

The Amygdaloid Complex: Anatomy and Physiology

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Sah, P., E. S. L. Faber, M. Lopez de Armentia, and J. Power. The Amygdaloid Complex: Anatomy and Physiology. *Physiol Rev* 83: 803–834, 2003; 10.1152/physrev.00002.2003.—A converging body of literature over the last 50 years has implicated the amygdala in assigning emotional significance or value to sensory information. In particular, the amygdala has been shown to be an essential component of the circuitry underlying fear-related responses. Disorders in the processing of fear-related information are likely to be the underlying cause of some anxiety disorders in humans such as posttraumatic stress. The amygdaloid complex is a group of more than 10 nuclei that are located in the midtemporal lobe. These nuclei can be distinguished both on cytoarchitectonic and connectional grounds. Anatomical tract tracing studies have shown that these nuclei have extensive intranuclear and internuclear connections. The afferent and efferent connections of the amygdala have also been mapped in detail, showing that the amygdaloid complex has extensive connections with cortical and subcortical regions. Analysis of fear conditioning in rats has suggested that long-term synaptic plasticity of inputs to the amygdala underlies the acquisition and perhaps storage of the fear memory. In agreement with this proposal, synaptic plasticity has been demonstrated at synapses in the amygdala in both in vitro and in vivo studies. In this review, we examine the anatomical and physiological substrates proposed to underlie amygdala function.

I. INTRODUCTION

The amygdala is an almond-shaped structure deep within the temporal lobe and was first identified by Burdach in the early 19th century. Burdach originally described a group of cells that are now known as the basolateral complex. Subsequently, a large number of structures that surround the basolateral complex have been identified in many species and constitute what is now known as the amygdaloid complex. This structure has attracted continued interest because of its central role in emotional processing. The word *emotion* is a difficult concept that describes subjective experiences and feelings such as pain, fear, desire, and hope as well as aspects of the behavior of individuals both public and private. In the past, emotions had traditionally been viewed as exclusively human and distinct from other aspects of brain function such as cognition and sensory perception. This separation between cognition and emotion persisted despite there being little doubt that emotions can have a major impact on various aspects of mental function. In the biological study of emotions, perhaps the single most influential contribution was that of Charles Darwin. In his seminal *Expression of Emotions in Man and Animals* published in 1872, Darwin (40) suggested that there are some fundamental aspects of emotion that find similar expression in the behavior of both man and animals. This was the first indication that it may be possible to make inferences about human emotion by examining animal behavior. Around the same time William James (87) and C. G. Lange (111) independently suggested that emotions are the cognitive responses that accompany our physiological responses to external stimuli. This idea came to be called the James-Lange theory of emotion. Thus, in James' words, when we see a bear "we don't run because we are afraid but are afraid because we run" (88). Together with Darwin's proposal, these ideas suggested that it is possible to study emotions by examining the physiological responses to stimuli.

The first neurophysiological theories of emotion emerged from the work of Cannon and Bard in the 1920s. Cannon and Bard were critical of the James-Lange theory and instead suggested that the hypothalamus and its projections to the cortex and brain stem were the central element that both evaluated and initiated emotional responses (25). Subsequently, Papez (197), reviewing the anatomical and clinical data in 1937, added more medial temporal structures to the circuitry involved in emotional expression. These ideas were further expanded by Paul McLean (172), who named these forebrain circuits the "visceral brain" and introduced the concept of the limbic system. While McLean included the amygdala in the limbic system, the involvement of the amygdala in emotional processing arose from the now classic studies of Klüver and Bucy (101, 102) who examined the behavioral effects

of medial temporal lobe lesions in monkeys. These animals showed a range of effects including marked changes in emotional behavior that were described by them as "psychic blindness" and has come to be known as the Klüver Bucy syndrome. However, these lesions were quite large and included the amygdala, hippocampus, and surrounding cortical areas. Subsequently, Weiskrantz (288) showed that more restricted amygdala lesions could replicate the results of Klüver and Bucy, cementing the fundamental role of the amygdala in emotional processing. These studies made it clear that the amygdala is an essential component of the circuitry that assigns emotional significance and produces appropriate behavioral responses to salient external stimuli (69, 96, 116, 231).

While initial studies on the role of the amygdaloid complex used avoidance conditioning and instrumental learning (245), the study of emotions reached a new level of analysis with the development of the study of fear conditioning. Fear conditioning is a simple Pavlovian conditioning task in which a neutral stimulus, such as a tone or a light, is paired with an aversive stimulus, typically a footshock. Following a relatively small number of such pairings, the neutral stimulus subsequently elicits a behavioral state similar to that evoked by the aversive stimulus alone. The fear response consists of freezing (a cessation of movement), sweating, and changes in heart rate and blood pressure. In humans, there are also cognitive effects such as feelings of dread and despair associated with these autonomic effects. This learned behavior is rapidly acquired and long lasting. The simple nature of this learning task, and the readily measured physiological changes that accompany it, have made the study of fear conditioning a very attractive model for the study of learning and memory consolidation. Furthermore, because of the physiological similarities between animal and human fear, fear conditioning is seen as relevant to the genesis of anxiety disorders in humans (41, 43, 237), thus providing an additional incentive to study fear. These advances have led to a rapid increase in the number of studies examining the role of the amygdala in fear, learning, and memory in general. Although some controversy persists in the precise role of the structures involved (114, 198), these studies have provided definitive evidence implicating the amygdala and its afferent and efferent projections in fear processing in mammals (1, 43, 96, 115).

In this review, we discuss the anatomy and physiology of the amygdala and the mechanisms proposed to underlie its involvement in fear conditioning.

II. THE AMYGDALOID COMPLEX

The amygdaloid complex, located in the medial temporal lobe, is structurally diverse and comprises ~13 nuclei. These are further divided into subdivisions that

have extensive internuclear and intranuclear connections. These nuclei and subnuclei are distinguished on the basis of cytoarchitectonics, histochemistry, and the connections they make (105, 208). The architectonic organization and connectivity of the amygdala have been extensively reviewed (4, 48, 159, 208). Although these reviews have mostly concentrated on the rat amygdala, it has also been studied in the monkey (8) and cat (213). These studies reveal that while there are many similarities between species, there are also clear differences in the organization and the relative sizes of the different amygdaloid nuclei. Because functional studies of the amygdala have largely been carried out in the rat, in this review we

mostly concentrate on results obtained in this species. We use the nomenclature introduced by Price et. al (213) with some modifications (159) (see below). In this classification, amygdala nuclei are divided into three groups (Fig. 1): 1) the deep or basolateral group, which includes the lateral nucleus, the basal nucleus, and accessory basal nucleus; 2) the superficial or cortical-like group, which includes the cortical nuclei and nucleus of the lateral olfactory tract; and 3) the centromedial group composed of the medial and central nuclei. Finally, there is a separate set of nuclei that do not easily fall into any of these three groups and are listed separately. These include the intercalated cell masses and the amygdalohippocampal area.

