

Brain Targets for Chronic Pain, Coupling with Network Desynchronization and Cognitive Deficits in Rodent Study

Abstract

Visceral hypersensitivity (VH) is a key factor of irritable bowel syndrome (IBS). The previous studies have identified an enhanced response of anterior cingulate cortex (ACC) to colorectal distension in VH rats, which can be observed up to 7 weeks following colonic anaphylaxis, independent of colonic inflammation. ACC is a component of a functional circuit that plays a crucial role in the mediation of perception and processing of chronic visceral pain. Overexpression of the NR2B receptor and T286CaMKII in ACC results in increased pain. The ACC also participates in the affective component of visceral pain. Using the colorectal distension-induced conditional place avoidance paradigm, it showed that glutamatergic activation of ACC mediates visceral pain memory in rats. Furthermore, postprandial release of CCK-8 can activate vagal afferent C fibers, and this enhances memory consolidation and retention involved in long-term visceral negative affective states.

Decision-making is a valuable model for monitoring higher-order cognitive functions in animals, which depends on the integrated function of several sub-regions of the ACC and amygdala. Using rat gambling task (RGT), it observed an impairment of decision-making behavior in VH rats. Electrophysiological study showed a reduction of long-term potentiation in the basolateral amygdala (BLA)-ACC synapses in VH rats. Further, multiple-electrode array recordings of local field potential in freely behaving rats revealed chronic visceral pain led to disruption of ACC spike timing and BLA local theta oscillation.

More recently, it shows that ACC-reactive astrogliosis and activity-dependent impairment of lactate release occur in VH rats. Exogenous lactate supply rescues chronic-visceral pain-caused impairments of ACC phase locking and decision making. Large-scale electrophysiological recordings indicate that optogenetic astrocytic activation improves decision-making performance and engages ACC phase locking and BLA-to-ACC information flow (*Cell Reports* 2017, 21, 2407–2418). Collectively, these observations support the idea of an “astrocyte-neuron L-lactate shuttle” and suggest that targeting astrocytes may help with cognitive dysfunctions under chronic visceral pain.