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THE ROLE OF THE AMYGDALA IN FEAR AND ANXIETY

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INTRODUCTION

Converging evidence now indicates that the amygdala plays a crucial role in the development and expression of conditioned fear. Conditioned fear is a hypothetical construct used to explain the cluster of behavioral effects produced when an initially neutral stimulus is consistently paired with an aversive stimulus. For example, when a light, which initially has no behavioral effect, is paired with an aversive stimulus such as a footshock, the light alone can elicit a constellation of behaviors that are typically used to define a state of fear in animals. To explain these findings, it is generally assumed (cf. McAllister & McAllister 1971) that during light-shock pairings (training session), the shock elicits a variety of behaviors that can be used to infer a central state of fear (unconditioned responses—Figure 1). After pairing, the light can produce the same central fear state and thus the same set of behaviors formerly produced by the shock. Moreover, the behavioral effects that are produced in animals by this formerly neutral stimulus (now called a conditioned stimulus—CS) are similar in many respects to the constellation of behaviors that are used to diagnose generalized anxiety in humans (Table 1). This chapter summarizes data supporting the idea that the amygdala, and its many efferent projections, may represent a central fear system involved in both the expression and acquisition of conditioned fear.

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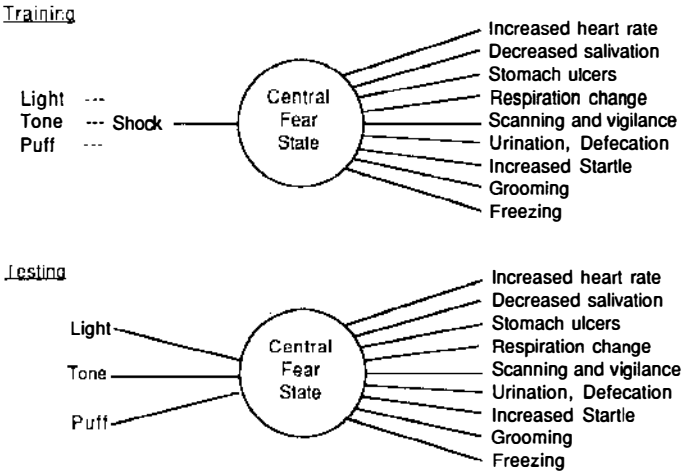

Figure 1 General scheme believed to occur during classical conditioning with an aversive conditioned stimulus. During training, the aversive stimulus (e.g. shock) activates a central fear system that produces a constellation of behaviors generally associated with aversive stimuli (unconditioned responses). After consistent pairings of some neutral stimulus such as a light or tone or puff of air with shock during the training phase, the neutral stimulus is capable of producing a similar fear state and hence the same set of behaviors (conditioned responses), formerly only produced by the shock.

Table 1 Comparison of measures in animals typically used to index fear and those in the DSM-III manual to index generalized anxiety in people

Measures of fear in animal models	DSM-III criteria—generalized anxiety
Increased heart rate	Heart pounding
Decreased salivation	Dry mouth
Stomach ulcers	Upset stomach
Respiration change	Increased respiration
Scanning and vigilance	Scanning and vigilance
Increased startle	Jumpiness, easy startle
Urination	Frequent urination
Defecation	Diarrhea
Grooming	Fidgeting
Freezing	Apprehensive expectation—something bad is going to happen

FEAR, ANXIETY, AND THE AMYGDALA

A variety of animal models have been used to infer a central state of fear or anxiety. In some models fear is inferred when an animal freezes, thus interrupting some ongoing behavior such as pressing a bar or interacting socially with other animals. In other models, fear is measured by changes in autonomic activity, such as heart rate, blood pressure, or respiration. Fear can also be measured by a change in simple reflexes or a change in facial expressions and mouth movements. Thus fear appears to produce a complex pattern of behaviors that are highly correlated with each other.

