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A reciprocal relationship exists between persistent pain and negative affective states such as fear, anxiety, and depression. Accumulating evidence points to the amygdala as an important site of such interaction. Whereas a key role of the amygdala in the neuronal mechanisms of emotionality and affective disorders has been well established, the concept of the amygdala as an important contributor to pain and its emotional component is still emerging. This article will review and discuss evidence from anatomical, neuroimaging, behavioral, electrophysiological, pharmacological, and biochemical data that implicate the amygdala in pain modulation and emotional responses to pain. The latero-capsular division of the central nucleus of the amygdala is now defined as the "nociceptive amygdala" and integrates nociceptive information with polymodal information about the internal and external bodily environment. Dependent on environmental conditions and affective states, the amygdala appears to play a dual facilitatory and inhibitory role in the modulation of pain behavior and nociceptive processing at different levels of the pain neuraxis. Only recently, electrophysiological, pharmacological, and biochemical neuroplastic changes were shown in the nociceptive amygdala in persistent pain. It is conceivable, however, that amygdala plasticity plays an important role in emotional pain behavior and its modulation by affective state. NEUROSCIENTIST 10(3):221–234, 2004.
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The amygdala is an almond-shaped structure in the medial temporal lobe. As part of the limbic system, the amygdala plays a key role in emotionality, the emotional evaluation of sensory stimuli, emotional learning, and memory, as well as affective disorders, including anxiety and depression (Davis 1998; Gallagher and Schoenbaum 1999; Maren 1999; Aggleton 2000; LeDoux 2000; Cardinal and others 2002; Davidson 2002; Zald 2003). The amygdala has been shown to exhibit a high degree of plasticity in various models of long-term synaptic and behavioral modification, including long-term potentiation, fear conditioning, kindling model of epilepsy, and chronic cocaine model of drug addiction (McKernan and Shinnick-Gallagher 1997; Neugebauer and others 1997; Maren 1999; LeDoux 2000; Neugebauer and others 2000).

Pain has a strong emotional component ("suffering"), and persistent pain is significantly associated with depression and anxiety disorders (Huyser and Parker 1999; Millan 1999; Wilson and others 2001; McWilliams and others 2003). The relationship between pain and negative affect appears to be reciprocal in that patients suffering from depression and anxiety experience pain more strongly, whereas fear and stress typically inhibit pain (Haythornthwaite and others 1991; Wilson and others 2001; Rhudy and Meagher 2003). Accumulating evidence points to the amygdala as a neural substrate of the interaction between pain and emotion (Heinricher and McGaraughty 1999; Fields 2000; Meagher and others 2001).

Persistent pain arises from pathological conditions such as injury and inflammation; it can be modified by emotional and social factors and is accompanied by neuroplastic changes in the peripheral and central nervous system. Neural plasticity may be defined as the capacity of neurons to change their function, electrophysiological properties, biochemical profile, or structure. Enhanced responsiveness to incoming signals by primary afferent nerve fibers and neurons in the central nervous system is referred to as peripheral and central sensitization, respectively. Sensitization is both the consequence and key mechanism of persistent pain states (Basbaum 1999; Besson 1999; Dubner and Gold 1999; Fields and Basbaum 1999; Millan 1999; Wood and Perl 1999; Yaksh and others 1999; Woolf and Salter 2000; Stucky and others 2001; Neugebauer 2002; Schaible and others 2002; Willis 2002).

Despite significant progress in pain research over the past decades, persistent pain remains difficult to treat and affects the quality of human life. "Pain is personal and subjective, is affected by mood and psychosocial factors, and demonstrates tremendous individual varia-

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tion" (National Institutes of Health 2001). The amygdala with its well-documented role in affective states and related disorders appears well positioned to play an important role in the emotional-affective component of persistent pain.

Anatomy: Amygdala as Part of the Pain System

The amygdala is composed of several anatomically and functionally distinct nuclei (see Table 1). Sensory information reaches the amygdala mainly through the lateral nucleus (LA), whereas the central nucleus (CeA) serves as the output nucleus for major amygdala functions, integrating inputs from other amygdala nuclei without forming substantial reciprocal intra-amygdaloid connections (Pitkanen and others 1997; Aggleton 2000; Price 2003). It is clear now that the amygdala is also part of the pain system (Fig. 1). Highly processed, affective and cognitive, polymodal information reaches the amygdala from the thalamus and cortical areas (Shi and Davis 1999; LeDoux 2000; Stefanacci and Amaral 2000; Price 2003) through connections with the LA and the basolateral nucleus of the amygdala (BLA), which then project to the CeA. These inputs from the LA and BLA to the CeA are part of the fear- and anxiety-related circuitry (LeDoux 2000). Through extensions of the spinohypothalamic and spinothalamic pain pathways, the LA-BLA-CeA circuitry also receives pain-related information from the thalamus (midline and posterior nuclei), granular and dysgranular insular cortex, and anterior cingulate cortex (Augustine 1996; Millan 1999; Shi and Davis 1999; LeDoux 2000; Price 2000; Stefanacci and Amaral 2000).

In addition to these indirect inputs through LA and BLA, there are direct nociceptive inputs to the latero-capsular part of the CeA (Fig. 1), which is now defined as the "nociceptive amygdala" because of its high content of nociceptive neurons (Bourgeais and others 2001; Neugebauer and Li 2002, 2003; Li and Neugebauer 2003). The term *nociception* refers to the neuronal processes resulting in a stimulus being perceived as painful. The latero-capsular CeA receives nociceptive-specific information from the spinal cord and brainstem through the spino-parabrachio-amygdaloid pain pathway (Gauriau and Bernard 2002) as well as through direct projections from the spinal cord (Burstein and Potrebic 1993; Wang and others 1999).

The CeA forms widespread connections with forebrain areas, hypothalamus, and brainstem (Fig. 2) to regulate emotional behavior (Davis 1998; LeDoux 2000; Bourgeais and others 2001). Neurons in the latero-capsular part of the CeA project heavily to the substantia innominata dorsalis, which provides connections with the agranular insular cortex, orbital and medial prefrontal cortices, cholinergic basal forebrain nuclei, bed nucleus of the stria terminalis, and medial dorsal thalamus, as well as the hypothalamus and brainstem areas (Bourgeais and others 2001). The latero-capsular CeA also forms direct and indirect (via medial CeA) connections with the medial dorsal thalamus through the ventral amygdaloid pathway (VAP), the hypothalamus via the stria terminalis and VAP, and the brainstem either directly through the VAP or indirectly via the hypothalamus (Davis 1998; LeDoux 2000; Price 2003). Brainstem targets include the periaqueductal grey (PAG), parabrachial nucleus (PB), reticular formation, dorsal nucleus of the vagus, solitary tract nucleus, and ventrolateral medulla (Davis 1998; LeDoux 2000; Price 2003).

Table 1. Major Amygdala Nuclei

LA	Lateral nucleus
BLA	Basolateral (or basal) nucleus
ABA	Accessory basal nucleus
MeA	Medial nucleus
CeA	Central nucleus

Through these connections with brain areas and systems involved in nociception and pain, fear and anxiety, attention and cognition, autonomic function and stress responses, and endogenous pain control, the CeA is well positioned to play a key role in the emotional-affective pain response and pain modulation (Bernard and others 1996; Heinricher and McGaraughty 1999; Millan 1999; Fields 2000; Rhudy and Meagher 2000; Bourgeais and others 2001; Gauriau and Bernard 2002).

Imaging Studies: Pain-related Activation and Deactivation

Neuroimaging pain studies using PET and fMRI have repeatedly identified pain-related signal changes in the amygdala in animals and humans. The experimental conditions included the application of brief noxious heat stimuli to the skin of humans (Derbyshire and others 1997; Becerra and others 1999; Bingel and others 2002; Bornhovd and others 2002), vascular pain induced in humans by balloon dilatation of a dorsal foot vein (Schneider and others 2001), noxious colorectal stimulation in patients with irritable bowel syndrome (Bonaz and others 2002; Naliboff and others 2003), and mechanical allodynia in neuropathic pain patients (Petrovic and others 1999), as well as in a rat model of peripheral mononeuropathy (Paulson and others 2002).

