Anxiety is a psychological, physiological, and behavioral state induced in animals and humans by a threat to well-being or survival, either actual or potential. It is characterized by increased arousal, expectancy, autonomic and neuroendocrine activation, and specific behavior patterns. The function of these changes is to facilitate coping with an adverse or unexpected situation. Pathological anxiety interferes with the ability to cope successfully with life challenges. Vulnerability to psychopathology appears to be a consequence of predisposing factors (or traits), which result from numerous gene–environment interactions during development (particularly during the perinatal period) and experience (life events). In this review, the biology of fear and anxiety will be examined from systemic (brain–behavior relationships, neuronal circuitry, and functional neuroanatomy) and cellular/molecular (neurotransmitters, hormones, and other biochemical factors) points of view, with particular reference to animal models. These models have been instrumental in establishing the biological correlates of fear and anxiety, although the recent development of noninvasive investigation methods in humans, such as the various neuroimaging techniques, certainly opens new avenues of research in this field. Our current knowledge of the biological bases of fear and anxiety is already impressive, and further progress toward models or theories integrating contributions from the medical, biological, and psychological sciences can be expected.

Keywords: anxiety; fear; emotions; animal models; neurobiology; behavior

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It is amazing to see how Letourneau’s views on emotions, more than a century ago, were in many ways premonitory. The fact that emotions are “intimately linked with organic life,” his precise description of the sequence of the physiological and behavioral reactions that accompany a strong emotion, such as fear, the idea that emotions involve specific areas of the brain, and the theory that activation of these areas is associated with an increased blood flow have all been largely confirmed by modern neuroscience.

The suggestion that temperament or personality traits influence the “affective style” and vulnerability to psychopathology is also an important aspect of our modern approach to anxiety and mood disorders. Two main questions addressed by earlier scientific theories of emotions was whether physiological changes precede the emotional experience, or if they are only a consequence of it. For James (1884) and Lange (1885), “[...] the bodily changes follow directly the perception of the existing fact, and [...] our feelings of the same changes as they occur IS the emotion.” In other words, according to the James-Lange theory of emotions, stimuli reaching the cerebral cortex induce visceral changes, which are then perceived as emotion. Cannon and Bard (1915–1932) criticized this theory and proposed that the neurophysiological aspects of emotions are subcortical and involve the thalamus. Stimuli from the environment activate the thalamus, which relays information to the cortex and viscera, and back again to the cortex to generate the “emotional state.”

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For a long time, emotions were considered to be unique to human beings, and were studied mainly from a philosophical perspective. Evolutionary theories and progress in brain and behavioral research, physiology, and psychology have progressively introduced the study of emotions into the field of biology, and understanding the mechanisms, functions, and evolutionary significance of emotional processes is becoming a major goal of modern neuroscience.

Three fundamental aspects of emotions

The modern era of emotion research probably started when it became obvious that emotions are not just “feelings” or mental states, but are accompanied by physiological and behavioral changes that are an integral part of them. This has progressively led to today’s view of emotions being experienced or expressed at three different, but closely interrelated levels: the mental or psychological level, the (neuro)physiological level, and the behavioral level. These three complementary aspects are present in even the most basic emotions, such as fear. A detailed account of the many “theories of emotion” is beyond the scope of this review. However, a brief historical survey of the more biologically oriented ones may help to set some important conceptual issues.

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Watson, the father of behaviorism, was also very critical of what he called the “introverted viewpoint” of James’ theory. He considered that there were only three types of unlearned emotional responses, which he called “fear,” “rage,” and “love” for convenience, although he wanted to “ [...] strip them out of all their old connotations.” These three emotional responses can be elicited by three sets of specific stimuli. Thus, a sudden noise or loss of physical support can induce an innate fear reaction, and restraint of bodily movements triggers rage. He also mentioned the fact that these emotional responses can be conditioned and that, although these reactions are usually accompanied by specific behaviors, “[...] visceral and glandular factors predominate.”

Papez’s (1937) theory of emotions also had a physiological basis. For him, connections between the cerebral hemispheres and the hypothalamus, and between the cerebral hemispheres and the dorsal thalamus mediate emotions. He held the view that emotion implies behavior (expression) and feeling (experience, subjective aspects). Expression depends on the hypothalamus, and experience on the cortex. Although the “circuit of Papez” is still presented as “the emotional brain” in some handbooks, it is clear...
that many details of his original theory are now outdated. More recently, Schachter (1975) emphasized the importance of cognitive processes: bodily states are interpreted in a cognitive context and are modulated by experience. He also showed that the visceral response appears to be a necessary, although not sufficient, condition for the occurrence of emotion.

The view that there is a limited set of emotions (eg, fear, anger, etc) with specific neurophysiological and neuroanatomical substrates that can be considered as “basic” and serve as the primitive building blocks from which the other, more complex emotions are built, was challenged as late as 1990. However, Ekman has convincingly argued that there is now enough evidence of universals in expression and in physiology to suggest a biological basis for these elementary emotions. Panksepp added to these arguments by stating that “genetically dictated brain systems that mediate affective-emotional processes do exist, even though there are bound to be semantic ambiguities in how we speak about these systems.”

The biology of fear and anxiety

Fear versus anxiety: is there a difference?

The main function of fear and anxiety is to act as a signal of danger, threat, or motivational conflict, and to trigger appropriate adaptive responses. For some authors, fear and anxiety are undistinguishable, whereas others believe that they are distinct phenomena. Ethologists define fear as a motivational state aroused by specific stimuli that give rise to defensive behavior or escape. Animals may learn to fear situations in which they have previously been exposed to pain or stress, and subsequently show avoidance behavior when they reencounter that situation. Young animals may show an innate fear reaction to sudden noise or disturbances in the environment, but rapidly become habituated to them. When they are used to a familiar environment, then a fear of novelty may develop. Ethologists have also made the important observation that fear is often mixed up with other aspects of motivation. Thus, conflict between fear and approach behavior may results in displacement activities (eg, self-grooming in rats). Such displacement activities may be the behavioral expression of an anxious state, but anxiety is a concept that is apparently not used by ethologists, perhaps because their definition of fear does in fact include all the more biological aspects of anxiety.