Anatomical Connections Between the Amygdala and Brain Areas Involved in Fear and Anxiety

The suggestion was made in several previous reviews (Gray 1989, Gloor 1960, Kapp et al 1984, 1990, Kapp & Pascoe 1986, Sarter & Markowitsch 1985) and supported by work in many laboratories that the central nucleus of the amygdala has direct projections to hypothalamic and brainstem areas that may be involved in many of the symptoms of fear or anxiety (summarized in Figure 2). Direct projections from the central nucleus of the amygdala to the lateral hypothalamus (Krettek & Price 1978a, Price & Amaral 1981, Shiosaka et al 1980) appear to be involved in activation of the sympathetic autonomic nervous system during fear and anxiety (cf. LeDoux et al 1988). Direct projections to the dorsal motor nucleus of the vagus nerve (Hopkins & Holstege 1978, Schwaber et al 1982, Takeuchi et al 1983, Veening et al 1984) may be involved in several autonomic measures of fear or anxiety, since the vagus nerve controls many different autonomic functions.

Projections of the central nucleus of the amygdala to the parabrachial nucleus (Hopkins & Holstege 1978, Krettek & Price 1978a, Price & Amaral 1981, Takeuchi et al 1982) may be involved in respiratory changes during fear, as electrical stimulation (Cohen 1971, 1979, Bertrand & Hugelin 1971, Mraovitch et al 1982) or lesions (Baker et al 1981, Von Euler et al 1976) of the parabrachial nucleus are known to alter various measures of respiration.

Projections from the amygdala to the ventral tegmental area (Beckstead et al 1979, Phillipson 1979, Simon et al 1979, Wallace et al 1989) may mediate stress-induced increases in dopamine metabolites in the prefrontal cortex (Thierry et al 1976). Direct amygdalar projections to the locus coeruleus (e.g. Cedarbaum & Aghajanian 1978, Wallace et al 1989), or indirect projections via the paragigantocellularis nucleus (Aston-Jones et al 1986) or perhaps via the ventral tegmental area (e.g. Deutch et al 1986), may mediate the response of cells in the locus coeruleus to conditioned

Figure 2 Schematic diagram showing direct connections between the central nucleus of the amygdala and a variety of hypothalamic and brainstem target areas that may be involved in different animal tests of fear and anxiety.

fear stimuli (Rasmussen & Jacobs 1986), as well as being involved in other actions of the locus coeruleus linked to fear and anxiety (cf. Redmond 1977). Direct projections of the amygdala to the lateral dorsal tegmental nucleus (e.g. Hopkins & Holstege 1978) and parabrachial nuclei (see above), which have cholinergic neurons that project to the thalamus (cf. Pare et al 1990), may mediate increases in synaptic transmission in thalamic sensory relay neurons (Pare et al 1990, Steriade et al 1990) during states of fear. This cholinergic activation, along with increases in thalamic transmission accompanying activation of the locus coeruleus (Rogawski & Aghajanian 1980), may thus lead to increased vigilance and superior signal detection in a state of fear or anxiety. In addition, release of norepinephrine onto motoneurons via amygdala activation of the locus coeruleus, or via amygdalar projections to serotonin-containing raphe neurons (Magnuson & Gray 1990), could lead to enhanced motor performance during a state of fear, because both norepinephine and serotonin facilitate excitation of motoneurons (e.g. McCall & Aghajanian 1979, White & Neuman 1980).

Projections of the amygdala to the nucleus reticularis pontis caudalis (Inagaki et al 1983, Rosen et al 1991) probably are involved in fear-potentiation of the startle reflex (Hitchcock & Davis 1991). The central nucleus of the amygdala projects to a region of the central grey (Beitz 1982, Gloor 1978, Hopkins & Holstege 1978, Krettek & Price 1978a, Post & Mai 1980) that has been implicated in conditioned fear in a number of behavioral tests (Borszcz et al 1989, Hammer & Kapp 1986, LeDoux et al 1988, Liebman et al 1970) and is thought to be a critical part of a general defense system (cf. Adams 1979, Bandler & Depaulis 1988, Blanchard et al 1981, Fanselow 1991, Graeff 1988, LeDoux et al 1988, Zhang et al 1990). Direct projections to the trigeminal and facial motor nuclei (Holstege et al 1977, Post & Mai 1980, Ruggiero et al 1982) may mediate some of the facial expressions of fear. Finally, direct projections of the central nucleus of the amygdala to the paraventricular nucleus of the hypothalamus (Gray 1989, Silverman et al 1981, Tribollet & Dreifuss 1981), or indirect projections by way of the bed nucleus of the stria terminalis and preoptic area, which receive input from the amygdala (De Olmos et al 1985, Krettek & Price 1978a, Weller & Smith 1982) and project to the paraventricular nucleus of the hypothalamus (Sawchenko & Swanson 1983, Swanson et al 1983), may mediate the prominent neuroendocrine responses to fearful or stressful stimuli.

