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Chronic pain-induced plastic change in the extended amygdala neural circuit causes maladaptive anxiety

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Chronic pain is often comorbid with psychiatric disorders such as depression and anxiety disorders, suggesting common neuronal mechanisms that underlie these pathological states, yet the mechanisms are still unclear. Here, using spared nerve injury model mice of chronic pain, we show the neuroplastic changes in the synaptic transmission in the bed nucleus of the stria terminalis (BNST) neurons projecting to the lateral hypothalamus (LH) which can lead to maladaptive anxiety. Consistent with previous reports, chronic pain increased anxiety-like behaviors in elevated plus maze and light-dark box tests. Whole-cell patch-clamp recordings revealed that chronic pain increased spontaneous IPSCs onto I_h-current negative LH-projecting BNST neurons. To test the causal role of this plasticity in behavioral anxiety, we inhibited or activated the LH-projecting BNST neurons using a DREADD technique and accessed anxiety-like behaviors. Inhibition of LH-projecting BNST neurons in naïve mice increased anxiety-like behaviors without affecting nociceptive behaviors. Furthermore, activation of LH-projecting BNST neurons ameliorated anxiety-like behaviors in chronic pain model mice. Collectively, these findings suggest the critical role of sustained suppression of the LH-projecting BNST neurons in maladaptive anxiety during chronic pain.