Many authors, however, have argued that differences in their etiologies, response patterns, time courses, and intensities seem to justify a clear distinction between anxiety and fear. Although both are alerting signals, they appear to prepare the body for different actions. Anxiety is a generalized response to an unknown threat or internal conflict, whereas fear is focused on known external danger. It has been suggested that “[…] anxiety can only be understood by taking into account some of its cognitive aspects, particularly because a basic aspect of anxiety appears to be uncertainty. Also, it is reasonable to conclude that anxiety can be distinguished from fear in that the object of fear is ‘real’ or ‘external’ or ‘known’ or ‘objective.’ The origins of anxiety are unclear or uncertain […]”. Other authors pointed out that “[…] situations lacking in clear indications of situational contingencies or likely outcomes are associated with considerable stress. The uncertainty regarding these situations highlights a lack of control that contributes to feelings of anxiety and makes coping more difficult.”

Barlow has described anxiety as “[…] a unique and coherent cognitive-affective structure within our defensive and motivational system […]. At the heart of this structure is a sense of uncontrollability focused largely on possible future threats, danger, or other upcoming potentially negative events, in contrast to fear, where the danger is present and imminent.”

The fact that anxiety and fear are probably distinct emotional states does not exclude some overlap in underlying brain and behavioral mechanisms. In fact, anxiety may just be a more elaborate form of fear, which provides the individual with an increased capacity to adapt and plan for the future. If this is the case, we can expect that part of the fear-mediating mechanisms elaborated during evolution to protect the individual from immediate danger have been somehow “recycled” to develop the sophisticated systems required to protect us from more distant or virtual threats.

Defense and coping strategies

Fear or anxiety result in the expression of a range of adaptive or defensive behaviors, which are aimed at escaping from the source of danger or motivational conflict. These behaviors depend on the context and the repertoire of the species. Active coping strategies are
used when escape from threat is possible, and the autonomic changes associated with these active strategies are mediated predominantly by sympathetic activation (hypertension, tachycardia). This is the fight-or-flight response originally described by Cannon.17 Passive coping strategies, such as immobilization or freezing, are usually elicited when threat is inescapable, and are usually characterized by autonomic inhibition (hypotension, bradycardia), and a more pronounced increase in the neuroendocrine response (activation of the hypothalmo-pituitary-adrenal axis and increased glucocorticoid secretion). This type of passive response was originally described by Engel and Schmale as a conservation-withdrawal strategy.18 The concept of alternative (active/passive) strategies itself owes much to the work of Henry and coworkers.19 Specific brain circuits appear to mediate distinct coping reactions to different types of stressors.20,21

According to Panksepp, flight and other active coping behaviors are unconditional responses to proximate threat, whereas passive coping strategies, such as freezing, are conditioned responses to distal stimuli predictive of danger. These two strategies have distinct and successive roles, and are modulated by the (cognitive) apprehension of the environment and probability of success, eg, whether or not there is a route of escape. Thus, when an animal faces a predator, freezing is preferentially activated when the source of known danger is still far away. When danger gets closer, and the stimulus passes through some critical “psychometric” distance, it becomes a true unconditional stimulus and a flight pattern is activated.22

Defensive behaviors have been studied in a large number of species,23 and it has recently been shown that human defensive behaviors to threat scenarios are not unlike those seen in nonhuman mammals.24 The importance of risk assessment in making a proper decision about the best strategy to be used in a particular context has been emphasized.25

It should be underlined, however, that the choice between an active or passive defense strategy does not entirely depend on contextual clues. Individual differences in coping styles do exist and may also influence this choice. In a given situation, some individuals may react actively (“proactive” style), whereas other individuals may react in a more passive way (“reactive” style). These coping styles are characterized by consistent behavioral and neuroendocrine patterns, and may explain individual differences in vulnerability to stress-induced diseases.26 Differences in coping styles have also been found between various strains of mice,27 or between genetically selected rat lines,28 which suggests that they have a genetic basis. The capacity to cope successfully with life challenges, whether innate or acquired, is probably a primary determinant of resistance to stress-induced diseases.29,30

Normal versus pathological anxiety

Although anxiety is a natural adaptive reaction, it can become pathological and interfere with the ability to cope successfully with various challenges and/or stressful events, and even alter body condition (eg, formation of gastric ulcers).

In 1926, following a major flooding disaster in Leningrad, Pavlov reported a state of “chronic inhibition” and learning impairment in the dogs that had been successfully trained for conditioned responses in his laboratory and had directly experienced the flood.31 This observation (which may be one of the first laboratory-based accounts of the symptoms of posttraumatic stress disorder) and other experiments were the basis for his later studies on “experimental neuroses” in dogs. Pavlov discovered large differences in dogs’ individual susceptibility to psychopathology, and attributed these differences to “nervous types.” He described four types analogous to the four temperaments of Hippocrates, which, according to him, resulted from the combination of three factors: the “strength” of the nervous system (its degree of resistance to excitation or inhibition), the equilibrium between excitation and inhibition processes, and the capacity to shift from inhibition to excitation and vice versa.32

Although Pavlov’s typology is outdated, it is now recognized that increased vulnerability to anxiety and its disorders is associated with particular traits or endophenotypes, ie, traits that may be intermediate in the chain of causality from genes to disease.33 These traits may be innate or acquired during development or through experience. Barlow has defined three interacting sets of vulnerability factors for the development of human anxiety disorders in humans: (i) a generalized biological vulnerability, mainly of genetic origin; (ii) a generalized psychological vulnerability, resulting in particular from early life experiences; and (iii) a specific psychological vulnerability, focused on particular events or circumstances.34 The lat-
ter set is probably implicated in the development of specific anxiety disorders (as opposed to generalized anxiety disorders), ie, social phobia, obsessive-compulsive and panic disorders, and specific phobias.

Increased anxiety in animal models, as a trait, can be attributed to at least two sets of factors: (i) a genetic predisposition, essentially linked to the expression of genes that are involved in the various neurochemical mechanisms underlying fear and anxiety; and (ii) the influence of environmental factors. These environmental factors can interact with the expression of the relevant genes during early development and determine the functional properties of the neural and biochemical systems involved in coping with stressful events. They can also modulate the learning processes that occur at a later stage, when the individual is confronted with various life events, and determine the capacity to cope successfully with aversive or threatening situations in adulthood.

These predisposing factors, either innate or acquired, determine individual “affective styles” or coping strategies, which are thought to play an important role in vulnerability to psychopathology.

