Review

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Neuronal Circuits for Fear Expression and Recovery: Recent Advances and Potential Therapeutic Strategies

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ABSTRACT

Recent technological developments, such as single unit recordings coupled to optogenetic approaches, have provided unprecedented knowledge about the precise neuronal circuits contributing to the expression and recovery of conditioned fear behavior. These data have provided an understanding of the contributions of distinct brain regions such as the amygdala, prefrontal cortex, hippocampus, and periaqueductal gray matter to the control of conditioned fear behavior. Notably, the precise manipulation and identification of specific cell types by optogenetic techniques have provided novel avenues to establish causal links between changes in neuronal activity that develop in dedicated neuronal structures and the short and long-lasting expression of conditioned fear memories. In this review, we provide an update on the key neuronal circuits and cell types mediating conditioned fear expression and recovery and how these new discoveries might refine therapeutic approaches for psychiatric conditions such as anxiety disorders and posttraumatic stress disorder.

Keywords: Amygdala, Anxiety disorders, Fear expression, Neuronal circuits, Prefrontal cortex, Single unit recordings

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Anxiety disorders are among the most common psychiatric conditions with a lifetime prevalence of around 6% in the population worldwide (1). In particular, posttraumatic stress disorder (PTSD) represents one of the most frequent anxiety disorders, which can develop following the experience of a traumatic event. Typically, PTSD patients present symptoms such as re-experiencing the traumatic experience, hyperarousal, and avoidance of situations, places, or objects that serve as reminders of the traumatic event. It is largely accepted that associative processes are involved in the etiology and maintenance of PTSD and anxiety disorders (2,3) and stimuli associated with the traumatic event can elicit conditioned fear responses (3). Despite a broad knowledge about brain structures involved in fear behavior, the mechanisms involved in the regulation of fear expression were, until recently, still largely unknown. Recent single unit recordings and optogenetic approaches have allowed a better identification of the circuits controlling fear expression in rodents. In the laboratory, fear behavior is classically studied using Pavlovian fear conditioning, which consists of repetitive associations of a neutral conditioned stimulus (CS), such as a sound or a context, with an unconditioned stimulus (US), usually a mild electric footshock. Following conditioning, re-exposure to the CS induces conditioned fear responses, including an immobility reaction termed freezing, which represents a reliable measure of the learned association (4). Inhibition of fear behavior can be observed following repetitive exposure to the CS without the US, a process termed fear extinction. Interestingly, fear extinction, which is known to represent a new learning process of the CS-no US association, is sensitive to contextual and temporal changes that can promote the recovery of the original fear memory (5,6). In this review, we will first provide a summary of data collected in humans and rodents that have allowed deciphering the gross anatomical structures involved in cued and contextual conditioned fear expression and recovery. Second, we will provide an update of the novel neuronal circuits that have recently been identified as central to fear expression and recovery. Lastly, we will discuss how these new discoveries may promote the development of new therapeutic strategies for anxiety disorders.

NEURONAL STRUCTURES MEDIATING FEAR EXPRESSION AND RECOVERY IN HUMANS

In humans, fear conditioning is usually studied by associating a CS, such as a tone or a visual cue, with an aversive US, such as a mild wrist or finger electrical shock. This aversive learning is evaluated by measuring skin conductance responses, which depend on the amygdala, a key structure for the processing of fear behavior (7–10). Functional neuroimaging approaches during and following fear conditioning in humans have been instrumental in deciphering the networks involved in physiologic or pathologic fear responses. However, because extinction learning is faster in humans compared with rodents and because some structures display within session habituation of functional magnetic resonance imaging (11,12), fear expression

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and extinction are usually explored simultaneously in human studies. We therefore review below studies related to both fear expression and extinction. These studies identified the amygdala, hippocampus, and prefrontal cortex as key structures for conditioned fear in normal and pathologic conditions. In functional neuroimaging studies, blood oxygen level-dependent (BOLD) signal (corresponding to changes in brain microvasculature oxygenation related to metabolic activity) revealed amygdala activation during fear conditioning in humans (11), particularly during fear expression (13–18). Amygdala activation was also observed several days after extinction of a conditioned threat memory but not if extinction was performed during fear memory reconsolidation (19). However, the above findings have not been consistently reproduced (20), probably due to the heterogeneity of fear conditioning paradigms used across neuroimaging studies. Finally, high-resolution functional imagery revealed different contributions of amygdala subnuclei during reversal of a conditioned fear procedure, with activation of the central and basolateral nuclei of the amygdala related to attentional and associative processes, respectively (21).

