

Anxiety and Anxiety Disorders

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Abstract

Anxiety is one of the important normally and regularly occurring emotions. Some of the actual public health problems like anxiety disorders are based on the pathology of feelings. Anxiety disorders comprise a heterogeneous group of disorders and each of these disturbances has a different etiology and outcome, and different physiological characteristics. Among the most important influences are actually genetic disposition, environmental impact upon one individual, and acute stressors that result in adaptational changes. Considering a large body of findings, several monoamine neurotransmitters and anxiogenic or anxiolytic-like neuropeptides are involved in the regulation of fear and anxiety.

Anxiety is one of the important normally and regularly occurring emotions, which can be observed throughout all human cultures and in several animal species. Some of the actual most prominent medical and public health problems like anxiety disorders or depression are based on the pathology of feelings (Damasio and Carvalho, 2013). While recent data show that the basic facial expression of emotions is also modulated by culture-specific influences, fundamental emotional expressions such as anxiety or fear originate presumably from the beginning of human ontogeny as biologically hardwired and universal signals (Jack et al., 2013).

Anxiety disorders comprise a heterogeneous group of disorders and each of these disturbances has a different etiology and outcome, and different physiological characteristics. Depending on actual classification rules according to the DSM 5 (2013), panic attacks and panic disorder, phobias, social phobia, and generalized anxiety disorder are summarized in anxiety disorders. In contrast to former classifications, post-traumatic stress disorder and obsessive compulsive disorder are no longer included, despite the fact that anxiety is a relevant dimension of these disorders. Moreover, anxiety has to be differentiated from fear and the so-called stress responses.

Anxiety derives from complex origins and among the most important influences are actually genetic disposition; environmental impact upon one individual, especially early adverse events; and acute stressors that result in adaptational changes. Considering a large body of findings, several monoamine neurotransmitters, for example, gamma-aminobutyric acid (GABA), serotonin, and noradrenalin, are involved in the regulation of fear and anxiety. In addition, an increasing variety of either anxiogenic neuropeptides like corticotropin-releasing factor (CRF), cholecystokinin tetrapeptide (CCK-4), vasopressin, and others, or anxiolytic-like neuropeptides like neuropeptide Y (NPY), neuropeptide S, and atrial natriuretic peptide (ANP) are most important in the modulation of anxiety.

Several neurobiologic findings also stem from investigations in humans by eliciting panic attacks. Panic attacks are unique in the spectrum of psychiatric disorders; since their core psychopathology is temporally limited, they can be provoked under laboratory conditions and can in part be conditioned. Due to the experimental character of these investigations, close comparisons with experiments in animals can be drawn. Hence

it has been proposed that panic disorder involves the same pathways that support conditioned fear in animals. However, while induction of panic anxiety has been studied intensively, little is known about the intrinsic mechanisms for the termination of panic and anxiety.

Anxiety or fear is, in addition to happiness, sadness, anger, disgust, and desire, one of the important normally and regularly occurring emotions, which can be observed throughout all human cultures and in several animal species (Ekman, 1982), but the facial expression of such basic emotions is also modulated by culture-specific influences. Anxiety per se is a complicated concept since several difficulties arise in defining this emotion and, in addition, it has to be differentiated from fear and stress (see below). Anxiety occurs, besides in anxiety disorders, also comorbid in several other psychiatric conditions. Moreover, anxiety refers to a variety of other emotional experiences, for example, apprehensiveness, tension, and agitation, which occur also in other emotional states. Anxiety is defined by subjective, behavioral, and physiological characteristics. Anxiety involves the experience of dread and apprehensiveness, and the physiological reactions of anxiety usually include trembling, sweating, elevated heart rate and blood pressure, and increases in muscle tone. Anxiety is defined as pathological when occurring inadequately or with much more pronounced severity and debilitating features. An additional defining criterion in standardized diagnostic manuals is the concomitant occurrence of anxiety and avoidance. Representatives for these diagnostic entities, in which anxiety is the leading symptom, are panic disorder and generalized anxiety disorder. Anxiety is experienced in phobic disorders when the subject is confronted with the feared stimulus, which results in its avoidance. One of the reasons for the declaratory confusion of the term *anxiety* is its psychological similarity to fear and its vegetative similarity to stress. Similar to anxiety, *fear* also includes the experience of dread, and fear seems to be largely included into the concept of anxiety. Moreover, anxiety and fear induce similar bodily reactions, which include the so-called *stress* responses. In general, these can be separated in active responses, known as 'fight or flight' reactions or behavioral inhibition, like freezing. The accompanying stress-related sequelae can again be divided into two large entities: the excitatory fight or flight response postulated by Cannon (1929), and the endocrine stress concept raised by Selye