Animal models

Some of the neurobiological mechanisms underlying anxiety may already be present in very simple organisms, such as the snail *Aplysia*, which can show forms of learning akin to anticipatory and chronic anxiety. However, most animal models of anxiety are based on the use of mammalian species, particularly rats and mice. These models fall into two broad categories. In the first one, animals are confronted with situations that generate an anxious state (state anxiety models). This state of anxiety can be either conditioned (eg, conditioned fear, avoidance, and punishment-induced conflict tests) or unconditioned (eg, aversive and ethological conflict tests). In the second category, the models are concerned with trait or “pathological” anxiety: genetic manipulations (transgenic or “knockout” animals) or selective breeding creates lines of rats or mice that permanently express an increased or decreased level of anxiety.

Functional neuroanatomy

As already suspected by Letourneau and others, emotional experience and the associated behavioral responses are likely to activate specific circuits in the brain. The search for the neuroanatomical substrates of fear and anxiety has been a successful field of research over the last decades.

For a long time, it was assumed that emotions, including fear and anxiety, were almost exclusively generated or processed in a “primitive” part of the brain, ie, the limbic system (“the emotional brain”). The view that emotions and cognitions are separate functions of the brain and must therefore have different underlying neuroanatomical substrates is probably responsible for this simplification. As pointed out by LeDoux in a recent review, modern research with the most advanced neuroimaging technologies still uses this dichotomic approach to higher brain functions as a post hoc explanation: “When a so-called emotional task is used, and a limbic area is activated, the activation is explained by reference to the fact that limbic areas mediate emotions. And when a limbic area is activated in a cognitive task, it is often assumed that there must have been some emotional undertone to the task.” However, neuroanatomical and behavioral data obtained during the last decades clearly indicate that this dichotomy between cognitive and emotional processes is obsolete.

The locus ceruleus and arousal

Autonomic activation and increased arousal are among the earlier psychophysiological responses observed in a state of fear or anxiety. Since the immediate consequences of autonomic activation (eg, tachycardia) are perhaps the most readily perceived when experiencing a state of fear or anxiety, it has been proposed that the ascending noradrenergic system originating from the locus ceruleus (LC) is the core around which feelings of anxiety are organized. The LC contains a large proportion of the noradrenaline (NA) cell bodies found in the brain and it is a key brain stem region involved in arousal (Figure 1). It is highly responsive to alerting/stressful stimuli. In rats, cats, and monkeys, increased LC neuronal firing rate is associated with alertness, selective attention to meaningful and/or novel stimuli, and vigilance. The meaning, as well as the intensity of stimuli, seems to be an important factor in LC response. In cats, confrontation with a novel, but non-threatening stimulus, such as a mouse, does not cause a specific increase in LC firing, whereas confrontation with a threatening stimulus (eg, a dog) causes a marked
increase in LC firing. Thus, novelty by itself is not sufficient to activate the LC/NA system, but stimuli that signal reward, as those that signal danger, may activate the system. Recent data suggest that a phasic mode of LC activity may promote focused or selective attention, whereas a tonic mode may produce a state of high behavioral flexibility or scanning attentiveness. Some LC neurons project to the paraventricular nucleus (PVN) in the hypothalamus and activate the hypothalamic-pituitary-adrenocortical (HPA) axis, triggering or facilita-

Figure 1. A schematic view of major brain circuits involved in fear and anxiety. External auditory, visual, olfactory, or somatosensory stimuli are relayed by the thalamus to the amygdala and cortex. The basolateral complex (BLA) of the amygdala is the input side of the system, which also receives contextual information from the hippocampal formation (entorhinal cortex, hippocampus, and ventral subiculum). After intra-amygdala processing of the emotional stimuli, the central nucleus of the amygdala (CeA), on the output side, activates the locus ceruleus (LC) and central and peripheral noradrenaline systems (via corticotropin-releasing factor [CRF] neurons), and the hypothalamus (paraventricular nucleus [PVN] and lateral hypothalamus [LH]). The bed nucleus of the stria terminalis (BNST), part of the “extended amygdala”) is also a control center for the neuroendocrine system by integrating information originating from both the hippocampus and the amygdala. In addition, the CeA directly activates various midbrain regions or nuclei responsible for different aspects of the fear/anxiety response: freezing or escape (periaqueductal gray [PAG]), increased respiratory rate (parabrachial nucleus [PBN]), startle (caudal reticulopontine nucleus of the reticular formation [RPC]), and the dorsal motor nucleus of the vagus (DMN) in the medulla, which (together with the lateral hypothalamus) is responsible for the increase in heart rate and blood pressure associated with emotional events. The prefrontal cortex (PFC) processes more elaborate (“cognitive”) information; it modulates the physiological, neuroendocrine, and behavioral responses (via the amygdala), and it is also involved in the extinction of fear- and anxiety-related conditional responses. ACTH, adrenocorticotropic hormone; ANS, autonomous nervous system; BP, blood pressure; GABA, γ-aminobutyric acid; Glu, glutamate; NA, noradrenaline (neurotransmitter) or nucleus ambiguus (structure); NTS, nucleus tractus solitarius.
tating the stress response associated with increased anxiety (Figure 1). However, although 6-hydroxydopamine lesions of the LC in rats affect the HPA axis response to acute stress, they do not appear to substantially affect its response to chronic stress. Noradrenergic LC neurons also project to the amygdala (mainly to the central nucleus of the amygdala [CeA]), the prefrontal cortex (PFC), the bed nucleus of the stria terminalis (BNST), the hippocampus, the periaqueductal gray (PAG), the hypothalamus, the thalamus, and the nucleus tractus solitarius (NTS), which are all areas involved in the fear/anxiety response (Figure 1). The LC is in turn innervated by areas such as the amygdala (which processes fear-related stimuli) and other areas receiving visceral stimuli relayed by the NTS. The LC is therefore in a key position to integrate both external sensory and internal visceral stimuli and influence stress- and fear-related neuroanatomical structures, including cortical areas.

