COMPARISON OF SALICYLATE & NOISE-INDUCED TINNITUS RAT MODELS

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Tinnitus, the perception of a "phantom" sound in the absence of external stimulation, is a common consequence of damage to the auditory pathway. It affects around 600 million people and may induce intolerable discomfort. Whereas some drug candidates are in the process of being developed, nowadays no effective treatment exists to cure tinnitus. Because it remains very difficult to detect tinnitus objectively in animal models, carry out new quantitative methods becomes the key step to develop new drug candidates in tinnitus treatment.

OBJECTIVE

The objective of this study is to compare the salicylate-induced & the noise-induced tinnitus rat models using three robust and validated experimental in vivo techniques: behavioral test, auditory cortex electrophysiology, and brain in vivo imaging.

MATERIALS AND METHODS

For salicylate-induced tinnitus model, salicylate (Fig. 1) is administered by intraperitoneal injection at 300 mg/kg/day. For acoustic trauma-induced tinnitus model, animals are exposed to an unilateral acoustic trauma (Fig. 2) of 116 to 118 dB SPL of two octaves (8-24 kHz) band noise centered at 16 kHz during 1h. Two hours after salicylate administration or 30 days after acoustic trauma, the presence of tinnitus is determined using gap prepulse inhibition test (GPIAS), unicellular electrophysiology of primary auditory cortex, and in vivo manganese enhanced MRI.

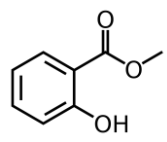

Fig. 1: Molecular structure of salicylate

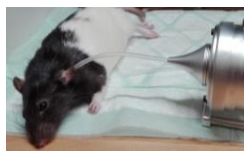

Fig. 2: Anesthetized rat during unilateral acoustic trauma

RESULTS

1/ Gap Prepulse Inhibition Acoustic Startle (GPIAS)

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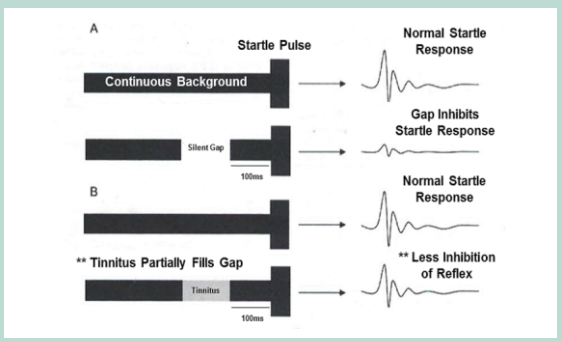
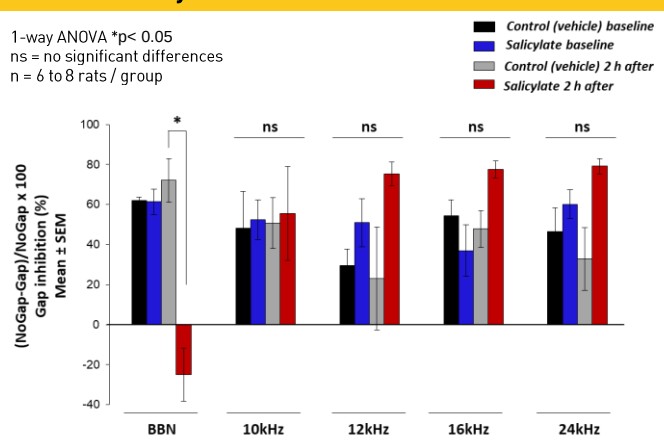


In normal animals, a silent gap before the startle stimulus will reliably inhibit the reflex. Animals with tinnitus exhibit deficits detecting the silent gap. Because the gap is not as easily detected, the reflex is not inhibited to the same degree. (Turner 2007).

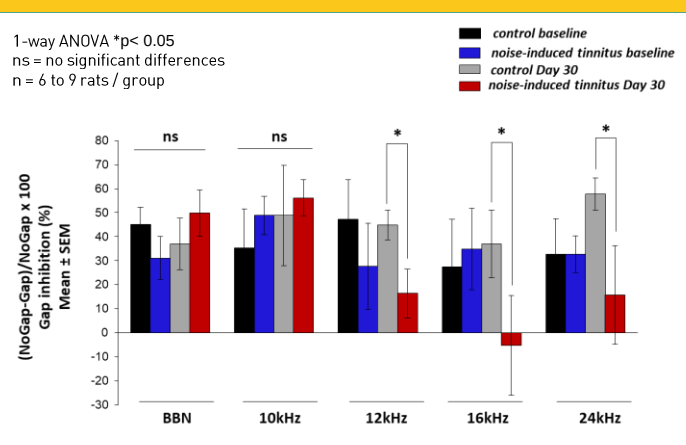
Salicylate-induced tinnitus model

1-way ANOVA *p< 0.05
ns = no significant differences
n = 6 to 8 rats / group



Noise-induced tinnitus model

1-way ANOVA *p< 0.05
ns = no significant differences
n = 6 to 9 rats / group



Two hours after salicylate administration, we observed a decrease of the inhibition of the startle reflex at the BBN (broadband noise). However, 30 days after acoustic trauma, we observed a decrease of the inhibition of the startle reflex at 12 kHz, 16 kHz, and 24 kHz but not at the BBN.