Bilateral activation of the amygdala in humans has been found to correlate with perceived pain intensity as shown in Figure 3 (Bornhovd and others 2002). Significantly enhanced blood oxygen level–dependent signals in the fMRI were evoked in the left and right amygdala by painful heat stimulation of the skin on the left hand of a healthy volunteer. Stimulus-response functions (SRFs) show a positive correlation between signal change in the amygdala and perceived intensity of painful stimuli (P2–4) compared to nonpainful stimuli (P1). Interestingly, stimuli that were not perceived (P0) evoked a signal comparable to that evoked by a painful stimulus (P3), which may be related to the anxiety arising from the anticipation of pain (Bornhovd and others

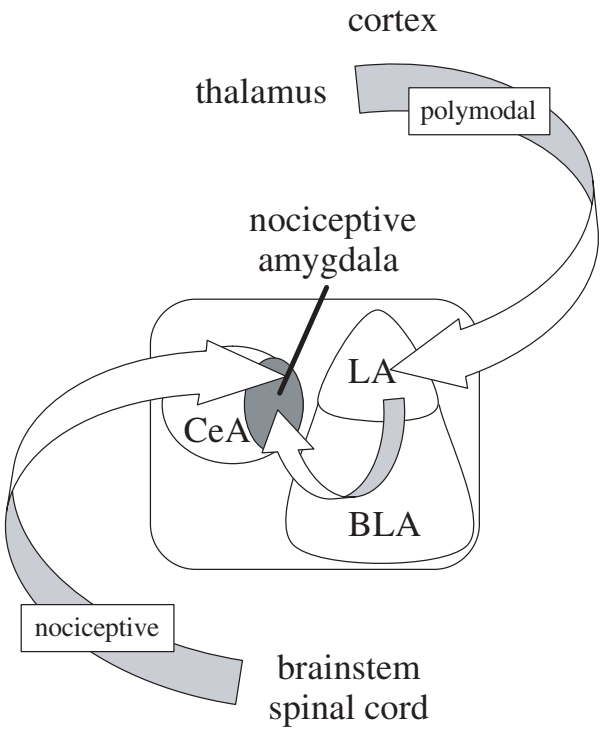

Fig. 1. Major sensory, including nociceptive, inputs to the amygdala. The latero-capsular part of the central nucleus of the amygdala (CeA) is termed *nociceptive amygdala*. It receives nociceptive-specific information from the spinal cord and brainstem through the spino-parabrachio-amygdaloid pain pathway, whereas highly processed polymodal, including nociceptive, information from the thalamus (midline and posterior nuclei) and cortex reaches the lateral and basolateral amygdala (LA and BLA, respectively). The CeA integrates polysensory and nociceptive-specific information, attaching emotional significance to painful stimuli.

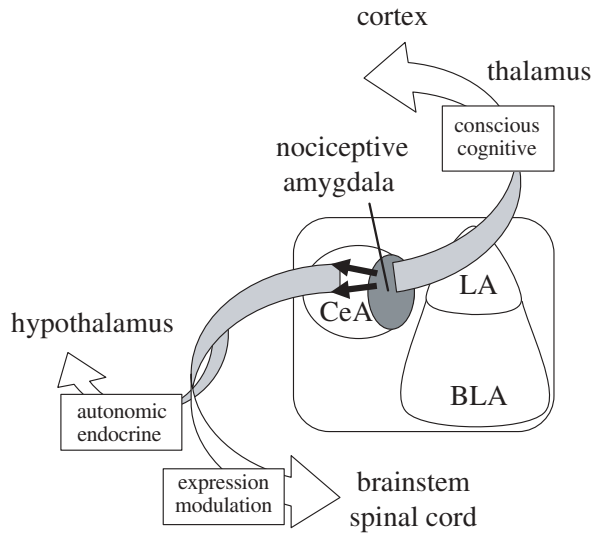

Fig. 2. Major pain-related outputs from the amygdala. The latero-capsular central nucleus of the amygdala (CeA, "nociceptive amygdala") forms widespread direct and indirect connections with forebrain and brainstem areas. Projections to thalamus and cortical areas may be related to cognitive and conscious components of pain. Autonomic and neuroendocrine pain responses involve the hypothalamus. Emotional expression and modulation of pain behavior are regulated by the CeA through projections (mainly via the ventral amygdaloid pathway) to brainstem areas that are part of an endogenous pain-modulating system, which includes circuits connecting periaqueductal gray matter, rostral ventromedial medulla (consisting of nucleus raphe magnus, nucleus gigantocellularis pars alpha, and adjacent reticular formation), and dorsal horn of the spinal cord. LA, lateral nucleus of the amygdala; BLA, basolateral nucleus of the amygdala.

2002). This phenomenon illustrates the difficulties with imaging a brain structure that is involved in a variety of different but somewhat related functions. It also emphasizes the importance of a careful selection of the baseline to which measures of brain activity levels are being compared to detect signal changes. The expectation of pain can cause changes in affective state and increase the experience of pain (Ploghaus and others 1999). The U-shaped SRF would be consistent with a role of the amygdala in the emotional evaluation of pain in the context of previous or concurrent experiences (Fields 2000; Rhudy and Meagher 2003).

Although the above-mentioned studies detected a correlation between amygdala responses and pain behavior in animals and pain experienced in humans, both activation and deactivation ("negative activation") were measured. It should also be noted that a number of previous neuroimaging pain studies were unable to detect signal changes in response to painful stimuli or in certain pain states. The basis of these discrepancies is yet to be understood, but general "neurophysiological and anatomical considerations in functional imaging of pain" (Davis 2003) also apply to the amygdala. The amygdala is a small structure with many diverse clusters of nuclei, subdivisions, and circuitry. The amygdala contains multiple neuronal populations responding to a variety of stimuli and conditions. Even the "nociceptive amygdala" comprises at least four classes of neurons (see Electrophysiology). PET and fMRI measure blood flow and blood oxygen level, respectively. The correlation between imaging signals and action potential firing of neurons is unknown (Davis 2003). As a key element in a variety of brain functions, the amygdala is easily affected by the behavioral condition, and therefore, the selection and definition of the appropriate baseline activity are of critical importance. Increased resolution and advanced analysis techniques may improve the analysis of pain mechanisms in the amygdala.

Behavior: Pain Enhancement versus Pain Inhibition

Several lines of evidence implicate the amygdala in pain modulation, and it appears that the amygdala is critically involved in both pain enhancement (hyperalgesia) and pain reduction (hypoalgesia or analgesia). Electrical stimulation of the amygdala elicits vocalizations that are accompanied by emotional reactions (Jurgens and others 1967; Jurgens 1982). Bilateral lesions or chemical inac-