The septohippocampal system and behavioral inhibition

The inhibition of ongoing behaviors is the first behavioral manifestation of an anxious or fearful state. In the 1970s, Gray suggested that vulnerability to anxiety is associated with individual differences in the activity of a septohippocampal behavioral inhibition system (BIS). According to Gray, this is one of the three major emotional systems, which also include the behavioral approach system (BAS) and the fight/flight system (F/FLS). The primary function of the BIS is to compare actual with expected stimuli. If there is a discrepancy between the actual and expected stimuli (ie, “novelty” or “uncertainty”), or if the predicted stimuli are aversive, the BIS is activated, arousal and attention to novel environmental stimuli is increased, and ongoing behaviors are inhibited. Thus, according to Gray, anticipatory anxiety reflects a central state mediated by BIS activation, which is elicited by threats of punishment or failure, and by novelty or uncertainty.

The central role of behavioral inhibition in generating an anxious state has also been pointed out by Laborit. Anxiety is associated with the “alarm reaction,” as defined in Selye’s original description of the stress response (or general adaptation syndrome). According to Laborit, anxiety appears when one realizes that a proper adaptive action is not possible, ie, that there is loss of control over the situation, and it depends on the activation of the HPA axis.

Panksepp has argued that the activities of the ascending NA systems and the descending BIS are not causally related to the affective experience of fear and anxiety. They may be correlated, supportive, or permissive systems for establishing brain states that participate in the many brain readjustments accompanying fear. These systems certainly participate in the genesis of fear and anxiety behaviors: the NA system is involved in the initial alarm reaction, whereas freezing promoted by septohippocampal inhibition may help regulate the intensity and duration of fear. However, according to Panksepp, the amygdala-central gray axis plays an essential role in creating the emotional state associated with fear and anxiety.

The amygdala-hypothalamus-central gray axis and fear

In all mammalian species, there are three distinct sites in the brain where electrical stimulation will provoke a full fear response: the lateral and central zones of the amygdala, the anterior and medial hypothalamus, and specific areas of the PAG. A circuit coursing from the lateral and central nuclei of the amygdala, throughout the ventral-anterior and medial hypothalamic areas, down to the mesencephalic PAG, may constitute the executive system for fear, since freezing, as well as flight behavior and the autonomic indices of fear (eg, increased heart rate and eliminative behavior) can be evoked along the whole trajectory of this system.

In rats, stepwise increases in the electrical stimulation of the dorsolateral periaqueductal gray (dlPAG) produce alertness, then freezing and finally escape, replicating the sequence of natural defensive reactions when exposed to threat. Recent data suggest that dlPAG stimulation produces freezing independently of any contextual fear conditioning, whereas stimulation of the ventral periaqueductal gray (vPAG) appears to be critical to the expression of conditioned fear. Because electrical or pharmacological stimulation of PAG produces a range of fear-related responses similar to those seen in a panic attack, this area could be directly implicated in panic disorder.

The amygdala and fear conditioning

The elegant studies carried out by LeDoux, based on a simple fear conditioning paradigm in rats, have emphasized the primary role of the amygdala in controlling
emotional behaviors. His approach is along the lines of earlier learning/behavioral theories, eg, those of Pavlov and Watson, which emphasize the role of conditioning processes in behavioral development. After a few pairings of a threatening stimulus (eg, electric shocks, the unconditioned stimulus [US]) with a formerly neutral cue (eg, a tone or visual signal, the conditioned stimulus [CS]), animals will experience a state of conditioned fear when only the cue is present. Conditioned fear provides a critical survival-related function in the face of threat by activating a range of protective (or defensive) behaviors. The neuroanatomical and neurochemical foundations of conditioned fear, based mainly on the behavioral models of freezing and fear-potentiated startle in rats have been worked out in detail. In LeDoux’s model, the amygdala and thalamic pathways are responsible for the primary appraisal of threat by allowing a rapid, automatic analysis of potentially dangerous stimuli. Additional brain structures, including the hippocampus and cortical pathways, provide more information on the situational context and relevant stimulus characteristics (Figure 1). Thus, the amygdala plays a central role by integrating rapid, direct thalamic inputs, eg, visual information, with more detailed information, eg, cortical integration of sensory information, originating from longer and slower neuronal pathways. Activation of the amygdala by threatening stimuli then influences cognitive processes, perception, selective attention, and explicit memory.

The cognitive representation of fear may preferentially involve the left amygdala, as shown by recent functional magnetic resonance imaging (fMRI) studies. Interestingly, a sex difference in amygdala activation during the perception of facial affect has recently been reported. Amygdala activation (measured by fMRI) differed for men and women depending on the valence of the expression: happy faces produced greater right than left amygdala activation for males, but not for females. Both sexes showed greater left amygdala activation for fearful faces. These data suggest that the left amygdala may be more involved in the representation of negative affect.

The role of the various amygdala nuclei in fear conditioning is now well established, notably by lesion studies. In rats, the central and medial nuclei of the amygdala are important in mediating conditioned aversive states, but conditioned freezing may be mediated independently. Thus, different types of fear-conditioned behavior may be mediated by separate nuclei within the amygdala.

The amygdala plays a pivotal role in coordinating the behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in rats. In a fear-conditioning paradigm, pretraining amygdala lesions blocked freezing behavior, ultrasonic vocalizations, adrenocortical activation, and dopaminergic metabolic activation in the medial prefrontal cortex (mPFC). Posttraining lesions blocked mPFC dopamine, serotonin (5-hydroxytryptamine [5-HT]), and NA activation and stress-induced freezing and defecation, and greatly attenuated adrenocortical activation.

### The amygdala and positive reinforcement and attention

The role of the amygdala is not limited to fear-conditioning and the processing of aversive stimuli. Studies in rats using food-motivated associative learning indicate that the basolateral amygdala may be involved in the acquisition and representation of positive reinforcement values (possibly through its connections with the ventral striatal dopamine systems and the orbitofrontal cortex). Therefore, the amygdala is probably a key structure for the integration of behavior in conflicting situations, when both potentially rewarding and aversive stimuli are present. Recent studies indicate that the human amygdala can also process both positively and negatively valenced stimuli.

Recent studies also indicate that the CeA may contribute to attentional function in conditioning, by way of its influence on basal forebrain cholinergic systems and on the dorsolateral striatum.

