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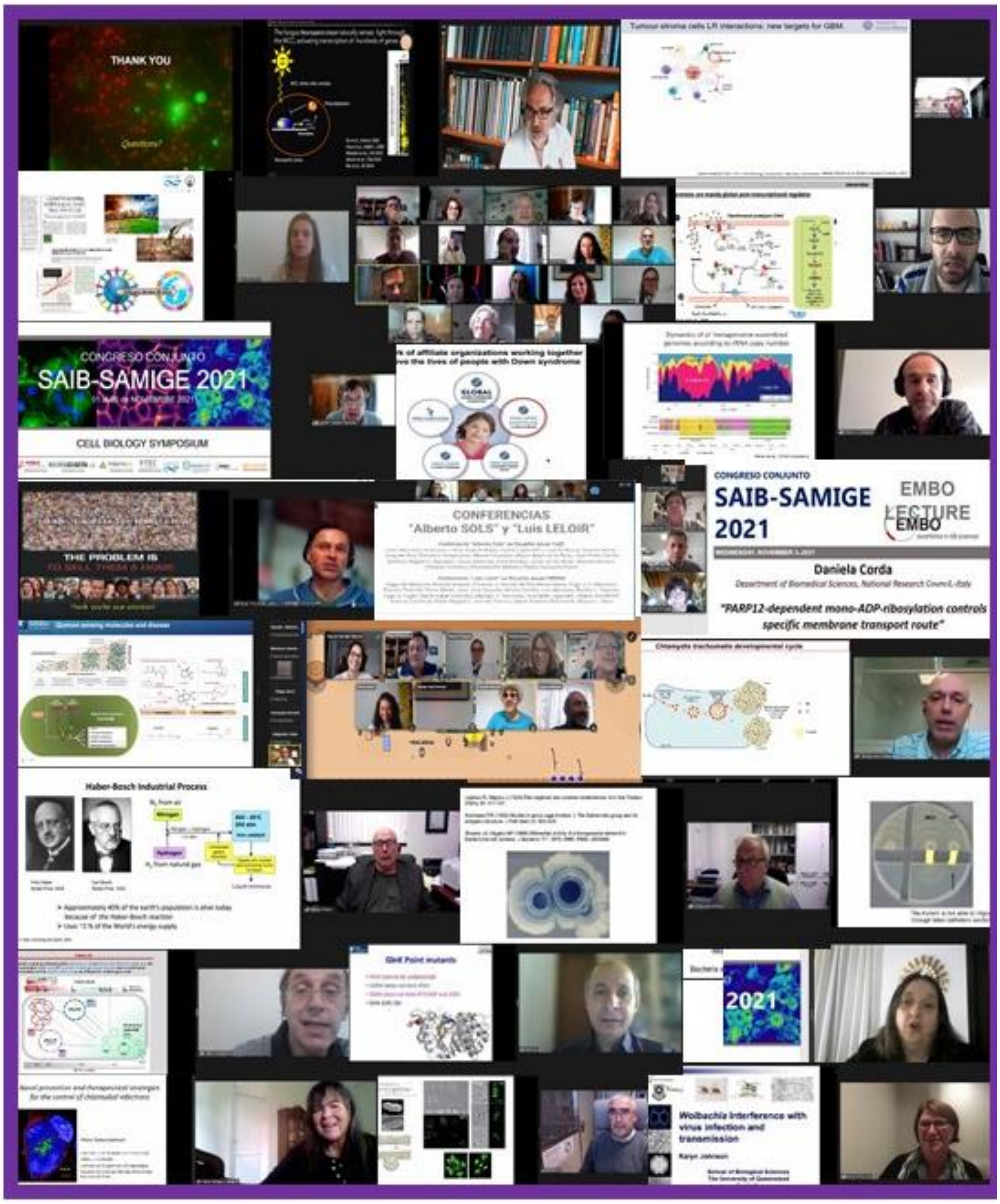
SAIB - SAMIGE Joint meeting
2021 *on line*