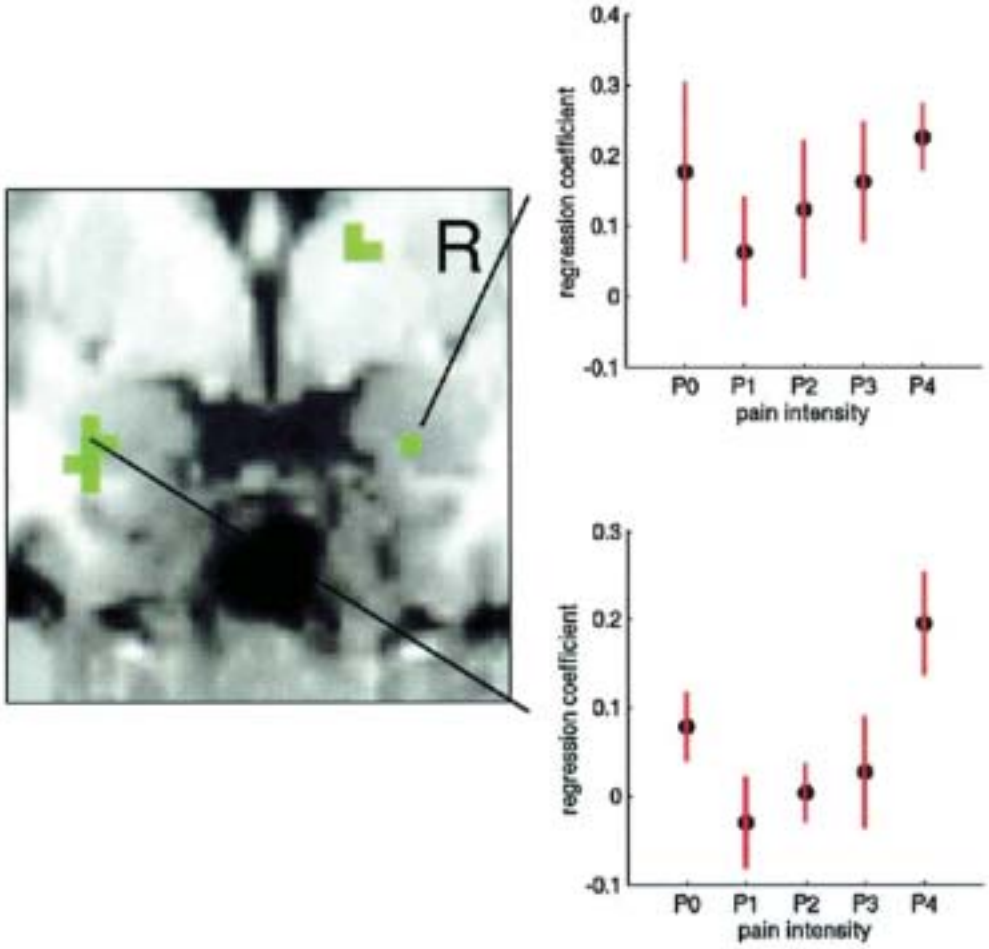

Fig. 3. Bilateral activation of the amygdala by painful stimuli. The T_1-weighted MRI (left) shows enhanced blood oxygen level–dependent (BOLD) signals evoked by noxious heat stimuli in a normal human subject. Stimulus-response functions (SRFs, right) suggest that amygdala activation is positively correlated with the perceived pain intensity of heat stimuli (P2–4) compared to nonpainful thermal stimuli (P1). SRFs were constructed by plotting the magnitude of the response (BOLD signal) for each trial type (P0–P4) as a function of rating. Interestingly, a stimulus that was not perceived (P0) evoked a greater signal than a nonpainful stimulus, comparable to that evoked by a painful stimulus (P3), suggesting perhaps a role of the amygdala in the anxiety arising from the anticipation of pain. Stimuli of four intensities (300–600 mJ) were applied to the dorsum of the left hand in randomized order, using an infrared laser. Stimuli were rated on a five-point scale: P0, pain not noticed; P1, sensation that felt warm but not painful; P2, lowest painful stimulus defined as the feeling when pulling a small hair on the dorsum of the hand; P3, pain intermediate between P2 and P4; P4, maximum pain in the experiment (600 mJ). Reproduced with permission by Oxford University Press, from Bornhovd and others (2002).

tivation of the amygdala, including the CeA, decreases emotional pain reactions such as vocalizations and vocalization after-discharges (Charpentier 1967; Calvino and others 1982; Werka 1997; Borszcz 1999), without affecting normal behavior or baseline nociceptive responses (Charpentier 1967; Calvino and others 1982; Helmstetter and Bellgowan 1993; Maier and others 1993; Fox and Sorenson 1994; Manning and Mayer 1995a, 1995b; Manning 1998; Watkins and others 1998; Tershner and Helmstetter 2000).

Although these data might suggest the involvement of the amygdala in pain production and expression, substantial evidence from numerous studies has clearly established a role of the amygdala in various forms of conditioned hypoalgesia and analgesia, that is, pain reduction and pain inhibition by aversive stimuli and stressors, some of which also evoke fear-related behavior (see references in Crown and others 2000; Rhudy and Meagher 2003). Amygdala lesions involving particularly the CeA reduced or abolished the expression of such conditioned hypoalgesia and/or analgesia (Helmstetter 1992; Helmstetter and Bellgowan 1993; Fox and Sorenson 1994; Watkins and others 1998; Crown and others 2000). These and other studies have led to the original concept of the amygdala, and the CeA in particular, being part of a descending endogenous pain control system that includes circuits in the brainstem (PAG and rostral ventromedial medulla [RVM]) and spinal cord (Helmstetter 1992; Heinricher and McGaraughty 1999; Millan 1999; Fields 2000; Rhudy and Meagher 2000; Bourgeais and others 2001; Gauriau and Bernard 2002).

Further evidence for an important role of the amygdala in descending inhibitory pain control came from bilateral or unilateral amygdala lesion studies that impli-

cated the CeA but not BLA in the analgesic effects of systemic morphine, a μ-opioid receptor agonist, in models of tonic and phasic pain (Manning and Mayer 1995a, 1995b; Manning 1998). Bilateral chemical inhibition of the CeA but not BLA also reduced the analgesic effects of systemic cannabinoid receptor activation in phasic and tonic pain models and the cannabinoid-induced inhibition of pain-related c-fos expression in the dorsal horn of the spinal cord (Manning and others 2003). The antinociceptive and analgesic effects of μ-opioid receptor activation in the BLA or CeA can be inhibited by lesions or chemical inactivation of the PAG and RVM (Helmstetter and others 1998; Pavlovic and Bodnar 1998; Tershner and Helmstetter 2000). Consistent with the participation of the amygdala in endogenous pain control, unilateral electrical stimulation of the amygdala, including the CeA and BLA, produced a reduction of phasic and tonic pain behavior (Mena and others 1995).

It does not come as a surprise, however, that a brain area such as the amygdala, which is involved in the reciprocal interaction between pain and affective state, not only modulates pain through descending inhibitory control systems but also contributes to the generation and enhancement of pain responses (Rhudy and Meagher 2003). Evidence for the latter function is provided by more recent behavioral studies using models of prolonged pain. Unilateral excitotoxin-induced lesions of the CeA significantly inhibited the second but not the first phase of formalin-induced pain behavior (Fig. 4) (Manning 1998), although it should be noted that no significant effect was detected in earlier studies (Helmstetter 1992; Manning and Mayer 1995a). Nociceptive processing and pain behavior in the formalin test, a model of inflammatory pain, follow a biphasic time course: The first phase represents acute nociception due to the activation of primary afferents, whereas the second phase includes an inflammatory state and reflects a combination of peripheral and central sensitization (Henry and others 1999). Nociceptive scores (flinches) were reduced in the second phase of the formalin test in rats with ipsilateral CeA lesions compared to nonlesioned "sham" rats (Fig. 4).

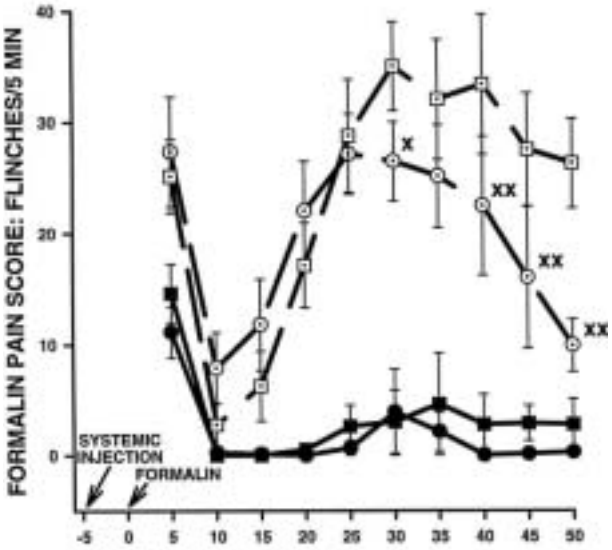

Fig. 4. Unilateral lesion of the central nucleus of the amygdala (CeA) reduces pain behavior in rats in the formalin pain test. Average nociceptive scores of rats with unilateral excitotoxin-induced lesions of the CeA (open circles) are significantly reduced in the second phase of the formalin test (30–50 min after injection of formalin into the ipsilateral hind paw) compared to nonlesioned sham rats (open squares). Formalin injection into the hind paw typically causes biphasic pain behavior, with the first phase (< 10 min) reflecting primary afferent activation and the second phase (> 15 min) resulting from both peripheral and central sensitization. Formalin (50 μl; 1%) was injected into one hind paw 7 days after the surgery for CeA lesion. The figure also shows the analgesic effects of systemic injection of morphine sulfate (6 mg/kg, s.c.) both in nonlesioned sham rats (filled squares) and in rats with CeA lesions contralateral to the injected hind paw (filled circles). Interestingly, unilateral CeA lesions did not affect morphine analgesia in rats with formalin pain induced in the contralateral hind paw (but CeA lesions ipsilateral to the formalin injection did; data not shown). Error bars indicate SEM. Flinch-frequency method of nociceptive scoring was performed measuring the total number of lifting, flinching, or shaking of the injected paw per 5-min interval. $^{x}P < 0.05$. $^{xx}P < 0.01$, Mann-Whitney U test, compared with unilateral CeA sham lesion rats. Reproduced from Manning (1998), copyright 1998 by the Society for Neuroscience.

