Neurobiology of Anxiety

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Definition

(on Yahoo web dictionary)

- Anxiety :
  A state of apprehension, ncertainty, and fear res lting from the anticipation of a realistic or fantasized threatening event or sit ation, often impairing physical and psychological f nctioning
- Fear :
  A feeling of agitation and anxiety ca sed by the presence or imminence of danger

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Another definition

(Yahoo Encyclopedia, Columbia university press.)

- **Anxiety**
  anticipatory tension or vague dread persisting in the absence of a specific threat.
  anxiety is generally related to an unconscious threat.
- **Physiological symptoms of anxiety**
  increases in pulse rate and blood pressure, accelerated breathing rates, perspiration, muscular tension, dryness of the mouth, and diarrhea
- **Fear**
  a realistic reaction to actual danger

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Brain structures related to anxiety

- The Amygdala
- Other Mesiotemporal cortical structures
- The sensory thalamus and cortices
- The orbital and medial prefrontal cortex
- The anterior insular
- The hypothalamus and brainstem nuclei

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Amygdala in fear learning

- Rapid response to simple perceptual elements of potentially threatening stimuli
  : monosynaptic projections from the sensory thalamus to the lateral amygdala
- Longer latency responses to more highly processed information about complex sensory stimuli and environmental contexts
  : Projections from sensory association cortices and mesiotemporal structures to the amygdala

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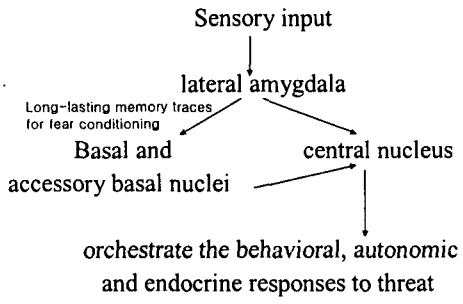
Within amygdaloid complex

(13 nuclei in rats)



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Learning of fear-conditioning

- Amygdala : rapid conditioning of fear response
- Medial temporal lobe : explicit or declarative memories about fear-related event
- Cortex : higher cognitive processing of fear experiences (attentional and mnemonic)

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Mesiotemporal cotical structures

- The perirhinal cortex
  : conveying information about complex visual stimuli to the amygdala during fear conditioning
- The temporopolar cortex
  : modulating autonomic aspects of emotional responses and processing emotionally provocative visual stimuli

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Prefrontal cortical structures

- The medial and orbital PFC : Modulating anxiety and other emotional behaviors
  - Interpreting the higher order significance of experiential stimuli
  - Modifying behavioral responses based upon competing reward vs. punishment contingencies
  - Predicting social outcomes of behavioral responses to emotional events
- Share extensive reciprocal projections with the amygdala

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Medial prefrontal cortex

- Include infralimbic cortex and anterior cingulate cortex (pregenual, subgenual)
- Critical roles in attenuating fear responses and extinguishing behavioral responses to fear-conditioned stimuli
- Pregenual ACC activity : related to anxious state
- Pregenual and subgenual ACC : reciprocal anatomical connections with posterior orbital cortex, amygdala, hypothalamus, NA, VTA, periaqueductal gray, raphe, LC and so on.

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Orbital and anterior insula cortex

- Physiologic activity of these area related to anxious state
- Modulating visceral and behavioral responses ass. with fearful, defensive, and reward-directed behavior

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Posterior cingulate cortex

- Exposure to aversive stimuli of various types activated the retrosplenial cortex and other portions of the post. cingulate cortex

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Neurochemical basis of anxiety

- Monoamine neurotransmitters
  - NE
  - 5-HT
  - Dopamine
- Peptidergic neurotransmitters
  - CRH
  - Neuropeptide Y
  - Substance P
- Amino Acid neurotransmitters
  - GABA
  - Glutamate

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Noradrenergic systems in anxiety

- Exposure to fear-conditioned stimuli (immobilization stress, foot-shock or tail-pinch)

↓

- Increase NE turnover in the LC, hypothalamus, hippocampus, amygdala and the cerebral cortex and firing activity in the LC

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HPA axis and CRH in anxiety

Exposure to acute stress

↓

↑ Release of CRH, ACTH and cortisol

Partial resistance to feedback inhibition of elevated cortisol

Rapid downregulation of GR

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Chronic stress and anxiety

- Adaption or sensitization of glucocorticoid response to chronic stress
- Factor : poorly understood
- Emotional experiences within critical periods of neurodevelopment (prenatal, early postnatal experiences) exert long-term effects on HPA axis function

  : adverse experiences – long-term hypersensitivity of HPA axis

  positive early life experiences – beneficial long-term consequences on the adaptive ability to stress or threat

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Critical period in neural plasticity

- A high degree of plasticity exists in stress-responsive neural systems during the prenatal and early postnatal periods

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Regional differences in the regulation of CRH function

- Acute or chronic administration of CORT

CRH mRNA expression	normal / stress
PVN of hypothalamus	↓ ↑
Ant. pituitary gland	↓ ↓
CE of amygdala, BNST	↑ ↑

- Positive feedback of glucocorticoid on extrahypothalamic CRH function in the amygdala or the BNST (the Bed Nucleus of the stria terminalis)

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CRH receptor subtypes and anxiety

- CRH1 receptor deficient mice :
  diminished anxiety and stress responses
- CRH2 receptor deficient mice :
  heightened anxiety response to stress
- Affinity of CRH is higher for CRH1 than CRH2
- CRH elicits anxiogenic effects
- CRH1 antagonist (antalarmin) inhibits the behavioral, sympathetic autonomic and neuroendocrine responses to acute social stress in monkeys

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Other NT in anxiety disorders

- Abnormalities in HPA axis, CRH, GABA receptor function, 5-HT function
  : inconsistent and inconclusive
- CCK receptor in animal models of anxiety
  - agonist (CCK-4) : anxiogenic
  - antagonist : anxiolytic

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Signal transduction pathways important for learning and memory of fear

- Fig.6 in Rosen et al, 2004

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Conditioned vs. Unconditioned Fear

- Animal studies on anxiety model
  - Pavlovian fear conditioning by pairing lights, tones, contexts and shocks
  - Ecologically, biologically based stimuli and approaches such as exposure to predators and odors from predators

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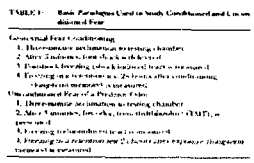
Behavioral paradigms

- Fear-potentiated startle and fear-induced freezing : universal fear responses
- Basic paradigms
  (Table 1 in Rosen et al, 2004)



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Lateral nucleus in the acquisition of fear-conditioning

- Fig. 4 in Rosen et al, 2004

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Conditioned vs. unconditioned fear in lesion of central nucleus

- Fig. 5 in Rosen et al. 2004

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Unconditioned fear and BNST

- Fendt et al, 2003

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A neural circuit in unconditioned fear response

- Ventromedial and premammillary nuclei of the hypothalamus : not confirmative
- The Bed Nucleus of the Stria Terminalis (BNST) : important in unconditioned fear

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Conditioned fear vs. unconditioned fear

- Conditioned fear : may be very labile and extinquised quickly
- Unconditioned fear : not very labile and acquired slowly, via evolutionary and adaptive processes or by repeated or prolonged presentation

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Conclusion

- Amygdala and related brain structures play important roles in fear conditioning and anxiety
- Critical periods may exist in neural plasticity of stress-response systems
- Long-term potentiation may be associated with fear conditioning
- However, there may be differences between the neural networks ass. with conditioned fear and unconditioned fear.

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