### The amygdala and social behavior and phobia

The amygdala may play an important role in regulating social behavior. Thus, in adult macaque monkeys, selective bilateral lesions of the amygdala result in a lack of fear response to inanimate objects and a “socially uninhibited” pattern of behavior. The amygdala may function as a protective “brake” during evaluation of a potential threat, and it has been suggested that social anxiety may involve a dysregulation or hyperactivity of the amygdala evaluative process. Studies in rats also suggest that the basolateral nucleus of the amygdala may play a crucial role in the consolidation of information that leads to the formation of a specific phobia.
The extended amygdala (BNST) and anxiety

Although the amygdala is clearly involved in conditioned fear, its role in anxiety is less evident, because it is often difficult to specify the stimuli that triggers anxiety.72,73 Thus, lesions of the rat amygdala that suppressed fear-elicited startle or freezing behavior did not affect measures of anxiety in the elevated plus-maze and shock-probe–burying tests, two classic tests of anxiety for rodents.74 Moreover, diazepam was effective in these tests, even in amygdala-lesioned rats, suggesting that the anxiolytic effects of benzodiazepines are not necessarily mediated by the amygdala.75 Recent studies in primates also suggest that the amygdala is involved in mediating some acute unconditioned fear responses in rhesus monkeys, but that it is unlikely to be a key structure regarding the dispositional behavioral and physiological characteristics of the anxious temperament.76 The BNST is considered to be part of the extended amygdala.77 It appears to be a center for the integration of information originating from the amygdala and the hippocampus (Figure 1), and is clearly involved in the modulation of the neuroendocrine stress response.78,79 Activation of the BNST, notably by corticotropin-releasing factor (CRF), may be more specific for anxiety than fear. Studies in rats with the startle reflex suggest that explicit cues such as light, tone, or touch activate the amygdala, which then activates hypothalamic and brainstem target areas involved in the expression of fear, whereas less specific (or more complex) stimuli of longer duration, such as exposure to a threatening environment or intraventricular administration of CRF, may preferentially involve the BNST.73

The PFC and the control of emotional responses

The primary roles of the PFC appear to be the analysis of complex stimuli or situations and the control of emotional responses. In a revised version of his original BIS model, Gray postulated that the PFC may modulate septohippocampal activity, and that lesions to this area would impair the processing of vital information for the subicular comparator, and subsequently affect behavioral inhibition and anticipatory anxiety.71 He also suggested that the role of cortical structures in anxiety was probably more prominent in primates, based on the increased anatomical relationship between the septohippocampal system and the prefrontal and cingulate cortices observed in monkeys. Recent studies in humans and primates have largely confirmed Gray’s hypothesis, and it is now clear that the various subdivisions of the human PFC (dorsolateral, ventromedial, and orbital sectors) have specific roles in representing affect in the absence of immediate rewards or punishments and in controlling emotional responses.80,81 There appear to be important functional differences between the left and right sides within each of these sectors. Earlier studies on patients with unilateral brain lesions have already emphasized the role of cerebral lateralization in emotional information processing.82 More recently, brain electrical activity measures and positron emission tomography (PET) studies have indicated that negative affect and anxiety are associated with increased activation of the right PFC; moreover, individual differences in baseline levels of asymmetric activation in the PFC may be associated with individual differences in affective styles and vulnerability to mood and anxiety disorders.81 There is also increasing evidence that the PFC plays an important role in controlling anxiety and the associated stress response in rats, and that cerebral laterality is an important feature of the PFC system. Thus, in a recent study right, but not left, lesions of the ventral medial PFC were shown to have anxiolytic effects, and were also more effective in suppressing the neuroendocrine and autonomic stress response.83

Neurochemical correlates

A large number of neurotransmitters, peptides, hormones, and other neuromodulators have been implicated in fear and anxiety. We shall only discuss a few representative examples.

The noradrenergic system

Several preclinical studies have shown that stress and anxiety cause a marked increase in NA release in several rat brain regions, including the hypothalamus, the amygdala, and the LC.84 In agreement with these data, yohimbine, an α2-adrenergic receptor antagonist that increases NA release in the brain, has been shown to have anxiogenic effects in rats.84 However, pharmacological experiments involving the administration of various α2A-receptor agonists or antagonists in several animal models of anxiety are...
inconsistent, perhaps due to their interaction with other monoaminergic receptors. In a recent study, local administration into the LC region of an antisense oligodeoxynucleotide (AS-ODN) corresponding to the α2A-receptor mRNA was shown to have an anxiolytic effect, but another study has also shown that genetic knockout of the α2A-receptor in mice resulted in a more anxious phenotype than that of the corresponding C57BL/6 wild type. The role of the various NA receptor subtypes in mediating NA action on fear- and anxiety-related behaviors is therefore not settled. The precise location of the receptor subtypes within the complex circuitry mediating fear and anxiety responses is probably critical.

**The serotonergic system**

Data on the role of 5-HT in anxiety are conflicting: there is no agreement whether 5-HT enhances or, conversely, decreases anxiety. Thus, a 5-HT2C agonist such as m-chlorophenylpiperazine (mCPP) has anxiogenic effects in humans and may induce panic attacks, obsessions, and other neuropsychiatric symptoms, whereas selective 5-HT reuptake inhibitors ( SSRIs ) and 5-HT1A or 5-HT3 receptor–selective drugs can have antianxiety effects in certain anxiety disorders and animal models. On the basis of data obtained from animal models, Graeff et al have proposed a “dual 5-HT fear hypothesis” postulating that 5-HT may enhance conditioned fear in the amygdala, while inhibiting innate fear in the dorsal PAG. The ascending 5-HT pathway originating from the dorsal raphe nucleus (DRN) and innervating the amygdala and frontal cortex facilitates conditioned fear, while the DRN-periventricular pathway innervating the periventricular and PAG matter inhibits inborn fight/flight reactions to impending danger, pain, or asphyxia. The same authors have also proposed that the pathway connecting the median raphe nucleus ( MRN ) to the hippocampus may promote resistance to chronic, unavoidable stress by facilitating hippocampal 5-HT1A transmission. These results demonstrate that it is not possible to conclude about an “anxiogenic” or “anxiolytic” role for 5-HT (or, for that matter, of any other neurotransmitter, peptide, or hormone) without considering its site of action in the brain and/or the receptor subtype implicated.