(1956). Complementarily, the results of several studies indicate that stress involves brain structures, which also mediate the perception of anxiety such as amygdala, hippocampus, and other limbic structures (see below).

Differentiation of Anxiety

Both anxiety and fear are regularly experienced within a range of normal emotional responses of everyday life. Specifically, fear is necessary to achieve personal growth and individual freedom during ontogeny.

Anxiety

Anxiety represents a basic emotional state, which is present in men and can be defined by affective (basic emotional feelings), perceptive (realization of bodily or psychomotor sensations), and cognitive components. Besides these subjective components, behavioral and physiological characteristics can be used to define anxiety phenomenologically. In contrast to experiencing anxiety during everyday life, anxiety as psychopathologic disturbance or anxiety disorder includes specific diagnostic criteria, neurobiological dysfunctions, and a specific genetic background and leads to social and occupational disabilities.

Fear

Fear is the normal reaction to threatening stimuli and is very common in everyday life. When fear is greater than warranted by the situation or starts to occur in inappropriate situations, a specific phobia arises, which belongs to the diagnostic entity of anxiety disorders. One distinction between fear in contrast to anxiety is based upon the presence of commonly defined stimuli, a realistic relation between dangerousness and elicited fear, and the potential to cope with or to adapt to the stimulus. Specific phobias are defined as persistent, irrational, exaggerated, and pathological dreads of a stimulus or situation combined with a compelling desire to avoid this feared challenge.

Stress

Stress is regularly experienced by all organisms, and refers generally to physical or psychological stimuli or alterations that are capable of disrupting the homeostasis of one individual or animal. With regard to psychological aspects of stress, predictability, control, and coping skills are important determinants, which, however, are also threatened during anxiety or fear. Hence, anxiety and fear also represent important psychological stressors with their physiological sequelae being similar to stress reactions. The differentiation between stress and fear is difficult in some situations like free speech, since psychological and biological aspects of stress are linked to each other and are mutually interdependent.

Anxiety Disorders

As defined by means of the diagnostic and statistical manual of mental disorders (DSM-V [American Psychiatric Association](#),

2013), anxiety disorders comprise a heterogeneous group, which share *anxiety* as a symptom. However, each of these disturbances has a different etiology and outcome, and different physiological characteristics.

Panic Attacks and Panic Disorder

Panic disorder is characterized by recurrent paroxysmal anxiety, which can even surmount the fear of death during an acute myocardial infarction. These attacks are regularly combined with bodily sensations such as tachycardia, suffocation, shaking, trembling, sweating, abdominal distress, and dizziness. They typically have a sudden onset and are either unpredictable or occur before or during specific situations. The duration of panic attacks is short and ranges between some minutes up to about few hours. If these attacks are affiliated to specific situations, they can lead to avoidance of these specific events and agoraphobia develops, which sustains for longer periods.

Phobias

Phobias are usually differentiated into distinct subtypes: (1) agoraphobia, as frequent sequel of panic disorder, (2) social phobias, and (3) simple phobias. Agoraphobia is the fear of being in situations from which escape is not immediately possible. The symptoms regularly include depersonalization, derealization, dizziness, and cardiac symptoms. Agoraphobia may occur without preceding a panic attack, but remain consolidated between attacks. Social phobias are characterized by the fear that someone may be exposed to a situation where this person is inappropriately scrutinized by others or where this person may behave inadequately. Exposure leads to prominent symptoms of anxiety including bodily alterations, and anticipatory anxiety leads to the avoidance of these situations. Simple phobias are characterized by a persistent fear of a defined object or situation such as fear of spiders or fear of height. The anticipatory anxiety is common and these stimuli are largely avoided, which can impair daily life routines for long periods.