The identity of the transmitters released onto these target sites by amygdaloid neurons is just beginning to emerge. Gray (1989) estimates that 25% of the neurons in the central nucleus of the amygdala and bed nucleus of the stria terminalis contain known neuropeptides. The main output neurons of the amygdala contain corticotropin-releasing factor, soma-

tostatin, and neurotensin, with smaller contributions from substance P and galanin-containing cells.

Elicitation of Fear by Electrical Stimulation of the Amygdala

Electrical stimulation of the amygdala can produce a complex pattern of behavioral and autonomic changes that highly resembles a state of fear. Stimulation of the amygdala can alter heart rate and blood pressure, both measures used to study cardiovascular changes during fear conditioning (Anand & Dua 1956, Applegate et al 1983, Bonvallet & Gary Bobo 1972, Cox et al 1987, Faiers et al 1975, Frysinger et al 1984, Galeno & Brody 1983, Gelsema et al 1987, Harper et al 1984, Heinemann et al 1973, Hilton & Zbrozyna 1963, Iwata et al 1987, Kaada 1951, Kapp et al 1982, Koikegami et al 1957, Morgenson & Calaresu 1973, Pascoe et al 1989, Reis & Oliphant 1964, Schlor et al 1984, Stock et al 1978, 1981, Timms 1981). These effects are often critically dependent on the state of the animal and level of anesthesia (e.g. Frysinger et al 1984, Galeno & Brody 1983, Harper et al 1984, Iwata et al 1987, Stock et al 1978, Timms 1981) and in some instances may result from stimulation of fibers of passage rather than cell bodies (cf. Lewis et al 1989). Amygdala stimulation can also produce gastric ulceration (Henke 1980b, 1982, Innes & Tansy 1980, Sen & Anand 1957), which may result from chronic fear or anxiety.

Electrical stimulation of the amygdala also alters respiration (Anand & Dua 1956, Applegate et al 1983, Bonvallet & Gary Bobo 1972, Harper et al 1984), a prominent symptom of fear, especially in panic disorders. Electrical stimulation of the central nucleus of the amygdala produces a cessation of ongoing behavior (Applegate et al 1983, Gloor 1960, Kaada 1972, Ursin & Kaada 1960). Cessation of ongoing behavior is the critical measure of fear or anxiety in several animal models, such as freezing (Blanchard & Blanchard 1969, Bolles & Collier 1976, Fanselow & Bolles 1979), the operant conflict test (Geller & Seifter 1960), the conditioned emotional response (Estes & Skinner 1941) that correlates with freezing (e.g. Bouton & Bolles 1980, Mast et al 1982), and the social interaction test (File 1980). Electrical stimulation of the amygdala also elicits jaw movements (Applegate et al 1983, Gloor 1960, Kaku 1984, Ohta 1984) and activation of facial motoneurons (Fanardjian & Manvelyan 1987), both of which may be included in the facial expressions seen during the fear reaction. These motor effects may be indicative of a more general effect of amygdala stimulation, namely that of modulating brainstem reflexes such as the massenteric (Gary Bobo & Bonvallet 1975, Bonvallet & Gary Bobo 1975), baroreceptor (Lewis et al 1989, Schlor et al 1984, Pascoe et al 1989), nictitating membrane (Whalen & Kapp 1991), and

startle reflex (Rosen & Davis 1988a,b). In most cases, stimulation of the amygdala facilitates these reflexes, although whether it does or not may depend on the exact amygdala sites being stimulated (see Whalen & Kapp 1991 for a discussion of this point). In humans, electrical stimulation of the amygdala elicits feelings of fear or anxiety, as well as autonomic reactions indicative of fear (Chapman et al 1954, Gloor et al 1981). Some of the emotional content of dreams may result from activation of the amygdala, stimulation of which increases ponto-geniculo-occipital activity that occurs during paradoxical (dream) sleep (cf. Calvo et al 1987).