2/ Manganese Enhanced MRI

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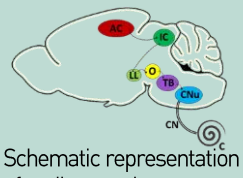
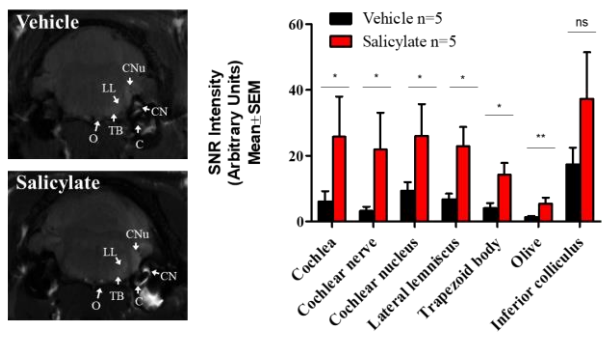
MRI system for small animal



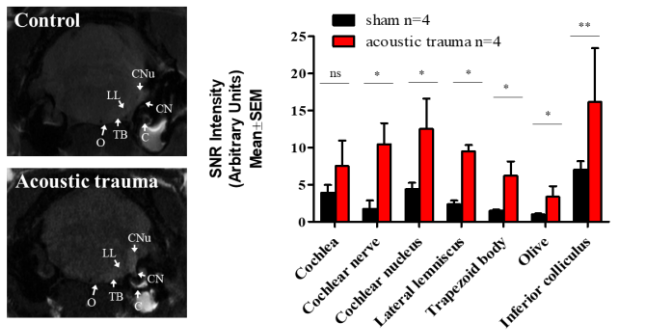
Schematic representation of auditory pathway

24 h before MRI session, animals received 30 µL transtympanic injection of manganese, $MnCl_2$ (0.2 mmol/kg), under isoflurane anesthesia.
Salicylate is administrated intraperitoneally at 300 mg/kg 6 h after manganese injection.

Salicylate-induced tinnitus model



Noise-induced tinnitus model



We observed an increase of MEMRI signals in different auditory brain structures compared to controls 24 hours after salicylate administration and 30 days after acoustic trauma. An increase of cochlea signal without differences in inferior colliculus is observed in salicylate model whereas opposite pattern is observed in noise-induced tinnitus model.

3/ Electrophysiology

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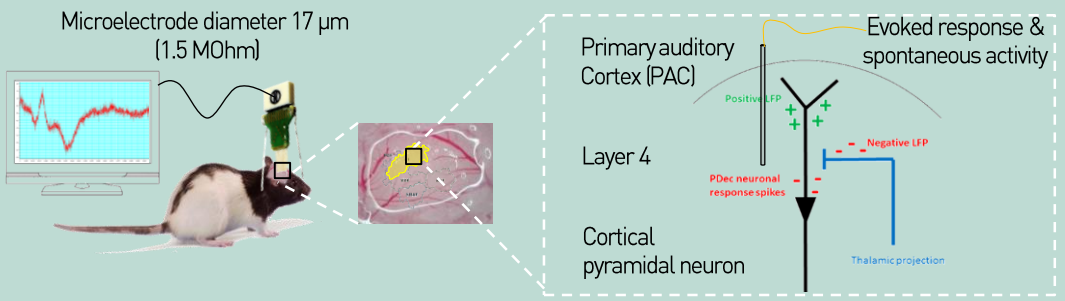
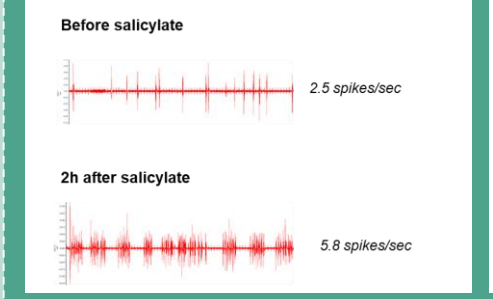
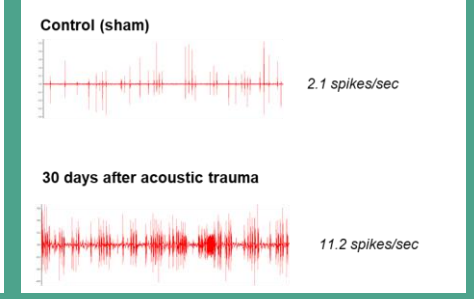


A single microelectrode of 17 µm of platinitum 10% iridium contact surface is placed into the layer 4 of the primary auditory cortex in order to measure the spontaneous spikes before and 2h after salicylate administration or 30 days after acoustic trauma.

Salicylate model



Noise model



Both salicylate and noise-induced tinnitus models presented similar increase of spontaneous activity of primary auditory cortex 2 h and 30 days after salicylate administration or acoustic trauma respectively.

The combination of behavioral test, electrophysiology recording, and *in vivo* imaging allows to measure putative signs of tinnitus in both rat models. Similar results were observed in electrophysiology and MEMRI imaging read-outs for salicylate and noise induced tinnitus model. However, using gap prepulse inhibition test, we observed that salicylate induced-tinnitus at the BBN whereas the acoustic trauma induced tinnitus at 12, 16, and 24 kHz but not at the BBN. Taken together, these data open the door for screening and characterization of new drug efficacy on tinnitus disorder.