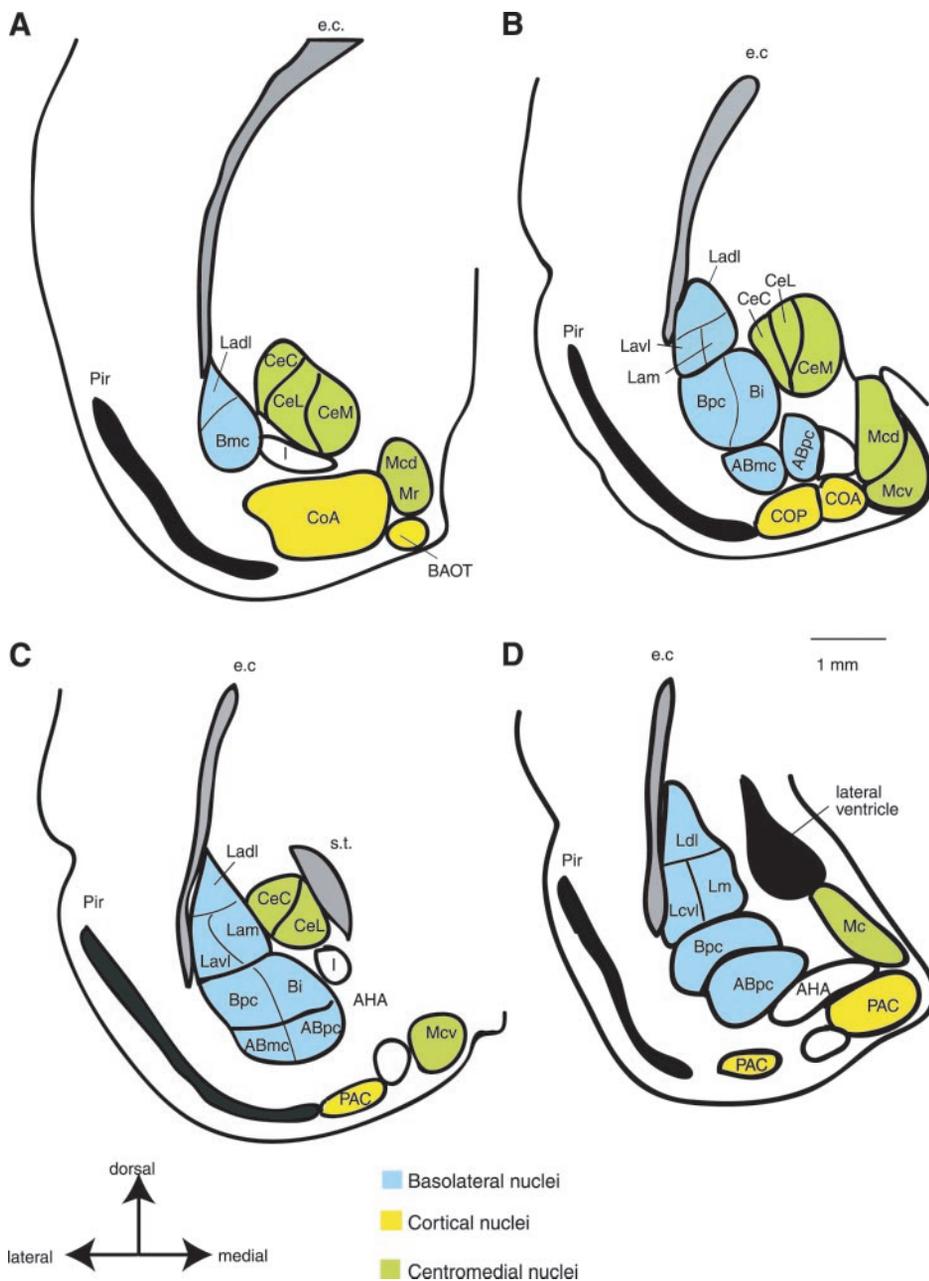


FIG. 1. Nuclei of the rat amygdaloid complex. Coronal sections are drawn from rostral (A) to caudal (D). The different nuclei are divided into three groups as described in text. Areas in blue form part of the basolateral group, areas in yellow are the cortical group, and areas in green form the centromedial group. ABmc, accessory basal magnocellular subdivision; ABpc, accessory basal parvicellular subdivision; Bpc, basal nucleus magnocellular subdivision; e.c., external capsule; Ladi, lateral amygdala medial subdivision; Lam, lateral amygdala ventrolateral subdivision; Mcd, medial amygdala dorsal subdivision; Mcv, medial amygdala ventral subdivision; Mr, medial amygdala rostral subdivision; Pir, piriform cortex; s.t., stria terminalis. See text for other definitions.

A. Basolateral Nuclei

The basolateral or deep nuclei comprise the lateral nucleus (LA), the basal nucleus (B), which is sometimes called the basolateral nucleus (BLA), and the accessory basal nucleus (AB), which is also known as the basomedial nucleus (Fig. 1). Often, these three nuclei are collectively referred to as the basolateral complex (91). The LA is located dorsally in the amygdala where it abuts the basal nucleus ventrally. It is bordered laterally by the external capsule and medially by the central nucleus. It has three subdivisions: the smaller celled dorsolateral subdivision, the larger celled ventrolateral subdivision, and the medial subdivision. The basal nucleus is located ventral to the LA and is subdivided into the rostral magnocellular subdivision and the more caudal intermediate and parvicellular subdivisions. The AB is found ventral to the basal nucleus and lies adjacent to the amygdalohippocampal area (AHA). It is comprised of the magnocellular subdivision, the intermediate subdivision, and the parvicellular subdivision (208, 210).

B. Cortical-like Nuclei

The second group is the superficial or corticomедial nuclei (150, 213) (Fig. 1). Although these superficial structures are called nuclei, many have cortical characteristics since they are located at the surface of the brain and have a layered structure (213). They comprise the nucleus of the lateral olfactory tract (NLOT), bed nucleus of the accessory olfactory tract (BAOT), the anterior and posterior cortical nucleus (CoA and CoP, respectively), and the periamygdaloid cortex (PAC). The BAOT is at the very rostral part of the amygdala where it is bordered laterally by the CoA. The CoA is a layered structure located lateral to the NLOT rostrally and the medial nucleus caudally. The CoP is also three layered and is located in the most caudal parts of the amygdala where it borders the AHA dorsally and the PAC laterally. The PAC is found ventral to the basal nucleus and is subdivided into three subdivisions: the periamygdaloid cortex, the medial division, and the sulcal division (208, 213).

C. Centromedial Nuclei

The centromedial nuclear group is found in the dorsomedial portion of the amygdaloid complex and consists of the central (CeA), medial (M), and the amygdaloid part of the bed nucleus of stria terminalis (BNST; Fig. 1). Traditionally these nuclei were pooled with the cortical nuclei. However, it has recently been suggested that the central, medial, and BNST have histochemical and developmental characteristics that are distinct from the cortical nuclei (see below). Thus, as initiated by McDonald

(159), we will also separate this group from cortical nuclei. The CeA is located dorsomedially in the rostral part of the amygdala, bordered laterally by the basolateral complex, dorsally by the globus pallidus, and medially by the stria terminalis. The CeA has four divisions: the capsular subdivision (CeC), lateral subdivision (CeL), intermediate subdivision (CeI), and medial subdivision (CeM) (92, 149). The medial nucleus is found near the surface bounded medially by the optic tract. It begins at the level of the NLOT and extends caudally. It has four subdivisions: rostral, central (dorsal and ventral), and caudal.

D. Other Amygdaloid Nuclei

The final group of nuclei comprising the remaining amygdala areas are the anterior amygdala area (AAA), the amygdalo-hippocampal area (AHA), and the intercalated nuclei (I) (8, 210, 213). The AHA is the most caudal of the amygdaloid nuclei and is comprised of the medial and lateral subdivisions. The intercalated nuclei are small groups of neurons found in clusters within the fiber bundles that separate the different amygdaloid nuclei (173).

E. Extended Amygdala

Although the above classification has been adopted by many, several authors have suggested that a different classification is more appropriate. Initially, based on the known connections of the amygdala, Alheid and Heimer and co-workers (4, 5) argued that the centromedial amygdala should be extended rostrally and medially. They pointed out that the amygdala innervates the BNST and the caudodorsal regions of the substantia inominata (ventral pallidum). Furthermore, these two regions have similar efferent connections to the descending projections of the amygdala. Thus they argued that these regions are part of the amygdaloid complex. By including these regions they suggested that the centromedial complex should be termed the "extended amygdala." More recently, Swanson and Petrovich (267, 269) have argued that the nuclei of the amygdaloid complex are a structurally and functionally heterogeneous group that have been arbitrarily grouped. They suggest that these nuclei should be divided into four functional systems. These systems would be the frontotemporal, autonomic, main olfactory, and accessory olfactory systems. In this classification, the basolateral nuclei, which embryologically are cortical-like nuclei, receive afferents from similar sources and contain cells resembling cortical neurons (see below) from part of the frontotemporal (cortical-like) system. The central nuclei, embryologically striatal in origin (214), contain cells morphologically similar to those in the striatum (214, 269) and make many connections with regions involved in autonomic control comprise the autonomic system. Fi-

nally, the cortical nuclei, and the medial nucleus, which are the major target of olfactory projections (see below), are part of the main and accessory olfactory systems.

