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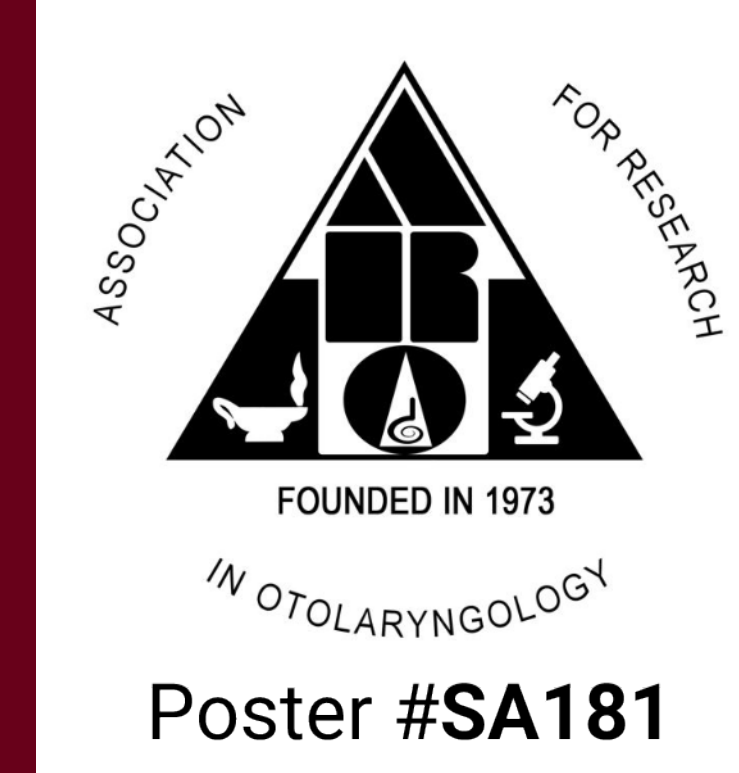
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BK channels as therapeutic targets for auditory impairments in neurodevelopmental disorders: preclinical findings from the CD mouse model of Williams-Beuren syndrome

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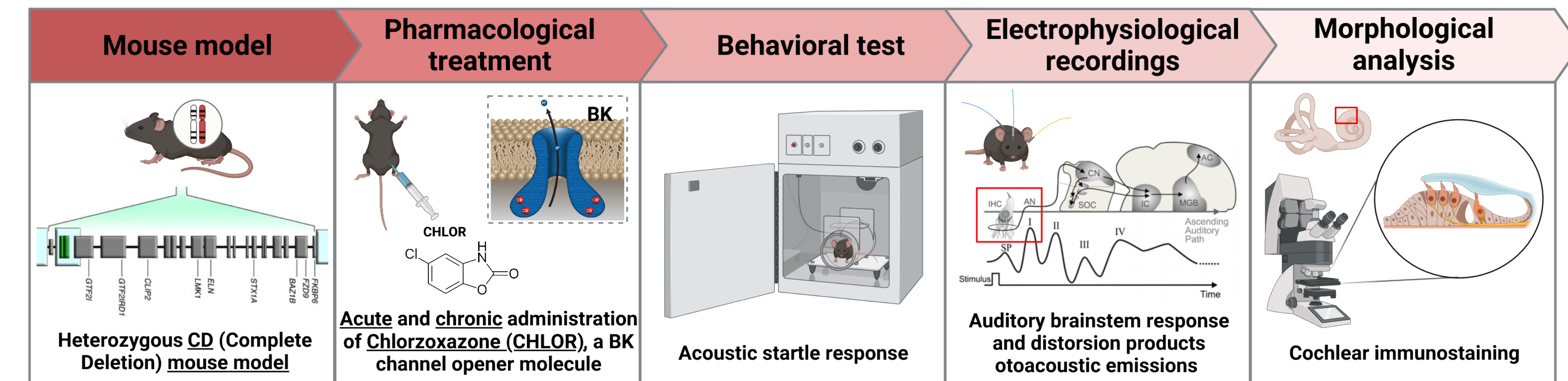


INTRODUCTION

Auditory impairments, such as hearing loss and hyperacusis (i.e., increased sound sensitivity), are commonly described in patients with neurodevelopmental disorders (NDDs) and may exacerbate the communication and social deficits typical of these pathological conditions. In particular, both hyperacusis and progressive hearing loss are frequently associated with Williams-Beuren syndrome (WBS), a rare genetic NDD, caused by a hemizygous deletion on chromosome 7, leading to the haploinsufficiency of about 30 genes. However, the cause of auditory dysfunction in WBS is still largely unknown.

