Fear is an adaptation to danger, but excessive fear underlies diverse forms of mental anguish and pathology. One neural site linked to a sense of adversity is the amygdala, and one neurohormone, corticotropin-releasing hormone (CRH), is localized within the central nucleus of the amygdala. Glucocorticoids enhance the production of CRH in this region of the brain, resulting in increased attention to external events and, when sustained for longer periods of time, perhaps contributing to anxious depression.

Keywords: amygdala; fear; angst

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Fear, as the perception of danger, is an adaptive response, and fundamental in problem-solving and survival. In fact, fear is an emotion that likely evolved as part of problem-solving. Appraisal mechanisms which discern danger become overactive, leading to increased perception of fear, which then leads to anxious thought, and perhaps to endless gloom. In psychological terms, both anxious and depressive states have a common core of heightened negative affect, a product of overactivity of the neural systems that underlie fear and that contribute to a number of affective disorders. While fear is a central state of the brain, changes in heart rate, blood pressure, respiration, facial muscles, and catecholamines, both peripheral and central, all influence the state of fear.

One should note at the outset that fear, of which there are several kinds (conditioned fear, fear of unfamiliar objects, fear to sensory stimuli, etc), is more than amygdala function, and amygdala function is more than fear; however, fear is one thing in which the amygdala participates, and exaggerated amygdala activation creates a vulnerability to affective disorders.

Anatomical considerations about the amygdala

Regions of the amygdala receive and send information from both cortical and subcortical regions. More specifically, the basolateral complex is comprised of the lateral, basal, and accessory basal nuclei, which are richly innervated by neocortical and subcortical uni- and polysynaptic sensory regions, which then relay information to the central nucleus of the amygdala. Intra-amygdala connectivity is widespread.
The central nucleus projects to numerous nuclei in the midbrain and brain stem to orchestrate the rapid and primary behavioral, autonomic, and endocrine responses to threat and danger.\(^3,5,17\) The central nucleus also receives visceral information from brain stem sites that include the solitary and parabrachial nuclei\(^18\) and reciprocally projects to these brain stem regions (eg, ref \(^19\)). Regions of the amygdala directly project to the nucleus accumbens, which led investigators\(^20,21,22\) to suggest an anatomical route by which motivation and motor control action are linked in the organization of active behavior (see also refs \(^21-25\)).

In addition to projections from the central nucleus of the amygdala to midbrain and brain stem targets important for mounting quick behavioral, autonomic, and endocrine responses to danger, the amygdala projections to the cortex and subcortical structures are also quite extensive.\(^13,14\) In rat, the sources are the lateral, basal, and accessory basal nuclei, and their projections are fairly restricted to the multisensory temporal lobe structures (perirhinal, pyriform, and entorhinal cortices) and prefrontal cortex.\(^26\) In primate brain, the primary visual cortex also receives input from the amygdala.\(^13\) These cortical structures also contribute the heaviest cortical input to the amygdala, suggesting that many of the connections between the amygdala and cortex are reciprocal. This is particularly the case with the amygdala and prefrontal cortex, both anatomically\(^27,28\) and functionally (for review see refs \(^27,28\)).

In addition to the basolateral nucleus of the amygdala, the central nucleus of the amygdala also plays a unique role in conditioned fear.\(^3,5\) The basolateral complex of the amygdala, with its rich afferents from the thalamus and cortical regions, is neuroanatomically situated to connect information about neutral stimuli with those that produce pain or are harmful.

The central nucleus can orchestrate behavioral responses related to fear via its direct connections to numerous midbrain and brain stem regions and circuits instantiating various fear-related behaviors.\(^3,17,18,20,23,25\) Thus, the central nucleus of the amygdala, via its projections to lower brain, orchestrates behavioral (freezing\(^5,17\)), autonomic, and endocrine responses to fear, while efferents of the basal nucleus of the amygdala participate in active avoidance behaviors to fear,\(^23,25,33\) likely through basal ganglia. The bed nucleus of the stria terminalis (BNST) is anatomically linked to the central/medial amygdala\(^24\) and is also distinguished from the basolateral complex as being part of an autonomic brain system.\(^25\) Importantly, the central nucleus and the BNST are not only the major efferent sources of input to midbrain and brain stem targets controlling autonomic responses to fear, but are the main recipients of autonomic information from the nucleus of the solitary tract and parabrachial nucleus.\(^13,19,35\) Corticotropin-releasing hormone (CRH) is one of the cell groups (neuropeptides) richly expressed in the central nucleus of the amygdala and in the lateral BNST, and therefore is of special interest, as it is tied to all of these behavioral and autonomic events (see below).