This grouping of the nuclei naturally divides the amygdaloid complex into distinct functional systems and fits well with the development of the structures. The classification that we have described above is largely in agreement with this proposal, with the basolateral nuclei constituting the frontotemporal group, the centromedial nuclei forming the autonomic group, and the cortical-like nuclei constituting the two olfactory groups.

III. AFFERENT AND EFFERENT CONNECTIONS

Data on afferent and efferent connections to the amygdaloid complex come from studies in which anterograde or retrograde tracers have been injected into various amygdaloid, cortical, and subcortical regions. These studies reveal that each amygdaloid nucleus receives inputs from multiple yet distinct brain regions (159, 208, 213). Efferent projections from the amygdala are also widespread and include both cortical and subcortical regions (208). There is a vast and complex literature on connections involving the amygdaloid complex, and there have recently been two detailed reviews (159, 208). Here we briefly summarize the main afferent and efferent connections to the amygdala. Studies carried out in rats, cats, and monkeys show that in most cases there are extensive similarities in the organization of inputs and outputs in the three species. We have chosen to concentrate on the connections in the rat, since most of the physiology has been performed in this species.

Based largely on the information content of the afferents, inputs to the amygdala can be separated into those arising in cortical and thalamic structures and those arising in the hypothalamus or brain stem. Cortical and thalamic inputs supply information from sensory areas and structures related with memory systems. Hypothalamic and brain stem inputs arise from regions involved in behavior and autonomic systems. The major source of sensory information to the amygdala is the cerebral cortex (159). These projections are glutamatergic, predominantly arising from layer V pyramidal neurons (7, 194). The majority are ipsilateral and enter the amygdala via the external capsule (145). Most cortical projections originate in association areas and transmit processed information by a series of cortico-cortical connections originating in the primary sensory cortex. These inputs can be divided into those that relay modality-specific sensory information, those that are polymodal, and those arising in the medial temporal lobe memory system. The different inputs and their distributions in the amygdala are summarized in Figure 2.

A. Sensory Inputs

The amygdala receives inputs from all modalities: olfactory, somatosensory, gustatory and visceral, auditory, and visual.

Olfactory projections arise from the main and accessory olfactory bulbs as well as the primary olfactory cortex. The main olfactory bulb projects mainly to the nucleus of the lateral olfactory tract, anterior cortical nucleus, and the periamygdaloid cortex, whereas the accessory olfactory bulb projects to the bed nucleus of the accessory olfactory tract, the medial nucleus, and posterior cortical amygdala (250). The piriform cortex and anterior olfactory nucleus have projections to the lateral amygdala, basal, and accessory basal nuclei (131). The dorsal endopiriform nucleus additionally projects to all cortical nuclei of the amygdala as well as the nucleus of the lateral olfactory tract, the periamygdaloid cortex, and medial amygdala (12). Thus all regions of the olfactory stream have projections to the amygdaloid complex.

For somatosensory inputs, few projections arise directly from primary somatosensory areas. Most afferents reach the amygdala via the dysgranular parietal insular cortex in the parietal lobe (256). These projections target the lateral, basal, and central nucleus (162, 256, 255). For the lateral amygdala, strong labeling is seen in the dorso-lateral subdivision while in the basal nucleus these inputs are not segregated (256). Somatosensory information also reaches the amygdala by projections from the pontine parabrachial nucleus and thalamic nuclei, the medial portion of the medial geniculate and the posterior internuclear nucleus (PIN), which have been suggested to be involved in the transmission of nociceptive information (16, 19, 121). Inputs arising in the PIN target all subdivisions of the LA, but also innervate the accessory basal nucleus and the medial subdivision of the central nucleus (15, 129).

Gustatory and visceral primary areas in the anterior and posterior insular cortices provide strong projections to the dorsal subdivision of LA, posterior basal nucleus, and central nucleus (255). Gustatory and visceral information also arrive from subcortical structures and, as with somatosensory projections, both cortical and subcortical inputs converge in the amygdaloid complex (159). Inputs from the posteromedial ventral thalamic nucleus (the thalamic gustatory nucleus) terminate in the LA, B, and CeL (185, 274), and those from the parabrachial nucleus, which receives projections from the nucleus of the solitary tract, target the CeL (15, 193).

Auditory and visual information also reach the amygdala from association areas rather than primary cortex. These pathways are thought to be particularly relevant during fear conditioning (see below). For auditory information, area Te1, the primary auditory cortex in rat, has no direct projections to the amygdala (145, 254). Injec-