Conversely, activation of glucocorticoid and mineralocorticoid receptors by corticosterone delivery into the CeA (stereotaxic implants) produced hypersensitivity to colorectal distension (CRD) and increased visceromotor responses in rats with sensitized colons, which was paralleled by increased indices of anxiety (Greenwood-Van Meerveld and others 2001). Corticosterone application to the CeA, which has been shown to increase the expression of the "stress hormone" corticotropin releasing factor in the amygdala, resulted in enhanced anxiety-like behavior (Fig. 5A). Rats with corticosterone implants spent significantly less time in the open arm of the plus maze assay than control (cholesterol-implanted) rats. Stimulation of the CeA with corticosterone also produced increased visceromotor responses to CRD in normal rats (Fig. 5B, right) and in rats with sensitized colons (Fig. 5C, right). Corticosterone delivery to the CeA appeared to mimic the visceral hypersensitivity that followed the sensitization of the colon with intracolonic acetic acid. In the absence of CRD, there was no significant difference between rats with corticosterone administration and control (cholesterol-implanted) rats (Fig. 5 B, C, left). These data suggest an important role of the amygdala, presumably the CeA, in the development of visceral hypersensitivity (Greenwood-Van Meerveld and others 2001).

The amygdala-mediated colorectal hypersensitivity involves the sensitization of lumbosacral spinal neurons through amygdala-dependent descending facilitation. Spinal neurons with nociceptive input from the colon and rectum show greater and longer lasting excitatory responses to CRD, and a larger number of these neurons

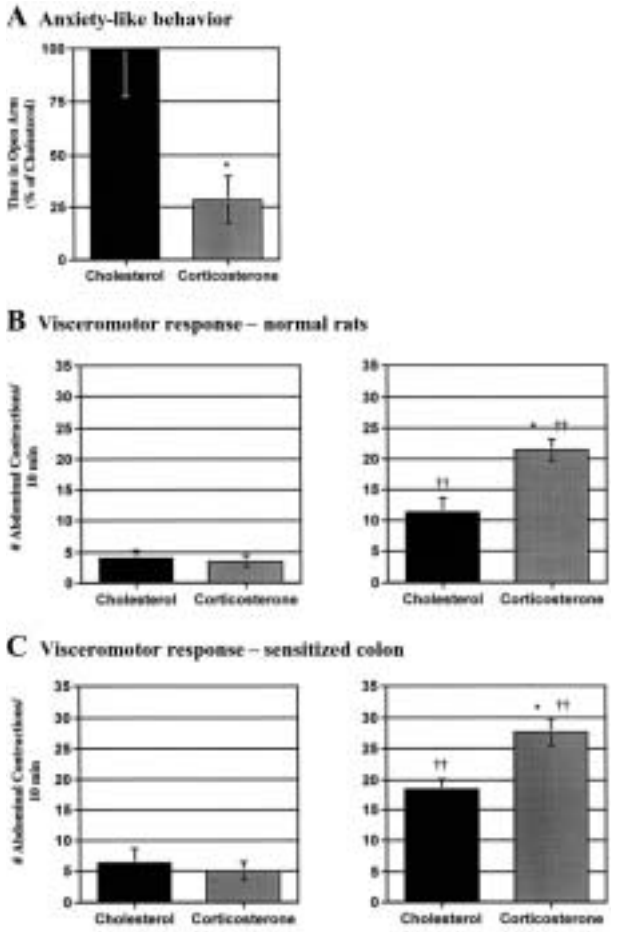

Fig. 5. Stimulation of the central nucleus of the amygdala (CeA) with corticosterone produces anxiety-like behavior and visceral hypersensitivity. Corticosterone implants were placed on the dorsal margin of the amygdala (CeA). *A*, Rats with stereotaxically delivered corticosterone to the CeA spent significantly less exploration time in the open arm of the elevated plus maze than control (cholesterol-implanted) rats (gray bar). **P* < 0.05. *B*, Effect of CeA stimulation with corticosterone on visceromotor responses in rats with normal (nonsensitized) colons. Control (cholesterol-implanted) rats and corticosterone-implanted rats showed no difference in the number of abdominal contractions under basal conditions (undistended colon, left), but innocuous colorectal distension with a balloon catheter (30 mmHg for 10 min, right) produced a significantly greater response in corticosterone-implanted rats compared to control rats. ††*P* < 0.05, undistended versus distended; **P* < 0.01, distended cholesterol versus corticosterone. *C*, Effect of colonic sensitization on the visceromotor responses of rats with corticosterone implants in the CeA and in control (cholesterol-implanted) rats. Acetic acid (0.6%, 1.5 ml) was slowly infused into the colon through a silastic tube running along the balloon catheter. Colon sensitization with acetic acid increased the visceromotor responses of rats with corticosterone implants and of control rats (right), but the response was greater in the group with corticosterone-stimulated CeA (right): 5.5-fold increase (corticosterone group) versus 2.6-fold increase (cholesterol group). No difference was found between corticosterone-implanted rats and control rats under basal conditions (undistended but sensitized colons, left). ††*P* < 0.05, undistended versus distended; **P* < 0.01, distended cholesterol versus corticosterone. Reproduced with permission by Elsevier from Greenwood-Van Meerveld and others (2001).

are spontaneously active in rats with elevated glucocorticoids in the CeA compared to control (cholesterol-implanted) rats (Qin, Greenwood-Van Meerveld, Myers, and others 2003; Qin, Meerveld, and others 2003). Similarly, spontaneous activity and responses of spinal neurons to urinary bladder distension are greater in rats with elevated glucocorticoids than in control (cholesterol-implanted) rats (Qin, Greenwood-Van Meerveld, and Foreman 2003). Importantly, the amygdala-mediated sensitization of spinal neurons to CRD or urinary bladder distension does not require altered visceral receptor sensitivity or primary afferent sensitization because the visceral tissue was not inflamed or injured in these studies. These data add strong support to the concept of the amygdala regulating descending facilitatory pathways, such as the amygdala-PAG-RVM–spinal cord pathway, to increase pain processing and contribute to chronic pain through the generation and maintenance of central sensitization in the spinal cord (Heinricher and McGaraughty 1999; Porreca and others 2002).

Although differences in experimental conditions, pain models, pain tests, and parameters measured in these studies need to be considered, it appears that the amygdala, including the CeA, has a dual pain-enhancing and pain-inhibiting function. This has been directly demonstrated in a behavioral study in which bilateral lesions of the CeA blocked shock-induced hyperalgesia measured as decreased threshold and increased intensity of vocalizations to electrical tail-shock and to noxious heat, without affecting baseline vocalization responses, but the CeA lesions also prevented shock-induced antinociception in the tail-flick test (Crown and others 2000). Electrophysiological data suggest that electrical and chemical stimulation in the CeA can both activate and inhibit neurons in the brainstem (PAG) that are part of descending pain modulation systems (Da Costa Gomez and Behbehani 1995). This bidirectional regulation of pain through the amygdala would be consistent with the reciprocal relationship between pain and negative affect, which includes pain enhancement by some affective states (mild shock, anxiety, depression) but pain inhibition by others (severe shock, stress, fear) (Crown and others 2000; Rhudy and Meagher 2000, 2003).

Electrophysiology: Nociceptive and Synaptic Plasticity

Now that the amygdala, and the CeA in particular, has emerged as an integral part of the pain system with important roles in both pain enhancement and pain inhibition, the issue of how the amygdala responds to pain and how pain affects amygdala activity becomes significant. As mentioned before, neuroimaging studies have provided heterogeneous information with regard to the relationship between amygdala function and pain in that both pain-related activation and deactivation have been reported. The analysis of pain mechanisms in the amygdala at the single-cell level provides important insight into how activity levels in the amygdala are modulated in

responses to nonpainful events, brief pain signals, and persistent pain states.

