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The amygdala: contributions to fear and stress

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Recent studies have identified major components of the neural system mediating the classical conditioning of defense or fear responses to sensory stimuli. The pathways involve transmission to the amygdala from sensory processing areas in the thalamus and cortex. Within the amygdala, the lateral nucleus receives the sensory inputs and the central nucleus provides the interface with motor systems controlling specific defense responses. Internal connections between the lateral and central nuclei allow the structures involved in receiving inputs and generating outputs to communicate. This circuitry contributes to stress reactions in two important ways. First, by way of these pathways environmental events that are interpreted as threatening activate the hypothalamic-pituitary-adrenal axis and thereby initiate so-called stress reactions. Second, nuclear regions of the amygdala contain receptors for adrenal steroids. Steroids released from the adrenal gland as a result of amygdala activity can therefore influence the processing of the environment by the amygdala. Although the amygdala is likely to play a major role in stress responses, relatively little work has been done to elucidate the nature of its role. This is an important topic for future research aimed at understanding how the biological cascade that constitutes the stress response fits into a broader network involved in emotional and cognitive information processing functions. In contrast to other models of stress, fear conditioning allows us to approach this complex problem armed with a clear understanding of major aspects of the circuitry involved in processing stress-inducing stimuli.

Key words: emotion / memory / classical conditioning / limbic system / learning / defense

FOR MANY YEARS, the limbic system concept[1] dominated thinking about the neural mechanisms of emotion. Recently, this concept has been called into question on the basis of anatomical[2,3] and functional[4,5] considerations. In retrospect, it seems that much of the strongest evidence for the involvement in limbic areas in emotion was due to the fact that the amygdala, a small region in the medial temporal lobe, was included within the limbic system concept.[4,6] The hippocampal formation, which was initially thought of as especially important to the emotional functions of the limbic system, now appears to be much more involved in cognitive processes than with emotion.[6,7]

The aim of this article is to examine the role of the amygdala in emotion, particularly in the emotion fear, and to consider the implications of this information for understanding the biology of stress. Fear is focused on because it has been extensively studied and much is known about its neural basis. Additionally, this emotion is directly relevant to the question of stress, especially the question of how stress reactions are initiated.

Neural basis of fear

The neural basis of fear has been studied using a variety of different approaches. These include studies of the neural pathways mediating defense reactions,[8-10] the Kluver-Bucy syndrome,[11-13] avoidance conditioning,[14,15] and fear conditioning.[16-18] These various approaches have produced a remarkably consistent picture of the neural system mediating fear. Below, studies of the neural basis of fear conditioning will be described, as these have provided the most detailed understanding of the underlying circuits.

Fear conditioning

Fear conditioning is a procedure in which an innocuous conditioned stimulus (CS), usually a light or tone, is paired with an aversive unconditioned stimulus (US), such as a brief shock to the feet. As a result of this pairing, the CS acquires aversive properties and will, when presented alone, elicit reactions that are characteristically elicited by threatening stimuli, such as the sight or sound of a predator.

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For example, rats freeze when they encounter a cat.[19] This occurs even in laboratory reared rats that have never had the opportunity to learn that cats are dangerous. Freezing is thus believed to be an innate, species-typical response that is exhibited when rats encounter danger. And through conditioning, novel stimuli can gain control over the circuits controlling these innate responses.[20,21] Thus, a rat that has been shocked in the presence of a tone CS will freeze when that CS is later given in the absence of the shock.

Fear conditioning has been quantified in experimental studies by measuring responses directly elicited by the CS, such as freezing[19,20,21], or a variety of autonomic[21-24] or endocrine responses.[25] Additionally, fear conditioning can be quantified by measuring the effects of CS presentation on other responses. For example, a CS that has been paired with shock will suppress ongoing behavior,[20,21,26,27] inhibit pain,[28,29] and potentiate reflex reactions.[30,31]

Each of the measures described above has been used to study the neural basis of fear conditioning. The circuitry involved is relatively insensitive to the kind of response that is measured, except for the components of the circuitry that are involved in the control of individual responses. Below, findings will thus be described more or less independently of the type of response that has been measured, except where indicated.