Indirect evidence that the anxiolytic action of 5-HT is mediated by the 5-HT1A receptor has been obtained by three independent groups who have reported an “anxious” phenotype in 5-HT1A receptor knockout mice compared with corresponding wild-type mice, using three different genetic backgrounds. Depending on this background, the null mutation may be associated with changes in GABAergic transmission. More recently, it has been shown that 5-HT1A receptor knockouts display an “anxious-like” phenotype not only at the behavioral, but also at the autonomic response level. This seems to provide a strong argument in favor of an important role of 5-HT1A receptor gene expression for anxiety-related behaviors. In contrast, 5-HT1B receptor knockout mice were found to be more aggressive, more reactive, and less anxious than their wild-type counterparts, suggesting that this receptor may also modulate 5-HT action on defense mechanisms. Serotonin transporter ( 5-HTT ) knockout mice ( 5-HTT−/− ) have also been produced, and shown to display elevated anxiety in various behavioral tests, and an increased stress response ( adrenocorticotropic hormone [ ACTH ] secretion) following a mild stress, which was also observed to a lesser degree in the 5-HTT+/− heterozygotes.

**The GABAergic system**

γ-Aminobutyric acid ( GABA ) is the most abundant inhibitory neurotransmitter in the brain. The GABAAR benzodiazepine receptor is an important target for several anxiolytic drugs and may therefore play an important role in anxiety-related disorders. Several GABA receptors have been described. The diazepam-sensitive α2-GABAAR subtype appears to be specifically involved in anxiolysis. This subtype is largely expressed in the hippocampus, the amygdala, and the striatum. Two mouse lines were generated with a knockin point mutation on the α2 or α3 subunit, which rendered them insensitive to diazepam. The anxiolytic action of diazepam was suppressed in mice with the α2(H101R) point mutation, but not in those with the α3(H126R) point mutation. Heterozygous γ2-knockout mice ( γ2+/− ) have been generated ( the homozygous mutation is not viable ). These mice show enhanced reactivity to natural aversive stimuli, increased passive avoidance responses, and a deficit
in ambiguous cue discrimination. They have been proposed as a model for trait anxiety characterized by harm avoidance behavior and explicit memory bias for threat cues (enhanced sensitivity to negative associations).

In contrast to the anxiolytic action of benzodiazepine-like compounds, inverse agonists of the GABA/benzodiazepine receptor such as the β-carbolines are well known to be anxiogenic. Recently, intrahippocampal injections of a novel inverse agonist (RY024) have been shown to produce a fear response (freezing) and to interfere with fear-conditioning in rats.

The neurosteroids

The neurosteroids are a novel, interesting class of neuromodulators synthesized in the brain directly from cholesterol. They appear to act essentially via an allosteric modulation of the GABA<sub>A</sub> receptor, although other receptors may also be involved. As early as 1987, Majewska suggested that neurosteroids could play an important role in mood regulation. Several studies have shown that positive allosteric modulators (which potentiate GABA action), such as progesterone and allopregnanolone, have anxiolytic effects in various animal models. Neurosteroid synthesis is regulated by a peripheral benzodiazepine receptor (PBR) located on the outer mitochondrial membrane, and part of the anxiolytic effects of benzodiazepine could in fact involve increased neurosteroid synthesis. Compounds with a selective affinity for the PBR, such as FG11-1-27, have shown an anxiolytic action in rats. Neurosteroids are currently attracting a lot of interest because of their potential role as natural, endogenous anxiolytics.

Hormones of the HPA axis

Hormones of the HPA axis, such as cortisol, or corticosterone (in rodents), ACTH, and CRF are usually increased in a state of fear and anxiety. They also appear to modulate the response to threatening events.

Corticotropin-releasing factor

Intracerebral administration of CRF has been shown to elicit anxious-like behavior in rats. More recent preclinical studies suggest that CRF and its receptors play a pivotal, integrative role in the stress response and anxiety-related behaviors. There are two major CRF systems in the brain: the neuroendocrine system in the PVN, and another system with CRF cells located in the amygdala (CeA) and BNST, which would be more directly related to the physiological and behavioral responses associated with fear and anxiety. Whereas glucocorticoids restrain CRF production in the PVN (the neuroendocrine negative feedback loop), they appear to increase CRF expression in the amygdala and BNST, thus promoting fear- and anxiety-related behavior. CRF neurons originating from the amygdala project onto the LC (Figure 1) and contribute to increased arousal in fear and anxiety states. In a rat model, a full postsynaptic CRF agonist, CRF(1-41), increased arousal at low dosage and had an anxiogenic action at higher doses. This suggests that progressively increasing levels of CRF in the brain may ensure the transition from the initial state of increased arousal to the anxious state of expectancy in stressful situations.

Transgenic mice overexpressing CRF show a behavioral and neuroendocrine profile consistent with an increased level of stress and anxiety, including elevated plasma ACTH and corticosterone levels, and generally exhibit the same behavioral changes as those observed in mice following exogenous CRF administration. Recent data indicate a desensitization of postsynaptic, but not presynaptic 5-HT<sub>1A</sub> receptors in mice overproducing CRF. Another line of transgenic mice overexpressing CRF (CRH-OE(2122)) has shown a reduced startle reactivity, habituation, and prepulse inhibition. Deletion of the CRF gene (CRF-KO mice) results in chronic glucocorticoid insufficiency, and this may cause severe developmental problems. Despite an impaired stress-induced activation of the HPA axis, the behavioral stress responses do not appear to be markedly affected in CRF-deficient mice, suggesting that other CRF-like molecules may be implicated in the behavioral effects mediated by CRF receptors. CRF-KO mice also display normal startle- and fear-conditioned responses.

CRF receptors and CRF binding protein

Deletion of the genes coding for CRF receptors 1 (CRF-R1) or 2 (CRF-R2) have more profound behavioral effects. CRF-R1-deficient mice display decreased anxiety and an impaired stress response, whereas deletion of the CRF-R2 gene has the reverse effect in males (but not in females): anxiety is increased in Crhr2-/-.
genic effects of CRF, whereas CRF-R2 may be involved in anxiolysis. Recently, mice deficient in both CRF-R1 and CRF-R2 receptors have been generated.127 These double mutants display altered anxiety-related behavior and an impaired HPA axis response to stress. Interestingly, the effects on anxiety are again sex-dependent: females show a decreased anxiety similar to that observed in Crhr1-/- mutants, whereas the genotype has no effect on male anxiety-related behaviors. These studies have also demonstrated a novel role of the mother’s genotype on the development of pup anxiety: pups born to a heterozygous or mutant mother display significantly more anxiety, regardless of that pup’s genotype.127 The CRF binding protein (CRF-BP) may play an important modulatory role in CRF action.128 Interesting data consistent with a modulatory action of CRF-BP have recently been obtained with transgenic and knockout models: transgenic males overexpressing CRF-BP tend to show less anxiety, whereas the behavior of CRF-BP-deficient mice was consistent with increased anxiety.129

