Are Different Parts of the Extended Amygdala Involved in Fear versus Anxiety?

Michael Davis

Although there is a close correspondence between fear and anxiety, and the study of fear in animals has been extremely valuable for understanding brain systems that are important for anxiety, it is equally clear that a richer animal model of human anxiety disorders would include measures of both stimulus-specific fear and something less stimulus specific, more akin to anxiety. Studies in patients with posttraumatic stress syndrome indicate these individuals seem to show normal fear reactions but abnormal anxiety measured with the acoustic startle reflex. Studies in rats, also using the startle reflex, indicate that highly processed explicit cue information (lights, tones, touch) activates the central nucleus of the amygdala, which in turn activates hypothalamic and brain stem target areas involved in specific signs of fear. Somewhat less explicit information, such as that produced by exposure to a threating environment for several minutes or by intraventricular administration of the peptide corticotropin-releasing hormone may activate a brain area closely related to the amygdala, called the bed nucleus of the stria terminalis, which in turn activates hypothalamic and brain stem target areas involved in specific signs of fear or anxiety. Because the nature of this information may be less specific than that produced by an explicit cue, and of much longer duration, activation of the bed nucleus of the stria terminalis may be more akin to anxiety than to fear. Biol Psychiatry 1998;44:1239–1247

Key Words: Startle, bed nucleus of the stria terminalis, conditioning

Introduction

Over the last several years, our laboratory has been studying how a simple reflex, the acoustic startle reflex, can be modified by prior emotional learning. Thus far, most of our work has concentrated on an experimental paradigm called the *fear-potentiated startle effect*, where the amplitude of the startle reflex in rats can be modified by a state of fear. More recently, however, we have found that other treatments, such as prolonged exposure to a bright light, also increase startle amplitude. Because this effect has a relatively slow onset and rate of decay, does not depend on prior conditioning, and is blocked by drugs that reduce anxiety in people, we have suggested that this *light-enhanced startle effect* may be more similar to anxiety than to fear. Moreover, we are finding that different parts of the brain may be important for fear-potentiated startle vs. light-enhanced startle, and, by inference, fear vs. anxiety.

The Fear-Potentiated Startle Effect

When the startle reflex is elicited by a loud sound 3–4 sec after a light has been turned on, there is no systematic change in the amplitude of the startle reflex; however, if the day before, or even a month before, the light had come on 3–4 sec before a shock for a few times, startle will be potentiated when elicited 3–4 sec after the light comes on. This fear-potentiated startle effect (first described by Brown et al 1951) only occurs following prior light–shock pairings and not when lights and shocks have been presented in an unpaired or "random" relationship (Davis and Astrachan 1978), indicating its dependence on prior Pavlovian fear conditioning. When the eyeblink component of the startle reflex is measured in humans, fear-potentiated startle can be produced using very similar conditioning procedures to those we use in rodents (Grillon and Davis 1997). If the light is presented over and over again, without further light–shock pairings, it no longer increases startle (Falls et al 1992), indicative of extinction of prior fear conditioning. This effect probably indicates that the light produces a state of fear that increases reflexive behavior, because drugs like diazepam or buspirone, which reduce fear in humans, block the increase in startle in the presence of the light but do not systematically alter startle in the absence of the light when appropriate doses are used (see Davis et al 1993 for review).

The Light-Enhanced Startle Effect

When the startle reflex is elicited by a loud sound 5–20 min after a bright light has been turned on, there is an increase in the startle reflex (Walker and Davis 1997a).

From the Ribicoff Research Facilities of the Connecticut Mental Health Center and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Dr. M. Davis, Emory University School of Medicine, 1639 Pierce Drive, Suite 4000, Atlanta, GA 30322.