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NEUROSCIENCE

NS-P01-90
CELLULAR AND FUNCTIONAL MECHANISMS INVOLVED IN HEARING LOSS IN A DFNA2 MOUSE MODEL

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Function impairment in the voltage-gated K^+ channel KCNQ4 is the main cause of DFNA2, a non-syndromic progressive hearing loss (HL). It occurs in two phases: initially, there is a mild HL at young ages, which then progresses to a profound HL in adulthood in the last phase. Previously, we reported that outer hair cell (OHC) death may contribute to the first phase and inner hair cell (IHC) and spiral ganglion neuron (SGN) degeneration would explain the last phase of DFNA2, in a mouse lacking KCNQ4 channel (*Kcnq4*$^{-/-}$). Now we correlate these findings with the molecular and functional alterations in this mouse model of HL. In 3-6 weeks-old (W) *Kcnq4*$^{-/-}$ animals, using immunofluorescence (IF), we found an increase of cleaved caspase-3 (CAS-3) expression in the OHCs area in the basal turn. Moreover, gene expression analysis by qPCR in young *Kcnq4*$^{-/-}$ mice revealed that pro-apoptotic *Bax* transcript level was ~6-fold higher than in the WT animals, while anti-apoptotic *Bcl2* gene expression was drastically reduced. Additionally, by IF, we found a lower synaptic density and mislocalization of the efferent terminals that contact OHCs from *Kcnq4*$^{-/-}$ mice. Previous studies showed that this model has an increase in the hearing threshold at low frequencies but with no decrease in IHC number. However, using the C3H mouse strain, we found loss of IHCs and SGNs in 1-year-old mice lacking KCNQ4 expression. To assess the auditory function in middle-aged mice, we initially performed the Preyer's reflex test. We determined that ~50% of *Kcnq4*$^{-/-}$ mice did not pass the test, indicating a profound HL. Auditory brainstem response (ABR) test exhibited a significant auditory threshold shift of ~60 dB SPL in the 5.6-45.25 kHz frequency range, pointing out that the electric transmission through the whole auditory pathway is affected by KCNQ4 absence. Following this, we observed CAS-3 expression in SGNs at 1-year-old mice. IHCs neither express CAS-3 nor the autophagy marker LC3-B2. However, they showed by scanning electron microscopy (SEM), different stereocilia alterations like fusion and missing ones in middle-aged *Kcnq4*$^{-/-}$ mice. Distortion product of otoacoustic emissions (DPOAE) test revealed an auditory threshold shift of ~20-30 dB SPL in the 8-32 kHz range, indicating that OHCs function is severely impaired in these mice. Despite this, cochlear microphonic signals were detected mainly at low frequencies, suggesting a mild activity of OHCs in the apical turn. Our results demonstrated that during the first stage of DFNA2, OHCs die by apoptosis while efferent synapsis is disorganized. In the second phase, apoptosis is present in SGNs but not in IHCs which are also lost. However, we found diverse stereocilia defects, which could account for their lack of auditory signal generation in middle-aged *Kcnq4*$^{-/-}$ mice. Collectively, these findings may help to understand the cellular and molecular mechanisms underlying the biphasic HL.

NS-P02-131
MATHEMATICAL MODELING OF AMPA RECEPTORS SUGGESTS A MECHANISM FOR SHORT-TERM BRAIN PLASTICITY BY MODULATING L-GLUTAMATE CURRENT SENSITIVITY

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AMPA receptors are ubiquitous tetrameric cation channels that mediate the first fast excitatory postsynaptic currents in most glutamatergic synapses in the central nervous system. Usually, the channel also desensitizes relatively quickly, resulting in an excitatory current that peaks quickly and has a low or non-existent steady-state current. The affinity to glutamate, usually inferred experimentally from the concentration of glutamate for which there is half-maximal peak current (current EC50), is considered "low", in the range of 10 to 200 μM (Traynelis et al., 2010). However, when the L-glutamate binding affinity is directly measured (binding EC50), it is much higher, around 0.5 μM (Abele et al., 2000). We have previously described a system-level mechanism called PRESS (pre-equilibrium sensing and signaling) which enables such shifts in the input dynamic range (Ventura et al., 2014; Di-Bella et al., 2018), and thus we asked if it operates on AMPAR. Here, using a simple kinetic one-channel-subunit model and a more complex four-subunits model, we show how the experimentally determined and relatively slow binding step, followed by the fast opening and desensitization steps, conforms very well to a PRESS mechanism, accounting for the large difference between binding and peak current EC50s. Our models also help explain how, through changes to the desensitization rates caused by association with transmembrane regulatory proteins, such as TARPs, PRESS could be a mechanism for adjusting the current dose-response curve closer to the binding curve, increasing the AMPA-R mediated currents.