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Dysregulation of aversive signaling pathways: a novel circuit endophenotype for pain and anxiety disorders

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Abstract

Aversive experiences activate dedicated neural instructive pathways which trigger memory formation and change behavior. The strength of these aversive memories and the degree to which they alter behavior is proportional to the intensity of the aversive experience. Dysregulation of aversive learning circuits can lead to psychiatric pathology. Here we review recent findings elucidating aversive instructive signaling circuits for fear conditioning. We then examine how chronic pain as well as stress and anxiety disrupt these circuits and the implications this has for understanding and treating psychiatric disease. Together this review synthesizes current work on aversive instructive signaling circuits in health and disease and suggests a novel circuit based framework for understanding pain and anxiety syndromes.

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Aversive experiences, such as those which are painful, produce strong memories and shape behavior in adaptive ways. For example, getting attacked by a dog while walking in your neighborhood results in detailed, lifelong memories of the experience and emotional responses upon re-exposure to the situation where the attack occurred. These conscious and emotional memories form because aversive experiences are transduced by dedicated neural pathways into 'instructive' signals which alter connectivity in brain networks responsible for storing memories resulting in aversive learning and adaptive changes in behavior.

In some clinical conditions aversive experiences produce disproportionate and dysfunctional emotional responses and memories. In chronic pain syndromes, for example, somatosensory/pain pathways become sensitized resulting in debilitating psychological symptoms [1,2]. In anxiety disorders such as post-traumatic stress disorder (PTSD), chronic stress or trauma can sensitize aversive learning circuits and produce strong, long lasting and incapacitating emotional memories and responses [3,4•,5]. Genetic and experiential factors are the root cause of most psychiatric disorders including chronic pain and anxiety. These factors produce psychiatric dysfunction through actions on specific brain circuits. To understand how psychiatric conditions emerge it is critically important to identify the circuits which mediate normal function and then determine how these systems are disrupted in disease conditions. Related to chronic pain and anxiety disorders, a potential underlying cause could be dysregulation of aversive instructive signaling pathways by genetic and experiential influences. This could result in exaggerated, persistent aversive learning as well as more generalized anxiety and depressed mood, symptoms which are characteristic of pain and anxiety syndromes.

In this review we discuss recent work elucidating the circuit mechanisms of aversive instructive signaling for auditory fear conditioning. We then explore the hypothesis that dysregulation of these instructive signaling circuits underlies chronic pain and anxiety disorders. We focus on fear conditioning because most of the research on aversive instructive circuits comes from this area and these same circuits likely participate in other forms of aversive learning. We note that the circuits underlying fear conditioning mediate only one aspect of the aversive experience [6] and further work on other forms of aversive learning will likely be required to accurately model human emotions/feelings and their psychiatric dysfunction.

The lateral and central nuclei of the amygdala: key sites of plasticity mediating fear learning

Auditory fear conditioning occurs when an auditory stimulus (conditioned stimulus, CS) is associated with an aversive outcome such as electrical shock (unconditioned stimulus, US) [7,8]. Following learning, presentation of the tone alone elicits a set of defensive responses

including behavioral freezing and changes in heart rate and blood pressure. The amygdala has emerged as a critical site of synaptic plasticity mediating fear learning (Figure 1), though there are likely other brain regions in the circuit which undergo plasticity [9–11]. Neurons in the lateral nucleus of the amygdala (LA) integrate auditory information from the thalamus and cortex with aversive nociceptive and neuromodulatory signals. During fear conditioning auditory thalamic and cortical inputs to LA (and possibly the basal nucleus of the amygdala, BA) are strengthened such that tone presentation alone following learning activates LA neurons to produce fear responses through output pathways in the central nucleus of the amygdala (CeA) (for recent reviews see [9,11–13]). Plasticity of LA inputs to the CeA also occurs during fear conditioning [14,15], possibly providing a gating mechanism for parallel plasticity occurring in the LA.