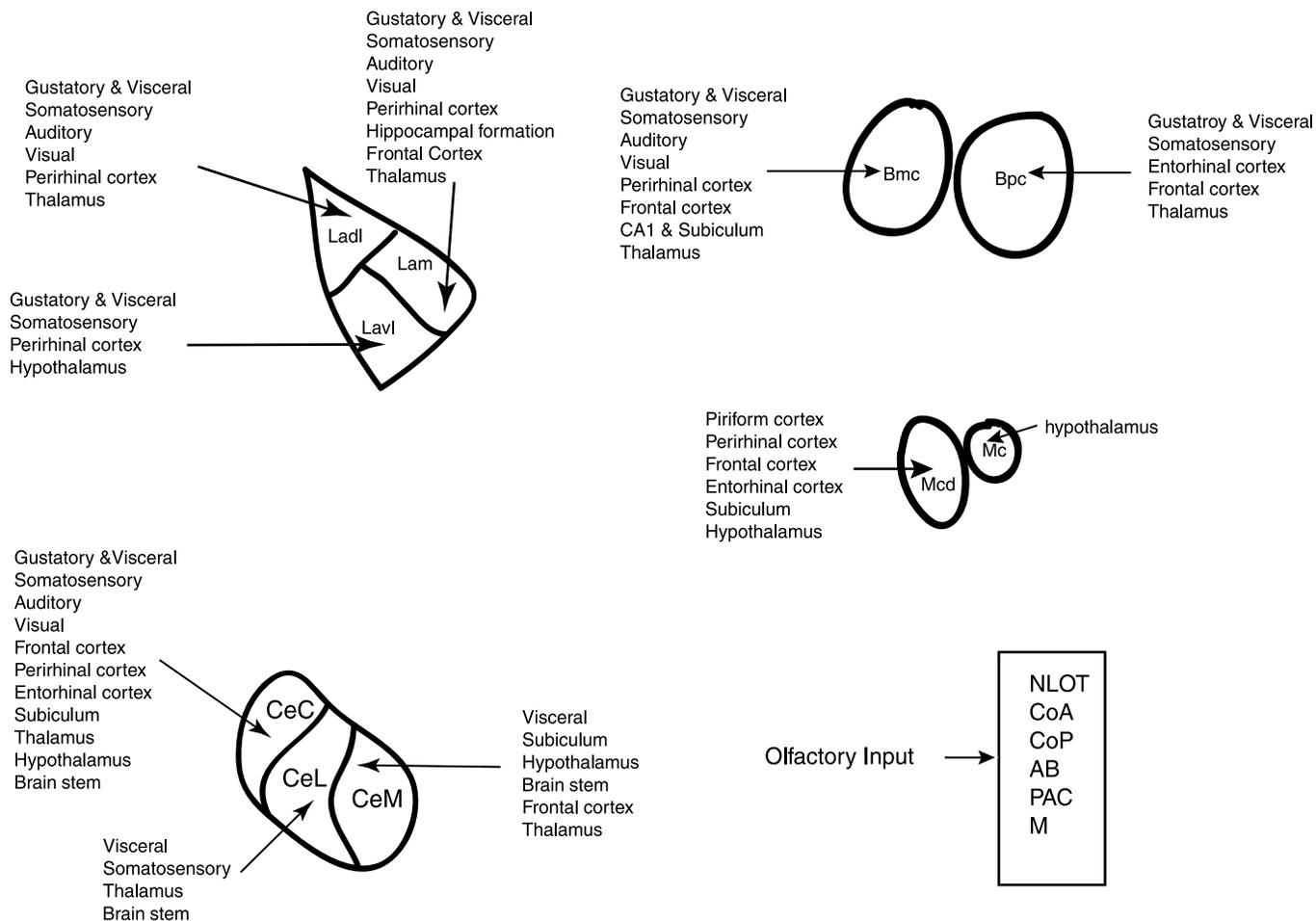


FIG. 2. Summary of the inputs to the amygdaloid nuclei. Neuromodulatory inputs (e.g., acetylcholine, serotonin) have been omitted for clarity. See Fig. 1 and text for definitions.

tions of anterograde tracers in Te3 show fibers in the LA, with the dorsolateral subdivision being the most common target (119, 254). Retrograde tracing studies have shown that these projections arise from cortical layers II and IV (119). Subcortical acoustic inputs arise from the thalamic medial geniculate nucleus and target the same areas of the LA (118, 119, 274). As with acoustic inputs, visual cortical projections to the amygdala also originate both from thalamic and high-order visual areas (253). Cortical projections from these areas (Oc2) follow a cascade to the amygdala in large part via Te2 (159, 253). These fibers terminate in the dorsal subdivision of the LA, the CeL, and some in the magnocellular basal nucleus.

B. Polymodal Inputs

There are several sources of polymodal sensory information to the amygdala. These include prefrontal cortex, perirhinal cortex, and hippocampus. The prefrontal cortex is a major source of cortical projections to the amygdaloid complex. Information from all sensory mo-

dalities converges in the prefrontal cortical areas (224), many of which are involved in behavior and reward circuitry in rats (231). In all species, a dense and topographically organized projection from the frontal cortex has been described (159). The basal nucleus is the main target of afferents from the prefrontal cortex, although projections to the LA as well as accessory basal, central, and medial nuclei have also been described (165).

Areas related to the long-term declarative memory system include the perirhinal cortex, the entorhinal cortex, the parahippocampal cortex, and the hippocampus (175). Projections between the amygdala and these structures are reciprocal and strong (159, 208). The medial division of the LA receives the heaviest projection from the perirhinal cortex, but projections to basal and cortical nuclei have also been described (257). The entorhinal cortex in comparison appears to project to most amygdalar nuclei (164). Inputs from hippocampus to the amygdala mainly originate in the subicular region, and although the basal nucleus is the main target, most other nuclei are also more sparsely innervated (26).

In summary, the amygdala receives sensory information from all modalities. These inputs target structures in the amygdaloid complex at all levels, from the traditionally considered input side of the complex (basolateral complex and cortical nuclei) to the output side (centromedial nuclei) (208). Thus there are extensive levels of convergence between different sensory modalities. In combination with access to information from the medial temporal memory systems, the amygdala is in a good position to form associations between current sensory inputs and past experience.

In addition to sensory information, the central, lateral, and medial nuclei receive substantial inputs from the hypothalamus while the other amygdalar areas receive very meager projections. For brain stem inputs, the central nucleus is a major target for a variety of inputs from the midbrain, pons, and medulla, while the other nuclei receive few or no inputs from these areas (208).

C. Efferent Connections

The amygdaloid nuclei have widespread projections to cortical, hypothalamic, and brain stem regions (Fig. 3). In general, projections from the amygdala to cortical sensory areas are light and originate in cortical and basolateral areas of the amygdala. The perirhinal area, along with other areas in the frontal cortex that project to the amygdala, receive reciprocal connections from the LA, B, AB, M, and periamygdaloid cortex (208). The cortical nuclei that receive olfactory projections all send substantial reciprocal projections back to the olfactory cortex.

The basolateral complex (LA, B, AB) has a substantial projection to the medial temporal lobe memory system with afferents to hippocampus and perirhinal cortex (205, 208). A large projection is also found to the nucleus accumbens (154). Similar to the LA, the basal nucleus also has substantial projections to hippocampus, but in addition

has a major projection to prefrontal cortex, nucleus accumbens, and the thalamus. Efferents from the basolateral complex arise from pyramidal-like neurons and are thought to be glutamatergic (204).

As mentioned above, the amygdala is involved in emotional responses, especially in fear and fear conditioning. These responses are characterized by freezing, potentiated startle, release of stress hormones, and changes in blood pressure and heart rate which are elicited by activation of the autonomic and hormonal systems (42, 115). Activation of the central nucleus induces this autonomic response by stimulating groups of neurons in the brain stem that control the autonomic system, or alternatively by stimulating hypothalamic nuclei that modulate these centers (97, 120). In agreement with these behavioral responses, the medial subdivision of the central nucleus has substantial projections to the hypothalamus, bed nucleus of the stria terminalis (49), and several nuclei in the midbrain, pons, and medulla (279). Projections to the brain stem are to three main areas: the periaqueductal gray, which leads to vocalization, startle, analgesia and cardiovascular changes (13, 226); the parabrachial nucleus, which is involved in pain pathways (67, 178); and the nucleus of the solitary tract (NTS), which is connected with the vagal system (275).

The hypothalamus contains a group of nuclei that have a major influence in the coordination of ingestive, reproductive, and defensive behaviors (267). The medial and capsular subdivisions of the central nucleus innervate mostly the dorsolateral and caudolateral regions of the hypothalamus (205). These areas of the hypothalamus project to autonomic cell groups in the brain stem and spinal cord (268). Efferents from the lateral subdivision of the central nucleus and from nuclei related with the olfactory system in the amygdala also project to these areas. Other hypothalamic nuclei innervated by the amygdala are the medial nuclei of the behavior control column

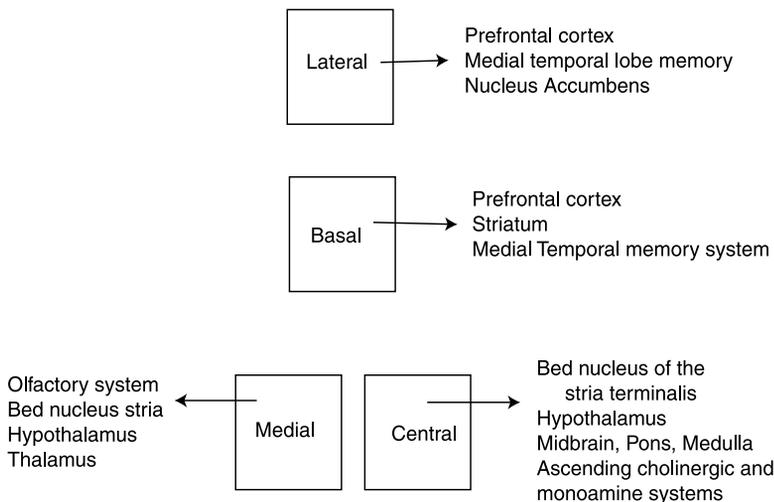


FIG. 3. Summary of the main outputs from the amygdaloid nuclei.

(205). The ventromedial nucleus, which is involved in reproductive behavior, is also innervated by nuclei related to the olfactory system in the amygdala, particularly the medial nucleus, posterior basal nucleus, and posterolateral cortical nucleus. The medial nucleus also sends projections to the hypothalamic neuroendocrine zone, mainly to the anterior paraventricular nucleus (45, 205).