Big Potassium (BK) channels play a crucial role in multiple aspects of auditory signaling and are known to be quantitatively and functionally altered in several NDDs. Hence, we tested the hypothesis that a reduction in BK channel expression and functionality underlies acoustic dysfunction in WBS and that the pharmacological activation of these channels may therefore represent an effective novel pharmacological approach.

METHODS



RESULTS

ACOUSTIC STARTLE RESPONSE (ASR)

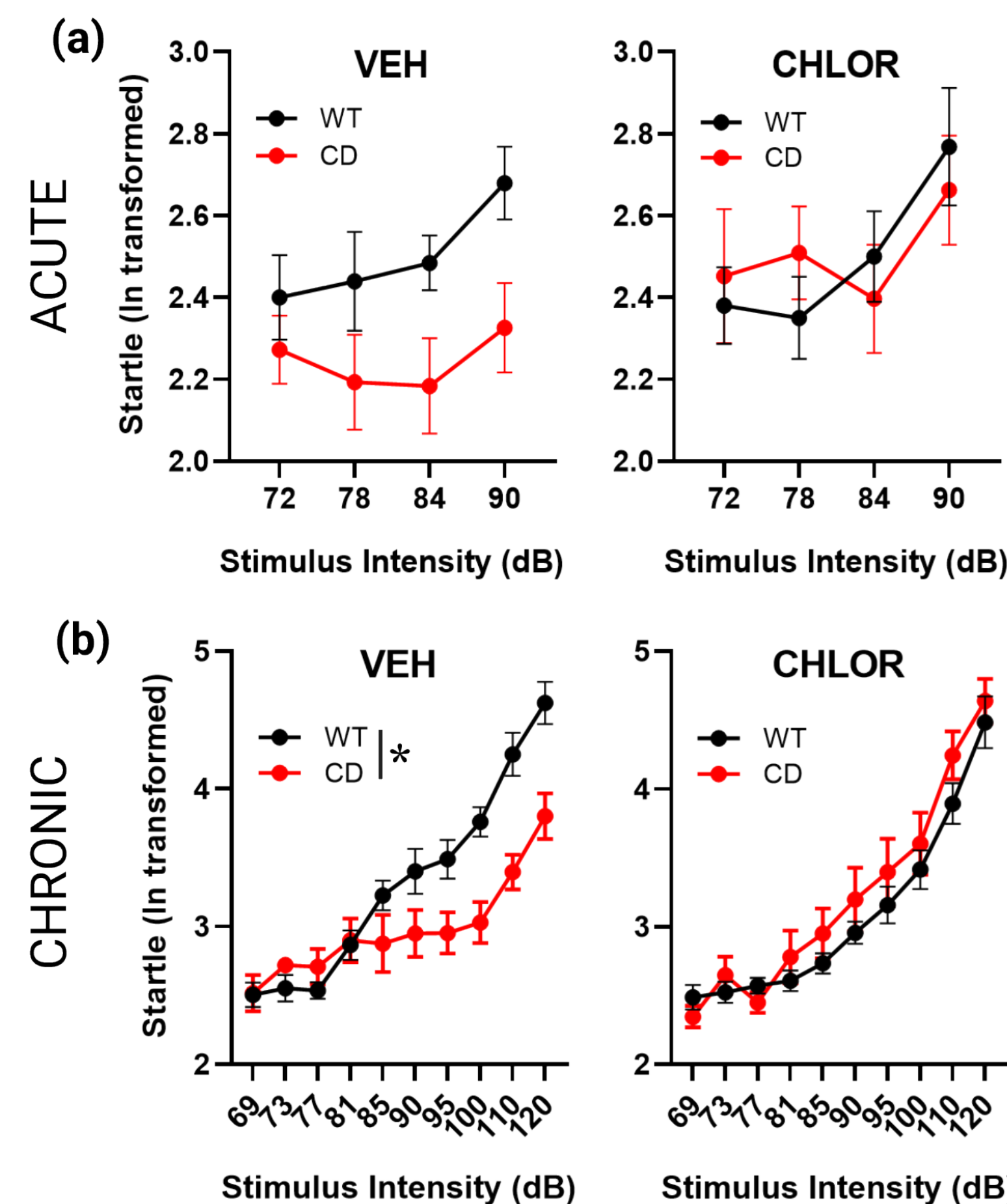


Fig.1 CD mice showed hypo-responsiveness in the ASR compared to WT (a,b). This phenotypic difference became significant with higher sound intensities. Chronic treatment with CHLOR rescued the hypo-acousis of CD mice (b).

AUDITORY BRAINSTEM RESPONSE (Click-ABR) AND DISTORSION PRODUCTS OTOACOUSTIC EMISSION (DPOAE)

