Inhibition of the Amygdala: Key to Pathological States?

GREGORY J. QUIRK[a] AND DONALD R. GEHLERT[b]

[a]*Department of Physiology, Ponce School of Medicine, Ponce, Puerto Rico, 00732-7004*

[b]*Lilly Research Laboratories, Indianapolis, Indiana 46285, USA*

ABSTRACT: **The amygdala plays an important role in associating sensory stimuli with aversive or appetitive outcomes. Conditioning procedures potentiate inputs to the amygdala, which facilitate emotional responses via subcortical and cortical outputs. Powerful inhibitory circuits exist that control expression of conditioned responses in the amygdala, including inhibition from prefrontal cortex. Deficient inhibitory tone in the amygdala could lead to overexpression of conditioned responses, producing pathological states such as anxiety disorders and drug-seeking behavior. Support for this comes from several lines of animal research: (1) GABA antagonist-induced priming of anxiety states, (2) extinction of conditioned fear, (3) modulation of inhibitory avoidance memory, and (4) cue-induced reinstatement of drug seeking. Cue-induced craving in humans is associated with feelings of fear and autonomic arousal, suggesting a link between fear and addiction in the amygdala. Future therapies aimed at increasing inhibitory tone in the amygdala, either locally or via the prefrontal cortex, may prevent anxiety disorders and addiction relapse. Novel neuropeptides, which can either excite or inhibit specific components of anxiety responses, offer promise in this regard.**

KEYWORDS: **amygdala; conditioning; response; behavior; drug seeking; GABA; anxiety; conditioned fear; avoidance; craving; addiction; neuropeptides**

Much of the work in the amygdala in the last two decades has focused on its ability to link sensory stimuli with affective outcomes and initiate emotionally appropriate behavior. The amygdala appears to be involved in learning aversive[1–5] as well as appetitive[6,7] associations. There is no doubt that such associations are important for survival, and some, in fact, may be genetically determined.[8] However, expression of emotional associations is not always appropriate and may be disadvantageous in certain situations. For example, a "fight or flight" response to a conditioned stimulus, with its associated hormonal, autonomic, and behavioral changes, would be pathological in situations in which danger is unlikely, such as during extinction.

Address for correspondence: Gregory J. Quirk, Ph.D., Department of Physiology, Ponce School of Medicine, P.O. Box 7004, Ponce, Puerto Rico 00732-7004. Voice: 787-813-1883; fax: 787-841-1040.

gjquirk@yahoo.com

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Thus, the expression of emotional associations stored in the amygdala must be tightly controlled and gated by contextual[9] and other cues. Accordingly, interest in the inhibitory mechanisms that control the expression of amygdala-based associations is increasing.[10] As emphasized by LeDoux,[11] failure in these inhibitory control mechanisms can lead to "overexpression" of conditioned associations, which could appear as the pathological states we know as anxiety disorders and addiction. Thus, understanding the mechanisms that control the expression of emotional associations in the amygdala could be an important step in advancing therapies for a variety of mental disorders.[12]

CLASSICAL CONDITIONING POTENTIATES AMYGDALA CONNECTIONS

Pairing discrete sensory or contextual stimuli with aversive or appetitive unconditioned stimuli leads to potentiation of amygdala inputs, especially in the basolateral complex (lateral and basal nuclei, BLA). In fear conditioning, tones or lights are often paired with footshocks. Plasticity in the sensory responses of lateral amygdala neurons during fear conditioning has been demonstrated in behaving animals[13–17] and in brain slices from fear-conditioned rats.[18] In addition to potentiating tone responses, fear conditioning also elevates spontaneous firing rates in anticipation of the shock[14] and can potentiate intra-amygdala connections.[15] These findings suggest that learned fear states are accompanied by increases in amygdala excitability, especially in the lateral nucleus. Once potentiated, lateral nucleus neurons excite basolateral and central nucleus neurons, whose outputs mediate autonomic and behavioral fear responses.[19,20]

It has been suggested that conditioned fear associations are indelible, based on the observation that cortical lesions prevent extinction of conditioned fear.[21] In fact, recent evidence shows that memory for conditioned fear to tones and contexts last the lifetime of the animal (see Fanselow and Gale, this volume). If true, powerful inhibitory processes must exist in the amygdala that prevent expression of conditioned responses at inappropriate times and in inappropriate contexts.

