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Research report

Serotonin in fear conditioning processes

Elizabeth P. Bauer*

Barnard College, Biology Department, 3009 Broadway, New York, NY 10027, United States

HIGHLIGHTS

- 5-HT_{2A} agonists are anxiogenic and enhance fear learning.
- 5-HT_{1A} agonists are anxiolytic and impair cued and contextual fear learning.
- Variation in 5-HT genes can influence fear conditioning and extinction.
- Roles of the amygdala, hippocampus and BNST in mediating acute SSRI effects.

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ABSTRACT

This review describes the latest developments in our understanding of how the serotonergic system modulates Pavlovian fear conditioning, fear expression and fear extinction. These different phases of classical fear conditioning involve coordinated interactions between the extended amygdala, hippocampus and prefrontal cortices. Here, I first define the different stages of learning involved in cued and context fear conditioning and describe the neural circuits underlying these processes. The serotonergic system can be manipulated by administering serotonin receptor agonists and antagonists, as well as selective serotonin reuptake inhibitors (SSRIs), and these can have significant effects on emotional learning and memory. Moreover, variations in serotonergic genes can influence fear conditioning and extinction processes, and can underlie differential responses to pharmacological manipulations. This research has considerable translational significance as imbalances in the serotonergic system have been linked to anxiety and depression, while abnormalities in the mechanisms of conditioned fear contribute to anxiety disorders.

1. Introduction

One hallmark of several anxiety disorders is an abnormality in acquiring or extinguishing conditioned fear memories [1,2]. Manipulations of the serotonin (5-HT) system are widely used to treat a variety of anxiety disorders such as panic disorder, social phobia, generalized anxiety disorder and obsessive-compulsive disorder [3–7]. Thus, an understanding of how the serotonergic system modulates fear learning processes has been of considerable interest for decades. The advantage of studying classical Pavlovian fear conditioning is that it is a model of emotional learning for which the underlying neural circuitry has been described in detail. The structures involved in fear learning and expression, including the amygdala, hippocampus and prefrontal cortices, contain dense concentrations of 5-HT receptors [8–10]. Moreover, 5-HT levels in the amygdala increase during both cued and context fear conditioning [11–13]. Here, recent advances in our understanding of the neural circuits involved in fear learning, expression and extinction are described. I then review the literature describing how manipulations of the serotonergic system affect each of these behavioral processes, attempt to reconcile seemingly contradictory findings and offer recommendations for future research.

2. The neural circuitry underlying classical fear conditioning

Pavlovian fear conditioning is one of the most comprehensively studied behavioral paradigms. In classical fear conditioning, an initially neutral stimulus, such as a tone or light (conditioned stimulus; CS) is paired with an aversive stimulus, such as a brief electrical footshock (unconditioned stimulus; US). As a result of this pairing, the CS acquires aversive properties. Afterwards, when presented alone, the CS elicits responses in the animal that are characteristic of fear, including autonomic changes such as increased heart rate and blood pressure, as well as behavioral reactions such as the cessation of movement (freezing) and/or fear-potentiated startle

* Corresponding author. Tel.: +1 212 854 2349; fax: +1 212 854 1950.
E-mail address: ebauer@barnard.edu

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[14,15]. While cued fear conditioning involves the association of the US with a discrete cued CS, animals are also capable of associating a collection of context cues with the US, producing context fear conditioning [16–18].

If an animal is exposed to repeated presentations of the CS in the absence of the US, a gradual reduction in the ability of the CS to elicit fear responses takes place [19]. This phenomenon, fear extinction, involves learning that the new CS no longer predicts the US. Rather than destroying the original memory, fear extinction is a new learning process that inhibits the original fear memory [20,21]. The gradual reduction in fear during CS presentations is referred to as within-session extinction. This new memory is consolidated and recalled at a later point in time, which is referred to as between-session extinction or extinction retention/recall.

To appreciate how the serotonergic system modulates fear learning it is important to keep in mind that fear conditioning involves different stages of memory. Initial learning of the CS-US association during training is referred to as fear acquisition. These memories are thought to consolidate into stable, enduring protein-synthesis dependent memories during the 24 h after fear acquisition [22,23]. When the CS is later presented alone, the fear memory is retrieved, leading to expression of the conditioned fear response. Thus if a manipulation (such as the administration of a drug) occurs immediately before training and impairs both short-term (STM) and long-term memory (LTM), it is said to disrupt the *acquisition* of a fear memory. However, a drug administered pre-training which does not affect STM but does impair LTM prevents memory *consolidation.* Similarly, a drug is given immediately after training which impairs the formation of LTM, also disrupts memory consolidation. Alternatively, if learning has already taken place and a drug is given immediately prior to testing, it can affect *expression* or *recall* of the fear memory. In this way, the timing of drug administration determines the stage of learning that is affected.