There are reasonable conceptual issues of what defines the amygdala,\(^25,36\) and the ultimate basis for deciding what is amygdala is still open to investigation (eg, the extent to which the amygdala is part of the striatum and/or the larger cortical areas, the link to the BNST). There is little doubt that the amygdala is importantly involved in diverse forms of motivated behaviors (eg, fear) and their aberration during pathological states.

**Fear, uncertainty, unfamiliar objects, and the amygdala**

Humans with damage to the amygdala have impaired fear-related behavior and autonomic responses to conditioned stimuli (eg, refs \(^37-41\)). Also, positron emission tomography (PET) imaging studies in normals have shown greater activation of the amygdala during fear and anxiety-provoking stimuli than during presentation of neutral stimuli.\(^42\) Such PET studies have revealed that the amygdala is activated when presented with fearful, unfamiliar, and uncertain faces.\(^2,43,44\) With the use of functional magnetic resonance imaging (fMRI), it has further been shown that the amygdala is activated and then habituates when subjects are shown fearful faces but not when they are shown neutral or happy faces;\(^45,46\) however, the amygdala is also responsive to a variety of facial responses.\(^47,48\) A number of studies have also demonstrated that anxiety disorder patients have excessive activation in the amygdala when presented with stimuli that provoke anxiety attacks.\(^1,10,27\)
CRH expression and the brain

One cell group within the amygdala (and the primary focus of this review) and elsewhere in the brain is CRH, which is well known to be both a peptide that regulates pituitary and adrenal function and an extrahypothalamic peptide hormone linked to a number of behaviors, including behavioral expressions of fear. The majority of CRH neurons within the paraventricular nucleus (PVN) are clustered in the parvicellular division. Other regions with predominant CRH-containing neurons are the lateral BNST and the central division of the central nucleus of the amygdala. To a smaller degree, there are CRH cells in the lateral hypothalamus and the prefrontal and cingulate cortex. In brain stem regions, CRH cells are clustered near the locus coeruleus (Barrington’s nucleus), parabrachial region, and regions of the solitary nucleus. The CRH family has at least two receptors, CRH1 and CRH2, localized in rodent and primate brain (eg, refs 57-60). Activation of both the CRH1 and CRH2 receptors is linked to a G protein, and activates adenylyl cyclase cascade and an increase in intracellular cyclic adenosine monophosphate (cAMP) and calcium levels; CRH appears to bind primarily to CRH1 receptors. The distribution of CRH1 receptor sites includes regions of the hippocampus, septum, and amygdala (medial and lateral region) and neocortex, ventral thalamic, and medial hypothalamic sites; sparse receptors are located in the PVN and the pituitary gland. The distribution is widespread in cerebellum in addition to brain stem sites such as major sensory nerves and the solitary nucleus. The distribution of CRH2 receptors is more limited than that of CRH1 receptors and is found primarily in subcortical regions including the amygdala, septum, BNST, and PVN and ventral medial nucleus of the hypothalamus.

Differential regulation of CRH by glucocorticoids

Glucocorticoids are importantly involved in the restraint of CRH production in regions of the PVN. This negative feedback is a fundamental way in which the hypothalamic-pituitary-adrenal (HPA) axis is restrained during stress and activity. Glucocorticoids directly control neuronal excitability. Some of the glucocorticoid effects on the brain are quite rapid, suggesting that corticosterone has nongenomic membrane effects via γ-aminobutyric acid (GABA)-ergic mechanisms. Neurons within the lateral BNST and within the PVN may activate or inhibit PVN function via GABAergic mechanisms. While the profound effect of inhibition is indisputable, there are neuronal populations within the PVN that project to the brain stem that are not inhibited by glucocorticoids, and the activity of which is actually enhanced. That is, CRH neurons en route to the pituitary are restrained by glucocorticoids, but CRH en route to other regions of the brain appears not to be restrained. Moreover, the activity of extrahypothalamic regions of the brain in which CRH is expressed (central nucleus of the amygdala or lateral BNST) is actually increased by glucocorticoid hormones.