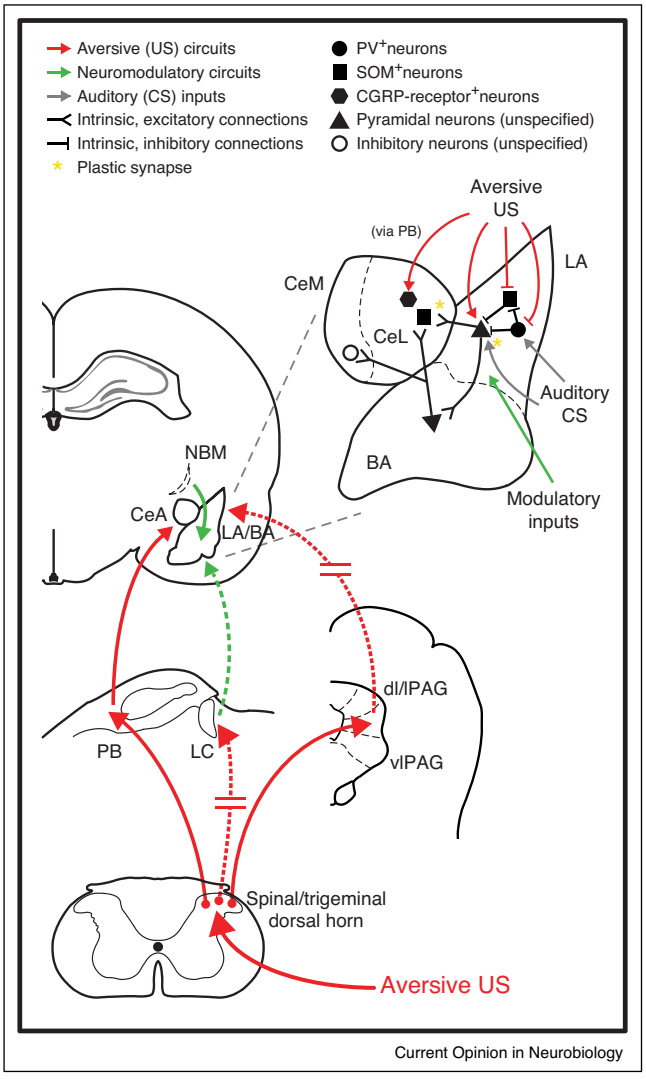
Instructive signals in the lateral amygdala for fear learning

Because plasticity mediating fear conditioning occurs in the LA, it is important to consider the signals within this nucleus which initiate plasticity and fear learning (Figure 1). In LA pyramidal neurons, aversive shock-evoked activity is necessary for strengthening auditory (and olfactory) synapses in LA as well as fear learning and local GABAergic mechanisms are important in regulating this process [16–18]. However, under normal learning conditions activation of LA pyramidal neurons is not sufficient to produce fear conditioning or plasticity unless β-adrenergic receptors (β-ARs) are co-activated [16,19]. Together, this suggests that parallel depolarizing and noradrenergic signals trigger neural plasticity in LA and fear learning.

In addition to noradrenaline, other neuromodulators such as acetylcholine and dopamine are important in fear learning [20••,21]. However, the mechanisms through which neuromodulators regulate plasticity are not known and could include direct modulation of intracellular signaling in pyramidal neurons and/or heterosynaptic control of pyramidal cell activity through local GABAergic networks [22,23]. Furthermore, it is unclear where many of these signals originate or what kinds of information they transmit to LA. Targeted manipulations of cellular level processes and recordings of amygdala projecting neuromodulatory cells could help determine the information conveyed to the amygdala by these neuromodulatory systems and how they control plasticity in LA.

Another important point to consider is that these intra-amygdala signals likely regulate plasticity in specific populations of LA/BA neurons. Recent studies have demonstrated functionally distinct aversive, rewarding and safety cell populations in the BA [24–28]. Furthermore, varying levels of intracellular signaling molecules such as CREB and cellular excitability can modulate

Figure 1



Working model of aversive signaling pathways to the amygdala for fear learning. During fear conditioning, auditory and aversive-nociceptive pathways converge in lateral amygdala (LA) pyramidal neurons (*inset*). Auditory input synapses are strengthened (denoted by yellow *) through a parallel hebbian/neuromodulatory mechanism involving activity in the auditory inputs, depolarization of postsynaptic pyramidal neurons by the shock and noradrenaline signaling. Aversive US information (*left image*) originating from peripheral nociceptive receptors reaches spinal or trigeminal dorsal horn, and is then relayed to PAG, LC, PB, and other brain regions. The PAG and PB may act as relays or modulators of aversive signals to LA/BA and CeA, through either monosynaptic (PB–CeA) or multi-synaptic connections (PAG–LA/B). In addition, the neuromodulatory inputs (from LC and NBM) onto LA/BA networks, along with local inhibitory interneurons (PV^+ and SOM^+ interneurons, *inset*), regulate the sensory-evoked activity and plasticity of LA/BA pyramidal neurons. Dotted lines indicate hypothetical functional/anatomical circuits, solid lines indicate established functional/anatomical pathways. LA/BA: lateral and basal nuclei of the amygdala; CeA: central nucleus of amygdala; CeL: central nucleus of amygdala, lateral division; CeM: central nucleus of amygdala, medial division; PV^+: parvalbumin-expressing; SOM^+: somatostatin-expressing; NBM: nucleus basalis of meynert; dl/l PAG: dorsolateral/lateral subregion of the periaqueductal grey; vlPAG: ventrolateral subregion of periaqueductal grey; LC: locus coeruleus; PB: parabrachial nucleus.