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Methods

SERT Knock-out (KO) (*Slc6a4* ^{-/-}), SERT Heterozygote (HET) (*Slc6a4* ^{+/-}), and control (C57BL/6J) mice were unilaterally noise exposed at 6 weeks-old. Unanesthetized mice were exposed to 116 dB, 16 kHz center frequency, 1 kHz band-pass filtered noise for 1 hour. Auditory brainstem response (ABR) and acoustic startle response (ASR) were tested before and after noise exposure to assess changes in hearing sensitivity and behavioral reactivity to loud noise, respectively. Open field and social interaction tests were also performed to investigate the effect of noise exposure on anxiety and social interaction behaviors.

Results

Unilateral noise exposure resulted in prominent high frequency hearing loss in the exposed ears in SERT KO, SERT HET, and control mice as measured by ABRs. Following noise exposure, SERT KOs displayed significantly larger ASR amplitudes compared to SERT HETs and controls, suggesting heightened reactivity to loud noise. Furthermore, SERT KOs exhibited significantly increased freezing time in an open field test and significantly reduced interaction time during a social interaction test after the noise exposure, indicating increased anxiety-like behaviors.

Conclusions

Our findings demonstrate that serotonergic system dysfunction affects behavioral reactivity to loud noise and increases anxiety-like behaviors following noise exposure. These results provide new insights into serotonin dysregulation and its relationship between emotional distress and hearing loss and identify a possible risk factor for negative psychological responses to hearing dysfunction.

PS 803

Synaptic NMDA currents and Short-Term Plasticity influence Spike Generation in Neurons of the Ventral Nucleus of the Lateral Lemniscus

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Neurons in the ventral part of the ventral nucleus of the lateral lemniscus (VNLL) receive large glutamatergic, somatic synapses that underlie the temporal precise generation of action potentials (APs). It remains unclear which synaptic components contribute to the precision and output generation during resting states as well as during ongoing activity. To determine the different synaptic contributions to the generation of APs, we

recorded from VNLL neurons in acute brain slices from gerbils aged between postnatal day 19 and 30. We found that fast glutamatergic synaptic transmission in VNLL neurons was based exclusively on AMPA and NMDA receptor currents. The small NMDA component increased the EPSC time course at potentials close to rest. During synaptic 20-pulse stimulation trains, EPSCs exhibited short-term plasticity with paired pulse facilitation at initial pulses for stimulus frequencies above 50 Hz, and a subsequent frequency-dependent depression. Using dynamic clamp recordings, the effects of NMDA currents and short-term plasticity on AP generation were decomposed. During more than 6 seconds of simulated ongoing activity with random frequencies, short-term depression reduced AP generation and prevented a single synapse to become permanently supra-threshold. The depression effectively low-pass filtered the input and only permitted reliable onset APs to input transients presented at frequencies below 50 Hz. Above 100 Hz stimulation, frequency ongoing generation of APs was supported by the NMDA component. Thus, interplay of short-term plasticity and NMDA currents form the physiological basis for prominent onset response to simulated activity transients and ongoing action potential generation during high frequency input stimulations.

PS 804

Synaptic activity at the MNTB is disrupted in a mouse model with enhanced efferent olivocochlear system

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The auditory system in many mammals is immature at birth but precisely organized in adults. Spontaneous activity in the inner ear plays a critical role in guiding this process. This is shaped by an efferent pathway that descends from the brainstem and makes transient direct synaptic contacts with inner hair cells (IHCs). In this work, we used an $\beta 9$ cholinergic receptor knock-in mouse model with enhanced medial efferent activity (*Chrna9L9^T*, *L9^T*) to understand the role of the olivocochlear system in the correct establishment of auditory circuits. Wave III amplitudes of auditory brainstem responses (which represent synchronized activity of synapses within the superior olivary complex) were smaller in *L9^T* mice, suggesting a central dysfunction. The mechanism underlying this functional alteration was analyzed in brain slices containing