Besides the amygdala, a subset of functional imaging studies observed an activation of the hippocampus (HPC) during fear behavior (18,22–25). Given the role of this structure in the processing of contextual information (26–28), these data suggest a role of the HPC in the encoding of the contextual features associated with fear expression. Finally, several studies reported a role of the prefrontal cortex (PFC) during fear acquisition and expression, as well as during fear extinction. Specifically, decreases and increases of BOLD signals were observed in the ventromedial PFC (vmPFC) [an equivalent of the rodent infralimbic cortex (IL) (17,29)] during fear acquisition/expression and extinction, respectively (17,22,25,30). Interestingly, analyses of the dorsal anterior cingulate cortex (dACC) [an equivalent of the rodent prelimbic cortex (PL) (16,31)] revealed an increase in BOLD signal during fear acquisition and expression (15,17,25). Thus, these data indicated opposing roles of the human vmPFC and dACC in processing fear-related behavior. Functional connectivity analyses, which look for significant BOLD signal correlations between brain regions, have revealed a functional coupling between the vmPFC, dACC, amygdala, and HPC during fear expression (22,25) and between vmPFC, amygdala, and HPC during fear extinction (32). Although these studies did not evaluate the direction of changes, they indicated that fear expression and extinction depend on the joint activity of these structures.

In the context of human psychiatric conditions, increased dorsomedial PFC activation, as measured with resting metabolic activity, was shown to be a risk factor for the development of PTSD (33). Interestingly, functional imaging analyses during recollection of traumatic events in PTSD patients revealed decreased activity in the vmPFC and increased activity in the amygdala (34–42) [for a review, see (43)]. In line with these results, increased amygdala and dACC activation was observed in PTSD patients during extinction in a safety context, whereas healthy subjects presented increased amygdala and prefrontal activation in the danger context, suggesting inappropriate modulation of brain activity according to contextual information in PTSD patients (44). Higher amygdala activation (45) and lower vmPFC activation (46) were also observed in PTSD patients, as compared with control subjects, during presentations of fearful faces during functional magnetic resonance imaging. Together, these data suggest that dysfunctional vmPFC–amygdala interactions are at the core of anxiety disorders including PTSD (32,47–51). Moreover, persistent conditioned fear in PTSD patients was suggested to be related to a failure of vmPFC and HPC activation and to a hyperactivation of dACC and amygdala (52). Importantly, this hypothesis has received strong support from work performed in rodents (see below). Altogether, these data provide strong arguments for the hypothesis that a dedicated brain network comprised of the amygdala, HPC, and prefrontal regions is involved in fear-related behavior.

NEURONAL CIRCUITS OF FEAR EXPRESSION AND RECOVERY IN RODENTS

Data collected in rodents using lesion and inactivation approaches have confirmed the involvement of the amygdala, hippocampus, and prefrontal cortex in the regulation of fear expression (Figure 1), and it is now largely accepted that fear behavior relies on a functionally conserved network of structures in mammals. These data, which have been previously reviewed (7–10,53–57), are discussed in Supplement 1. More recently, optogenetic technical developments have provided unprecedented details of the circuits and mechanisms regulating fear expression. Optogenetic technology consists of the expression of light-sensitive proteins in neurons whose excitation at specific wavelengths can activate or inhibit neuronal activity at the millisecond timescale. Currently, these techniques represent one of the best strategies to identify neuronal populations and to manipulate dedicated circuits. Recently identified circuits are further described in the following sections.

Central Amygdala-Periaqueductal Gray Matter Neuronal Circuits in Fear Expression

One circuit, which includes the basolateral amygdala (BLA), central nucleus of the amygdala (CEA), and the periaqueductal gray matter (PAG), has been shown to drive the expression of fear behavior following auditory fear conditioning (Figure 2A). In this circuit, the PAG, which is involved in the genesis of various conditioned fear responses (58–60) and the generation of aversive instructive learning signals (61,62), receives direct anatomical and functional inputs from the CEA (63–65). Recent studies suggest that expression of fear behavior is driven by the activation of the medial division of the central nucleus of the amygdala (CEm) neurons projecting to the PAG (63,66). Indeed, CEm output neurons are tonically controlled by lateral subdivision of the central amygdala (CEl) inhibitory neurons and display CS-evoked firing activity during freezing (63,66,67). More specifically, the CEl contains two populations of inhibitory neurons forming a disinhibitory microcircuit controlling the activity of PAG-projecting CEm neurons. This microcircuit is composed of CEl inhibitory neurons activated during CS presentations (CEl_{ON} neurons), which inhibit protein kinase C-delta-expressing (PKC-δ^{+}) CEl neurons (CEl_{OFF} neurons) (Figure 2A). CS-evoked inhibition of CEl_{OFF}