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This effect also is significantly decreased by drugs like buspirone (Walker and Davis 1997b) and chlordiazepoxide (Walker and Davis, unpublished observations). This may indicate an unconditioned anxiogenic effect of bright light that enhances startle, consistent with several other behavioral measures (Crawley 1981; File 1980; see Walsh and Cummins 1976 for review). Recently, we have found that humans show a significant increase of startle amplitude (i.e., of the eyeblink response) in the dark (Grillon et al 1997). The species difference may reflect fear of the light in a nocturnal species (rats) compared to fear of the dark in a diurnal species (humans). When the lights are suddenly turned off, many people feel more anxious, especially if they were afraid of the dark when they were young (Grillon et al 1997). In patients with posttraumatic stress disorder, startle is increased in the dark to a greater degree than that seen in combat control subjects (Grillon et al in press). These individuals report that the darkness makes them think of being back at their guardpost in Vietnam and anxious about being hit by an incoming mortar.

As far as we can tell, light-enhanced startle in rats does not depend on prior conditioning. Moreover, at least in rats, this method of increasing startle does not extinguish, because it does not decrease in magnitude either within or across several test sessions (Walker and Davis 1997a). Hence, this method of increasing startle seems to reflect an unconditioned, rather than a conditioned, anxiogenic effect. It is less certain whether dark-enhanced startle in people results from prior conditioning, although explicit conditioning in the laboratory is not required to see this phenomenon.

Corticotropin-Releasing Hormone (CRH)-Enhanced Startle

Intraventricular administration of the peptide CRH produces a variety of behavioral and neuroendocrine effects similar to those seen during fear and anxiety. Intraventricular administration of the CRH antagonist alpha-helical CRH_{9-41} blocks the behavioral and neuroendocrine effects of natural stressors or conditioned fear (Dunn and Berridge 1990). (Swerdlow et al 1986) reported that intraventricular administration of CRH increased the acoustic startle reflex and that this effect could be blocked by the benzodiazepine chlordiazepoxide, suggesting that the excitatory effect of CRH on startle reflected an anxiogenic effect of the hormone. We have confirmed and extended this work showing that intraventricular infusion of CRH (0.1–1.0 μg) produced a pronounced, dose-dependent enhancement of the acoustic startle reflex in rats (Liang et al 1992b) that lasts for several hours. This effect still occurs after adrenalectomy, indicating that it is not dependent on the release of corticosterone from the adrenal glands (Lee et al 1994). Thus CRH-enhanced startle represents yet another example of a long-lasting, unconditioned, anxiogenic effect.

The Primary Acoustic Startle Pathway

One of the advantages of using the startle response is that these different conditioned and unconditioned anxiogenic effects are being measured by modification of a simple reflex, which has a nonzero baseline. The nonzero baseline is important because potentially it allows one to separate the effects of a treatment on the hypothetical state of interest (e.g., fear) from the effects of the treatment on the response that is used to measure that hypothetical state. For example, although freezing is a sensitive measure of fear, it is only measurable during a state of fear. Thus if some treatment blocks freezing it is concluded that it blocks fear; however, that treatment might simply prevent animals from holding still, without actually affecting fear itself.

The other advantage of using a reflex is that it can be elicited by a stimulus that is controlled by the experimenter so that different response levels can be produced. If some treatment reduces or increases the reflex response, the experimenter can increase or decrease the loudness of the startle stimulus to produce a response level in the treatment condition equivalent to that in the control condition, allowing assessment of fear or anxiety at equivalent parts of the measurement scale.

Finally, because reflexes generally have short latencies, it is possible to determine the neural pathway that mediates the reflex, which can then serve as a starting point to determine the neural pathways involved in fear or anxiety. In fact, the extraordinary short latency of the acoustic startle reflex (e.g., 8 msec measured electromyographically in the hindleg) means that it must be mediated by a simple neural pathway. In 1982, our laboratory proposed that acoustic startle was mediated by four synapses; three in the brain stem (the ventral cochlear nucleus; an area just medial and ventral to the ventral nucleus of the lateral lemniscus; and the nucleus reticularis pontis caudalis) and one synapse onto motoneurons in the spinal cord (Davis et al 1982). Electrolytic lesions of these nuclei eliminated acoustic startle and single pulse electrical stimulation of these nuclei elicited startlelike responses with a progressively shorter latency as the electrode was moved farther down the startle pathway. Furthermore, local infusion of excitatory amino acid antagonists such as AP5 into the area just medial and ventral to the ventral nucleus of the lateral lemniscus markedly decreased acoustic startle amplitude (Spiera and Davis 1988).