Corticosteroids

Corticosteroids effects on anxiety-related behaviors may be mediated by both genomic and nongenomic mechanisms (control of neuronal excitability). Hippocampal corticosteroid receptors play an important role in the termination of the acute stress response.130 Studies with a model of posttraumatic stress disorder in rats suggest an alteration of the mineralocorticoid receptor (MR) vs glucocorticoid receptor (GR) balance, as measured by the expression of mRNA levels in the hippocampus, during the recovery phase following acute stress: the MR/GR ratio was decreased, but only in animals with an enhanced fast feedback.131 Recent data also suggest that, at low circulating levels, corticosteroids exert a permissive action (via MRs) on acute freezing behavior and other acute fear-related behaviors. At higher levels, corticosteroids enhance acquisition, conditioning, and consolidation of an inescapable stressful experience, as well as processes underlying fear potentiation, via GR-dependent mechanisms.132 Mice with targeted mutation of the MR and GR receptors display altered anxiety-related behaviors.133

Other peptides, neurotransmitters, and hormones

Several peptides, such as cholecystokinin (CCK), neuropeptide Y (NPY), tachykinins (substance P, neuropeptides A and B), and natriuretic peptides (atrial natriuretic peptide or C-type natriuretic peptide) may play important roles in fear- and anxiety-related behaviors.134 CCK may be particularly relevant for panic disorders.135,136 and may influence cognitive processes.137 Excitatory amino acids (EAA), such as glutamate, are also important. In rats, microinjections of EAA into the dorsolateral PAG induce a flight reaction. Part of the effects mediated by N-methyl-d-aspartate (NMDA) receptors may involve nitric oxide (NO). Nitric oxide synthase (NOS) inhibitors injected in the dorsolateral PAG have been shown to have anxiolytic effects, and psychological stress (restraint) induced an increased expression of neuronal NOS in the same area and in other areas related to defense mechanisms, suggesting that NO may participate in these defensive responses.138 We have also shown that anticipatory anxiety can lead to a decreased secretion of luteinizing hormone (LH) and testosterone in young, healthy male subjects.139

Genetic and environmental factors

Individual differences in sensitivity to threat or stress, and particular coping or affective styles appear to be critical predisposing factors for anxiety-related disorders. Genetic and environmental factors have been implicated, and how these factors interact during development is one of the major questions addressed by recent clinical and fundamental research.

Genetic determinants

A genetic basis for anxiety-related behaviors is now clearly established, notably through several family, twin, and adoption studies. In mice, targeted gene mutations have shown that modifying the expression of particular genes can have a profound effect on anxiety-related behavioral phenotypes.139,140 Some examples were mentioned in the preceding section. Natural variations in trait anxiety, or emotionality, in inbred rat and mouse strains are being extensively studied.141-148 Some of these strains show differences in sensitivity to anxiolytic agents such as diazepam.147,148 Crossbreeding of inbred rodents strains has shown the quantitative nature of many anxiety-related traits.149,150 The quantitative trait locus (QTL) method is based on a comparison between the allelic frequency of DNA
markers and quantitative behavioral traits. It has been used to assess gene effects on fear, emotionality, and anxiety-related behaviors in mice from various genetic backgrounds. Loci on mouse chromosomes 1, 4, and 15 were found to operate in four tests of anxiety, whereas loci on chromosomes 7, 12, 14, 18, and X influenced only a subset of behavioral measures. A QTL influencing anxiety has also been found recently on rat chromosome 5.

Selective breeding of mice and rats has also been used to create lines that show extreme behavioral characteristics within the range of the normal population. Various selection criteria can be used, which may not be directly related to anxiety. Thus, rat lines initially selected for their good versus poor performance in two-way, active avoidance were subsequently shown to differ in trait anxiety, or emotionality. For instance, the Roman high- (RHA/Verh) and low- (RLA/Verh) avoidance rat lines display clear differences in emotionality and anxiety-related behaviors. The more anxious (RLA/Verh) rats display increased neuroendocrine and autonomic reactivity to mild stressors. Differences in vasopressin, oxytocin, and CRF action at the level of the amygdala, dopaminergic and GABAergic neurotransmission, basal vasopressin mRNA expression in the hypothalamic PVN, and 5-HTT levels in the frontal cortex and hippocampus have been reported. We have shown an increased capacity (enzymatic activities) for the production of progesterone-derived, anxiolytic neurosteroids in the frontal cortex and BNST of RHA/Verh rats, which may explain in part the differences in emotional reactivity of these two lines. These two rat lines also differ in their respective coping styles and response to novelty, and this model may therefore prove useful for studying the interaction between anxiety and defense mechanisms.

Recently, two Wistar rat lines have been selected and bred for high anxiety-related behavior (HAB) or low anxiety-related behavior (LAB) on the elevated plus-maze, a classical test for anxiety in rodents. The neuroendocrine, physiological, and behavioral characteristics of these two lines are being extensively studied, and show some similarities, but also differences, as compared to the Roman rat lines. Further comparison between lines such as the RHA/RLA and HAB/LAB rats, which have been selected on different behavioral criteria (avoidance versus anxiety in the elevated plus-maze test), but show a similar, anxiety-related behavioral phenotype, may be extremely fruitful to delineate brain mechanisms underlying specific aspects of anxiety disorders.

Environmental influences

The role of environmental influences in the etiology of anxiety is also well established. Early adverse experience is a major developmental risk factor for psychopathology. Prenatal stress in animal models has been shown to permanently alter brain morphology, anxiety-related behavior, coping, and regulation of the HPA axis in adulthood. Naturally occurring variations in maternal care can also alter the regulation of genes controlling the behavioral and neuroendocrine responses to stress, as well as hippocampal synaptic development. These effects are responsible for stable, individual differences in stress reactivity, as well as the maternal behavior of female offspring. They could constitute the basis of a nongenetic mechanism for the transmission of individual differences in stress reactivity and coping styles across generations.