Connections of the amygdala involved in fear conditioning

The amygdala consists of a number of distinct nuclei.[32] Studies examining the role of the amygdala in fear conditioning have made considerable progress in isolating the key nuclei and their connections. Below, these pathways will be described in terms of inputs to, outputs of, and connections within the amygdala.

Input pathways

The afferent pathways to the amygdala in fear conditioning are best understood in the auditory modality. These differ depending upon the sensory processing demands of the conditioning task. For *simple fear conditioning* (one tone paired with shock), lesions of the auditory cortex do not interfere with conditioning, but lesions of the medial geniculate body (MGB) or inferior colliculus do.[21] These data suggest that the acoustic CS is transmitted through the auditory system to the MGB and from there to some region other than the auditory cortex. Anatomical tracing studies demonstrate that the MGB, in addition to projecting to the auditory cortex, also sends efferents to the amygdala.[33-36] While the central (CE) and lateral (LA) nuclei of the amygdala both receive thalamic afferents, only LA receives inputs from thalamic areas that receive inputs from the inferior colliculus.[35] The projections originate in the extralemniscal regions of the auditory thalamus,[18,34,35] where cells tend to be broadly tuned, rather than in the leminiscal areas that have narrow tuning and tonotopic organization. Selective lesions of LA interferes with fear conditioning.[37] Together, these finding suggest that LA is the sensory interface of the amygdala in fear conditioning.[37]

Although the auditory cortex is not a necessary part of the circuitry involved in simple fear conditioning, the auditory cortex can mediate fear conditioning when the thalamo-amygdala system is destroyed.[38] While not necessary, cortico-amygdala projections are certainly sufficient in mediating simple fear conditioning.

Ablation of the auditory cortex interferes with *differential fear conditioning* (two tones, one paired with shock the other not).[39] Such lesions do not prevent responding to the CS+, they simply prevent the differential responding to CS+. As a result, the animals respond to both the CS+ and CS-. When the auditory cortex is destroyed, these responses to CS+ and CS- are most likely mediated by thalamo-amygdala projections. This suggests that thalamo-amygdala projections, with their tendency towards broad tuning, may tend to overgeneralize fear reactions to stimuli other than the CS and that auditory cortex (and its cortico-amygdala projection) is needed for responding to a specific and restricted CS. Conversely, as the sensory processing demands of the task are increased beyond the limits of thalamic neurons, the cortical system and cortico-amygdala projections become involved. The cortico-amygdala and thalamo-amygdala projections converge in LA,[40] suggesting that the monosynaptic arrival of inputs in the amygdala from the acoustic thalamus might influence the processing of inputs arriving later over multisynaptic cortico-amygdala pathways.[6]

The hippocampus is not required for either simple or differential fear conditioning but is required for contextual conditioning. Contextual conditioning involves conditioning to cues other than the CS