Because electrolytic lesions of the area just medial and

ventral to the ventral nucleus of the lateral lemniscus eliminated the acoustic startle reflex, we concluded that this area must be part of a primary acoustic startle pathway (Davis et al 1982). When we did the initial work on this project techniques were not yet available to selectively destroy cells vs. cells plus fibers passing through the area of the lesion. By using newly developed techniques that allowed selective destruction of cell bodies without a concomitant loss of fibers of passage, we now believe that a synapse, obligatory for the startle reflex, does not exist at this level of the brain stem. First, while very discrete *N*-methyl-D-aspartate (NMDA)-induced lesions of cell bodies in the nucleus reticularis pontis caudalis completely eliminated startle, NMDA-induced lesions of the ventral nucleus of the lateral lemniscus or the area just ventral and medial to it did not, provided the lesion did not extend to the nucleus reticularis pontis caudalis (Lee et al 1996). Second, local infusion of the NMDA antagonist DL-2-amino-5-phosphonopentanoic acid (AP5) into the nucleus reticularis pontis caudalis reduced startle by 80–90% (Miserendino and Davis 1993), at doses 1/60 of those that depressed startle after infusion into the area of the ventral lateral lemniscus (Spiera and Davis 1988). Moreover, comparably low doses of the non-NMDA antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) also depressed startle after local infusion into the nucleus reticularis pontis caudalis (Miserendino and Davis 1993), but had no effect when infused into the area of the ventral lateral lemniscus, even using much higher doses (Lee and Davis, unpublished). Hence, we believe that the depressant effects produced by excitatory amino acid antagonists infused into the area of the ventral lateral lemniscus (Spiera and Davis 1988) resulted from spread to the nearby nucleus reticularis pontis caudalis (about 1 mm caudal) and that, if there is a synapse here, it does not use excitatory amino acids acting on a known receptor subtype.

All the data still pointed to the critical importance of the nucleus reticularis pontis caudalis in the acoustic startle reflex. Recent evidence indicates that auditory input gets to the nucleus reticularis pontis caudalis via projections from cochlear root neurons. These are very large cells (35 μm in diameter) embedded in the cochlear nerve in rodents (about 20 on each side) and humans, called "cochlear root neurons" (see Lopez et al 1993 for a review). These neurons receive direct input from the spiral ganglion cells in the cochlea, making them the first acoustic neurons in the central nervous system. They send exceedingly thick axons (sometimes as wide as 7 μm) through the trapezoid body, at the very base of the brain, directly to an area just medial and ventral to the lateral lemniscus and continue on up to the deep layers of the superior colliculus; however, they give off thick axon collaterals that terminate directly in the nucleus reticularis pontis caudalis (Lingenhohl and Friauf 1994; Lopez et al 1993) exactly at the level known to be critical for the acoustic startle reflex onto cells that then project to motoneurons in the spinal cord (Lingenhohl and Friauf 1994).

Bilateral, chemically induced lesions of the cochlear root neurons essentially eliminate acoustic startle in rats. Thus far there has been an excellent correlation between the number of root neurons destroyed and the decrease in startle (Lee et al 1996). In animals with only unilateral cochlear root neuron damage there was a preferential loss of the ipsilateral pinna reflex, and a partial decrease in whole body startle. In animals with bilateral damage to the cochlear root neurons there was a marked decrease in whole body startle and the pinna reflex on both sides. Although damage to the auditory root, where the cochlear root neurons reside, has not been fully ruled out, other tests indicated that these animals could clearly orient to auditory stimuli (e.g., suppression of licking) and had normal compound action potentials recorded from the cochlear nucleus (Lee et al 1996).

Although there is some disagreement (Frankland et al 1995), we now believe that the acoustic startle pathway may be simpler than we had originally thought, consisting of only three synapses onto 1) cochlear root neurons; 2) neurons in the nucleus reticularis pontis caudalis; and 3) motoneurons in the facial motor nucleus (pinna reflex) or spinal cord (whole body startle; Figure 1).