CRH, glucocorticoids, and fear-related behaviors

Central CRH activation has been consistently linked to the induction of fear, uncertainty, unfamiliarity, and uncontrollability in animal studies. Central infusions of CRH induce or potentiate a number of fear-related behavioral responses, and infusion of CRH antagonists both within and outside the amygdala reduce fear-related responses. One study, for example, reported that injection of a CRH antagonist into the basolateral complex of the amygdala, one of the regions in the amygdala which contains glucocorticoid receptors, immediately following footshock diminished retention of aversive conditioning in an inhibitory avoidance task. It was also shown in this study that the expression of CRH in the central nucleus of the amygdala increased 30 minutes following footshock. The results indicated that, similar to glucocorticoids and norepinephrine magnifying memory, CRH in the amygdala modulated learning and memory for aversive events. While glucocorticoids are essential in the development of fear, perhaps by the induction of central CRH, glucocorticoids, and CRH both play a larger role in the organization of behavior. Nonetheless, glucocorticoids are secreted under a number of experimental conditions in which fear, anxiety, novelty, and uncertainty are experimental manipulations. In contexts where there is loss of control, or the perception of a loss of control (worry is associated with the loss of control), glucocorticoids are secreted. This holds across a number of contexts.
species, including humans; perceived control reduces the levels of glucocorticoids.88 These findings are congruent with those of Curt Richter91 who observed an enlarged adrenal gland in stressed, fearful wild rats when compared with unstressed laboratory analogs. Glucocorticoids in the basolateral complex of the amygdala appear to be necessary for aversive and fear conditioning. For example, injection of the glucocorticoid receptor antagonist RU-486 into the basolateral complex of the amygdala will reduce the consolidation of aversive conditioning92 in addition to other forms of conditioning, including contextual fear.93 Other experiments have shown that glucocorticoid injections into the amygdala can facilitate aversive conditioning.33 Experiments like these, which use post-training injection procedures, demonstrate that glucocorticoids are necessary for consolidation of the memory of aversive conditioning and may facilitate the memory process.94-95 Glucocorticoid levels impact on learned fear.94-97 For example, in one study rats received conditioning trials in which the unconditioned stimulus (footshock) was presented concurrently with the conditioned stimulus (auditory tone). For several days after conditioning the rats were treated with corticosterone; conditioned fear-induced freezing was enhanced.96 Corticosterone, by the induction of central CRH expression, facilitates fear-related behavioral responses.76 Thus, in one study looking at contextual fear conditioning, groups of rats that were chronically treated with corticosterone displayed more fear conditioning than the vehicle-treated rats. Glucocorticoid antagonists disrupt contextual fear conditioning.94-95 Thus, the data suggest that repeated high levels of corticosterone can facilitate the retention of contextual fear conditioning, perhaps by the induction of CRH gene expression in critical regions of the brain such as the amygdala.

Importantly, amygdala infusion of corticosterone aimed at the central nucleus also increases milder forms of anxiety as measured with rats in the elevated plus maze.90 Shepard et al have, furthermore, demonstrated that implants of corticosterone resulted in an increase in CRH expression in the central nucleus of the amygdala. In addition, the corticosterone implants to the central nucleus of the amygdala increased levels of CRH expression in the dorsal lateral BNST96 and administration of the type 1 CRH receptors decreased this fear-related response.100 In other tests, pretreatment with the type-1 receptor CRH antagonist ameliorated fear-inducing events, or reactivity to the events,100 (see also refs 101-103 for the role of the CRH type-1 receptor; and 104, 105 for the role of the type II receptor). Furthermore, Cook demonstrated that the CRH response in the amygdala of sheep to a natural (dog) and unnatural (footshock) adversity is regulated by glucocorticoids.106 Following acute exposure to the dog, for example, amygdala CRH had a large increase during exposure to the dog and a second peak corresponding to the increase in cortisol. Administration of a glucocorticoid receptor antagonist blocked the second CRH peak in the amygdala without affecting the first peak.