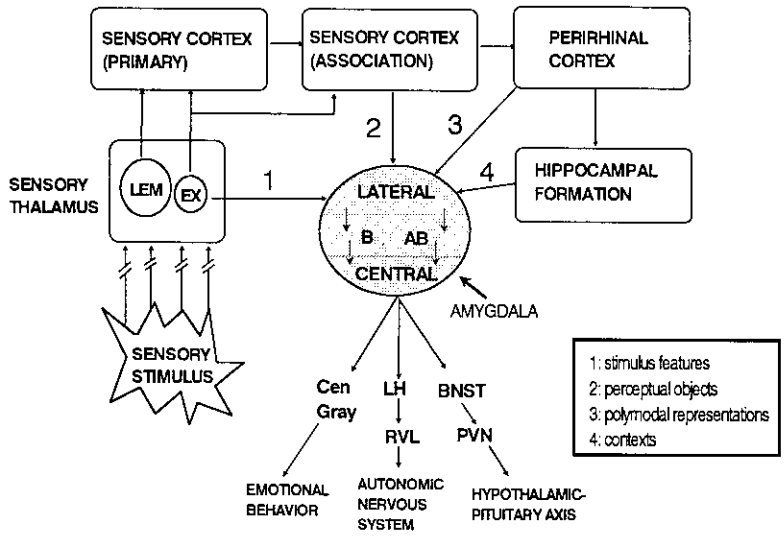

Figure 1.

that are present in the apparatus where conditioning takes place. Normally, some conditioning occurs to these cues. Damage to the hippocampus or the amygdala prevents such contextual conditioning from taking place without affecting conditioning to the CS.[41-44] The hippocampal formation gives rise to projections to the amygdala, including projections to LA,[45,46] suggesting that the amygdala may be involved in the association of the context with the US just at it is involved in forming associations between a simple or discriminated CS and the US.

Output pathways

Considerable evidence now points to the central nucleus of the amygdala as the structure by which information leaves the amygdala in the fear conditioning circuitry. Lesions of CE prevent both simple and differential conditioning of fear responses.[16-18,47] Further, unit activity recorded in the central amygdala is modified by explicit pairing of the CS and US but not by unpaired presentations in a differential conditioning procedure.[48] The central nucleus projects to brainstem areas involved in autonomic and somatomotor response control[49-51] and electrical or chemical stimulation of the central nucleus elicits autonomic and behavioral fear responses.[17,52] Lesions of the central nucleus interfere with both behavioral (freezing) and autonomic conditioned responses (see above). Lesions of areas that the central nucleus projects to separately interfere with behavioral or autonomic responses,[23,53,54] as well as with the potentiation of reflexes[16,31] or suppression of pain[29] elicited by as CS. These lesions thus disrupt response control, rather than fear learning, mechanisms. The central nucleus of the amygdala is the final site of response-independent processing in the fear conditioning pathway and is clearly the origin of the major amygdala outputs aimed at specific response systems.

Intraamygdala connections

If inputs come into the amygdala by way of LA and if outputs leave by way of CE, then it would seem necessary for connections to exist linking these two regions. Indeed, LA projects to CE both directly and by way of the basal (basolateral) and accessory basal (basomedial) nuclei.[32,55,56] At this point, it is not clear whether one of these intraamygdala pathways is crucial in fear conditioning, or whether the pathways are redundant.

Summary

These various observations allow a first approximation of the structures and pathways underlying auditory fear conditioning from sensory to motor neurons (Figure 1). The circuitry involves transmission of inputs through the auditory system to the acoustic thalamus. Projections from the auditory thalamus to LA directly or by way of auditory cortex can mediate CS transmission to the

amygdala in simple conditioning but projections through cortex are required for differential conditioning. Projections to LA from the hippocampus may be involved in contextual conditioning. LA then projects to CE, both directly and by way of intraamygdala connections. Efferent to CE, the pathway diverges, with different projections mediating different responses. These findings suggest an input-output description of the through-processing circuitry at the level of brain nuclei and pathways. However, other brain areas certainly also contribute, possibly modulating activity in the through processing circuit. Obvious examples include the various chemically specific brainstem pathways that project diffusely to the amygdala and the rest of the forebrain.[57]

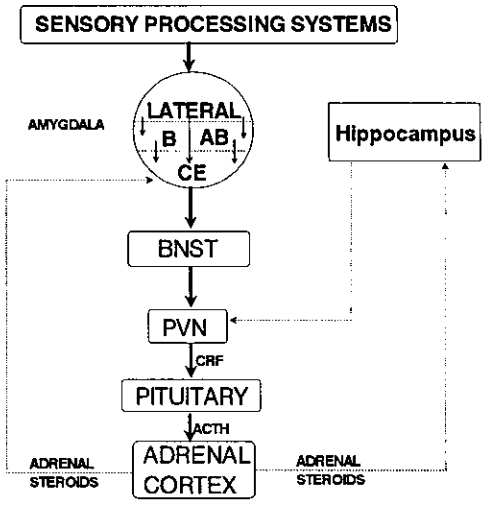

Figure 2.