Differential Effects of Inactivation of the Amygdala vs. the Bed Nucleus of the Stria Terminalis on Fear-Potentiated Startle, Light-Enhanced Startle, and CRH-Enhanced Startle

The Role of the Amygdala in Fear-Potentiated Startle

In addition to its role in appetitive (Cador et al 1989; Everitt et al 1989) and attentional processes (e.g., Gallagher and Holland 1992; Kapp et al 1992), converging evidence now indicates that the amygdala, and its many efferent projections, may represent a central fear system involved in both the expression and acquisition of conditioned fear (Davis 1992; Gloor 1960; Gray 1989; Kapp and Pascoe 1986; Kapp et al 1984; LeDoux 1987; Sarter and Markowitsch 1985). The amygdala receives highly processed sensory information from all modalities through its lateral and basolateral nuclei. In turn, these nuclei project to the central nucleus of the amygdala, which then projects to a variety of hypothalamic and brain stem target areas that directly mediate specific signs of fear and anxiety (cf. Davis 1992). Electrical stimulation of the

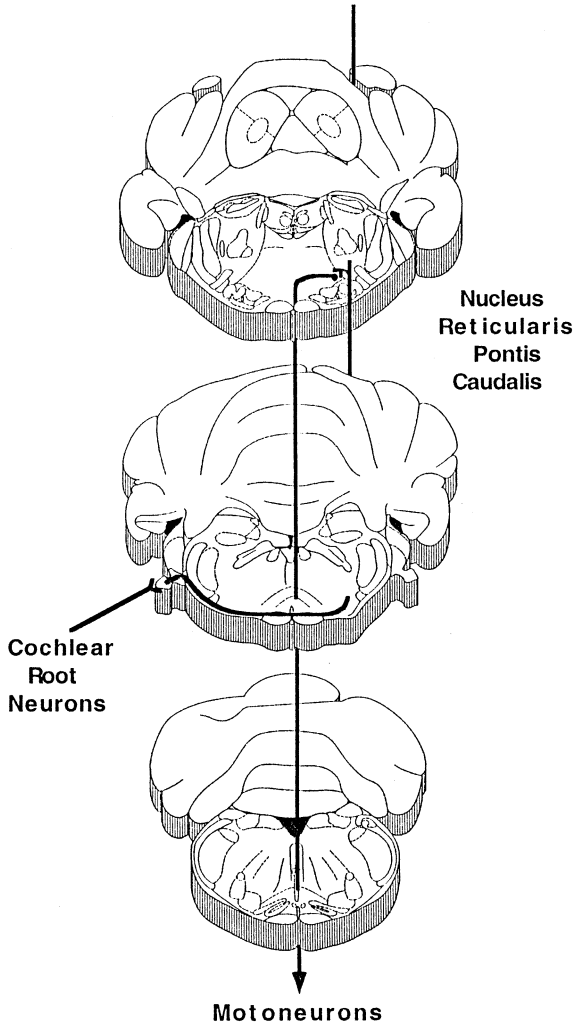

Figure 1. Schematic diagram of the primary acoustic startle pathway in the rat. (From Lee et al 1996 with permission from the Society for Neuroscience.)

amygdala elicits many of the behaviors used to define a state of fear, whereas stimulation of selected target areas of the amygdala produces more selective effects. Conditioned fear may result when a formerly neutral stimulus now comes to activate the amygdala by virtue of pairing that stimulus with an aversive event.

Lesions of the central nucleus of the amygdala block the expression of fear-potentiated startle using either a visual (Hitchcock and Davis 1986) or auditory conditioned stimulus (Campeau and Davis 1995; Hitchcock and Davis 1987). Blockade of glutamate receptors in the central nucleus of the amygdala via local infusion of a non-NMDA glutamate receptor antagonist has a similar effect (Kim et al 1993). The central nucleus of the amygdala projects directly to the nucleus reticularis pontis caudalis (Rosen et al 1991), and lesions at several points along this pathway blocked the expression of fear-potentiated startle (Hitchcock and Davis 1991). Both conditioned fear and sensitization of startle by footshocks appear to ultimately modulate startle at the level of the nucleus reticularis pontis caudalis (Berg and Davis 1985; Boulis and Davis 1989; Krase et al 1994). Selective destruction of cell bodies via local infusion of neurotoxic doses of NMDA into the lateral and basolateral nuclei caused a complete blockade of fear-potentiated startle when the lesions were made either before or after training (Sananes and Davis 1992). All animals had sparing of the central nucleus of the amygdala. This blockade of fear-potentiated startle did not seem to result from a disruption of vision, and other studies found that NMDA-induced lesions of these amygdaloid nuclei also blocked fear-potentiated startle using an auditory conditioned stimulus (Campeau and Davis 1995). These results are consistent with other work that indicates that the lateral nucleus of the amygdala provides a critical link for relaying auditory information involved in fear conditioning to the amygdala (LeDoux et al 1990).