There is a body of evidence suggesting that the BNST may be important for unconditioned fear107 and that perhaps CRH plays an important role.93 Lesions of the BNST do not interfere with conditioned fear-related responses, unlike lesions of regions of the amygdala which interfere with fear-potentiated startle or conditioned freezing.108,109 However, inactivation of the BNST can interfere with unconditioned startle responses108 and with longer-term CRH effects on behavior.109 High chronic plasma levels of corticosterone in adrenally intact rats facilitated CRH-induced startle responses.110 Perhaps what occurs normally is that the glucocorticoids, by increasing CRH gene expression, increase the likelihood that something will be perceived as a threat, which results in a startle response.

Lesions of the BNST also interfere with unconditioned freezing of rats to a fox odor,111 while amygdala lesions do not.11,112 Corticosterone can potentiate freezing to predator odor,11 (Rosen et al, unpublished observations). Perhaps the BNST may be linked to CRH-facilitated unconditioned adaptive anxiety and to general anxiety associated with drug abuse and to symptoms associated with pathological generalized anxiety disorder.114-116

Depression, anxiety, CRH, cortisol, brain

A genetic predisposition for a hyperactive amygdala has long been thought to result in a vulnerability to exaggerated fear and perhaps anxiety/depression.11,117 There is a substantial number of findings of increased activity in the amygdala of depressive patients,28,44,118 correlating with negative affect in other medication-free depressives119 and patients suffering from a number of anxiety disorders.2 In addition, a finding in depressive patients, particularly in those with comorbid anxiety, is hypercortisolism.120-122 Interestingly, antiglucocorticoids are, in a
number of contexts, reported to ameliorate depressive symptoms,123,124 which perhaps results in a reduction in central CRH expression. Importantly, depressive patients tend to have higher levels of CRH in cerebrospinal fluid than normal controls.125-129 There is some evidence that TYPE 1 receptor regulation can impact on depression.130 One study has found a significant positive correlation between activity in the amygdala measured by PET and plasma cortisol levels in both unipolar and bipolar depressives.131 Interestingly, patients with major depression show exaggerated responses in the left amygdala to sad facial expressions.132,133 Acute infusions of cortisol in normal patients resulted in exaggerated amygdala responses to sad faces.46 This correlation may reflect either the effect of amygdala activity on CRH secretion or cortisol actions directly in amygdala. It is intriguing to speculate that the findings that patients with a first episode of depression have an enlarged amygdala133 may be due to increased chronic levels of glucocorticoids and blood flow in the amygdala.134 Interestingly, fearful anxious children in whom cortisol was elevated in development117,135 also display a hyperactive amygdala to social performance as adults.11 Importantly, there is evidence of increased dendritic hybridization in amygdala and decreased dendritic hybridization of the hippocampus in animals under duress.136 Glucocorticoids are known to produce morphological changes in brain, typically decreases in hippocampal and prefrontal neurons’ dendritic trees.137,138 Moreover, studies have linked increased glucocorticoid production to changes in neuronal morphology in the basolateral complex of the amygdala following repeated stress136,139 and such changes in plasminogen activator in cell bodies within the amygdala promotes corticotropin-releasing factor (CRF) activity; the administration of antalarmin, a CRF TYPE 1 antagonist, does the converse.140 An fMRI study reported that, whereas the amygdala in both normals and depressives responded to aversive stimuli, the amygdala response of normals habituated quickly while the familial depressives’ amygdala remained active significantly longer.14 Whether CRH and cortisol are involved in the sensitized responses awaits further study. We do know that in animal studies, increased CRH increases the salience of familiar incentives8,87,142 and perhaps glucocorticoids magnify the CRH effect.8,45,142 Data on anxiety also indicate that the amygdala and cortisol are interactive in several anxiety disorders and for which cortisol, and the return to normal function, may be therapeutic.143 Although the research has developed along two separate paths, activity in the amygdala in a number of different anxiety disorders has been shown to be highly reactive to triggers that evoke anxious reactions29 and the HPA axis is hyper-responsive in anxiety disorders, particularly post-traumatic stress disorder (PTSD).144-46 PTSD patients also have high norepinephrine/cortisol ratios144,147 In research on cortisol measures, PTSD patients have basal hypocortisolemia but increased reactivity of the HPA axis to cortisol, suggesting that CRH and adrenocorticotropic hormone (ACTH)-secreting cells are sensitized to cortisol in PTSD patients.145 Indeed, CRH has been found to be elevated in cerebrospinal fluid of PSTD patients.147,148 PTSD patients have normal resting (nonprovoked) levels of amygdala activity, but the amygdala is highly responsive to anxiety provocation.149-152 While most of these studies do not demonstrate an abnormal response of the amygdala per se, particularly because normal humans also demonstrate increased amygdala activity to fearful or aversive stimuli (however, they do suggest that the amygdala has a lower threshold for responding to fearful stimuli in anxiety disorder patients).153 While focus here has been on the amygdala and, to a lesser extent, on the BNST, a fundamental part of fear circuitry is the prefrontal cortex (eg, refs 27,154,155). The medial prefrontal cortex (mPFC), for example, plays a role in inhibition of fear responses and extinction.154,156 There is evidence that regions of the prefrontal cortex regulate glucocorticoid responses to duress.157-159 The prefrontal cortex has relatively dense expression of glucocorticoid receptors in most regions, including the infralimbic cortical areas and CRH neurons are also located in most regions of the prefrontal cortex.49,50 Rosen and Schulkin, unpublished data. Chronic glucocorticoid treatment has been shown to alter apical dendrites of medial prefrontal neurons.157