ANXIETY AND PANIC

The physiology of GABAergic inhibitory circuits within the amygdala has been elegantly demonstrated by Paré and colleagues[22] (see also Paré *et al.*, this volume). The spontaneous firing rates of lateral and central nucleus neurons are some of the lowest in the brain,[14,15,23] suggesting pronounced inhibition. The behavioral effects of blocking this inhibition are readily apparent when GABA antagonists are microinjected into the amygdala. This approach has been explored extensively by Shekhar and colleagues, using a modified social interaction test, a validated model of anxiety-like behavior (see Shekhar, this volume). In early studies, infusions of the benzodiazepine antagonist flumazenil and the $GABA_A$ receptor antagonist bicuculline (BMI) were found to block the anxiolytic-like actions of systemically administered chlordiazepoxide.[24] These studies established the importance of inhibitory transmission within the BLA for the efficacy of anxiolytic compounds.

Subsequent studies have illustrated the importance of inhibitory neurotransmission in the normal functioning of the BLA. Infusion of BMI into the BLA of rats produced a dose-dependent reduction in social interaction. The investigators then explored the effects of repeated "subthreshold" doses of BMI on behavior.[25] When repeated over a period of 5 days, the animals exhibited an anxiety-like response to the fifth dose. In addition to decreased social interaction, animals also exhibited an increase in heart rate and blood pressure, consistent with a clinical anxiety episode in patients.[25] No changes in EEG were noted in this experimental paradigm, which was described as "priming" to differentiate it from the epileptogenic "kindling." These $GABA_A$-mediated effects can be reversed by blocking excitatory transmission in the BLA,[26,27] thus confirming the importance of inhibitory transmission in the normal regulation of BLA excitability.

The priming effect obtained with subthreshold doses of GABA antagonists suggests that blocking inhibitory transmission in the BLA induces intra-amygdala plasticity, which can lead to increased fear and anxiety. Primed rats also have a lower threshold for developing autonomic and behavioral anxiety responses when infused with sodium lactate.[28] In the clinic, sodium lactate initiates panic attacks in patients with panic disorder, suggesting that a priming-like effect may be operating in the amygdala of these patients. Thus, a loss of inhibitory tone could underlie panic attacks and other anxiety disorders.

EXTINCTION OF CONDITIONED FEAR

Another example of the importance of inhibition of fear is found during extinction, when the conditioned stimulus no longer predicts the unconditioned stimulus. Behavioral experiments since the time of Pavlov[29] have suggested that extinction does not erase the conditioned association, but forms a new memory that inhibits expression of the conditioned response. Deficits in extinction of conditioned fear have been proposed as a basis for the sustained anxiety responses seen in posttraumatic stress disorder (PTSD) and treatment-resistant phobias.[30,31]

An important question is, what are the structures that learn extinction of conditioned fear and inhibit the amygdala's output? Work from Davis and colleagues suggests that the amygdala itself learns extinction via an NMDA receptor-dependent mechanism (see Davis *et al.*, this volume). Cortical inputs to the amygdala have also been implicated in extinction. For example, lesions of the medial prefrontal cortex prevent recall of extinction learning.[15,32,33] Rats with damage to the ventral medial prefrontal cortex (infralimbic and prelimbic areas) acquired conditioned freezing to a tone normally and could extinguish their freezing responses the same day.[34] The next day, however, freezing responses spontaneously recovered to maximal levels as if rats had never received extinction (FIG. 1A). A deficit in long-term, but not short-term, extinction memory suggests that the ventral medial prefrontal cortex may be involved in consolidation and/or storage of extinction memory. Consistent with this hypothesis, infralimbic neurons recorded in this same paradigm show no tone responses during either conditioning or extinction phases of training (Milad and Quirk[65]). The next day, however, when rats must recall extinction learning, infralimbic neurons show robust tone responses consistent with the hypothesis that infralimbic cortex signals memory for extinction (FIG. 1B).