Generalized Anxiety Disorders

This disorder is characterized by excessive worry and by an unspecific, unrealistic, and excessive apprehension about a large variety of future events, which are difficult to control for the person. In addition, symptoms of physiological arousal such as restlessness, autonomic hyperreactivity, sleep disturbances, and muscle tension are characteristics. It has been classified as a chronic disorder lasting longer than 6 months.

Sources of Anxiety in Humans

Anxiety has to be derived from complex origins and interplay of genetic, biological, social, and psychological events and influences. Among the most important factors are the genetic or biological disposition, the developmental and environmental impact upon one individual, and acute stressors and experiences that challenge one person and lead to a variety of adaptational changes.

Genetic and Biological Disposition

Hints for a genetic background of anxiety disorders and indicators for their heritability have been considered as long as for mood disorders, despite the change of diagnostic criteria and labels for different anxiety disorders over the years. Among anxiety disorders, the genetics of panic disorder and generalized anxiety disorder have been most studied. Although panic disorder is the most common anxiety disorder, its underlying etiology is still not well understood. However, several studies have consistently shown that genetic factors explain about half of the variance and that most cases have a complex genetic basis. Existing data suggest that the genetic structures underlying panic disorder seem to be heterogeneous and seem also to differ between cases. The pattern of genes involved might differ in familial versus nonfamilial cases, in early- versus late-onset cases, in different comorbid conditions, but also gender effects and potential subphenotypes have to be considered (Schumacher et al., 2011). From a methodological point of view, family studies, twin studies, linkage and association studies have to be differentiated. Regarding panic disorder, it has been shown that relatives of patients have an increased risk of a similar disturbance. Among relatives a risk of up to 30% is reported, which is significantly different from a lifetime prevalence of about 2% in the general population. Also, twin studies support a heritable component since several studies indicate that the concordance rates for panic disorder are higher in mono- than in dizygotic twins. Linkage studies have been attempted several times, but no single gene loci could be identified. Considering the great complexity of this disorder, it is to be expected that single gene loci are unlikely to be responsible for the diagnostic entity *panic disorder*. However, association studies might lead to the detection of genes responsible for an enhanced vulnerability to anxiety disorders. Interestingly, while single polymorphisms like the transporter for the neurotransmitter serotonin seem to be linked to an altered sensitivity for panic attacks, the respective studies are possibly influenced by selection biases of investigated subjects, which illustrate the complexity of genetic correlations.

Support for a genetic basis of anxiety stems also from preclinical studies. By selective breeding, different lines of rats can be established that differ markedly in their innate anxiety behavior. In genetic knockout, strategies in mice for specific receptors was shown that deficiency of receptors, which are considered to be involved in anxiety and stress reactions, is correlated with a lower innate anxiety behavior. These receptors include particularly the CRF receptor (Steckler and Holsboer, 1999).

Regarding neurogenesis, genetic and epigenetic factors may also regulate the proliferation, survival, and integration of cells into the hippocampus, which is involved in information processing of fearful events. Future studies may therefore elucidate the effect of modulating neurogenesis in animal models of anxiety disorders and the development of proneurogenic compounds may have therapeutic potential (Kheirbek et al., 2012).

Social and Environmental Influences

Although the strong impact of untoward events during childhood is evident, it is worth remembering that simple

relationships cannot be constructed. Besides family conflict situations, several factors such as parental support, child-rearing style, and personality traits have been linked to incidence of anxiety disorders in adolescence. Childhood separation anxiety, childhood parental loss, common stressful events, and major life events were predictive for individual susceptibility to develop panic disorder. Interestingly, also the liability to experience a panic attack after inhaled carbon dioxide as panicogenic agent (see below) was increased (Ogliari et al., 2010).