Conclusions

Although the amygdala has been known to be involved in the emotion of fear since the seminal studies of Kluger and Bucy160 showed a taming effect of amygdala lesions in monkeys, research in the last two decades has produced great advances in determining the neuroanatomy of fear.
circuits. Not only has the amygdala been found to be critical for many types of fear, but fear circuits that connect the amygdala to many other brain regions have been described, which suggests that these circuits have evolved to function as neurobehavioral systems for particular kinds of cognitive and behavioral strategies. Understanding the neural circuitry that underlies fear/anxiety leads one to be in a better position for clinical judgment about treatment for states such anxious depression.

Normal fear is an adaptation to danger; chronic anxiety and depression are the overexpression of the neural systems involved in adaptation to danger. Coping with anxious depression is metabolically expensive; expectations of adversity predominate. Moreover, anxious depression is a condition in which there can be both high systemic cortisol and elevated CRH in the cerebrospinal fluid.118,125,161,162 Anxious depressed patients also tend to have increased glucose metabolic rates in the amygdala.118,134 The cortisol that regulates CRH gene expression in the amygdala may underlie the fear and anxiety of the anxiously depressed person.3,85 The exaggerated amygdala response that can occur because of life events and genetic predisposition (eg, refs 11, 77, 90, 129) contributes to the anxious/depressed person’s altered perception and experience of the world, leading to a chronic sense of anticipatory angst.

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### Angustia existencial y la amígdala

El miedo es una adaptación al peligro pero el miedo excesivo es la expresión de diversas formas de angustia y enfermedad mentales. Una localización neural relacionada con el sentido de la adversidad es la amígdala; el neuropéptido hormona liberadora de corticotropina (CRH), se localiza en el núcleo central del cuerpo amigdalino. Los glucocorticoides refuerzan la producción de CRH en esta región cerebral, con lo que aumenta la atención a los acontecimientos externos y, si se sostiene durante largos períodos, puede contribuir a la depresión ansiosa.

### Angoisse existentielle et amygdale

La peur est une adaptation au danger, mais une peur excessive est à l’origine de diverses formes d’angoisse et de pathologies. L’amygdale est un site cérébral traitant le concept d’adversité. La CRH (corticotropin-releasing hormone) est un neuropeptide situé dans le noyau central de l’amygdale. Les glucocorticoides augmentent la sécrétion de CRH dans cette région du cerveau, conduisant ainsi à une attention accrue aux événements extérieurs. En se pérennisant sur de plus longues périodes, cette sécrétion pourrait contribuer au trouble anxio-dépressif.
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