Electrophysiological pioneer studies from Bernard's group (Bernard and others 1992, 1996; Gauriau and Bernard 2002) and recent data from our laboratory (Neugebauer and Li 2002, 2003; Li and Neugebauer 2003) have now established the latero-capsular part of the CeA as the "nociceptive amygdala." Using extracellular single-unit recordings in anesthetized animals (rats), the processing of nociceptive information from superficial (skin) and deep tissue (joints and muscles) was analyzed in CeA neurons. Although potentially confounding effects of anesthesia need to be considered, the advantage of the anesthetized preparation is that it allows a single-cell analysis at the systems level and at the same time provides a stable environment through the constant control of body temperature, metabolism, and respiratory and cardiovascular parameters. This is of critical importance for the study of a brain structure such as the amygdala that is sensitive to changes in the internal and external bodily environment.

The main findings of these electrophysiological single-unit studies of nociceptive processing in the CeA can be summarized as follows (Bernard and others 1992; Neugebauer and Li 2002, 2003; Li and Neugebauer 2003). The vast majority (around 80%) of CeA neurons respond exclusively or predominantly to noxious (i.e., painful in the awake subject) stimulation of superficial and deep body tissue. CeA neurons typically have large, often symmetrical bilateral receptive fields that can include the whole body, arguing against a sensory-discriminative role of the amygdala. CeA neurons encode mechanical and thermal nociceptive information with sigmoidal rather than monotonically increasing SRFs (see Fig. 6 C, D), consistent with a role in other than sensory-discriminative aspects of pain. Background activity is variable but can be substantial, suggesting a continuous activity level. Electrical orthodromic stimulation in the pontine PB produces monosynaptic responses of latero-capsular CeA neurons consistent with input from the spino-parabrachio-amygdaloid pain pathway (Gauriau and Bernard 2002). Several types of CeA neurons have been identified that may reflect different contributions of the amygdala to pain: Nociceptive-specific (NS) neurons are activated exclusively by noxious stimuli and preserve information about "pain"; multireceptive (MR) neurons, which respond to innocuous but more strongly to noxious stimuli, integrate pain signals with other sensory information; nonresponsive (noSOM) neurons, which do not have a somatic receptive field under normal conditions, may contribute specifically to persistent pain; and inhibited neurons show a reduction of background activity in response to noxious stimuli. These neurons could participate in the dual pronociceptive and antinociceptive function of the amygdala by enhancing or decreasing output to pain modulation systems.

The effect of persistent pain on the nociceptive amygdala was not known until recently when two major subpopulations of CeA neurons, MR neurons and noSOM neurons, but not NS neurons, were shown to exhibit substantial nociceptive and synaptic plasticity in a model of persistent arthritic pain (Li and Neugebauer 2003; Neugebauer and Li 2003; Neugebauer and others 2003). In this model, a monoarthritis is induced in one knee by intra-articular injections of kaolin and carrageenan, which cause an acute-onset inflammation that develops progressively within a few hours, reaches a maximum plateau after 6 hours, and persists for weeks. The arthritis results in well-documented pain behavior (decreased hind limb withdrawal thresholds, reduced exploratory behavior, increased vocalizations), and sensitization of primary afferent nerve fibers and spinal cord neurons (see Li and Neugebauer 2003; Neugebauer and Li 2003; Neugebauer and others 2003). In the amygdala, MR neurons with excitatory input from the knee joint responded more strongly to noxious than to innocuous mechanical stimuli under control conditions (see individual example in Fig. 6A). Within hours after induction of arthritis, these neurons typically developed enhanced responses to mechanical stimuli (Fig. 6B), indicating an enhanced gain as evidenced by the upward shift of the SRFs (Fig. 6 C, D) (Neugebauer and Li 2003). Importantly, enhanced information processing was not limited to input from the arthritic knee but also included inputs from noninjured parts such as the ankle and resulted in the expansion of the total receptive fields of these neurons. In addition, the responses of CeA neurons to a constant input evoked by orthodromic electrical stimulation in the PB also increased in the arthritic pain state, suggesting that these neurons are in fact "sensitized" (Neugebauer and Li 2003).

Although the sensitization of CeA neurons to such a variety of inputs is consistent with their involvement in functions other than sensory-discrimination, it is not simply the result of a generally increased excitability state in the amygdala but is input specific and dependent on the response properties of the neuron under normal conditions. Responses of MR neurons to mechanical but not thermal stimuli changed; NS neurons showed no changes of their responses to mechanical, thermal, and electrical stimulation; noSOM neurons developed prolonged responses to mechanical but not thermal stimuli after induction of arthritis (Neugebauer and Li 2003). These data suggest that prolonged pain is accompanied by enhanced responsiveness of a subset of CeA neurons. MR neurons could serve to integrate and evaluate information in the context of prolonged pain. Recruitment of noSOM neurons would increase the gain of amygdala processing. NS neurons preserve the distinction between nociceptive and non-nociceptive inputs.

The sensitization of CeA neurons measured in vivo is maintained independently of continuous sensory input from peripheral and spinal nociceptive processes, as shown in subsequent in vitro studies (Neugebauer and others 2003). Brain slices containing the CeA were obtained from arthritic rats at the time of maximum sensitization of CeA neurons measured in the in vivo stud-