Because the central nucleus of the amygdala projects directly to the nucleus reticularis pontis caudalis (Rosen et al 1991) and lesions at several points along this pathway blocked the expression of fear-potentiated startle (Hitchcock and Davis 1991), we suggested that this direct pathway may mediate both fear potentiated startle and sensitization of startle produced by prior footshocks (Hitchcock and Davis 1991; Hitchcock et al 1989); however, those studies only used electrolytic lesions of the amygdalofugal pathway at several levels including the ventrolateral central gray so that obligatory synapses at points along this pathway could not be ruled out (Hitchcock and Davis 1991). Recent data now suggest that a synapse between the amygdala and central gray may be required for both fear-potentiated startle and shock sensitization because fiber sparing chemical lesions of the central gray have been reported to block both phenomena (Fendt et al 1996; Franklin and Yeomans 1995).

Effects of Glutamate Antagonists Infused into the Bed Nucleus of the Stria Terminalis vs. the Amygdala on Light-Enhanced Startle

Because, as mentioned above, local infusion of glutamate antagonists into the central nucleus of the amygdala completely blocks the expression of fear-potentiated startle (Kim et al 1993), we wondered whether this treatment would also block light-enhanced startle. As a control, we measured the effects of local infusion of glutamate antagonists into the bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis is considered to be part of the so-called extended amygdala because it is highly similar to the central nucleus of the amygdala in terms of its transmitter content, cell morphology, and efferent

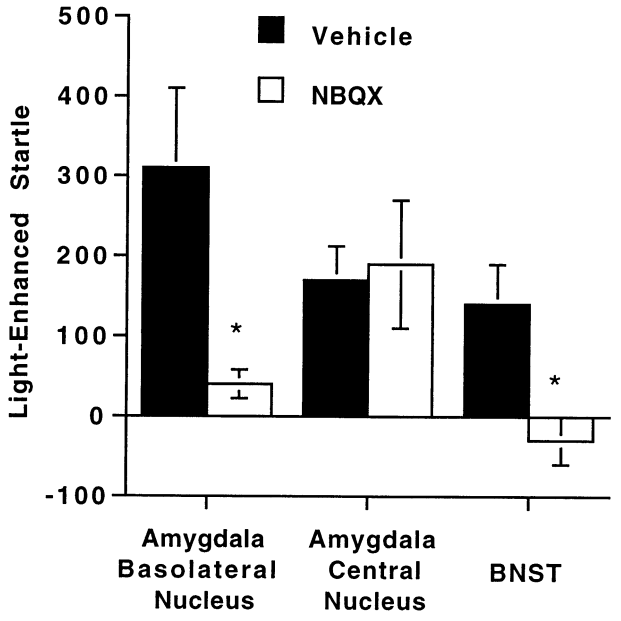

Figure 2. Mean change in startle amplitude from the dark phase to the light phase (light-enhanced startle) after infusion of the glutamate antagonist NBQX or its vehicle into either the basolateral nucleus of the amygdala, the central nucleus of the amygdala, or the lateral bed nucleus of the stria terminalis (BNST).

connections (cf. Alheid et al 1995); however, lesions of the bed nucleus of the stria terminalis fail to block either fear-potentiated startle (Hitchcock and Davis 1991) or conditioned freezing using an explicit cue (LeDoux et al 1988), suggesting that it may not be involved in explicit cue conditioning. On the other hand, several ongoing studies in our laboratory suggested that the bed nucleus of the stria terminalis might be involved in elevations of startle that were more long-lasting than the increase in startle observed in explicit cue conditioning. For example, lesions of the bed nucleus of the stria terminalis blocked long-term sensitization of the startle reflex (Gewirtz et al 1998) or the excitatory effect of the peptide CRH on startle (Lee and Davis 1997 and see below).