Finally, electrical stimulation of the amygdala has been shown to increase plasma levels of corticosterone, thus indicating an excitatory effect of the amygdala on the hypothalamo-pituitary-adrenal axis (Dunn & Whitner 1986, Feldman et al 1982, Mason 1959, Matheson et al 1971, Redgate & Fahringer 1973, Smelik & Vermes 1980, Setekleiv et al 1961, Yates & Maran 1974). As mentioned above, some of these excitatory effects may be mediated through the preoptic area and bed nucleus of the stria terminalis, which receive input from the amygdala (De Olmos et al 1985, Krettek & Price 1978a, Weller & Smith 1982) and project to the paraventricular nucleus of the hypothalamus (Sawchenko & Swanson 1983, Swanson et al 1983). Electrical stimulation of these nuclei increases plasma corticosterone levels (Dunn 1987, Saphier & Feldman 1986). Elevated plasma levels of corticosterone produced by amygdala stimulation can be attenuated by bilateral lesions of the stria terminalis, medial preoptic area, and the bed nucleus of the stria terminalis (Feldman et al 1990). Direct projections from the medial nucleus of the amygdala to the hypothalamus exist as well (Gray et al 1989, Silverman et al 1981, Tribollet & Dreifuss 1981), and these projections may also mediate some of the excitatory effects of the amygdala on the hypothalamic-pituitary axis.

The highly correlated set of behaviors seen during fear may result from activation of a single area of the brain (the amygdala, especially its central nucleus), which then projects to a variety of target areas, each of which is critical for specific symptoms of fear and the perception of anxiety. Moreover, it must be assumed that all of these connections are already formed in an adult organism, because electrical stimulation produces these effects in the absence of prior explicit fear conditioning. Thus, much of the complex behavioral pattern seen during fear conditioning has already been "hard wired" during evolution. For a formerly neutral stimulus to produce the constellation of behavioral effects used to define a state of fear or anxiety, it is only necessary for that stimulus to activate the amygdala, which in turn will produce the complex pattern of behavioral changes by virtue of its innate connections to different brain target sites. Plasticity during fear conditioning probably results from a change in synaptic inputs

prior to or in the amygdala, rather than from a change in its efferent target areas. The ability to produce long-term potentiation (Clugnet & LeDoux 1990, Chapman et al 1990) in the amygdala and the finding that local infusion of NMDA antagonists into the amygdala blocks the acquisition (Miserendino et al 1990) and extinction (Falls et al 1992) of fear conditioning is consistent with this hypothesis.

The Role of the Amygdala in Fear Elicited by a Conditioned Stimulus

If fear conditioning results from an activation of the amygdala, one would expect that a conditioned stimulus would activate units in the amygdala and that lesions of the amygdala would prevent a conditioned stimulus from producing fear. Thus far, recording single unit activity in the amygdala has been difficult because many of the cells are small and have very low spontaneous rates of firing. Nonetheless, several studies have shown that a neutral stimulus paired with aversive stimulation will alter neural firing in the amygdala (Applegate et al 1982, Henke 1983, Pascoe & Kapp 1985b, Umemoto & Olds 1975). In addition, many studies indicate that lesions of the amygdala block the effects of a conditioned stimulus in a variety of behavioral test situations. Lesions of the amygdala eliminate or attenuate freezing normally seen in response to a stimulus formerly paired with shock (Blanchard & Blanchard 1972, LeDoux et al 1988, 1990); in the presence of a dominant male rat (Bolhuis et al 1984, Luiten et al 1985); or in a continuous passive avoidance test (Slotnick 1973). Lesions of the amygdala counteract the normal reduction of bar pressing in the operant conflict test (Shibata et al 1986) or the conditioned emotional response paradigm (Kellicut & Schwartzbaum 1963, Spevack et al 1975). In birds, lesions of the archistriatum, believed to be homologous with the mammalian amygdala, block the development of a conditioned emotional response (Dafters 1976) or heart rate acceleration in response to a cue paired with a shock (Cohen 1975). In both adult (Gentile et al 1986, Kapp et al 1979) and infant mammals (Sananes & Campbell 1989), lesions of the central nucleus block conditioned changes in heart rate. Ibotenic acid lesions of the central nucleus of the amygdala (Iwata et al 1986) or localized cooling of this nucleus (Zhang et al 1986) also block conditioned changes in blood pressure. Lesions of the lateral amygdala (basal, lateral, and accessory basal nuclei) attenuate and lesions of the medial amygdala (corticomedial and central nucleus) eliminate negative contrast following sucrose reduction (Becker et al 1984), a measure of emotionality sensitive to anxiolytic drugs (cf. Flaherty 1990). Perhaps similarly, lesions of the amygdala block the effects of positive behavioral contrast (Henke 1972, Henke et al 1972), decreased responsiveness to shifts in reward magnitude in monkeys (Schwartzbaum 1960) and rats (Kemble & Beckman 1970),