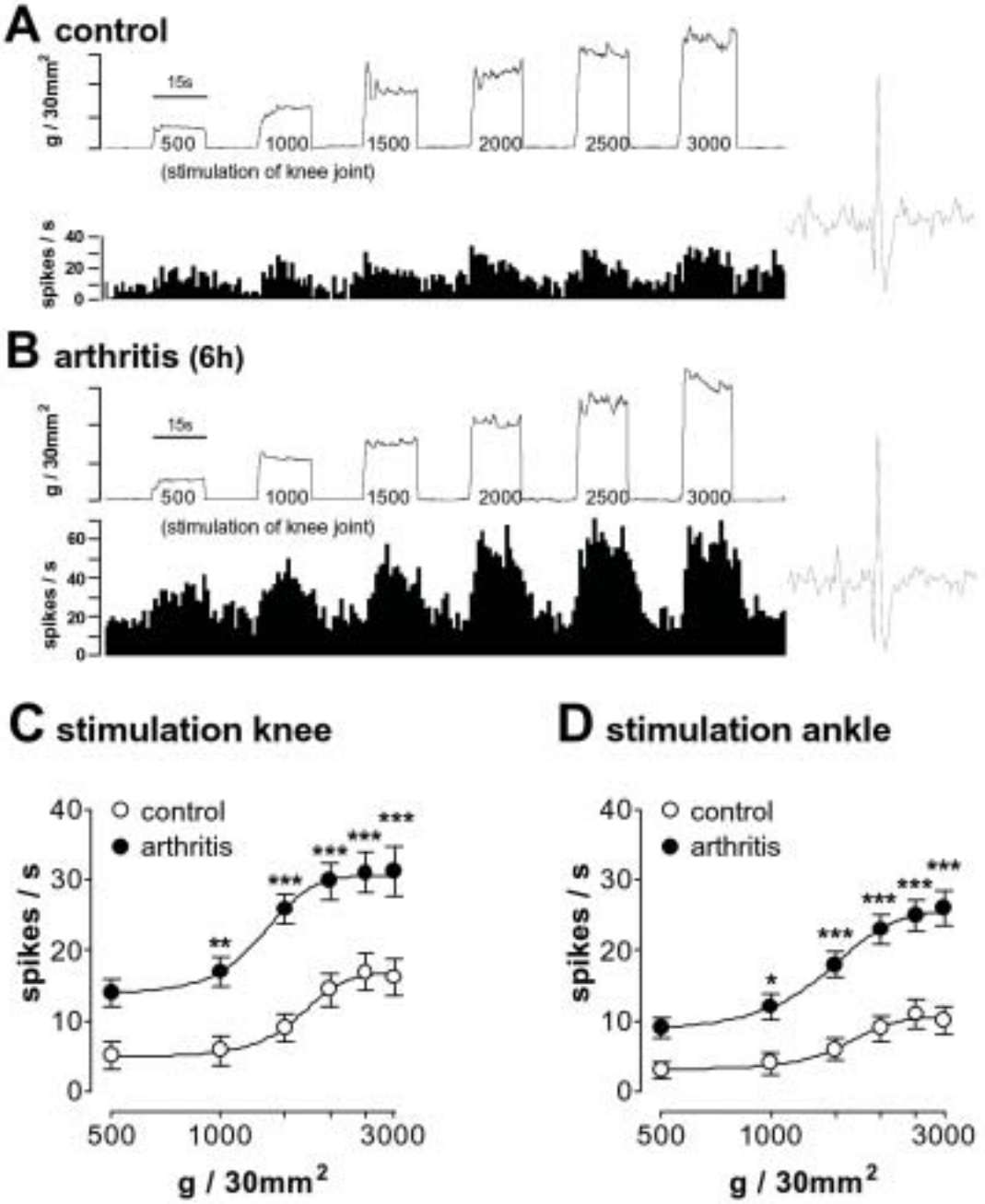

Fig. 6. Enhanced nociceptive processing in the central nucleus of the amygdala (CeA) neurons in vivo in persistent pain. Stimulus-response functions for mechanical stimulation of deep tissue are altered in the arthritis pain model. Extracellular recordings from an individual CeA neuron (same neuron in *A* and *B*) show the increased responses of a multireceptive neuron to brief (15 s) graded mechanical stimulation of the knee joint (top traces) 6 hours after induction of arthritis (*B*) compared to control (*A*). The monoarthritis was induced in one knee joint (contralateral to the recording site) by intra-articular injections of kaolin and carrageenan. Individual action potentials displayed on the right next to corresponding histograms on the left illustrate that spike configuration, shape, and size remained constant throughout the experiment. Stimulus-response functions (*C*, *D*) were constructed from the averaged responses of individual CeA neurons to graded mechanical stimuli in the innocuous (< 500 g/30 mm^2) and noxious range (> 1500 g/30 mm^2). Stimuli were applied to the arthritic knee and the nonarthritic ankle. Stimulus-response curves for mechanical stimulation were best described by a sigmoid nonlinear regression. Note the logarithmic scale. Each symbol represents the mean ± SEM. The stimulus-response relationships before and after induction of arthritis were significantly different. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$, two-way ANOVA followed by Bonferroni posttests. Reproduced with permission by the American Physiological Society, from Neugebauer and Li (2003).

ies (see above). Whole-cell voltage-clamp recordings of CeA neurons showed that synaptic transmission of both nociceptive-specific inputs from the pontine PB area (PB-CeA synapse) and polymodal thalamo-cortical inputs (BLA-CeA synapse) was enhanced in the arthritis pain model compared to control neurons from normal

and sham rats (Fig. 7). Lower thresholds for excitatory postsynaptic currents (EPSCs) and orthodromic spike generation at the BLA-CeA synapse and lower EPSC spike thresholds at the PB-CeA synapse in the arthritis pain state resulted in significantly enhanced input-output relationships in neurons from arthritic animals compared to control neurons (Fig. 7).

In addition to such synaptic plasticity, CeA neurons recorded in slices from arthritic rats also developed increased excitability compared to control CeA neurons. In the arthritis model, the resting membrane potential of CeA neurons was significantly depolarized; input resistance was significantly decreased; average slope conductance calculated from the linear portion of the current-voltage relationship was greater; action potentials generated by intracellular injections of depolarizing currents could be evoked at more hyperpolarized resting membrane potentials (Neugebauer and others 2003). These data suggest altered membrane properties of CeA neurons in the arthritis pain model. As a consequence of these neuroplastic changes, both the input to and the output from the CeA are enhanced during arthritis-induced prolonged pain. The altered input is reflected in the enhancement of synaptic transmission, and the increased output will result from the depolarization of CeA neurons in arthritis, which renders the neurons more excitable.

Taken together, the anatomical, imaging, behavioral, and electrophysiological data suggest that pain-related sensitization, synaptic plasticity, and increased excitability of CeA neurons should activate cortical systems concerned with cognitive-affective functions as well as descending systems involved in the expression of pain behavior. These hypotheses need to be addressed experimentally.

Pharmacology and Biochemistry: Mechanisms of Pain-related Plasticity

The mechanisms of pain-related plasticity are not yet known. Understanding the pharmacological and chemical mechanisms, however, may provide novel and improved targets for the relief of pain and its emotional-affective components, at least as far as they involve amygdala functions. Our initial studies addressed the role of metabotropic glutamate receptors (mGluRs). Glutamate is a major neurotransmitter in the nervous system, and G-protein-coupled mGluRs have been implicated in neuroplasticity associated with normal brain functions but also in a variety of neurological and psychiatric disorders (Schoepp and others 1999; Neugebauer 2002; Varney and Gereau 2002). Eight mGluR subtypes have been cloned to date and are classified into groups I (mGluR1,5), II (mGluR2,3), and III (mGluR4,6,7,8). Group I mGluRs typically couple through $G_{q/11}$ proteins to the activation of phospholipase C, resulting in phosphoinositide hydrolysis, release of calcium from intracellular stores, and protein kinase C activation, although other signal transduction mecha-

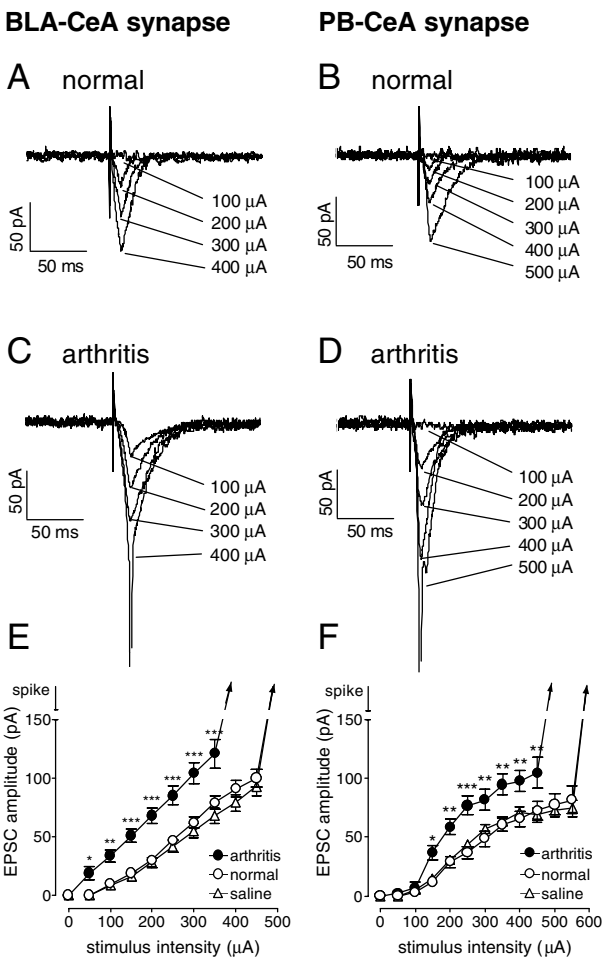

Fig. 7. Synaptic plasticity in the central nucleus of the amygdala (CeA) in vitro in persistent pain induced in vivo. Input-output relationships at the nociceptive parabrachial nucleus (PB)–CeA and the polymodal basolateral nucleus of the amygdala (BLA)–CeA synapses show enhanced synaptic transmission in the arthritis pain model. Coronal brain slices containing the CeA were obtained from control (uninjected normal and saline-injected sham) rats and from rats with a kaolin/ carrageenan–induced monoarthritis in the left knee (6–8 h postinduction). Whole-cell voltage-clamp recordings were made from neurons in the latero-capsular part of the CeA. Monosynaptic excitatory postsynaptic currents (EPSCs) were evoked by electrical stimulation of afferent fibers from the parabrachial area (PB-CeA synapse) and from the basolateral amygdala (BLA-CeA synapse). Input-output relationships were obtained by increasing the stimulus intensity in 50 µA steps and measuring the peak amplitudes of evoked EPSCs. *A–D*, Individual examples of one CeA neuron recorded in the brain slice from a normal rat (*A*, *B*) and another CeA neuron from an arthritic rat (*C*, *D*). *A*, *C*, At the BLA-CeA synapse, lower thresholds for EPSCs and orthodromic spike generation were recorded in arthritis. *B*, *D*, EPSCs evoked at the PB-CeA synapse in arthritis had lower spike thresholds. *E*, *F*, Significantly enhanced input-output relationships in neurons from arthritic animals (n = 20) compared to control neurons (N = 36: normal uninjected rats, n = 26; saline-injected shams, n = 10), suggesting enhanced synaptic transmission at the BLA-CeA (*E*) and the PB-CeA (*F*) synapses (two-way ANOVA followed by Bonferroni posttests). $^{*}P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$. Neurons were held at –60 mV. Reproduced from Neugebauer and others (2003). Copyright 2003 by the Society for Neuroscience.