To evaluate the role of the bed nucleus of the stria terminalis versus the amygdala in light-enhanced startle, animals were implanted with bilateral cannulas in either the bed nucleus of the stria terminalis, the basolateral complex of the amygdala (i.e., the lateral and basolateral nuclei), or the central nucleus of the amygdala (Walker and Davis 1997b). One week later animals were tested for light-enhanced startle shortly following bilateral infusion of the glutamate antagonist NBQX into the different brain areas. Figure 2 shows the results. Local inactivation of either the basolateral nucleus of the amygdala or the bed nucleus of the stria terminalis significantly decreased light-enhanced startle. Other studies showed that this could not be attributed to a general depressant effect on baseline startle. To our surprise, however, infusion of the glutamate antagonist into the central nucleus of the amygdala had no effect.

These data indicate an important role for both the lateral/basolateral amygdala complex and the bed nucleus of the stria terminalis in light-enhanced startle. It is possible, however, that the cannulas in the central nucleus of the amygdala were misplaced, and that this accounted for the lack of an effect of inactivation of the central nucleus on light-enhanced startle. To evaluate this, the rats used in the light-enhanced startle experiment were trained and tested for fear-potentiated startle after infusion of NBQX into either the amygdala or bed nucleus of the stria terminalis. Figure 3 shows that consistent with previous results, infusion of the glutamate antagonist into the central nucleus of the amygdala completely blocked the expression of fear-potentiated startle. This was also true after an infusion of NBQX into the basolateral nucleus of the amygdala. In contrast, infusion of NBQX into the bed nucleus of the stria terminalis had no effect on fear-potentiated startle. These data indicate, therefore, that the location of the cannulas into the central nucleus of the amygdala was adequate to allow infusion of NBQX to totally block fear-potentiated startle. Hence, the ineffectiveness of NBQX infused into the central nucleus of the amygdala to block light-enhanced startle cannot be attributed to misplaced cannulas. Moreover, these data show a

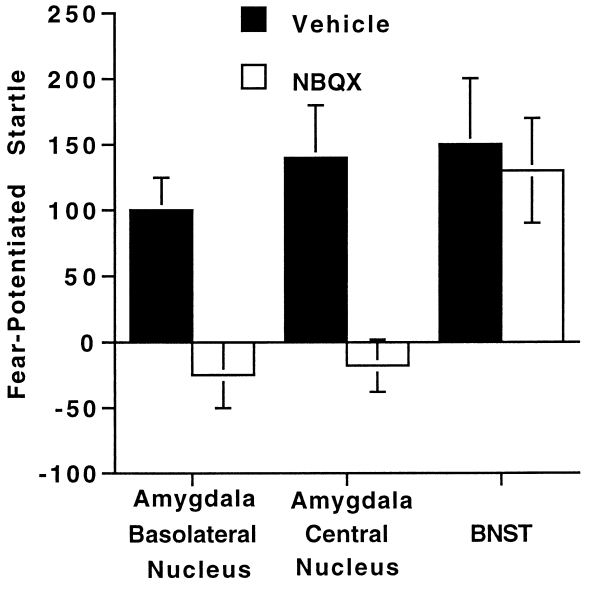

Figure 3. Mean change in startle amplitude on the light–noise vs. the noise alone trials (fear-potentiated startle) after infusion of the glutamate antagonist NBQX or its vehicle into either the basolateral nucleus of the amygdala, the central nucleus of the amygdala, or the lateral bed nucleus of the stria terminalis (BNST).