and effects of frustrative nonreward (e.g. Henke 1977, 1973). Lesions of the central nucleus or of the lateral and basal nuclei of the amygdala block fear-potentiated startle (Hitchcock & Davis 1991, 1987, Sananes & Davis 1992). This, along with a large literature implicating the amygdala in many other measures of fear such as active and passive avoidance (for reviews see Kaada 1972, Sarter & Markowitsch 1985, Ursin et al 1981) and evaluation and memory of emotionally significant sensory stimuli (Bennett et al 1985, Bresnahan & Routtenberg 1972, Ellis & Kesner 1983, Gallagher et al 1980, Gallagher & Kapp 1981, 1978, Gold et al 1975, Handwerker et al 1974, Kesner 1982, Liang et al 1985, Liang et al 1986, McGaugh et al 1990, Mishkin & Aggleton 1981) provide strong evidence for a crucial role of the amygdala in fear.

The Role of the Amygdala in Unconditioned Fear

Lesions of the amygdala are known to block several measures of innate fear in different species (cf. Blanchard & Blanchard 1972, Ursin et al 1981). Lesions of the cortical amygdaloid nucleus and perhaps the central nucleus markedly reduce emotionality in wild rats measured in terms of flight and defensive behaviors (Kemble et al 1984, 1990). Large amygdala lesions or those which damaged the cortical, medial, and, in several cases, the central nucleus dramatically increase the number of contacts a rat will make with a sedated cat (Blanchard & Blanchard 1972). Some of these lesioned animals crawl all over the cat and even nibble its ear, a behavior never shown by the nonlesioned animals. Following lesions of the archistriatum, believed to be homologous with the mammalian amygdala, birds become docile and show little tendency to escape from humans (Phillips 1964, 1968), consistent with a general taming effect of amygdala lesions reported in many species (cf. Goddard 1964). Finally, lesions of the amydaloid complex inhibit adrenocortical responses following olfactory or sciatic nerve stimulation (Feldman & Conforti 1981) and attenuate the compensatory hypersecretion of ACTH that normally occurs following adrenalectomy (Allen & Allen 1974). Lesions of the central nucleus have been found to attenuate ulceration significantly (Henke 1980a) and elevated levels of plasma corticosterone produced by restraint stress (Beaulieu et al 1986, 1987). Moreover, lesions of the medially projecting component of the ventroamygdalofugal pathway, which carries the fibers connecting the central nucleus of the amygdala to the hypothalamus, attenuate the increase in ACTH secretion following adrenalectomy, whereas lesions of the stria terminalis do not (Allen & Allen 1974). Finally, lesions of the amygdala have been reported to block the ability of high levels of noise, which may be an unconditioned fear stimulus (cf. Leaton & Cranney 1990), to produce hypertension (Galeno et al 1984) or activation of tryptophan hydroxylase (Singh et al 1990).

Other measures that have been used to index innate fear have produced less consistent data concerning amygdala lesions, however. Large electrolytic lesions of the amygdaloid complex (Bresnahan et al 1976, Corman et al 1967, Eclancher & Karli 1979, Greidanus et al 1979, Jonason & Enloe 1971, Schwartzbaum & Gay 1966), or electrolytic or ibotenic acid lesions of the central nucleus of the amygdala (e.g. Grijalva et al 1990, Jellestad et al 1986, Werka et al 1978) or of the lateral and basal nuclei (Jellestad & Cabrera 1986) produce an increase in exploratory behavior in the open field test. This does not seem to occur, however, when (*a*) open field testing is preceded by other tests on the same animals (Grossman et al 1975), (*b*) test conditions are especially familiar (e.g. McIntyre & Stein 1973), (*c*) testing occurs after considerable handling and a long time after surgery (Kemble et al 1979), or (*d*) the lesions are very small (Riolobos et al 1987), and may depend on the age of the animal when the lesions are performed (Eclancher & Karli 1979). Because increased exploratory behavior is not always associated with changes in corticosterone (Jellestad & Cabrera 1986, Jellestad et al 1986) or other measures usually associated with a loss of fear of the open field, these authors have concluded that increased locomotor activity cannot easily be explained by a general loss of fear after amygdala lesions. Moreover, other measures of neophobia, such as the time to begin eating in a novel environment, do not show consistent changes with lesions of the amygdala, as one might expect from a lesion that reduced fear (cf. Aggleton et al 1989). However, the exact way neophobia is measured may determine whether it is a valid measure of fear, at least based on the measurement of corticosterone (e.g. Misslin & Cigrang 1986).