In 1958, Levine reported that rats handled for the first 21 days of life exhibit reduced fearfulness compared with nonhandled controls. Since then, several studies have shown the beneficial effects of neonatal handling and a progressive habituation to stress on adults’ stress responses and anxiety-related behaviors. Neonatal handling can even reverse the behavioral abnormalities induced by prenatal stress. These effects appear to be mediated essentially by the CRF/HPA axis system, although the serotonergic and catecholaminergic systems could be also involved. A study has shown that neonatal handling increases the expression of the peripheral benzodiazepine receptor (PBR), which has been implicated in the synthesis of endogenous, natural anxiolytic agents such as the neurosteroids, in rat adrenals, kidney, and gonads. It is likely that increased adrenal production of naturally anxiolytic compounds such as allopregnanolone contributed to the decrease in anxiety reported in this study.

Sex differences in the effects of neonatal handling have been recently reported: neonatal handling may provide males with a greater capacity to actively face chronic stressors. Recent data indicate that neonatal handling can also affect memory processes involved in contextual fear conditioning.

In the Roman rat lines, neonatal handling has been shown to alter the behavioral phenotype of the more anxious
RLA/Verh rats so that, in adulthood, they behave in the same way as their nonhandled, hypoemotional RHA/Verh counterparts. Females were found to be more sensitive than males to the positive influences of early stimulation. The effects of neonatal handling on RLA/Verh rats were not limited to behavioral stress responses and coping behaviors, but were accompanied by a concomitant decrease in stress-induced ACTH, corticosterone, and prolactin release, indicating that the neurochemical substrates underlying these responses were also permanently affected by early experience.

This and other examples indicate that the developmental processes that determine individual sensitivity to stressors, or emotionality, and coping behaviors involve complex interactions between genetic and environmental factors, and that anxiety-related phenotypes cannot be predicted on the sole basis of a genetic predisposition or early adverse experience.

Conclusions

The biological bases of fear and anxiety are now recognized, and the major brain structures and neuronal circuits involved in emotional information processing and behavior are delineated. Emotional and cognitive processes cannot be dissociated, even when considering such a basic emotion as fear. The cognitive apprehension of events and situations is critically involved in emotional experiences and also influences coping strategies or defense mechanisms. This is reflected in the important role now attributed to the PFC in controlling emotional behavior in humans and animals.

Molecular biology techniques, such as those used to create transgenic and knockout mice, have been successful in exploring the role of various neurotransmitters, peptides, hormones, and their receptors in mediating the appraisal of stressful stimuli, information processing through the various neuronal circuits, and the physiological responses and behaviors associated with fear and anxiety.

It is now clear that individual differences in affective or coping styles, which are also observed in nonhuman species, are directly associated with vulnerability to psychopathology. Studying these individual differences, including sex-related differences, in humans and in animal models will give interesting clues about the brain mechanisms of emotional behavior.

Finally, the study of genetic predisposition and environmental influences, particularly during early development, in determining vulnerability traits and anxiety-prone endophenotypes is certainly becoming one of the major, and perhaps most promising, domains of contemporary research with respect to our understanding of the etiology of anxiety and mood disorders.

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La biología de las conductas relacionadas con el miedo y la ansiedad

La ansiedad es una condición psicológica, fisiológica y conductual que se induce en los animales y en el hombre por una amenaza al bienestar o a la sobrevivencia, sea presente o potencial. Se caracteriza por un aumento del alerta, expectación, activación autonómica y endocrina, y patrones conductuales específicos. La función de estos cambios es facilitar la adaptación ante una situación adversa o inesperada. La ansiedad patológica interfiere con la capacidad para adaptarse exitosamente a los desafíos de la vida. La vulnerabilidad a la psicopatología parece ser una consecuencia de factores predisponentes (o rasgos) los cuales se deben a numerosas interacciones entre los genes y el ambiente durante el desarrollo (especialmente durante el período perinatal) y a lo largo del curso de la vida (acontecimientos vitales). En esta revisión se examinará la biología del miedo y la ansiedad desde aproximaciones sistemáticas (relaciones cerebro-conducta, circuitos neuronales y neuroanatomía funcional) y moleculares/celulares (neurotransmisores, hormonas y otros factores bioquímicos) poniendo especial atención a los modelos animales. Estos modelos han constituido un medio para establecer los correlatos biológicos del miedo y la ansiedad; sin embargo, el reciente desarrollo de métodos de investigación no invasores en humanos, como las diversas técnicas de neuroimágenes, ciertamente abre nuevas vías de investigación en este campo. Nuestro conocimiento actual de las bases biológicas del miedo y la ansiedad ya es notable y se puede esperar que a futuro se progrese hacia modelos o teorías que integren contribuciones desde las ciencias médicas, biológicas y psicológicas.

Biolgie des comportements liés à l’anxiété et à la peur

L’anxiété est un état psychologique, physiologique et comportemental provoqué chez les animaux et les humains par une menace qui s’exerce sur le bien-être ou la survie, qu’elle soit réelle ou potentielle. Elle est caractérisée par une hypervigilance, une attente excessive, une activation des systèmes autonome et neuroendocrine et par des schémas comportementaux spécifiques. Ces modifications doivent faciliter l’adaptation à une situation hostile ou inattendue. L’anxiété pathologique interfere con la capacidad de s’adapter avec succès aux aléas de la vie. La susceptibilidad à la psychopatologie para resulter de facteurs prédisposants (ou de caractères), eux-mêmes issus de nombreuses interactions génome-environnement pendant la phase de développement (particulièrement durant la période périnatale) et de l’expérience (événements de la vie). Dans cet article, la biologie de la peur et de l’anxiété sera examinée d’un point de vue systématique (relations cerveau-comportement, circuits neuronaux et neuroanatomie fonctionnelle) et d’un point de vue cellulaire et moléculaire (neurotransmetteurs, hormones et autres facteurs biochimiques), avec une référence particulière aux modèles animaux. Ces modèles ont contribué à l’établissement de corrélations biologiques de la peur et de l’anxiété, bien que les avancées récentes des méthodes d’investigation non invasives chez les humains, telles les diverses techniques de neuroimagerie, ouvrent certainement de nouvelles voies de recherche dans ce domaine. Nos connaissances actuelles des bases biologiques de la peur et de l’anxiété sont déjà impressionnantes et nous pouvons espérer des progrès supplémentaires de la part de modèles ou de théories intégrant les données des sciences médicales, biologiques et psychologiques.

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