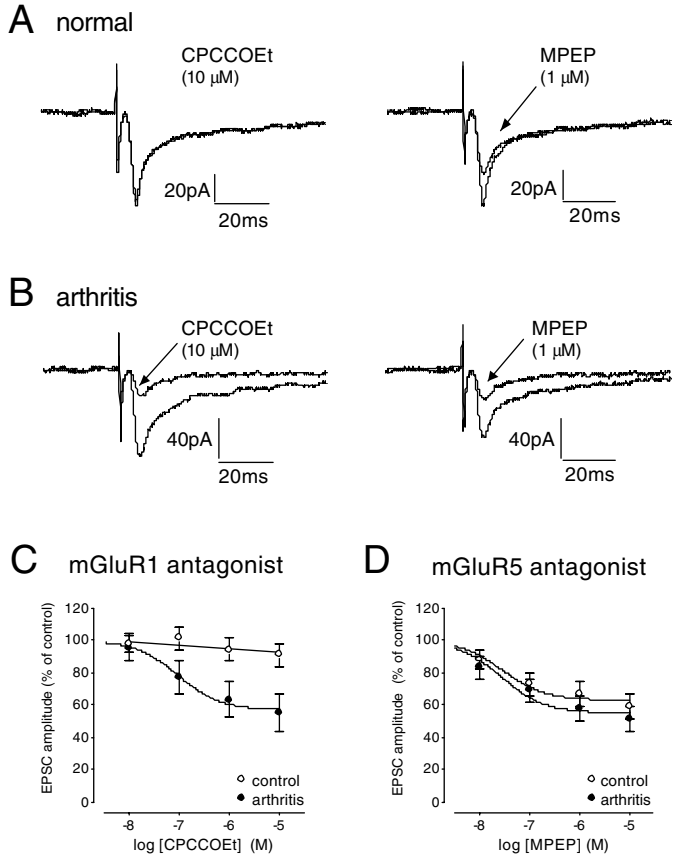

Fig. 8. Differential changes of metabotropic glutamate receptor 1 (mGluR1)– and mGluR5-mediated effects in pain-related plasticity in the central nucleus of the amygdala (CeA). *A*, In a CeA neuron recorded in a brain slice from a normal rat, MPEP (mGluR5 antagonist) inhibited synaptic transmission, whereas CPCCOEt (mGluR1 antagonist) had no effect. *B*, In a CeA neuron from an arthritic rat (6 h postinduction by intra-articular kaolin/carrageenan injections), both CPCCOEt and MPEP inhibited synaptic transmission, suggesting a change in the endogenous activation of mGluR1 in the arthritis pain model. Each trace is the average of 8 to 10 monosynaptic excitatory postsynaptic currents (EPSCs) recorded at –60 mV. Drugs were applied by superfusion of the slice in ACSF for at least 10 minutes. *C*, CPCCOEt inhibited synaptic transmission in neurons from arthritic rats (EC_{50} = 94 nM, n = 9) but not in neurons from normal rats (n = 11), suggesting a change in the activation state of mGluR1 in the arthritis pain model. *D*, The inhibitory effects of MPEP on synaptic transmission were not significantly different in control CeA neurons from normal rats (EC_{50} = 28.3 nM, n = 10) and in arthritis (EC_{50} = 27.7 nM, n = 9; $P > 0.05$, two-way ANOVA). Reproduced from Neugebauer and others (2003). Copyright 2003 by the Society for Neuroscience.

nisms have also been described (Schoepp and others 1999; Neugebauer 2002; Varney and Gereau 2002).

Pharmacological data from electrophysiological studies in vivo (Li and Neugebauer 2003) and in vitro (Neugebauer and others 2003) show that mGluR1 function is enhanced in the arthritis pain model and contributes to CeA sensitization and synaptic plasticity, whereas mGluR5 is involved in brief nociception and normal synaptic transmission as well as in nociceptive and synaptic plasticity. When administered into the CeA by microdialysis in vivo, a group I mGluR1 and mGluR5 agonist (DHPG) potentiated the responses of extracellularly recorded CeA neurons to innocuous and noxious stimuli. This effect was mimicked by an mGluR5 agonist (CHPG). In the arthritis pain state, the facilitatory effects of DHPG but not CHPG increased. Conversely, an mGluR1 antagonist (CPCCOEt) had no effect before arthritis but inhibited the responses of sensitized neurons in the arthritis pain state, whereas an mGluR5 antagonist (MPEP) inhibited brief nociceptive responses under normal conditions and prolonged nociception in arthritis (Li and Neugebauer 2003). The increased function of mGluR1 but not mGluR5 in the amygdala in persistent pain was also apparent in electrophysiological studies using brain slices in vitro (Neugebauer and others 2003). Potentiation of synaptic transmission at the PB-CeA and the BLA-CeA synapses by a group I mGluR1 and mGluR5 agonist (DHPG) was increased in slices from arthritic animals, whereas the effects of an mGluR5 agonist (CHPG) remained unchanged. Accordingly, an mGluR5 antagonist (MPEP) inhibited basal synaptic transmission under normal conditions, whereas an mGluR1 antagonist (CPCCOEt) had no effect. However, in brain slices from arthritic animals, the mGluR1 antagonist also significantly reduced transmission at this synapse (Fig. 8). Consistent with a role of mGluR1 in nociceptive processing and synaptic plasticity, CPCCOEt and DHPG were more potent at the nociceptive PB-CeA synapse than at the polymodal BLA-CeA synapse, whereas the reverse was true for MPEP and CHPG, suggesting a closer association of mGluR5 with non-nociceptive processing and basal synaptic transmission.

Several mechanisms could explain the enhanced sensitivity to mGluR1 agonists and antagonists observed in the CeA in persistent pain, including enhanced receptor affinity, altered coupling to second messenger systems, or decreased desensitization, but the most obvious possibility is increased receptor expression. In fact, western blot analysis of mGluR1 and mGluR5 protein in CeA tissue from normal rats and from arthritic rats (Neugebauer and others 2003) showed that the expression of mGluR1 protein was significantly increased in

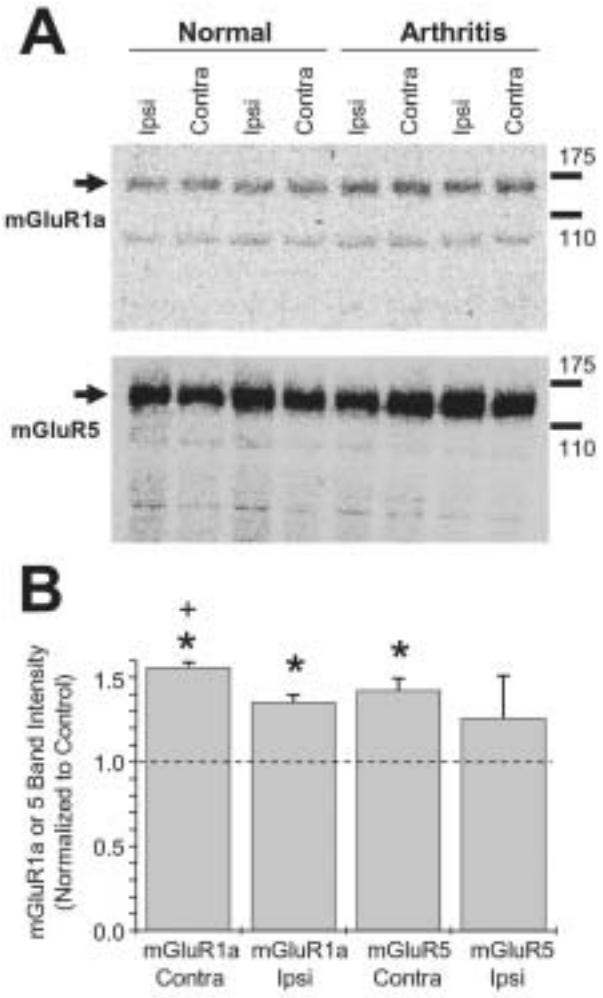

Fig. 9. Up-regulation of metabotropic glutamate receptor 1 (mGluR1) and mGluR5 in the central nucleus of the amygdala (CeA) in persistent pain. Group I mGluR1 and mGluR5 expression increased in the amygdala 5 to 6 hours after kaolin/carrageenan–induced arthritis in the knee. *A*, upper panel, mGluR1a immunoblot of CeA membranes from normal and arthritic rats; ~150 kD band is mGluR1a, whereas the lower band probably represents a proteolytic fragment or cross-reactive protein. Lower panel, mGluR5 immunoblot of CeA membranes from normal and arthritic rats; ~150 kD band represents mGluR5 immunoreactivity. *B*, Densitometry of mGluR1a and mGluR5 immunoreactivity suggests an increase in group I mGluR expression in arthritic rats with a greater increase in the contralateral (contra) amygdala (n = 3 in duplicate, $+P < 0.05$ when compared to the ipsilateral (ipsi) side with paired t-test; $*P < 0.05$ when compared to normal rats using a one-sample t-test). Reproduced from Neugebauer and others (2003). Copyright 2003 by the Society for Neuroscience.