Implications for understanding stress reactions

Although stress is a fairly ambiguous term, it is generally used to refer to the bodily response that occurs in the presence of challenges to psychological and/or physiological homeostasis. A hallmark of stress reactions is the activation of the pituitary-adrenal axis, which results in the release of ACTH from the pituitary gland and the subsequent release of steroids from the cortex of the adrenal gland.[25,58]

Conditioned fear stimuli are known to elicit pituitary-adrenal axis activation.[25,59] In contrast to other commonly used forms of stressful stimulation that rely on physical stimulus properties (painful stimulation, extreme ambient temperatures, restraint, circulatory hemorrhage), conditioned fear stimuli initiate stress reactions purely on the basis of the learned significance of the stimulus. In the absence of prior conditioning, the conditioned stimulus itself (a tone or flashing light) is innocuous and has no stressful consequence.

It is well established that the paraventricular nucleus (PVN) of the hypothalamus, is a key link in this chain of events leading to pituitary-adrenal activation. PVN contains neurons that release corticotrophin releasing factor (CRH) in the pituitary and thereby initiate the release of ACTH.[60] CE, the amygdala output station in conditioned fear, projects to PVN directly and by way of the bed nucleus of the stria terminalis (BNST).[51,61] While BNST lesions do not interfere with the expression of freezing or autonomic conditioned responses,[53] lesions of CE or of BNST prevents the release of ACTH from the pituitary in the presence of conditioned fear stimuli.[59,62]

Together, these findings suggest a clear scenario as to how stress responses can be initiated by environmental events (Figure 2). Information about threatening events is transmitted from sensory processing systems to the amygdala, and ultimately to nucleus CE, by way of the various input pathways described above. CE sends the signals to PVN by way of BNST. PVN then releases CRF in the pituitary gland, which starts the pituitary-adrenal cascade that typifies stress reactions.

Adrenal corticosteroids reach the brain through the circulation and bind to steroid receptors in many regions, including the hippocampus and amygdala.[63-66] Steroid binding in the hippocampus is well known to be involved in negative feedback regulation of the pituitary-adrenal axis.[63,64,66] Additionally, with prolonged or repeated stress circulating steroids result in structural pathological changes in the hippocampus[64] and functional changes in processes mediated by the hippocampus.[67,68]

Little is known about the effects of steroid binding in the amygdala during stress. However, recent studies have shown that CRF messenger RNA is increased in CE with chronic corticosteroid treatment[69,70] and similar treatment potentiates conditioned fear responses.[71] This effect of CRF is unique to the amygdala since in other areas CRF mesage is either increased or does not change.[71] It thus seems likely that the amygdala is crucially involved in the initiation of at least some stress

reactions and may also be greatly influenced by the same reaction. However, considerably more work is needed in this area to uncover the role of the amygdala in stress and the effects of stress on the amygdala.[65]

The use of fear conditioning as a model for studying stress allows us to approach this complex problem armed with a clear understanding of major aspects of the circuitry involved in processing the stress-inducing stimulus. In this respect, fear conditioning offers important advantages over other models of stress. Unlike most other approaches to stress, studies of fear conditioning allow the understanding of pituitary-adrenal responses and their consequences in a broader context of information processing by the brain. The eliciting conditions in fear conditioning are very specific. The CS enters the brian through a particular sensory processing system and reaches the amygdala from this system. By studying how the CS is processed in the amygdala and its afferent pathways, we can discover how the brain processes the signals that lead to stress and can therefore begin to understand stress as an interpretation of the environment as well as a response of the body.

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