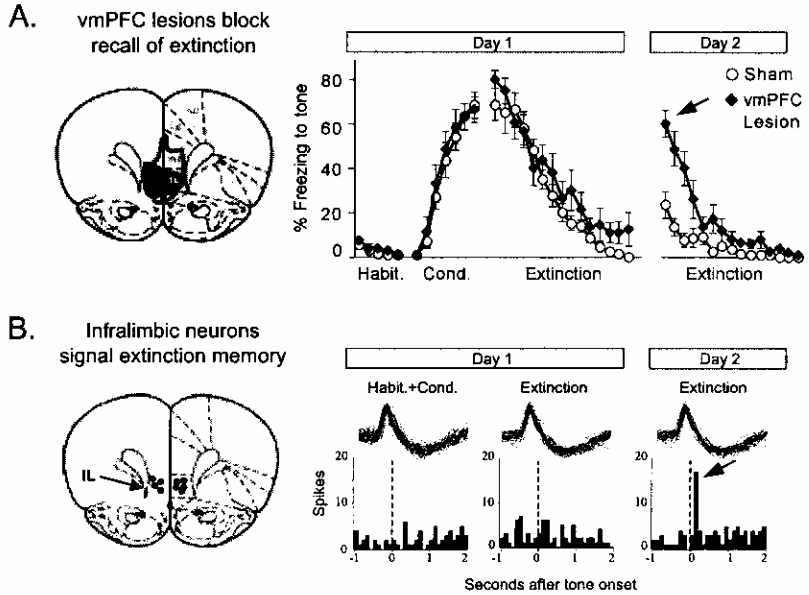

FIGURE 1. The infralimbic cortex (IL) plays a role in recall of extinction of conditioned fear. (**A**) Lesions of ventral medial prefrontal cortex (prelimbic and infralimbic areas) have no effect on acquisition or extinction of conditioned freezing to a tone paired with footshock, but they prevent recall of extinction the following day (adapted from Ref. 34). (**B**) Paralleling these lesion findings, a representative IL neuron does not respond to tones during either conditioning or extinction sessions, but it shows a robust tone response the following day when the rat is recalling extinction. This suggests that IL neurons signal memory for extinction of conditioned fear. (Adapted from Ref. 65.)

Infralimbic neurons could reduce the expression of fear via robust projections to the amygdala[35] and/or direct projections to freezing centers in the periaqueductal gray.[36] Of particular interest is the projection from infralimbic to the capsular division of the central nucleus of the amygdala.[35] FIGURE 2 is an adaptation of a figure by McDonald and colleagues, showing an anterograde label in the amygdala following injection of PHL-A in infralimbic cortex. The capsular division of the central nucleus contains GABAergic intercalated cells that have been shown to exert powerful inhibitory control over central nucleus neurons that project out of the amygdala (see Paré *et al.*, this volume). Infralimbic input to intercalated cells could be a pathway by which infralimbic tone responses reduce freezing. Further physiological and anatomical studies are needed to determine if infralimbic axons actually make contact with intercalated cells. If so, deficient activity in infralimbic and other parts of the medial prefrontal cortex might explain the exaggerated fear responses seen in PTSD. In support of this, PTSD patients show abnormally low medial prefrontal cortex activity together with abnormally high amygdala activity, when reexposed to

