Involvement of ASIC1a in ASIC4-positive BNST/amygdala neurons in modulating anxiety and fear.

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Background
ASIC4 is a member of acid-sensing ion channels and widely expressed in the CNS. However, the physiological function of ASIC4 remains unclear

Aims & Objectives
Here we used genetic approaches to probe the role of ASIC4 in anxiety-associated nuclei in mouse models.

Methods
Chemo-optogenetic system
Anxiety-related Behavior
Electrophysiological
Western blotting
viral injection

Results
We discovered that chemo-optogenetically activating ASIC4-positive cells induced anxiety-like responses in mice. Studies of mice with a disrupted ASIC4 gene in specific brain regions suggested that ASIC4 in the amygdala and the bed nucleus of the stria terminalis (BNST) are implicated in fear and anxiety. Interestingly, conditional knockout of ASIC1a in ASIC4 positive cells resulted in reduced anxiety behavioral phenotypes in both fear and anxiety. In situ hybridization data suggested a possible surface membrane protein modulation role for ASIC4 in regulating ASIC1a, so we performed point-mutations on two glycosylation sites, Asn191 and Asn341, which resulted in differential effects on ASIC4 biogenesis. Furthermore, these Asn191 and Asn341 mutations increased ASIC1a surface protein expression and current density. More importantly, expression of ASIC4 in the amygdala and bed nucleus of the stria terminalis of ASIC4 knockout mice using viral vector-mediated gene transfer resulted in rescue of the anxious phenotypes

Discussion & Conclusion
Together, these data suggest ASIC4 plays an important role in fear and anxiety-related behaviors, with the glycosylation of ASIC4 as one of the possible mechanisms.