Other data indicate that the amygdala appears to be involved in some types of aversive conditioning, but this depends on the exact unconditioned aversive stimulus that is used. For example, electrolytic lesions of the basal nucleus (Pellegrino 1968), or fiber-sparing chemical lesions of most of the amygdaloid complex (Cahill & McGaugh 1990), attenuate avoidance of thirsty rats to approach an electrified water spout through which they were previously accustomed to receiving water. Importantly, however, these same lesioned animals did not differ from controls in the rate at which they found the water spout over successive test days or their avoidance of the water spout when quinine was added to the water (Cahill & McGaugh 1990). This led Cahill and McGaugh to suggest that "the degree of arousal produced by the unconditioned stimulus, and not the aversive nature per se, determined the level of amygdala involvement" (p. 541). Although many studies have shown that electrolytic lesions of the amygdala can interfere with taste aversion learning, an elegant series of experiments have now shown that these effects result from an interruption of gustatory fibers passing through the amygdala on route to the insular cortex (Dunn &

Everitt 1988). In these studies, ibotenic acid lesions of the amygdala fail to block taste aversion learning, whereas ibotenic acid lesions of the gustatory insular cortex do. Once again, the amygdala does not seem critical for all types of aversive conditioning but only conditioning that involves an obvious fear component such as that produced by aversive shocks.

Finally, the amygdala may also be importantly involved in stimulus-response associations that do not obviously involve aversive conditioning (e.g. Aggleton & Mishkin 1986, Cador et al 1989, Everitt et al 1989, Gallagher et al 1990, Kesner et al 1989, Murray 1990, Murray & Mishkin 1985, Peinado-Manzano 1990; but see Zola-Morgan et al 1989). Hence, some of the deficits in aversive conditioning following alterations of amygdala function may be part of a more general deficit in attention (Gallagher et al 1990, Kapp et al 1990).

Conditioned Fear vs Anxiety

Clinically, fear is regarded to be more stimulus-specific than anxiety, despite very similar symptoms. Figure 2 suggests that spontaneous activation of the central nucleus of the amygdala would produce a state resembling fear in the absence of any obvious eliciting stimulus. In fact, fear and anxiety often precede temporal lobe epileptic seizures (Gloor et al 1981), which are usually associated with abnormal electrical activity of the amygdala (Crandall et al 1971). An important implication of this distinction is that treatments that block conditioned fear might not necessarily block anxiety. For example, if a drug decreased transmission along a sensory pathway required for a conditioned stimulus to activate the amygdala, that drug might be especially effective in blocking conditioned fear; however, if anxiety resulted from activation of the amygdala not involving that sensory pathway, that drug might not be especially effective in reducing anxiety. On the other hand, drugs that act specifically in the amygdala should affect both conditioned fear and anxiety. Moreover, drugs that act at various target areas might be expected to provide selective actions on some but not all of the somatic symptoms associated with anxiety.

Effects of Drugs Infused into the Amygdala on Fear and Anxiety

The central nucleus of the amygdala is known to have high densities of opiate receptors (Goodman et al 1980), whereas the basal nucleus, which projects to the central nucleus (Aggleton 1985, Krettek & Price 1978b, Millhouse & DeOlmos 1983, Nitecka et al 1981, Ottersen 1982, Smith & Millhouse 1985, Russchen 1982), has high densities of benzodiazepine receptors (Niehoff & Kuhar 1983). Local infusion of opiate agonists into the central nucleus of the amygdala blocks the acquisition of con-