It is important to keep in mind when studying fear conditioning and fear processes that the terms “fear” and “anxiety” can refer to conscious feelings and also to behavioral and physiological responses (see [24–26] for discussions of this idea). All animals, including humans, can detect threats and respond defensively. Studies that measure freezing behavior, or avoidance, or blood pressure are measuring behavioral or autonomic reactions to perceived threats. The conscious perception of fear and anxiety, however, can only be experienced by organisms capable of such conscious experience. In humans, emotions, including panic, can be consciously perceived even when the amygdala or insula is damaged [27,28], even though animals or humans with amygdala damage are not capable of Pavlovian fear conditioning [29,30]. Nevertheless, because the terms “fear conditioning” and “fear expression” are so widely used, this review will continue to use these terms.

The robustness of the Pavlovian fear conditioning paradigm has led to a detailed understanding of the key neuronal circuits, neurochemicals and molecular mechanisms underlying fear learning, fear extinction and associative plasticity in general (for recent reviews, see [31–34]). Lesion, inactivation and unit recording studies originally identified the lateral nucleus of the amygdala (LA) as the main input station of the amygdala where CS and US sensory inputs from both cortical and subcortical areas synapse on individual LA neurons [29,35–39]. Activation of individual LA neurons by CS inputs is enhanced by US-mediated depolarization during fear learning [38,40]. As a result of contingent CS-US pairings, subsequent presentations of the CS alone evoke larger responses in LA neurons [37,38,41]. Several recent reviews explore the complex molecular mechanisms underlying the formation of the CS-US association [31,33].

In the original model of fear conditioning, the central nucleus (CE) functioned as the main output of the amygdala. Neurons in the medial division (CeM) project to several fear effector systems in the hypothalamus and brain stem including the periaqueductal gray (PAG) which controls freezing behavior [15,42,43]. Disinhibition of the CeM allows for the expression of a range of defensive behaviors including freezing [44]. Newer research suggests that neurons in the lateral division of the Ce (CeL) contribute to fear acquisition. Pretraining inactivation of the entire CE, or CeL specifically, interferes with the acquisition of auditory fear conditioning [44,45]. Blockade of NMDA receptors or disruption of protein synthesis within the CE also impairs fear learning [45,46]. Neurons within the CeL receive input from the BLA and project to the CeM [44,47]. Plasticity of these glutamatergic inputs to CeL is induced by fear conditioning such that activation of these CeL neurons is necessary for fear memory recall [48]. Therefore, during CS presentations, subsets of LA and CeL neurons become active, disinhibiting CeM output neurons [44,48].

The bed nucleus of the stria terminalis (BNST), considered part of the extended amygdala, receives a strong glutamatergic input from the basolateral nucleus of the amygdala (BLA; which is composed of the LA and basal nuclei) and is reciprocally connected with the CE [49,50]. The CE and the BNST share a similar pattern of efferent targets including brainstem areas involved in fear and anxiety [49,51]. Unlike the BLA and CE, lesions of the BNST do not disrupt auditory fear conditioning or expression [15]. However, lesions or reversible inactivation of the BNST do attenuate the expression of context fear conditioning [52,53]. The BNST also contributes to an animal’s response to unpredictable stressful events and anxiety [54–57]. These data have led to the hypothesis that there is a distinction between fear (imminent threat or phasic fear) and anxiety (potential threat or sustained fear), which are mediated by the amygdala and BNST, respectively [56,58].

Animals are not only capable of associating discrete cues with an aversive stimulus, but can also associate a collection of contextual cues with a shock. A role for the hippocampus in this process is implicated by studies demonstrating that electrolytic lesions of the dorsal hippocampus before or after training impair context conditioning [16,17,59,60]. More recent experiments using optogenetic techniques reveal that during fear conditioning, subsets of granule cells in the dentate gyrus encode the memory of the context [61,62]. This memory of the context can be recalled when those specific subpopulations of neurons are activated [62,63]. Lesions or functional inactivation of the ventral hippocampus, however, produce inconsistent effects on context fear. Some studies show that the ventral hippocampus is required for the formation of a context representation [64–67], while others fail to replicate these findings [68]. Rather, the dentate gyrus of the ventral hippocampus seems to mediate anxiety [61]. Importantly, only the ventral hippocampus projects directly to the amygdala, thus damage to the ventral portion interferes with the transfer of information from the dorsal hippocampus to the amygdala [69,70]. Moreover, the ventral hippocampus modulates activity of BLA neurons [71]. The ventral hippocampus also sends a strong projection to the prelimbic cortex, which in turn forms a reciprocal connection with the BLA [72,73]. Finally, the BNST also receives input from both the ventral hippocampus and ventral subiculum and BLA [49]. However, lesions of the BNST selectively disrupt the expression of context but not cued fear conditioning [53,74].

After fear learning has taken place, it can be expressed via disinhibition of CeM neurons [44]. The increased responsiveness of CeM output neurons to the CS depends on disinhibition of CeL neurons as well as excitation from glutamatergic neurons in the BLA [44,75,76]. Indeed, the activity of BLA neurons correlates with high or low fear behavior (freezing) [71]. The prelimbic cortex (PL) integrates information from the BLA and ventral hippocampus, with increased activity in this area of the prefrontal cortex also correlating with increased fear expression [77,78].

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