Prospectively ascertained child maltreatment was associated with anxiety disorders, indicating that maltreatment in fact carries an association of anxiety disorders as well as depression and alcohol abuse (Scott et al., 2010). Besides these factors, age also contributes to the expression of anxiety. Anxiety and anxiety disorders have a higher incidence in adolescence that cannot be reduced only to the use of different diagnostic tools, but seems to be related to other reasons.

Life Events

The amygdala and the prefrontal cortex show structural plasticity. Acute and chronic stress cause (see above) an imbalance of neural circuitries involved in anxiety and mood that can increase or decrease expression of those behaviors. In the short term, during increased fearful vigilance and anxiety in a threatening environment, these changes may be adaptive. However, when the danger passes and the behavioral state persists along with changes in neural circuitries, such maladaptation may require intervention in the case of anxiety disorders (McEwen et al., 2012). In context with environmental and developmental influences, traumatic events, which are regularly out of the realm of normal human experience, are of special importance. A traumatic event can lead to increased anxiety after the event, but may have also long-term effects that emerge with future traumas.

Neuronal Basis of Anxiety

Both the increasingly differentiated analysis of anatomical structures, and biochemical and neurophysiological pathways has led to a more detailed concept about the neurobiology of anxiety and especially of panic attacks.

Neuroanatomical Structures

While fear is one of the best investigated emotions in terms of brain mechanisms, a direct comparison of animal models of fear is limited with respect to the spectrum of human anxiety disorders. It has been proposed that panic disorder involves the same pathways that support conditioned fear in animals. These findings support the theory that panic attacks arise from loci in the brain stem that control especially serotonergic and noradrenergic neurotransmission and respiratory control. In addition, also glutamate receptors seem to play a role in fear memory. Further, it was postulated that anticipatory anxiety arises from kindling of limbic areas and phobic avoidance from precortical activation.

Sensory inputs for conditioned stimuli are mediated through the connection of the anterior thalamus to the lateral

and then to the central nucleus of the amygdala. The amygdala is a structure that plays a prominent role in both fear and anxiety: the two components of the amygdala are the central nucleus of the amygdala and the bed nucleus of the stria terminalis. These regions exhibit a high degree of connectivity and play a central role in generating negative emotional responses like fear and anxiety to environmental or conditioned stimuli (Johansen et al., 2011). Interestingly, besides its role in fear processing, the amygdala is considered as structure that detects salient and personally relevant stimuli in cooperation with ventral and dorsal medial prefrontal cortex with both engaged in the processing of socially relevant stimuli (Fossati, 2012).

The central nucleus of the amygdala coordinates physiological and behavioral responses related to anxiety. Efferents of this nucleus have several targets, for example, the parabrachial nucleus producing an increase in respiratory rate, the lateral nucleus of the hypothalamus activating the sympathetic system, the locus coeruleus resulting in an increase in noradrenalin release with its sequelae of increased blood pressure and heart rate and behavioral fear responses, and the nucleus paraventricularis of the hypothalamus causing an increase in corticosteroids via release of neuropeptides like CRF. As outlined by LeDoux (1998), the overlap between effects of brain stem activation by the central nucleus of the amygdala in animals with physiological effects in humans during panic attacks is striking. Besides these connections, mutual interactions between the amygdala and the thalamus, the prefrontal and the somatosensory cortex are obvious. An impairment of the cortical processing could lead to a misinterpretation of viscerosensory cognitions, leading to the activation of the above-mentioned systems. Because of these complex interactions with the autonomic and endocrine regulation, panic attacks apparently result in equivocal physiological and behavioral sequelae (see below) (Gorman et al., 2000).

Transmitter Systems

At least four monoamine transmitter systems, i.e., the noradrenergic, serotonergic, glutamatergic, and GABA system, are involved since several pharmacological compounds provide therapeutic benefit via respective receptors. However, additional neurotransmitter systems have been proposed to underlie anxiety and fear, such as the endocannabinoid system which gives new challenges to investigators.

From clinical experience, the involvement of the GABA system in anxiety and anxiety disorders seems highly important, and for short-term treatment, ligands at the GABA-A receptor like benzodiazepines are extremely helpful due to their rapid onset of anxiolytic action. However, all GABAergic compounds have more or less sedative properties and may induce tolerance, abuse liability, and withdrawal symptoms.