In addition to these direct projections to the hypothalamus, the CeA has a strong projection to the BNST, which also innervates hypothalamic nuclei. Furthermore, both CeA and BNST have strong projections to ascending monoaminergic and cholinergic neuron groups. These include the noradrenergic locus coeruleus, the dopaminergic substantia nigra and ventral tegmental area, the serotonergic raphe, and the cholinergic nucleus basalis (8, 43, 213). These systems innervate large regions of the forebrain and temporal lobe memory systems as well as providing inputs to the amygdaloid complex. Rather than the fast, point-to-point excitation mediated by most glutamatergic afferents, these ascending systems provide modulatory inputs that affect information processing over large cell assemblies.

Large numbers of neurons in the medial subdivision of the central nucleus and medial nucleus are GABAergic, and these projections from the central nucleus have been

suggested to be inhibitory (209, 244). Functionally, activation of CeA neurons in the rat results in rises in blood pressure and heart rate. A GABAergic projection from the CeA suggests these fibers are likely to innervate local inhibitory cells in brain stem nuclei. However, no direct evidence for this is available.

IV. INTRA-AMYGDALOID CONNECTIONS

Tract tracing studies have revealed that amygdala nuclei have extensive intranuclear and internuclear connectivity (105, 208). These studies indicate that sensory information enters the amygdala through the basolateral nuclei, is processed locally, and then follows a predominantly lateral to medial progression to the centromedial nuclei which act as an output station (210). However, little is known about the synaptic physiology of these circuits in the amygdala and how these networks integrate incoming information. The connections between the different nuclei in the amygdala have been described in great detail (208, 210). Here we summarize results (Fig. 4) obtained in the rat, although data are also available in cat (105, 204, 260, 261) and monkey (8). We restrict the discussion to connections involving the basolateral com-

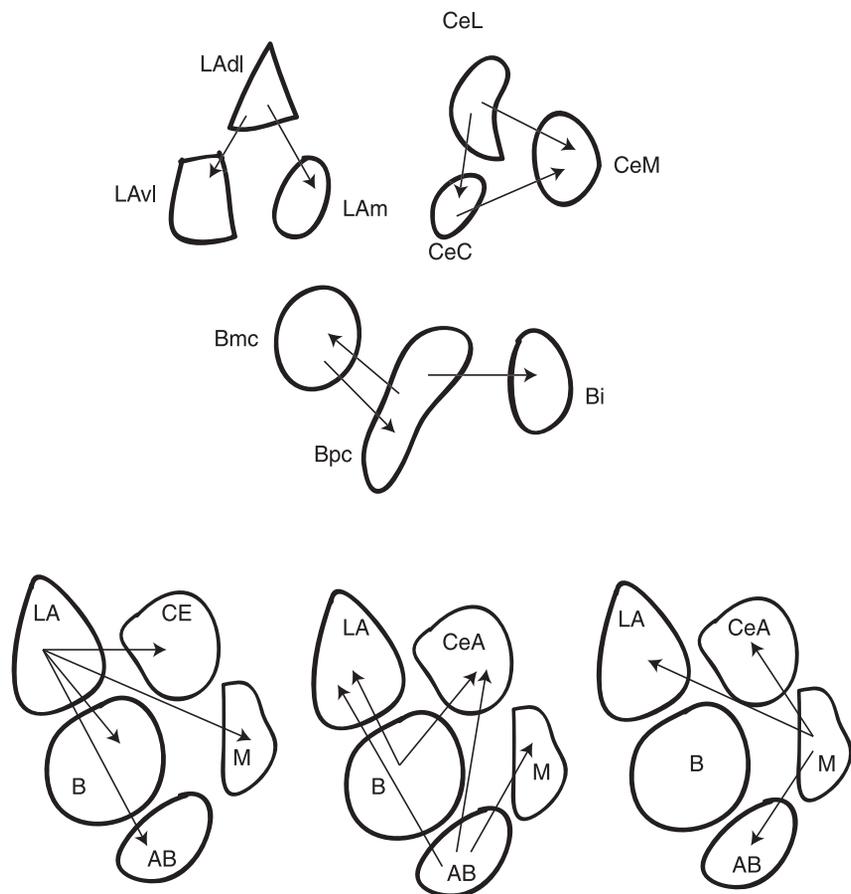


FIG. 4. Intra-amygdaloid connections as described by anatomical tract tracing studies. Most of the connections between nuclei within the amygdala are glutamatergic. See Fig. 1 and text for definitions.

plex and centromedial nuclei since these nuclei are the best understood functionally.

Within the LA, extensive rostrocaudal as well as interdivisional connections have been described (211). The dorsolateral subdivision projects to the medial subdivision and to lateral aspects of the lateral subdivision. As described above, unimodal sensory inputs enter the LA laterally while the polymodal afferents and projections from declarative memory systems are largely confined to the medial subdivision (208). The presence of the lateral to medial intranuclear connections within the LA suggest that the medial subdivision might be a site for integration of sensory information with assessments of past experience. The LA sends extensive projections to the basal and accessory basal nuclei and the capsular part of the central nucleus (211, 260). Of these, the heaviest projection is to the accessory basal nucleus. Finally, the lateral nucleus also sends projections to the periamygdaloid cortex. Despite early studies suggesting the contrary (8, 213), all these regions, except the central nucleus (92), send reciprocal connections back to the LA (248, 249). It is notable that most reciprocal projections terminate in the medial and ventrolateral subdivisions in the lateral amygdala, while the dorsolateral subdivision is largely spared. Furthermore, these reciprocal connections are modest compared with the lateromedial intranuclear connections. Most projections to and from the LA make asymmetrical synapses, indicating they are excitatory (249, 260). However, some of the reciprocal connections from the basal nuclei make symmetrical synapses, suggesting that they are inhibitory (249).

The basal and accessory basal nuclei, which receive strong cortical inputs, have extensive internuclear as well as intranuclear connections. Within the basal nucleus, all subdivisions have extensive rostrocaudal connections. The parvicellular subdivision has extensive projections to the magnocellular and intermediate subdivisions (246). The largest projection from basal nuclei is to the medial subdivision of the central nucleus (204, 246, 247). These afferents form asymmetric synapses with spines and dendrites in the central nucleus and are therefore thought to be glutamatergic (204). Because the hypothalamic and brain stem projections from the amygdala responsible for the autonomic responses of amygdala function largely originate from the medial subdivision of the central nucleus, these projections from the basal nuclei to the central nucleus have a key role in controlling the output of processed information from the amygdaloid complex. The accessory basal nucleus has extensive rostrocaudal connections and sends afferents to the LA, CeA, and medial divisions (247).

The central nucleus, which forms a major output of the amygdala, receives inputs from all the other amygdaloid nuclei but sends very meager projections back to these nuclei (92). The amygdaloid inputs to the central

nucleus are largely restricted to the medial and capsular subdivisions. Within the CeA there are extensive intradivisional and interdivisional connections (92) with each of the four subdivisions making extensive intranuclear connections. The capsular and lateral subdivision make significant projections to the medial and capsular subdivisions with a light projection to the intermediate subdivision. The medial division largely sends projections out of the amygdala, but also has a moderate projection to the capsular subdivision (92). It is notable that the lateral subdivision, which forms the largest projections to the other central subdivisions, receives few reciprocal connections. Interestingly, the lateral subdivision receives extra-amygdaloid inputs from both cortical and subcortical sources (208), suggesting that this might also be a site for integration of inputs to the amygdaloid complex.