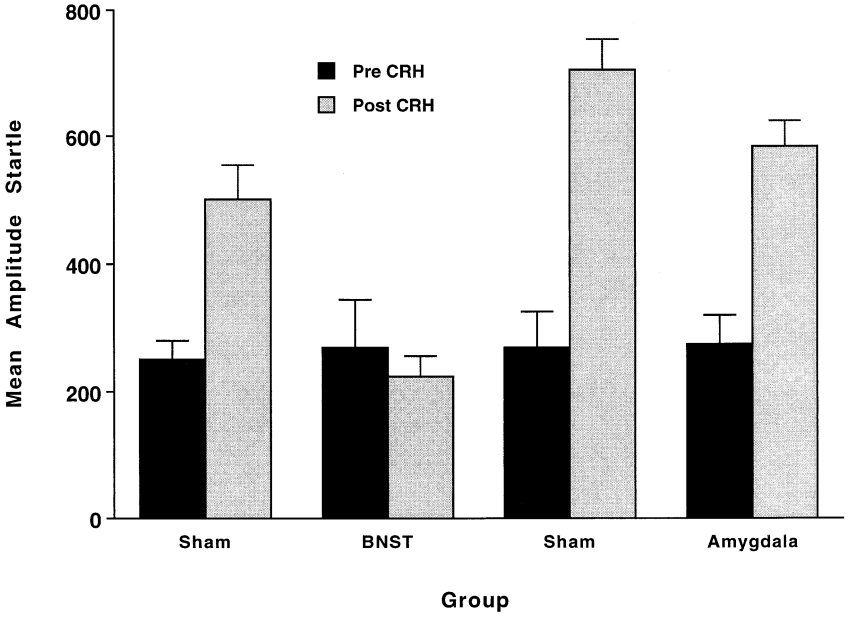

Figure 4. Mean startle amplitude prior to and after intraventricular infusion of CRH in animals previously given either sham lesions or chemical lesions of either the bed nucleus of the stria terminalis (BNST) or the amygdala (either the basolateral nucleus or the central nucleus). (Adapted from Lee and Davis 1997.)

double dissociation between inactivation of glutamate receptors in the central nucleus of the amygdala vs. the bed nucleus of the stria terminalis in relationship to fear-potentiated vs. light-enhanced startle.

The Role of the Bed Nucleus of the Stria Terminalis vs. the Amygdala in CRH-Enhanced Startle

As mentioned earlier, intraventricular infusion of the CRH produces a marked increase in startle that has a slow onset and decay, is not dependent on prior fear conditioning, and is blocked by anxiolytic compounds. Because CRH-enhanced startle has certain similarities to light-enhanced startle, we wondered whether it too would be dependent on the bed nucleus of the stria terminalis and perhaps not the central nucleus of the amygdala. To test this, rats were given chemical lesions of either the central nucleus of the amygdala, the basolateral nucleus of the amygdala, or the bed nucleus of the stria terminalis combined with implantation of intraventricular cannulas. Two weeks later they were tested for startle before and after intraventricular infusion of CRH. Remarkably, chemical lesions of the amygdala failed to block CRH-enhanced startle (Lee and Davis 1997). On the other hand, NMDA-induced lesions of the bed nucleus of the stria terminalis completely blocked CRH-enhanced startle (Figure 4). In other animals we found that local infusion of very low doses of CRH directly into the bed nucleus of the stria terminalis produced a rapid and large increase in startle amplitude. Moreover, local infusion into the bed nucleus of the stria terminalis of the CRH antagonist, alpha-helical CRH_{9-41}, blocked the excitatory effect on startle normally seen after intraventricular administration of CRH, whereas local infusion into the amygdala had no effect. These data provide compelling evidence that the bed nucleus of the stria terminalis, and not the amygdala, is the primary receptor site mediating the startle-enhancing effects of CRH given intraventricularly. A previous finding that large electrolytic lesions of the amygdala blocked CRH-enhanced startle (Liang et al 1992a) probably resulted from destruction of fibers projecting from the bed nucleus of the stria terminalis to the startle pathway.