In the past, for many years the balance between GABAergic and glutamatergic systems was pursued in anxiety research. Decreasing the activity of glutamatergic neurotransmission may attenuate excitation in the CNS, thus resulting also in anxiolysis. Moreover, glutamate (especially NMDA receptors) may be involved, besides in fear acquisition, also in fear extinction, which is important in treatment: modulating glutamate neurocircuitries may result directly in therapeutic effects of cognitive therapies.

Further, the monoamine transmitters, serotonin and noradrenalin, and neuropeptides like CRF are important in the regulation of anxiety and fear. Moreover, serotonin neurons in the raphe nuclei have an inhibitory effect on noradrenergic neurons at the locus coeruleus. In addition, these neurons act at the periaqueductal gray modifying the escape responses and are also thought to inhibit the hypothalamic release of CRF. From a clinical point of view, these findings are supported by therapeutic effects of serotonin reuptake inhibitors. These pharmaceuticals inhibit the uptake of serotonin back into the presynaptic neuron and increase the amount of serotonin in the synapse to bind both to pre- and postsynaptic sites with more than 13 subtypes of serotonin receptors (Kent et al., 1998): a long-term increase of serotonergic transmission by these compounds exerts antipanic and anxiolytic effects.

Another important system is the noradrenergic system (Sullivan et al., 1999). Noradrenalin neurons largely originate in the locus coeruleus and some other nuclei in the medulla and pons. Projection sites include the prefrontal cortex, the amygdala, the hippocampus, the hypothalamus, the thalamus, and the nucleus tractus solitarius. Conversely, the locus coeruleus is innervated by the amygdala. Therefore, the locus coeruleus seems to integrate external sensory and visceral afferents influencing a wide range of neuroanatomical structures related to fear and stress. Clinically it has been proven that, for example, noradrenergic alpha-2 receptor antagonists such as yohimbine can be used to provoke panic attacks acting, whereas clonidine, an alpha-2 adrenergic agonist, exerts anxiolytic-like effects in experimentally induced panic attacks (see below).

All in all it may be summarized that besides serotonin and noradrenalin also glutamatergic and GABAergic transmitters are interacting in complex circuitries, which involve also neuropeptides such as CRF (Arborelius et al., 1999; Koob, 1999). Neurons containing CRF and its receptors have been shown to be distributed throughout the brain, especially the amygdala, the hypothalamus, and the locus coeruleus, and CRF has emerged as a neurotransmitter/modulator that plays a central role not only in stress regulation, but also in anxiety and depression. CRF neurons project from the amygdala to the locus coeruleus. Hence, there are strong hints that CRF could act as a modulator of cognitive and physiological symptoms of anxiety. CRF initiates on one hand a humoral cascade, which enhances via the secretion of corticotropin the release of glucocorticoids, which in turn act at central glucocorticoid and mineralocorticoid receptors. On the other hand, CRF seems directly involved in the modulation of anxiety and depression within the central nervous system. Stress results in increased CRF concentrations in the locus coeruleus and CRF increases the firing rate of noradrenergic neurons. In contrast, noradrenalin also potently stimulates the release of CRF. The involvement of CRF is interesting also with respect to respiratory alterations during panic attacks, which have led to the 'suffocation false alarm theory' (Klein, 1993), since CRF seems to be an important modulator of respiratory centers in the brain stem. Several studies support the contention that antagonists and inhibitors of the synthesis of CRF exert anxiolytic-like effects. Antagonists of CRF receptors have also been examined in clinical trials for their anxiolytic and antidepressant potency.

Since serotonin reuptake inhibitors are involved in the inhibitory regulation of noradrenergic neurons of the locus coeruleus and are thought to reduce the hypothalamic release of CRF, these complex interactions suggest that noradrenergic, serotonergic, and CRF-regulated neurotransmission are linked together with other transmitter circuitries mediating the responses to anxiety, fear, and stress.