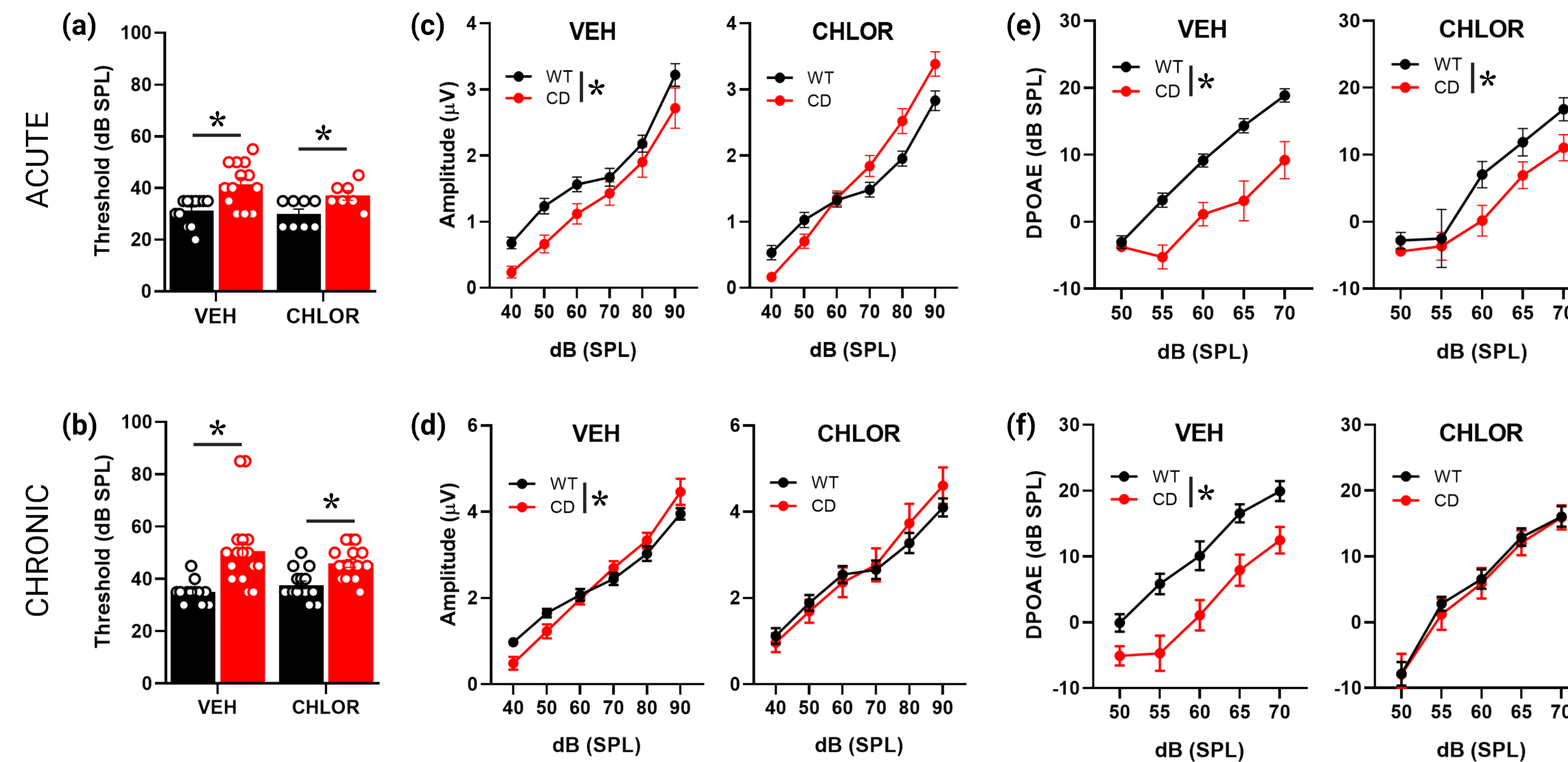


Fig.2 CD mice showed increased hearing threshold (a,b) and decreased wave I amplitude (c,d), especially at lowest intensities, compared to WT littermates, which together indicate hearing loss and impaired peripheral synaptic transmission. CD mice also showed reduced DPOAEs (e,f), suggesting outer hair cells dysfunction. Both acute and chronic CHLOR rescued wave I amplitude deficits of CD mice, but not the increased hearing threshold. Chronic treatment with CHLOR, but not acute, rescued impaired DPOAEs in CD mice.

ORGAN OF CORTI IMMUNOSTAINING

BK CHANNELS IMMUNOSTAINING

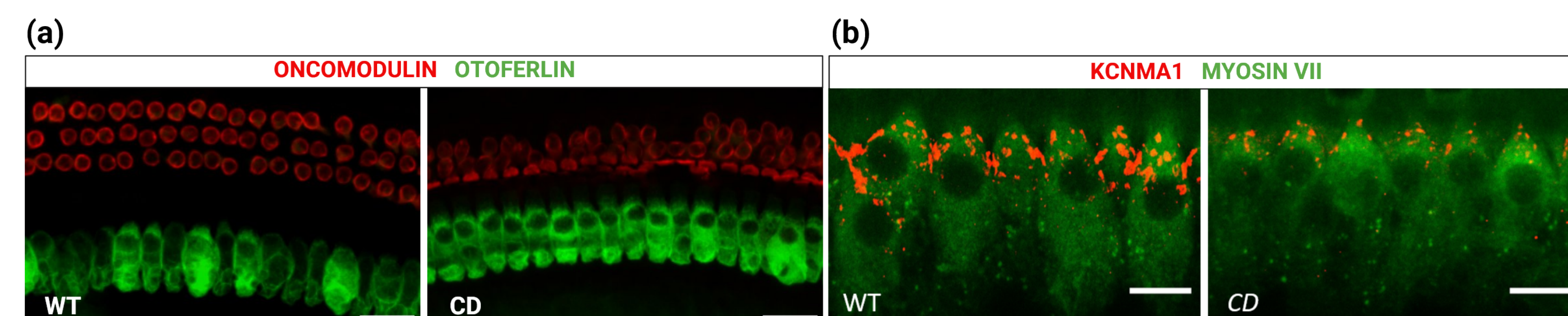


Fig.3 (a) Immunostaining of the Organ of Corti in WT and CD mice. Red indicated oncomodulin staining of the three rows of outer hair cells (OHC); green indicated otoferlin staining of the one row of inner hair cells (IHC). Images were taken from the mid-basal turn of the cochlea and revealed impaired cytoarchitecture of OHC in CD mice; no morphological alterations were detected in IHC. (b) Immunostaining of cochlear BK channels in IHC in WT and CD mice. Red indicated BK channels at the apical end of IHC in dense clusters above nuclei; green indicated myosin VII staining, a cytoplasmic IHC marker. Images revealed a markedly reduced channel expression in IHC in CD mice.