ditioned bradycardia in rabbits (Gallagher et al 1981, 1982) and has anxiolytic effects in the social interaction test (File & Rogers 1979). Furthermore, local infusion of benzodiazepines into the amygdala has anxiolytic effects in the operant conflict test (Hodges et al 1987, Nagy et al 1979, Petersen & Scheel-Kruger 1982, Petersen et al 1985, Scheel-Kruger & Petersen 1982, Shibata et al 1982, 1989, Thomas et al 1985), and in the light-dark box measure in mice (Costall et al 1989) and antagonizes the discriminative stimulus properties of pentylenetetrazol (Benjamin et al 1987). The anticonflict effect can be reversed by systemic administration of the benzodiazepine antagonist flumazenil (Hodges et al 1987, Petersen et al 1985, Shibata et al 1989) or co-administration into the amygdala of the GABA antagonist bicuculline (Scheel-Kruger & Petersen 1982) and mimicked by local infusion into the amygdala of GABA (Hodges et al 1987) or the GABA agonist muscimol (Scheel-Kruger & Petersen 1982). In general, anticonflict effects of benzodiazepines occur after local infusion into the lateral and basal nuclei (Petersen & Scheel-Kruger 1982, Petersen et al 1985, Scheel-Kruger & Petersen 1982, Thomas et al 1985) (the nuclei of the amygdala that have high densities of benzodiazepine receptors) and not after local infusion into the central nucleus (Petersen & Scheel-Kruger 1982, Scheel-Kruger & Petersen 1982). Shibata et al (1982) found just the opposite effect, however, perhaps because of local anesthetic effects, which can occur when high doses of these compounds are infused into the central nucleus (e.g. Heule et al 1983). More recently, it has been shown that the anterior parts of the basal and central nucleus are especially important for conflict performance based on both lesion and local infusion of benzodiazepines (Shibata et al 1989). Taken together these results suggest that drug actions in the amygdala may be sufficient to explain both fear-reducing and anxiety-reducing effects of various drugs given systemically. Local infusion into the amygdala of the benzodiazepine antagonist flumazenil significantly attenuated the anticonflict effect of the benzodiazepine agonist chlordiazepoxide given systemically (Hodges et al 1987). However, in a very important recent experiment, Yadin et al (1991) found that chlordiazepoxide actually had a more potent anticonflict effect in animals previously given lesions of the amygdala, even though the amygdala lesion itself released punished behavior. Clearly, more work has to be done to locate the site of the anxiolytic action of benzodiazepines given systemically.

Recently, a new class of anxiolytic compounds acting as 5-HT_3 receptor subtype antagonists have been shown to produce anxiolytic effects after local infusion into the amygdala (Costall et al 1989). Such infusions also can block some of the signs of withdrawal following subchronic administration of diazepam, ethanol, nicotine, or cocaine (Costall et al 1990) or

increases in levels of dopamine or the serotonin metabolite 5-HIAA in the amygdala after activation of dopamine neurons in the ventral tegmental area (Hagan et al 1990). The latter effects, which may relate to how sensory information is gated in the amygdala (Maeda & Maki 1986), were more pronounced in the right amygdala vs the left (Hagan et al 1990), consistent with other lateralized effects reported previously (Costall et al 1987). Measures of emotionality, including fear-potentiated startle in humans, also show lateralization (cf. Lang et al 1990), consistent with a greater participation of the right vs the left hemisphere and hence perhaps the right amygdala. Future studies employing local infusion of benzodiazepine or opiate antagonists into the amygdala, coupled with systemic administration of various agonists, may be able to determine whether local binding to receptors in the amygdala is necessary to explain their anxiolytic effects. Eventually, local infusion of various drugs into specific target areas may be used to evaluate whether highly specific anxiolytic actions are produced. These results could then serve as a guide for eventually producing more selective anxiolytic compounds.

CONCLUSIONS

An impressive amount of evidence from many laboratories using a variety of experimental techniques indicates that the amygdala plays a crucial role in conditioned fear and probably anxiety. Many of the amygdaloid projection areas are critically involved in specific signs that are used to measure fear and anxiety. Electrical stimulation of the amygdala elicits a pattern of behaviors that mimic natural or conditioned states of fear. Lesions of the amygdala block innate or conditioned fear and local infusion of drugs into the amygdala have anxiolytic effects in several behavioral tests. Finally, the amygdala may be a critical site of plasticity that mediates both the acquisition and extinction of conditioned fear. A better understanding of brain systems that inhibit the amygdala and of the role of the amygdala's very high levels of peptides (cf. Gray 1989) may eventually lead to the development of more effective pharmacological strategies for treating clinical anxiety disorders.

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