arthritic animals compared to controls, suggesting that the enhanced mGluR1 function reflects either increased production of mGluR1 mRNA and protein or increased stability of the protein that is produced (Fig. 9). There was also a significant increase in mGluR5 levels in the CeA from arthritic animals, but this increase of mGluR5 did not translate into functional changes, perhaps because contribution of normal mGluR5 levels to synaptic transmission is already maximal or the increase in mGluR5 levels occurs on CeA cells other than those involved in pain-related plasticity.

Importantly, the mGluR1 and mGluR5 agonists and antagonists did not significantly alter the membrane properties of CeA neurons in the electrophysiological in vitro studies, suggesting that other mechanisms account for the increased neuronal excitability of CeA neurons in persistent pain. Our group is currently probing the function of N-methyl-D-aspartate receptors, which play important roles in various forms of neuroplasticity, and neuropeptides, which are abundantly present in the CeA.

Strong evidence for pain-related biochemical changes in the CeA also comes from studies that analyzed the expression of the immediate-early gene, c-Fos, a neuronal activity marker. The CeA was one of the brain areas where immunocytochemical labeling for c-Fos was detected only in rats that received noxious CRD but not in unstimulated, loosely restrained rats, suggesting that Fos expression following noxious visceral stimulation exceeded that induced by restraint stress (Traub and others 1996). Interestingly, many cortical (including cingulate and insular cortices) and subcortical (including PAG, PB, and thalamic and hypothalamic nuclei) areas, which are linked to the nociceptive amygdala, were labeled in the control rats but showed significantly more Fos expression following noxious CRD (Traub and others 1996). The c-fos mRNA expression in the latero-capsular CeA was induced following intraperitoneal injection of acetic acid as a noxious visceral stimulus (Nakagawa and others 2003). Intraplantar formalin injection as a noxious somatic stimulus, however, increased c-fos mRNA expression in the LA and BLA but not CeA (Nakagawa and others 2003), suggesting differential stimulus- or input-specific patterns of activation in the amygdala. Finally, consistent with a role of the amygdala in shock-induced hypoalgesia, Fos expression induced by colonic distension was reduced in the CeA of rats that received a brief session of stressful foot shocks compared to control rats (Stam and others 2002). These data suggest pain-related biochemical changes occur in the CeA and can be modified by certain behavioral conditions. A detailed analysis of the transmitter systems and signal transduction pathways involved in pain mechanisms in the amygdala will allow the design of target-specific drugs to modify pain-related activity in the amygdala for new therapeutic strategies.

Summary, Conclusions, and Outlook

A well-documented reciprocal relationship exists between pain and negative affective states. Accumulating evidence suggests that this interaction is mediated through the amygdala, a key player in emotionality and related disorders. The amygdala, particularly the latero-capsular part, which is now defined as the nociceptive amygdala, is closely linked to the pain system through ascending pain pathways such as the spino-parabrachio-amygdaloid pain pathway and descending inhibitory and facilitatory pathways such as the amygdala-PAG-

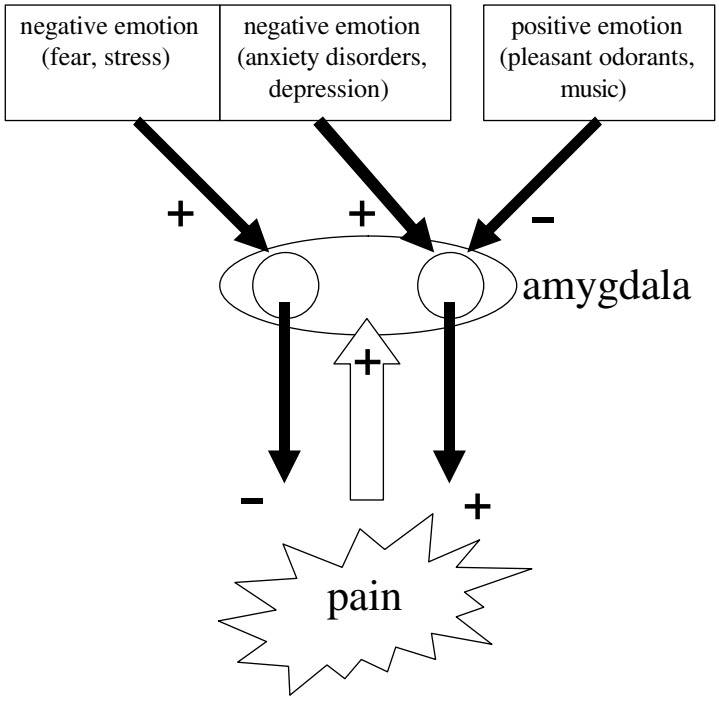

Fig. 10. Pain, emotions, and the amygdala: a hypothetical model. Negative affective states are generally associated with increased amygdala activity, whereas positive emotions have been shown to deactivate the amygdala. The amygdala is linked to both facilitatory and inhibitory pathways to modulate pain. Pain in turn enhances amygdala activity. Negative emotions associated with pain reduction (fear and stress) would activate amygdala-linked inhibitory control systems, whereas negative affective states that correlate with increased pain (depression and anxiety disorders) would activate pain-facilitating pathways. Positive emotions inhibit amygdala coupling to pain facilitation.

RVM–spinal cord pathways. The amygdala is well positioned to integrate nociceptive-specific information from the spinal cord and brainstem with highly processed polymodal information from the thalamus and cortex. This may be a mechanism by which the amygdala attaches emotional significance to painful events.

The amygdala also modulates pain behavior and experience. It is clear now that the amygdala can both enhance and inhibit pain processing and pain responses, perhaps dependent on the context, affective and pain state, and the activity level in the amygdala itself. Persistent pain states in turn modulate activity in the CeA, causing electrophysiological, pharmacological, and biochemical neuroplastic changes. The influence of such a heightened level of amygdala activity on pain-enhancing and pain-inhibiting systems needs to be examined. Conversely, the presumably differential effects of positive emotions and various negative affective states on pain processing in the amygdala remain to be analyzed.

Figure 10 depicts a hypothetical model of interaction between emotions and pain through the amygdala: Negative emotions such as fear and stress that produce hypoalgesia activate amygdala connections with descending inhibitory pathways; negative affective states such as anxiety and depression that enhance pain activate amygdala outputs to facilitatory pathways (Heinricher and McGaraughty 1999; Fields 2000; Rhudy and Meagher 2000, 2003; Porreca and others 2002). Positive emotions that decrease the unpleasantness of pain inhibit amygdala-mediated pain facilitation (Blood and Zatorre 2001; Villemure and others 2003). Activity-dependent targeting of pharmacologically and biochemically phenotyped neurons belonging to these different amygdala circuits may provide a new avenue for improved therapeutic strategies to relieve pain and its affective components. Pain facilitation versus pain inhibition could also be related to different types of amygdala plasticity (long-term potentiation versus long-term depression), and targeting the underlying mechanisms may yield useful therapeutic tools. Reversing abnormal activity levels in the amygdala may contribute to pain relief by restoring balance to the bodily environment. This would be consistent with homeostasis being an integral and vital function of the limbic system, of which the amygdala is part.

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