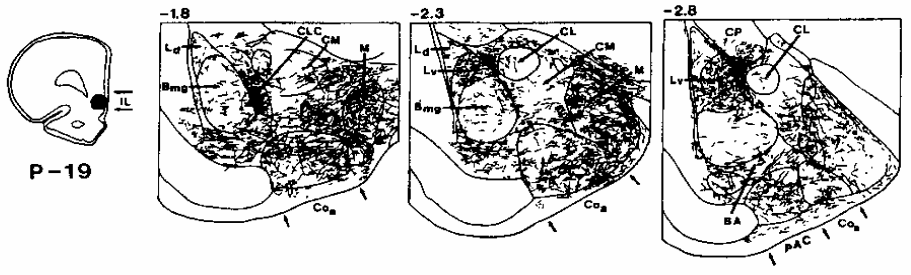

FIGURE 2. The work of McDonald and colleagues showing anterograde label in the rat amygdala following an injection of the tracer PHL-A in the infralimbic cortex. Note the dense labeling of fibers in the capsular region of the central nucleus (CLC), which contains GABAergic intercalated cells that inhibit central nucleus output. Ld, dorsolateral subdivision of the lateral nucleus; Bmg, basal magnocellular nucleus; CLC, lateral capsular subdivision of the central nucleus; CM, medial subdivision of the central nucleus; M, medial amygdala; Co, cortical amygdala. (Adapted with permission from Ref. 35.)

traumatic reminders,[37,38] supporting the idea that the amygdala is not sufficiently inhibited by the prefrontal cortex in PTSD.

CONSOLIDATION OF TRAUMATIC MEMORIES

The amygdala has extensive ascending projections to the striatum and neocortex, directly and via the cholinergic basal nuclei. Extensive evidence collected by McGaugh[39] and colleagues has demonstrated that the amygdala is responsible for enhancing memory consolidation during periods of emotional arousal (see McIntyre *et al.*, this volume). Norepinephrine released from the adrenal medulla during stress activates vagal afferents that stimulate noradrenergic release in the basolateral amygdala via brain-stem ascending systems.[39] Activation of β-adrenergic receptors in the BLA is necessary for long-term retention of inhibitory avoidance, in which a rat must learn to avoid entering a chamber in which it received shock. Water-maze learning is similarly enhanced by β-adrenergic activation in the amygdala,[40] suggesting that the memory-enhancing effect of norepinephrine generalizes to other forms of memory. In addition to norepinephrine, the adrenal gland releases glucocorticoids during stress that enhance noradrenergic effects in the BLA by facilitating the cAMP cascade triggered by β-adrenergic activation.[41] Thus, McGaugh and colleagues suggested that the BLA acts as a bridge between the peripheral arousal systems and brain regions involved in memory consolidation.

In humans, emotionally arousing scripts are better remembered than nonemotional scripts, and this memory-enhancing effect is blocked with β-receptor antagonists.[42] Recall of emotional information is correlated with amygdala activity at the time of encoding, as revealed by PET.[43] Whereas increased memory for emotional events is adaptive, a disinhibited amygdala could result in overconsolidation of trau-

matic memories with pathological consequences. Inhibiting noradrenergic activation associated with trauma might prevent the development of PTSD.[44]

DRUG ADDICTION

In addition to aversive learning, the amygdala is also importantly involved in appetitive learning. Lesions of the BLA block conditioned reinforcement, second-order pavlovian and instrumental responding, reevaluation of food rewards, and conditioned place preference (for reviews, see Refs. 6 and 45 and Everitt, this volume). Pairing sensory stimuli with appetitive outcomes such as sucrose or rewarding brain stimulation increases the sensory responses of lateral and basolateral amygdala neurons.[46,47] Involvement in appetitive conditioning suggests a possible role of the amygdala in addiction. See and colleagues have used cue-induced reinstatement of drug seeking to study the role of the BLA in addiction (see See *et al.*, this volume). Rats learn to self-administer cocaine in the presence of cues that predict drug availability. Once self-administration is extinguished by pairing bar-presses with saline instead of drug, pressing can be reinstated with drug-associated cues. The ability of drug-associated cues to reinstate drug seeking is blocked by lesions[48] or inactivation[49] of the BLA. Interestingly, manipulations of the BLA have no effect on cocaine self-administration, suggesting that the role of BLA is to form drug-cue associations rather than to mediate the rewarding effects of the drugs themselves.

