accumulation may reflect the progressive axonal injury present outside macroscopic lesions in patients with longer disease duration. The progressive axonal injury may also result from macroscopic white matter lesions that induce distant brain injury secondary to Wallerian degeneration [17].

> *"...a combination of proton and sodium MRI techniques in parallel with the assessment of clinical disability would allow the better depiction of the occurrence and degree of axonal injury."*

Zaaraoui *et al.* hypothesized that sodium accumulation in the brain detected by sodium MRI may be a biomarker for the degeneration of nerve cells that occurs in patients with MS. Therefore, sodium MRI may help to monitor the occurrence of tissue injury and disability. To reach this goal, further studies need to be performed on larger groups of patients and during longitudinal follow-up to better depict and understand the patterns of brain sodium accumulation and their clinical impact during the course of MS [17].

The view of physicians & the future of sodium MRI in MS

Conventional and advanced proton MRI techniques are powerful tools used daily by physicians in the diagnosis and monitoring of the evolution of MS. However, these MR techniques suffer from a lack of specificity in identifying and quantifying neuronal injury *in vivo*, especially in the early stages of the disease. In the near future, proton MRI techniques will probably be combined with sodium MRI, which is more prone to detect the occurrence and to monitor the evolution of neuronal injury. On an individual level, longitudinal studies involving a combination of proton and sodium MRI techniques in parallel with the assessment of clinical disability would allow the better depiction of the occurrence and degree of axonal injury. Furthermore, these combined tools would allow the assesment of new drugs for neuroprotection such as sodium-channel blockers to prevent or repair accumulation of disability. Recently, a Phase 2 trial study was performed in patients with secondary progressive MS to assess whether the sodium-channel blocker lamotrigine is neuroprotective, as found in experimental models of MS [18]. The study failed to demonstrate an effect of neuroprotection. It can be assumed that the use of sodium MRI in the upcoming studies may be of paramount interest to depict and quantify the degree of neuroprotection of these drugs more accurately.

While the feasibility of using sodium MRI to examine the human brain was first demonstrated in 1985 [12], its application in clinical research has been limited for two decades due to methodological drawbacks. Nowadays, the increasing availability of high-field (≥3 Tesla) and ultra-high-field MR scanners (≥7 Tesla) contribute to improving the sensitivity of sodium MRI by offering better signal-to-noise ratio, higher spatial resolution and shorter acquisition time. Moreover, the emergence of promising techniques, such as inversion recovery and triple quantum-filtered sodium imaging [19], enable the selective measurement of different sodium compartments. Several progresses are still required. For example, the assessment of the *in vivo* longitudinal and transverse sodium relaxation times and the assessment of the nonuniform B_1 magnetic fields have to be taken into account to improve the sodium absolute quantification.

Conclusion

In conclusion, brain sodium MRI is an emerging tool that enables depiction of cerebral sodium accumulation related to neuronal injury as evidenced in MS [16,17] and also in brain tumors, stroke [14] and Huntington's disease [20]. Sodium MRI may be useful when applied to other neurological diseases, such as epilepsy, or channelopathies to monitor the occurrence of tissue injury and disability.

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References

1 Compston A, Coles A. Multiple sclerosis. *Lancet* 372(9648), 1502–1517 (2008).

2 Kutzelnigg A, Lucchinetti CF, Stadelmann C *et al.* Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain* 128(Pt 11), 2705–2712 (2005).

3 Lassmann H. Axonal and neuronal pathology in multiple sclerosis: what have we learnt from animal models. *Exp. Neurol.* 225(1), 2–8 (2010).

4 Craner MJ, Hains BC, Lo AC, Black JA, Waxman SG. Co-localization of sodium channel Nav1.6 and the sodium-calcium exchanger at sites of axonal injury in the spinal cord in EAE. *Brain* 127(Pt 2), 294–303 (2004).

5 Smith KJ. Sodium channels and multiple sclerosis: roles in symptom production, damage and therapy. *Brain Pathol.* 17(2), 230–242 (2007).

6 Stys PK. General mechanisms of axonal damage and its prevention. *J. Neurol. Sci.* 233(1–2), 3–13 (2005).

7 Waxman SG. Axonal conduction and injury in multiple sclerosis: the role of sodium channels. *Nat. Rev. Neurosci.* 7(12), 932–941 (2006).

8 Andrews HE, Nichols PP, Bates D, Turnbull DM. Mitochondrial dysfunction plays a key role in progressive axonal loss in multiple sclerosis. *Med. Hypotheses* 64(4), 669–677 (2005).

9 Mahad D, Lassmann H, Turnbull D. Review: mitochondria and disease progression in multiple sclerosis. *Neuropathol. Appl. Neurobiol.* 34(6), 577–589 (2008).

10 Waxman SG. Mechanisms of disease: sodium channels and neuroprotection in multiple sclerosis-current status. *Nat. Clin. Pract. Neurol.* 4(3), 159–169 (2008).

11 Boada FE, Laverde G, Jungreis C, Nemoto E, Tanase C, Hancu I. Loss of cell ion homeostasis and cell viability in the brain: what sodium MRI can tell us. *Curr. Top. Dev. Biol.* 70, 77–101 (2005).

12 Hilal SK, Maudsley AA, Ra JB *et al. In vivo* NMR imaging of sodium-23 in the human head. *J. Comput. Assist. Tomogr.* 9(1), 1–7 (1985).

13 Ouwerkerk R. Sodium MRI. *Methods Mol. Biol.* 711, 175–201 (2011).

14 Thulborn KR, Davis D, Snyder J, Yonas H, Kassam A. Sodium MR imaging of acute and subacute stroke for assessment of tissue viability. *Neuroimaging Clin. N. Am.* 15(3), 639–653, xi–xii (2005).

15 Nagel AM, Laun FB, Weber MA, Matthies C, Semmler W, Schad LR. Sodium MRI using a density-adapted 3D radial acquisition technique. *Magn. Reson. Med.* 62(6), 1565–1573 (2009).

16 Inglese M, Madelin G, Oesingmann N *et al.* Brain tissue sodium concentration in multiple sclerosis: a sodium imaging study at 3 Tesla. *Brain* 133(Pt 3), 847–857 (2010).

17 Zaaraoui W, Konstandin S, Audoin B *et al.* Distribution of brain sodium accumulation correlates with disability in multiple sclerosis: a cross-sectional 23Na MR imaging study. *Radiology* 264(3), 859–867 (2012).

18 Kapoor R, Furby J, Hayton T *et al.* Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Neurol.* 9(7), 681–688 (2010).

19 Stobbe R, Beaulieu C. *In vivo* sodium magnetic resonance imaging of the human brain using soft inversion recovery fluid attenuation. *Magn. Reson. Med.* 54(5), 1305–1310 (2005).

20 Reetz K, Romanzetti S, Dogan I *et al.* Increased brain tissue sodium concentration in Huntington's disease – a sodium imaging study at 4T. *Neuroimage* 63(1), 517–524 (2012).