Besides CRF, several other neuropeptides are involved in the regulation of anxiety: it was consistently demonstrated that NPY has an inhibitory role in fear acquisition and facilitates fear extinction in animals. In line, also in man abnormally low levels of plasma and cerebrospinal fluid levels of NPY have been found in patients with anxiety disorders (Bowers et al., 2012). Another neuropeptide, i.e., neuropeptide S is of special interest since it exerts anxiolytic effects in animals (Dine et al., 2013), however, effects in humans are still pending.

Models of Anxiety

Anxiety is not merely one of the most important naturally occurring emotions throughout phylogeny and ontogeny, but is also provokable by different means and can then be readily observed under experimental conditions. Both in humans and in animals, a variety of investigations have been conducted, which allow thorough insights into the pathophysiological conditions and the cognitive and neurobiological processes involved in these specific emotional states.

Animal Models

Animal studies in anxiety can be used both for investigating the physiological and anatomical substrates of anxiety and for studying pharmacological strategies for potential anxiolytic or anxiogenic effects (Westenberg et al., 1996). Basically there are three types of animal behavioral models to detect anxiolytic-like effects. They can be classified in two major groups, i.e., conditioned behavior comprising conflict tests and cognitive-based tests, and unconditioned tests, i.e., ethological behavior. Conditioned behavior detects responses controlled by operant conditioning procedures. Unconditioned behavior is mainly based upon naturally occurring behavior and is called an ethological-based model. A different type is separation models, which mainly investigate the behavior of an offspring during separation from its mother and involves the investigation of developmental disturbances.

Conditioned Emotional Responses

The most important conditioned models comprise conflict models where behavior is suppressed by aversive stimulation. The release of the suppressed behavior without altering the levels of punished responding following pharmacological intervention is estimated as the anxiolytic-like effect. Using these models in rodents, for example, benzodiazepines are consistently effective, whereas for other compounds such as serotonin reuptake inhibitors anxiolytic-like effects are difficult to find. Other important models are the fear-potentiated startle response where the startle response of rats is augmented by fear conditioning. During the conditioning phase, another stimulus is presented signaling the presence of, for example, a shock

stimulus. During the startle response, presentation of the stimulus enhances the startle amplitude. Also in this paradigm, benzodiazepines exert anxiolytic effects. In addition to these models, a variety of other conditioned responses and active and passive avoidance reactions can be determined.

Ethological Models

In contrast to the conditioned responses, the ethological models are based upon naturally occurring behavior. The most important and frequently used models are the elevated plus-maze, the open-field, and the dark-light-box models. The elevated plus-maze uses the conflict between exploration and aversion to elevated open places. In this test, anxiety is generated by placing the animal on an elevated open arm, where height and openness rather than light are responsible for anxiogenic effects. The device is shaped as a plus sign with two open arms and two arms enclosed by high walls. The time that rodents spend on the open arms and the number of entries, both, are indicative for anxiolytic-like effects. The open-field test investigates the distance traveled by rodents in a locomotor box within a given time interval. Usually, rodents avoid open areas and try to remain at the edge of the locomotor box. The overall distance traveled and the transitions of the central area of the box are related to the anxiolytic potency by a treatment. The dark-light box uses the number of transitions between a light and a dark, closed compartment as measure of anxiety, since rodents prefer the dark compartment. Peptide-receptor ligands such as CRF (Arborelius et al., 1999) and CCK-4 (Bradwejn and Vasar, 1995) show anxiogenic effects in all three paradigms, whereas other substances such as ANP (Wiedemann et al., 2001) and NPY (Heilig and Widerlöv, 1995) indicate anxiolytic-like effects.

Human Models

The interest in human models of anxiety has been catalyzed to a large extent by findings that panic attacks can be stimulated by a variety of different psychological, physiological, and pharmacological paradigms. Attempts to alter basic anxiety levels and especially those via induction of psychological stress have led to equivocal findings. This might indicate that within the above-mentioned neuroanatomical and physiological systems strong interfering factors exist, which modulate the responses to anxiety and stress.