In summary, there are extensive connections within and between the different nuclei of the amygdaloid complex. These connections indicate that there is extensive local processing of information entering the amygdala before it leads to the appropriate behavioral outcomes. These intranuclear and internuclear connections have mostly been studied using anatomical tract tracing techniques, coupled in some cases with electron microscopic examination of the synaptic specializations. However, physiological studies indicate that amygdala nuclei contain many types of cells that cannot be readily distinguished on anatomical grounds alone (see below). Furthermore, reconstructed neurons in the lateral and basal nuclei show large dendritic trees, and neurons that have cell bodies in a particular nuclear subdivision (e.g., the dorsolateral subdivision of the lateral nucleus) may well have dendrites that extend into the next division (e.g., the medial subdivision of the lateral amygdala) (56, 200, 219). This implies that inputs that anatomically terminate in a particular subdivision of these nuclei may well innervate neurons whose cell bodies are in a different subdivision. Thus the physiological impact of these local connections and their implications for information processing remain elusive.

V. MORPHOLOGY AND PHYSIOLOGY: BASOLATERAL COMPLEX

The cell types present in the amygdala were, as in most other brain regions, initially described using Golgi techniques. More recently, single-cell recordings have been made in both in vivo and in vitro preparations, the cells filled with dyes, and their morphology reconstructed after physiological recording. These studies have allowed a correlation of morphological and physiological properties of neurons in several nuclei. Although Golgi studies have been carried out in most regions of the amygdala, investigations of the electrophysiological characteristics

of neurons have centered mainly on the basolateral complex in vitro in the rat (56, 61, 219, 283) and in vivo in the cat (107–109, 196, 201).

A. Morphology

Initially, two main types of neuron were described based on Golgi studies. The first type comprises ~70% of the cell population and has been described as pyramidal (73, 174, 283), spiny, or class I cells (153, 150). Many have pyramidal-like somata with three to seven dendrites emanating from the soma. The secondary and tertiary dendrites of these cells are spiny. One of the dendrites is usually more prominent than the others and thus has been likened to the apical dendrite of cortical neurons (56, 73). Some neurons appear to have two apical dendrites and are more like the spiny stellate cells of the cortex (155). Unlike pyramidal neurons in the cortex or hippocampus, these cells are not arranged with parallel apical dendrites but are randomly organized, particularly close to the nuclear borders (56, 155, 201, 219, 283). Thus, while this cell type has been described as pyramidal, these neurons differ from cortical pyramidal neurons in several ways. The primary dendrite of the apical and basal dendrites is of equivalent length, the dendrites taper rapidly, the distal dendrites do not have an elaborate terminal ramification, and as mentioned above, there is no rigid orientation of the pyramids in one plane (56, 112). Because of these clear differences, it may be more appropriate to call these cells pyramidal-like or projection neurons (56, 201). The axons of these cells originate either from the soma or from the initial portion of the primary dendrite (56, 150). They give off several collaterals within the vicinity of the cell before projecting into the efferent bundles of the amygdala, showing that they are projection neurons (150, 260). For neurons within the basolateral complex, cells described as pyramidal comprise a morphological continuum ranging from pyramidal to semi-pyramidal to stellate (56, 156, 201, 219, 283). However, it should be noted that when reconstructed in coronal sections, cells can sometimes appear stellate because they have a largely rostro-caudal orientation (56, 174, 204, 283). In general, neurons in the B are somewhat larger than in the LA with an average soma diameter of ~15–20 μm compared with 10–15 μm in the LA (150, 174). No clear morphological distinctions have been found between neurons in the different subdivisions of the lateral or basal nuclei. As mentioned above, the large dendritic arbors of pyramidal-like neurons indicate that the dendritic trees of these cells would cover the boundary between subdivisions (56, 200). These considerations call into question the functional parcellation of neurons in the basolateral complex into different subdivisions.

The second main group of cells found within the

basolateral complex has slightly smaller somata (~10–15 μm) and resembles nonspiny stellate cells of the cortex. These were termed “S,” for spiny cells by Hall (73) and “stellate” or “class II” cells by Millhouse and De Olmos (174). These cells have two to six primary dendrites that lack spines and form a relatively spherical dendritic field (109, 150). There is no apparent apical dendrite and, as with the pyramidal like neurons, they form a heterogeneous population that has been subdivided into multipolar, bitufted, and bipolar cells according to their dendritic trees by McDonald (150). These neurons are clearly GABAergic (160) and are local circuit interneurons. Their axons originate from the soma or from the proximal portion of a primary dendrite (150). Consistent with local circuit interneurons, the axons branch several times and thus have a “cloud of axonal collaterals and terminals” near the cell body (174). Some of these interneurons form a pericellular basket or axonal cartridge around the perikarya and initial segment of pyramidal cells, respectively, allowing a tight inhibitory control over the output of the cell (28, 109, 161, 261).

Like interneurons in other cortical areas, these cells express several calcium binding proteins (98, 163). About one-half of the cells express parvalbumin, whereas the other half express calbindin and/or calretinin in their cytosol (98, 158), suggesting that there are different classes of interneurons in the basolateral complex. However, there is significant overlap between these three markers. While the calretinin and parvalbumin positive neurons form separate populations, a large proportion of the parvalbumin positive cells also express calbindin (98, 163). The functional relevance, if any, of these different populations of interneurons is currently not known.

In addition, although uncommon, several other types of cells have also been described in the basolateral complex on the basis of distinctive axonal or dendritic patterns. These have been termed extended neurons, cone cells, chandelier cells, and neurogliaform cells (61, 95, 153, 150, 174). Extended cells are large cells with long thick dendrites with few branches and few spines and are found in the rostral parts of the basal nucleus. Cone cells, which have only been described in the rat, have large cell bodies (~20–30 μm) and cone-shaped dendritic trees that are nonspiny and are found in the dorsal angle of the lateral nucleus (174). Chandelier cells resemble cortical chandelier cells and have clustered axon varicosities that form synapses with the initial segment of pyramidal like neurons (150). Finally, neurogliaform cells are another type of small nonspiny stellate neuron found in the basolateral complex (95, 153, 150). These cells are small (~10 μm) with a restricted spherical dendritic tree and branching axons that travel little further than the confines of their dendritic trees. They form numerous synaptic connections along the dendrites of pyramidal-like neurons

and therefore probably represent inhibitory local circuit neurons (150).

B. Physiology

Electrophysiological studies of neurons in the basolateral complex have been made *in vivo* from cats and *in vitro* in acute brain slices, largely from the rat. These neurons have been divided according to whether they are located in the lateral or basal nucleus. However, no attempt has been made to separate neurons located in different subdivisions. In our experience, this is largely because internuclear boundaries that can be delineated in Nissl-stained sections are not readily apparent in acutely prepared coronal brain slices when viewed under the light microscope. However, the lateral and basal nucleus can be readily distinguished (Fig. 5).

Recordings both *in vivo* and *in vitro* from neurons in the LA show extremely low levels of spontaneous activity (135, 200, 201). Based on their firing properties in response to current injections, neurons in the LA have been broadly divided into two types (Fig. 6) (135, 201). The first type, comprising ~95% of total cells, fires broad action potentials (half-width ~1.2 ms measured at 28–30°C) and shows varying degrees of spike frequency adaptation in response to a prolonged depolarizing current injection. Action potential trains are followed by a prolonged (1–5 s)

afterhyperpolarization (AHP), which is largely responsible for the spike frequency adaptation (57). The second population fires short-duration action potentials (half-width ~0.7 ms) and shows little spike frequency adaptation in response to a prolonged depolarizing current injection (109, 135, 201) (Fig. 6). Due to the similarities with cortical and hippocampal neuron firing properties (109, 135), the first type was classified as pyramidal or projection neurons and the second as interneurons. This electrophysiological distinction between projection neurons and local circuit interneurons is similar to that seen in other brain regions (37, 148). A detailed analysis of repetitive firing patterns of pyramidal neurons in the lateral nucleus has recently been carried out using whole cell patch-clamp recordings from coronal rat brain sections (56). These characteristics were then correlated with morphological properties by filling cells with neurobiotin. In this study, cells were classified according to the degree of spike frequency adaptation that they displayed in response to a prolonged current injection. It was found that pyramidal-like neurons formed a continuum of firing properties (Fig. 7). At one end of the spectrum cells fire two to three spikes only and show marked spike frequency accommodation, whereas at the other end of the spectrum cells fire repetitively throughout the current injection with little accommodation (Fig. 7A) (56, 65). In between were cells that fire several times but show clear