Differential Roles of the Bed Nucleus of the Stria Terminalis and the Central Nucleus of the Amygdala in Fear vs. Anxiety

We have found a clear distinction between the central nucleus of the amygdala and the bed nucleus of the stria terminalis in relationship to fear-potentiated startle versus CRH-enhanced and light-enhanced startle (Table 1). Lesions or chemical inactivation of the central nucleus of the

Table 1. Differential Effects of Inactivation of Glutamate Transmission in the Central Nucleus of the Amygdala vs. the Bed Nucleus of the Stria Terminalis (BNST)

Effect on startle	Amygdala	BNST
Stimulus-specific fear (short light paired with shock)	Blockade	No blockade
Anxiety or sensitization (long exposure to bright light, no previous shock pairing)	No blockade	Blockade
CRH-enhanced startle (unconditioned anxiogenic effect of a peptide)	No blockade	Blockade

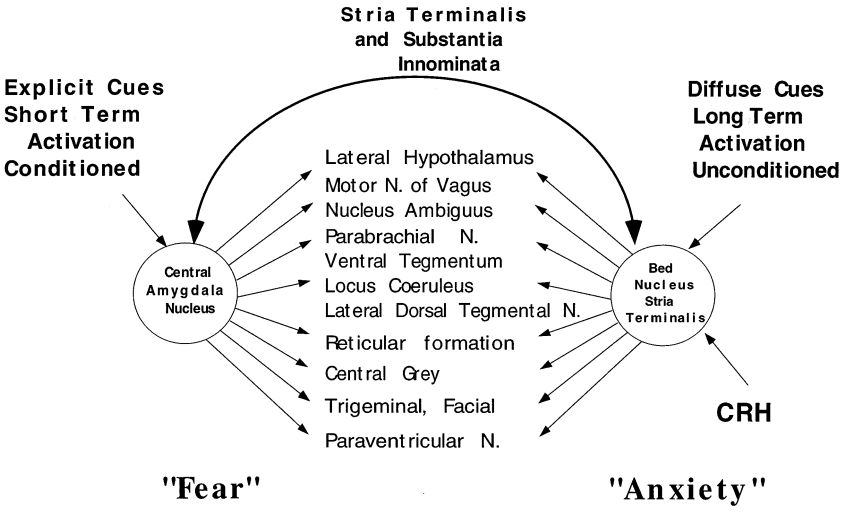

Figure 5. Hypothetical schematic suggesting that the central nucleus of the amygdala and the bed nucleus of the stria terminalis may be differentially involved in fear vs. anxiety, respectively. Both brain areas have highly similar hypothalamic and brain stem targets known to be involved in specific signs and symptoms of fear and anxiety; however, the stress peptide CRH appears to act on receptors in the bed nucleus of the stria terminalis rather than the amygdala, at least in terms of an increase in the startle reflex. Furthermore, the bed nucleus of the stria terminalis seems to be involved in the anxiogenic effects of a very bright light presented for a long period of time but not when that very same light has previously been paired with a shock. Just the opposite is the case for the central nucleus of the amygdala, which is critical for fear conditioning using explicit cues such as a light or tone paired with aversive stimulation (i.e., conditioned fear). (Adapted from Davis et al 1997 with permission from the New York Academy of Sciences.)

amygdala completely block the expression of fear-potentiated startle but have no effect whatsoever on either light-enhanced startle or CRH-enhanced startle. Conversely, lesions or chemical inactivation of the bed nucleus of the stria terminalis significantly attenuated either light-enhanced startle or CRH-enhanced startle without having any effect whatsoever on fear-potentiated startle.

We suggest that the bed nucleus of the stria terminalis may be a system that responds to signals more akin to anxiety than those akin to fear, whereas the central nucleus of the amygdala is clearly involved in fear and perhaps not as much in anxiety (Figure 5). Both these structures have very similar efferent connections to various hypothalamic and brain stem target areas known to be involved in specific signs and symptoms of fear and anxiety (cf. Davis 1992). Both receive highly processed sensory information from the basolateral nucleus of the amygdala and hence are in a position to respond to emotionally significant stimuli. CRH is known to be released during periods of stress or anxiety, some of which may come from CRH containing neurons in the central nucleus of the amygdala that project to and act on receptors in the bed nucleus of the stria terminalis (Sakanaka et al 1986). Thus, phasic activation of the amygdala by certain stressors could lead to a long-term activation of the bed nucleus of the stria terminalis via CRH. Assuming that phasic activation is like fear, whereas sustained activation of similar structures is like anxiety, this would suggest differential roles of the amygdala vs. the bed nucleus of the stria terminalis in fear vs. anxiety, respectively. Because of the potential clinical implications of this distinction, further investigation of the functional similarities and differences between these two parts of the extended amygdala is currently under way.

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