^{23}Na MRI, A NEW QUANTITATIVE METHOD FOR THE DETECTION OF TINNITUS IN AN ANIMAL MODEL

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Tinnitus is an auditory phantom sensation experienced in the absence of an external stimulus. This disorder is present in more than 10% of the adult population worldwide and may induce intolerable discomfort. Because it remains very difficult to detect tinnitus objectively in animal models, carrying out new quantitative methods is a key step in the development of new compounds for treating tinnitus. In the MRI field, the MEMRI tool is often used to detect tinnitus in animal models. To circumvent the toxicity of MnCl2 and its non-translational method, a non-invasive protocol without a contrast agent injection was developed based on sodium MRI (23Na MRI). 23Na MRI provides physiological information complementary to proton MRI (1H MRI). Therefore, 23Na MRI is applied to clinical applications (tumors, strokes, multiple sclerosis and muscular disease) to assess diseases and therapies non-invasively.

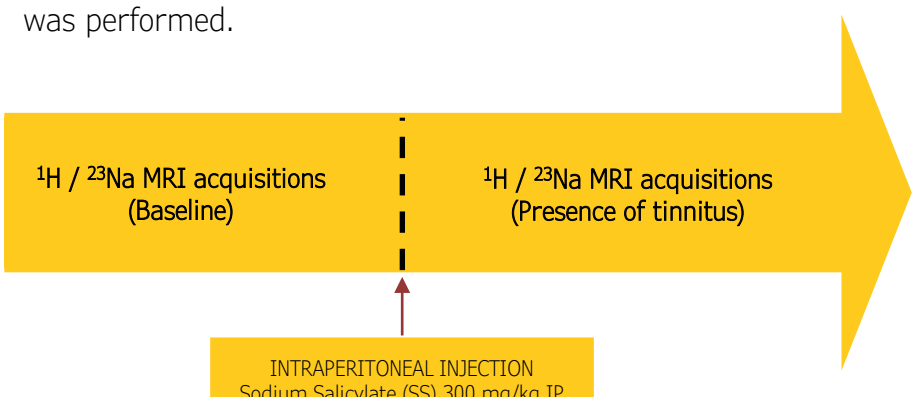
OBJECTIVE

The objective of the study was to develop a new translational experimental protocol allowing to demonstrate the presence of tinnitus, from the combination of 1H and ^{23}Na MRI on a salicylate-induced tinnitus model.

MATERIALS AND METHODS

- MRI experimental protocol

Two series of Proton/Sodium acquisitions were performed on each rat under isoflurane anesthesia. The first series of acquisitions served as the baseline (before salicylate administration). An injection of salicylate (300 mg/kg/IP route) was then performed. Two hours after injection of the drug, a second series of acquisition of the drug was performed.



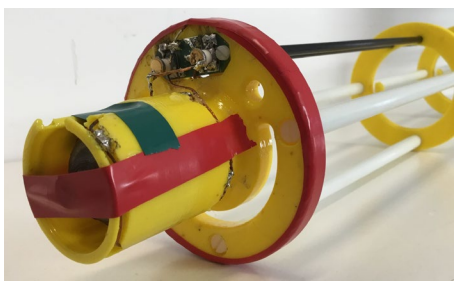


Figure 1: Design of 23Na brain saddle coil 106 MHz (BNIF, France) applied on 9.4T MRI scanner (Agilent Varian, Santa Clara, CA, USA).

- Image of MRI Analysis

From a superposition of ^{1}H and ^{23}Na MRI images, ROIs in the inferior colliculus (IC) and the cerebral cortex (CC) were defined. ^{23}Na MRI signal levels were referenced according to the concentration (154mM) of NaCl tubes positioned close to the brain of the rat. Only the long NMR relaxation component was present in the reference tubes (Figure 2).

The distribution of ^{23}Na concentration was determined by integrating the ^{23}Na MRI signals corresponding to short (5ms) and long (25ms) relaxing components (intra and extra cellular) from an auditory ROI (IC) and a non-auditory ROI (CC) (Table 1). However, in the experimental conditions of the study, ^{23}Na MRI signals correspond predominantly to long relaxing components (extracellular).

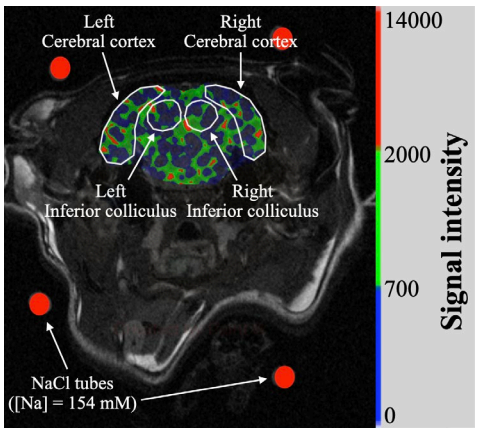


Figure 2: ^{23}Na MRI image (RGB colormap) superimposed over ^{1}H MRI image

Biological tissues

	Intracellular compartment	Extracellular compartment
Sodium concentration	[Na] = 10-15 mM	[Na] = 140-150 mM
Relaxation component	T2* (5 ms)	T2* (25 ms)

Table 1: Schematic models of intracellular and extracellular compartments in biological tissues such as CC and IC (Ridley et al. 2018; Thulborn et al. 1999)

RESULTS

$$Sodium\ Marker\ (SM) = \frac{Signal\ intensity\ (after\ SS) - Signal\ intensity\ (without\ SS)}{Signal\ intensity\ (without\ SS)} \times 100$$

A)

ROI (Region of Interest)	Animals				
	N°1	N°2	N°3	N°4	N°5
Right Inferior colliculus	+	+	-	+	+
Left Inferior colliculus	+	-	-	+	-
Right cerebral cortex	+	+	+	+	+
Left cerebral cortex	+	-	-	+	+
Whole brain	+	+	-	+	+

B)

ROI (Region of Interest)	Animals				
	N°1	N°2	N°3	N°4	N°5
Right Inferior colliculus	32,8	14,3	-6,6	1,8	64,8
Left Inferior colliculus	38,3	-8,6	-18	66,5	-29,7
Right cerebral cortex	10,4	73,4	40,2	53,1	19,8
Left cerebral cortex	24,7	-20,8	-12,4	9,1	32,1
Whole brain	13,0	17,5	-4,7	10,8	8,8

Table 2: Summary of individual sodium marker (SM) data
A) positive and negative signs B) numerical values in different auditory areas

Increases of sodium markers (SM +) were observed in the right inferior colliculus (IC) for 4 rats out of 5, in the right cerebral cortex (CC) for all rats and in the left CC for 3 rats out of 5. In the whole brain, an increase of sodium markers (SM+) from 8,8 to 17,5% was demonstrated for 4 rats out of 5. On the contrary, a decrease (SM -) was found in the left IC for 3 out of 5 rats.

CONCLUSION

Preliminary results revealed a potential increase of sodium in the volume of extracellular space in the inferior colliculus, in the tinnitus animal model. However, this increase in extracellular space does not appear to be specific to the auditory system, as sodium salicylate may provoke side effects in the brain (tinnitus, hypersensitivity, central nervous system disorders).

PERSPECTIVES

In future ^{23}Na MRI experiments, it would be interesting to validate this technique on a noise-induced tinnitus model. Indeed, validation of a more translational tinnitus model with ^{23}Na MRI could open up a new axis in clinical tinnitus research.