BK CURRENTS RECORDINGS IN MOUSE INNER HAIR CELLS

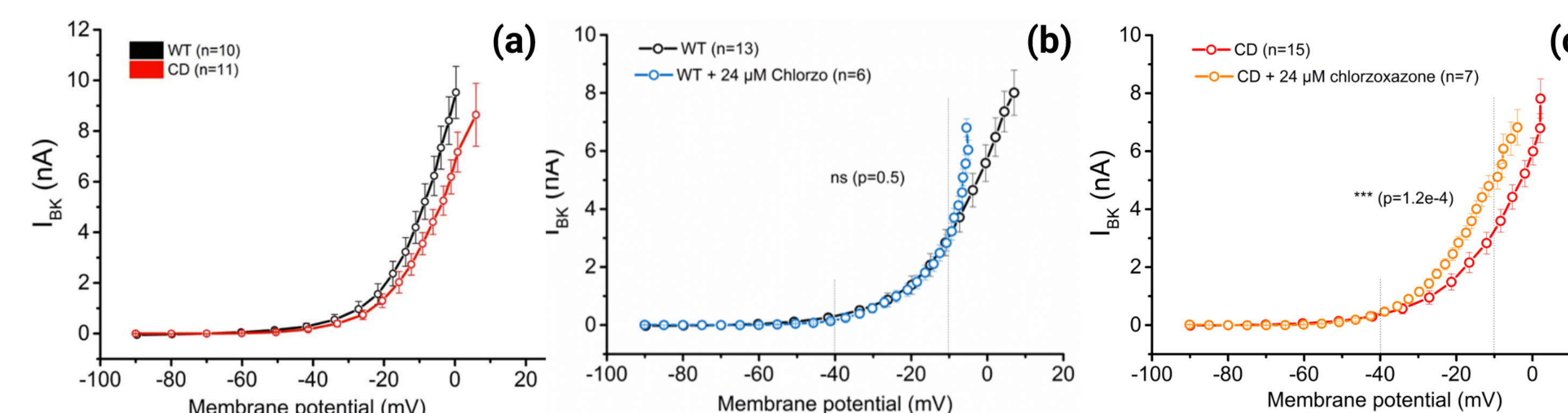


Fig.4 Whole cell patch clamp recording of BK current in IHC of adult WT and CD mice. Outward current were generated by depolarizing stimulation from -90mV to 10mV. No difference was observed between WT and CD mice (a). BK current patch clamp recordings in IHC before and after bath application of 24µM CHLOR in WT (b) and CD (c) mice. CHLOR potentiated the BK currents only in CD mice by shifting channel voltage dependence of 10mV.

CONCLUSION

CD mice displayed reduced acoustic startle response and increased hearing thresholds, recapitulating the hearing loss of WBS patients. Electrophysiological recordings also revealed a reduced wave I amplitude, suggesting a defect in the synaptic transmission at the periphery of the auditory pathway (i.e. the synaptic connection between inner hair cells and auditory nerve fibers). Moreover, DPOAEs were significantly decreased in CD mutants, indicating a defect of outer hair cells. Such impairments were indeed associated with a disorganized structure of outer hair cells and reduced BK expression in inner hair cells, as revealed by immunohistological analysis.

Both the acute and chronic administration of CHLOR, a BK agonist, rescued the behavioral and electrophysiological alterations of CD mice. In particular, chronic treatment was able to rescue the auditory hypo-responsiveness of CD mutants, as well as the reduced wave I amplitude and DPOAEs.

No differences were found in BK currents between CD and WT mice. However, CHLOR administration had a potentializing effect in CD mutants only, suggesting that a higher sensitivity of BK channels may be associated with CD mutation.

Taken together, our results provide preclinical evidence supporting the therapeutic potential of CHLOR to treat auditory impairments in WBS and highlight the value of BK channels as potential therapeutic targets for rare NDDs.