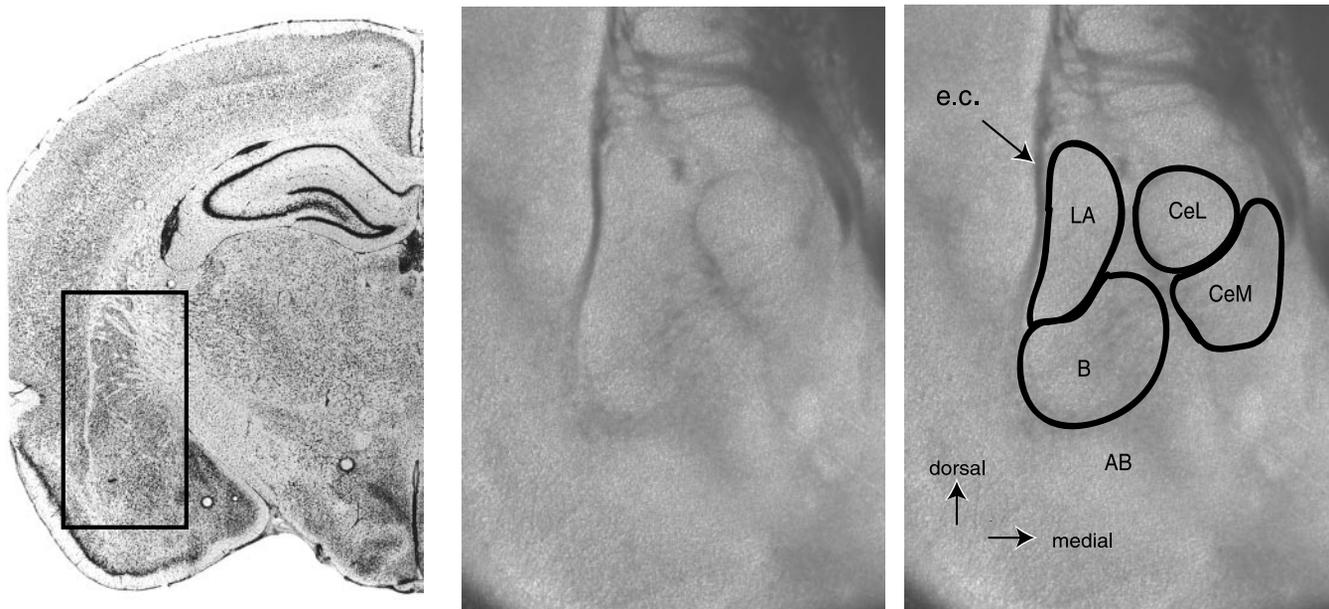


FIG. 5. An example of the amygdaloid region as it appears in acutely prepared coronal sections. *Left*: a Nissl-stained hemisection of a rat brain around bregma-3. The areas shown in the outlined region are shown in an acutely prepared coronal brain slice as it appears under brightfield illumination (*middle*). Shown is the region containing the basolateral complex and central nucleus. *Right*: approximate regions of the lateral (LA), basal (B), accessory basal (AB) and central nucleus have been outlined. In the central nucleus, the approximate locations of the lateral (CeL) and medial (CeM) subdivisions have also been shown. [Adapted from Paxinos G. and Watson C. *The Rat Brain in Stereotaxic Coordinates* (2nd ed.). Sydney, Australia: Academic, 1986.]

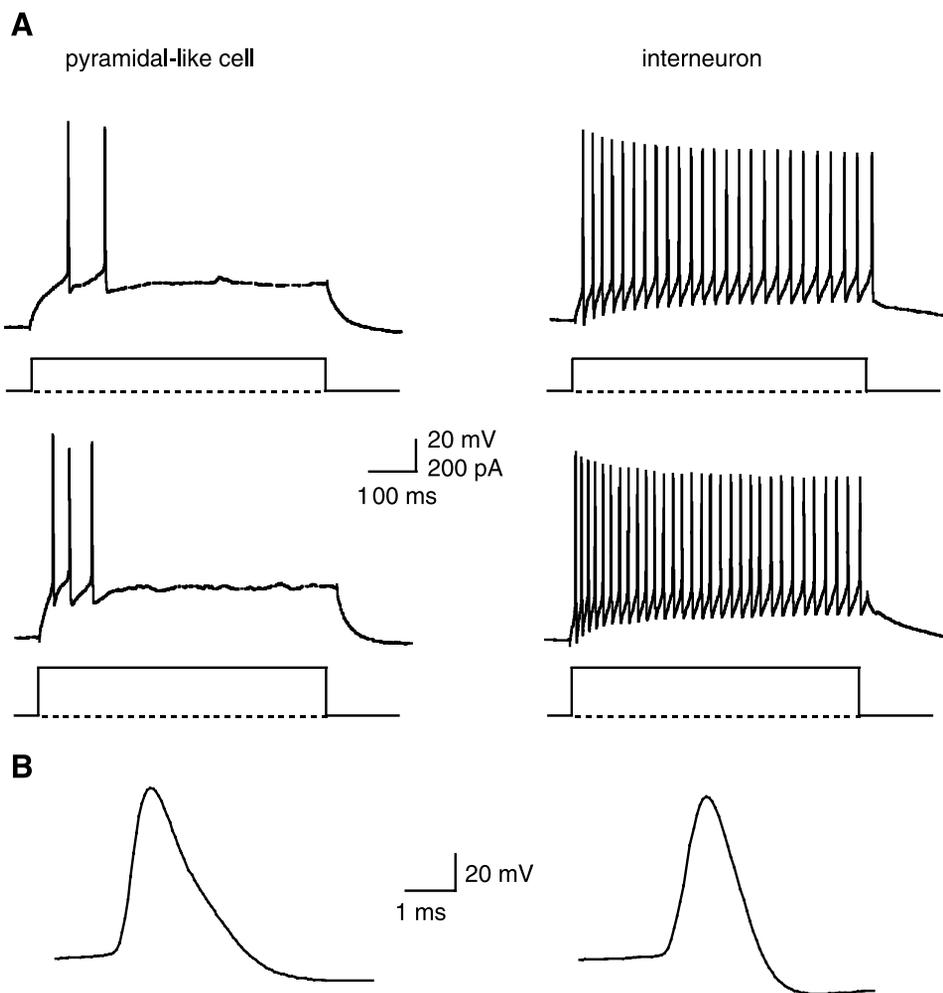


FIG. 6. Pyramidal-like neurons and interneurons can be distinguished on electrophysiological grounds. Traces show recordings from typical pyramidal-like neuron and interneuron in the basolateral complex. Traces on the *left* are from a typical pyramidal-like neuron, and those on the *right* are from an interneuron. *A*: injection of a 400-ms depolarizing current injection in pyramidal neurons evokes action potentials that show spike frequency adaptation, while similar current injections into interneurons evoke a high-frequency train of action potentials that do not adapt. *B*: action potentials in interneurons have a shorter duration than in pyramidal cells.

spike frequency adaptation. The majority of the cells lay at the end of the spectrum that fired fewer spikes and showed marked accommodation. These neurons did not show any difference in resting membrane properties. Quantitative analysis of the morphological properties of neurons at each end of the electrophysiological spectrum revealed no significant differences between cells (56, 65). Thus it was concluded that these neurons have differential distributions of voltage-gated and calcium-activated potassium channels that determine their repetitive firing properties (56, 57). In accordance with this, cells that show spike frequency adaptation were shown to have larger AHPs than those that fire repetitively (Fig. 7B) (56). This wide distribution of firing properties is consistent with the distribution of morphological features that have been described for projection neurons in the basolateral complex (see above). However, no correlation was found between the cells' firing properties and their morphology (56).