State and Trait Anxiety

When investigating human anxiety, the distinction between state and trait anxiety is most important and still expanding. State anxiety can be defined as a transitory emotional state consisting of feelings of apprehension, nervousness, and physiological sequelae such as an increased heart rate or respiration (Spielberger, 1979; Endler and Kocovski, 2001). While everyone can experience state anxiety occasionally, there are large differences among individuals in the frequency, duration, and severity. State anxiety can be determined by several rating instruments developed in the past. Trait anxiety represents a fairly stable characteristic related to personality. Experiencing more frequently state anxiety combined with a general view of the world as being threatening and dangerous is used as marker of trait anxiety. The initiation and maintenance of trait anxiety have been related to several factors as outlined above.

Challenge Studies

The profound interest in state anxiety and especially panic attacks stems from a large variety of investigations provoking anxiety and panic attacks experimentally (Nutt and Lawson, 1992). Panic attacks are unique in the spectrum of psychiatric disorders since their core psychopathology of paroxysmal anxiety is temporally limited and can be provoked and investigated under laboratory conditions. Information provided by these studies has led to new cognitive and physiological theories about the basis of panic anxiety and anxiety diseases. Moreover, owing to the experimental character of these investigations, closer comparisons with experiments in animals can be drawn in contrast to other psychiatric animal models. Panic attacks can be elicited by various means, which are listed in Table 1. As indicated, the different paradigms can be differentiated into cognitive, metabotropic, and direct receptor-mediated mechanisms. Especially naturally occurring, cognitive, and metabotropic panic attacks share many features. One of the most amazing findings is that, despite the dramatic anxiety felt, a uniform stress response either of the hypothalamo-pituitary-adrenocortical (HPA, Selye, 1956) or the sympathetic system (Cannon, 1929) is largely missing. These findings led to the hypothesis that in addition to a variety of stimulating agents, strong inhibitors also exist, which physiologically antagonize the altered transmitter and modulator systems involved in panic anxiety. Considering the hypothesis that CRF is one important modulator of anxiety in humans and rodents, it is astonishing that no activation of the HPA system occurs in naturally occurring or metabotropic panic attacks. In contrast, compounds interfering with monoamine and peptide receptors stimulate the HPA activity and the noradrenalin system. Of the latter group, one of the most potent panicogens is CCK-4 (Bradwejn and Vasar, 1995), which seems to exert its effect via CRF. CCK-4 leads dose-dependently to an increase of panic anxiety and a rise of stress hormones. Interestingly, during placebo stimulation following CCK-4 stimulations a psychophysiological conditioning effect could be observed with panic anxiety not accompanied by increases in HPA-axis activity (Hinkelmann et al., 2010). Up to now only a few modulators have been identified, which exert anxiolytic-like

Table 1 Experimentally induced panic attacks

<i>Panicogen</i>	<i>Heart rate stimulation</i>	<i>Respiratory stimulation</i>	<i>HPA stimulation</i>	<i>NE stimulation</i>
Cognitive stimuli	+	+	–	–
<i>Metabotropic agents</i>				
L-Lactate	+	+	–	–
D-Lactate	+	+	–	–
Bicarbonate	–	+	–	–
CO ₂	+/-	+	–	–
<i>Receptor ligands</i>				
Yohimbine	+	–	+	+
Fenfluramine	+	–	+	–
β-Carboline	+	–	+	+
Caffeine	+	+	+	–
CCK-4	+	+	+	(+)
CRF	+	+	+	(+)

HPA, hypothalamo-pituitary-adrenocortical system; NE, noradrenergic system; CCK-4, cholecystokinin tetrapeptide; CRF, corticotropin-releasing factor.

effects and, in addition, are able to inhibit the exaggerated HPA system activity. One of these inhibitors might be ANP, which is secreted in the atria of the heart and in various brain regions involved in anxiety. Hence it may be speculated that peptides such as ANP might help to explain the so far unknown mechanisms of terminating panic anxiety (Wiedemann et al., 2001). Despite a tremendously increased knowledge about the induction of anxiety, fear, and stress, the mechanisms of coping and terminating these emotional alterations need further investigations.

See also: Behavior Therapy: Psychiatric Aspects; Cognitive Behavioral Therapy; Hysteria: History and Critiques; Obsessive-Compulsive Disorder; Psychoanalysis: Current Status; Somatoform Disorders.

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