Recent data from human studies is consistent with the notion that relapse may be due to an overactive amygdala, deprived of sufficient inhibition from the prefrontal cortex. Using PET imaging, researchers found increased activation of the amygdala together with inactivation of the medial prefrontal cortex in cocaine addicts re-exposed to drug-associated cues.[50,51] Furthermore, cocaine patients exhibit reduced gray matter in the ventral medial prefrontal cortex, relative to non-cocaine-exposed individuals.[52] Building on their functional imaging data, Childress and colleagues are using the $GABA_B$ agonist baclofen to reduce cue-induced craving as well as the amygdala overactivity seen in cocaine patients (see Childress *et al.*, this volume). Thus, augmenting inhibitory tone in the amygdala may hold promise as treatment for relapse.

FEARFUL ADDICTS?

These data suggest that potentiation of connections within the BLA are responsible for drug-seeking behavior. This resembles the models of amygdala involvement in fear and anxiety just summarized. If plasticity in the amygdala is involved in both addictions and conditioned fear, are there any data linking the two? Interestingly, states of cocaine craving in humans are accompanied by feelings of anxiety and fear as well as increases in heart rate and cortisol levels.[53] Footshocks can reinstate drug-seeking behavior,[54] and amygdala lesions block this effect.[55] Dopamine D1 receptors in the BLA are necessary for both cue-induced reinstatement[56] and second-order fear conditioning.[57] Finally, cocaine users have an increased incidence of panic attacks.[58] Taken together, these observations suggest that emotional associations formed in the amygdala may be responsible for triggering pathological behavior

such as drug seeking and persistent anxiety, if they are not sufficiently inhibited. They also suggest the possibility of "cross-talk" between fear and addiction within amygdala circuits.

It is well established that benzodiazepines, which act by potentiating GABAergic transmission, reduce anxiety in experimental models when injected into the BLA.[59] This corresponds to the high density of benzodiazepine binding sites in the amygdala, especially in the BLA.[60] Recently, it was demonstrated that neuropeptides are important in regulating BLA excitability. For example, infusion of the excitatory peptides CRF and urocortin into the BLA reduces social interaction latency.[61] Unlike $GABA_A$ receptor blockade, urocortin does not alter heart rate or blood pressure,[62] suggesting the existence of separate processing channels for behavioral versus autonomic anxiety responses in the BLA. By contrast, the inhibitory peptide neuropeptide-Y acts as an anxiolytic when infused into the BLA.[63,64] Strategies to block excitatory tone using a CRF antagonist or to enhance neuropeptide-Y–mediated inhibitory tone may facilitate extinction and reduce subsequent pathology. Given the wealth of neuropeptides expressed in the amygdala, our understanding of the importance of these systems is currently in its infancy. Thus, a better understanding of the action of these neuropeptides may lead to more-targeted therapies able to inhibit the specific components of amygdala-linked pathologies.

CONCLUSION

During arousing and emotionally charged situations, the basolateral amygdala encodes associations between sensory stimuli and emotional outcomes. Emotional associations stored in the amygdala are in a position to trigger behavioral responses via subcortical and cortical projections. The amygdala also exerts a powerful influence on the storage of emotional memories in other structures. Emotional learning situations are accompanied by potentiation of connections to and within the amygdala, especially in the basolateral complex. Adequate levels of inhibition may be required to prevent expression of emotional associations at inappropriate times or in inappropriate contexts. A reduction in inhibitory tone in the amygdala, either generated intrinsically or due to decreased activity of prefrontal inputs, may lead to pathological expression of conditioned responses in both aversive and appetitive domains.

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