the medial nucleus of the trapezoid body (MNTB), where neurons are topographically organized along a medio-lateral axis. Electrophysiological recordings evidenced MNTB synaptic alterations. Spontaneous synaptic response (mEPSCs) displayed no changes in its amplitude among genotypes, while mEPSCs mean frequency displayed a significant increase in the *L9'T* lateral region (M: 2.52 ± 0.56 Hz; L: 345 ± 1.94 Hz; Mann-Whitney test, $Z: -2.11$, $p=0.035$). Moreover, evoked synaptic transmission was altered in the transgenic mice. While no significant differences in the unitary medial and lateral EPSC amplitudes were recorded in WT mice (M: 7.59 ± 1.12 nA, $n=9$, 7 animals; L: 7.35 ± 0.95 nA, $n=10$, 8 animals, ANOVA, $F: 0.027$, $p=0.87$), evoked synaptic currents in the lateral side (5.07 ± 0.87 nA, $n=12$, 11 animals) of *L9'T* mice were smaller compared to those of the medial side (8.05 ± 1.37 nA, $n=11$, 11 animals; ANOVA, $F: 5.07$, $p=0.0357$). These abnormalities were further supported by morphological alterations. Rhodamine-dextran labeling evidenced multiple innervation in *L9'T* MNTB principal cells suggesting an impairment during development. At the *in-vivo* level, multielectrode recordings showed that the overall level of MNTB activity was reduced in the *L9'T*. The average multi-unit activity in WT (11.49 ± 3.58 Hz, $n=6$ animals) was larger than in *L9'T* mice (2.53 ± 0.43 Hz, $n=8$ animals; Mann-Whitney U Test, $Z=2.19$, $p=0.028$). The present results suggest that the transient cochlear efferent innervation to IHCs during the critical period before the onset of hearing is involved in the refinement of topographic maps as well as in setting the correct synaptic transmission at central auditory nuclei.

PS 805

Arrangement of Contact Sites from Single Excitatory Fibers on Medial Superior Olive Dendrites

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Neurons in the medial superior olive (MSO) detect interaural time differences (ITD) in the microsecond time range. The temporal precision of the underlying cellular integration process for this coincidence detection is based on pre- and postsynaptic and morphological specializations. Thick bipolar dendrites with large potassium conductances accelerate the EPSP time course while still introducing a propagation time for distal EPSPs towards the soma, which is at least in the same range as physiologically relevant ITDs. Therefore, the arrangement of synaptic contacts of an input fiber may also be crucial to the size of the binaural coincidence time window.

To quantify the morphological arrangement of excitatory inputs on dendrites of MSO neurons and its impact on coincidence detection we combined axonal tracing, quantitative morphometry and computational modelling. Labelled axons terminating on MSO neurons followed closely the dendritic structure from distal sites to the terminal bouton with very little branching. Contact sites of labelled axons were identified as swellings adjacent to MAP2 labelled dendrites, a morphological feature that was VGluT positive. Single axons carried usually more than one swelling. Axonal swellings tended to cluster along the dendrite and the majority of terminal boutons were close to the soma. A single contact site harbors more than one active zone. Thus, a single fiber exerts strong excitation to the MSO dendrite along its whole extent. The influence of the distributions of axonal contact sites and travel times were examined in multi-compartmental models of an MSO neuron with conduction velocities known from either myelinated or un-myelinated axons. Distributed contact sites along the dendrite produced shorter EPSP peak latencies, normalized the EPSP time course and lead to larger summed EPSPs when compared to the same synaptic drive applied at a single site. Distributed synaptic sites also improved ITD sensitivity by sharpening the coincidence detection window, but sharpening only occurred when active low threshold potassium channels were present in the model. In a passive membrane model, distributed synapses actually widened the coincidence detection window, as predicted by cable theory. Thus, the arrangement of excitatory inputs of single fibers generally strongly affects the neuron's ability to transfer information about ITDs. Simulations also showed that, as expected, myelination further shortened EPSP peak latencies, but, interestingly, had no effect on coincidence window and EPSP amplitude, and hence did not facilitate ITD encoding.

PS 806

Cochlear protection after noise exposure requires 5-HT3A receptor via efferent feedback system

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The cochlear efferent feedback system plays important roles during auditory processing, including the regulation of the dynamic range of hearing, and provides protective