Finally, one other cell type, termed a single firer, that stands out from the above classification has also been described in the LA and comprises ~3% of recorded cells

(33, 56, 61, 297). In this cell type only a single action potential is evoked in response to a prolonged current injection; the excitability could not be enhanced by giving larger current injections or by depolarizing the cell. Despite the marked accommodation that it showed, no prolonged AHP followed the action potential (243). These cells appear to express a dendrotoxin-sensitive voltage-gated potassium current that is responsible for their marked spike frequency adaptation (E. Faber and P. Sah, unpublished observations). Thus this cell was considered to be in a discrete class from the above neurons. Faulkner and Brown (61) recovered one of these cells for morphological analysis and found that it was pyramidal-like but with few spines. In contrast, Yajeya et al. (296) who recovered two of these neurons reported them to have a round soma from which four or five spiny dendrites emanated in a spherical fashion. Yajeya et al. (297) have proposed the single firing neurons to represent the neurogliaform (type III) cells described by McDonald (150).

Intracellular recordings from LA neurons made *in vitro* in the cat and guinea pig and *in vivo* in cats have found a large proportion of LA projection neurons to

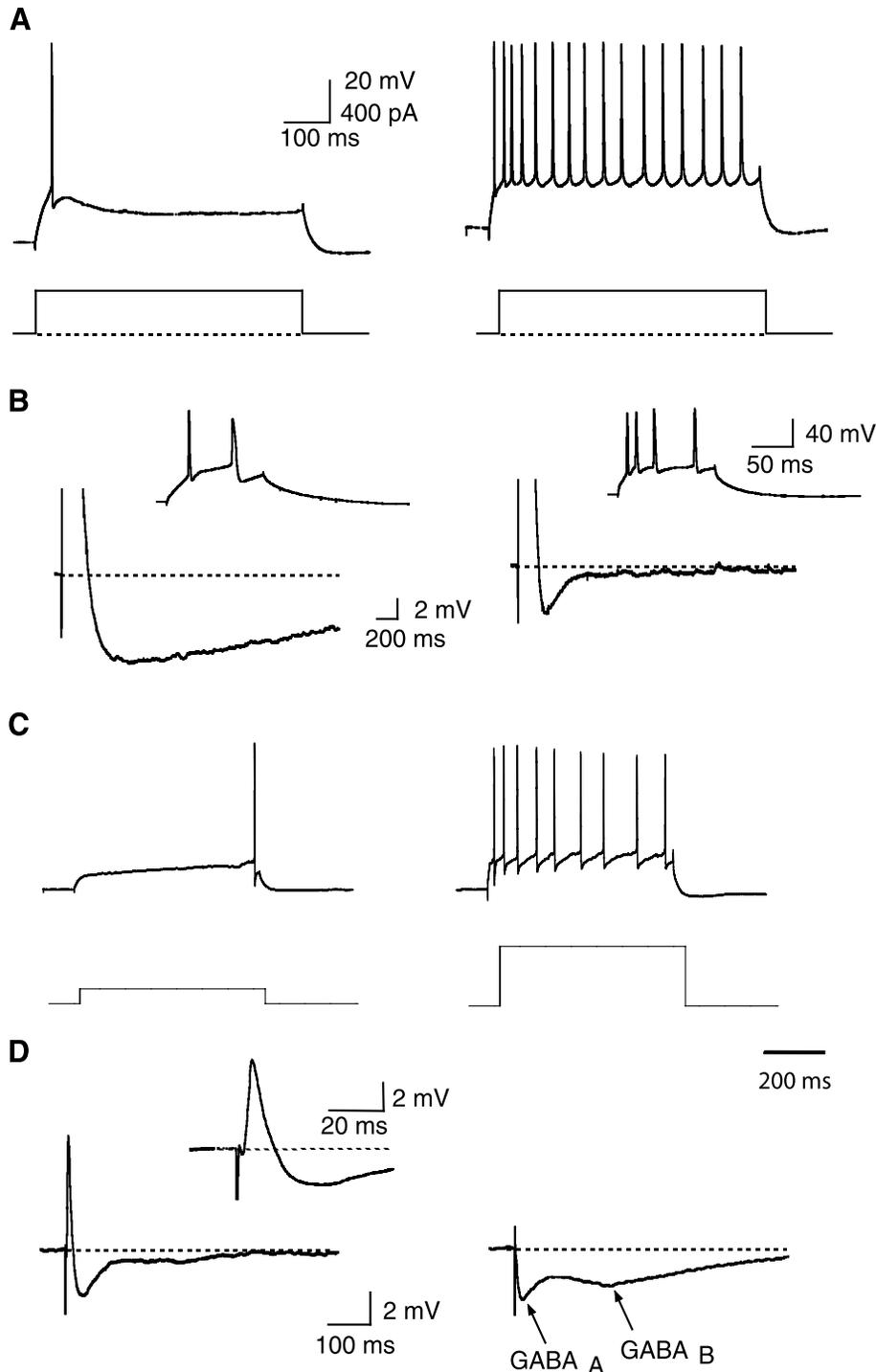


FIG. 7. Electrophysiological and synaptic properties of different types of pyramidal neuron in the basolateral complex. The traces on the *left* show recordings from neurons which show marked spike frequency adaptation, while the traces on the *right* are recordings from a repetitively firing neuron. *A*: response to 600-ms depolarizing current injection (400 pA). The neuron on the *left* fires a single action potential, whereas the cell on the *right* fires repetitively throughout the current injection. Spike frequency adaptation is due to activation of a slow afterhyperpolarization (AHP) that follows a train of action potential. The recording on the *left* shows the AHP that follows two action potentials in a cell which shows complete spike frequency adaptation. *Inset*: response to a 100-ms, 400-pA current injection which evoked two action potentials. Traces on the *right* show the AHP evoked in a cell which fires repetitively during a prolonged current injections. Note that the AHP that is evoked is much smaller despite twice the number of action potentials in response to the current injection. *C*: late firing neuron from the basal nucleus. Traces show the response to a just threshold current injection and one that is suprathreshold. Note the long delay to action potential initiation during a threshold current injection (*left*). A suprathreshold current injection removes the long delay (*right*). *D*: stimulation of the external capsule evokes a depolarizing excitatory postsynaptic potential (*inset* on *left*) followed by a hyperpolarizing inhibitory postsynaptic potential (IPSP). The IPSP has two components: a fast component mediated by activation of GABA_A receptors and a slow component mediated by activation of GABA_B receptors. The amplitudes of the two components are highly variable between cells, and two examples are shown.

display intrinsic voltage-dependent oscillations. These increased in frequency in a voltage-dependent manner until repetitive spiking was evoked with larger depolarizing current injections (196, 201). As first reported in entorhinal cortex (6), these oscillations have been suggested to be due to the activity of subthreshold tetrodotoxin-sensitive sodium channels (196). Upon depolarization, these cells fire a burst of action potentials followed by a slow rhythmic firing of single spikes, but do not fully accom-

modate. Action potentials are followed by an AHP. A small number of nonoscillating bursting neurons were also described that fired a burst of two to three action potentials before firing in a sustained fashion and showing no accommodation. As with the results described *in vitro* (56, 65), no morphological differences were found between neurons with different firing properties (201).

Thus, although there are some similarities, there are also clear differences in the description of pyramidal

neurons recorded in vivo in cat and those recorded in vitro in the rat. First, the in vitro recordings from neurons in rat slices using whole cell patch-clamp techniques have not shown the membrane oscillations described in vivo. Second, while the firing patterns were not described in detail for recordings in vivo, these studies did not describe any fully accommodating projection neurons in the LA, the major cell type described in vitro. The reason for this disparity is not clear. However, the recordings in vivo were made with sharp intracellular microelectrodes, which leads to a lower input resistance due to the membrane leak around the electrode. This would have attenuated the impact of the AHP in the neurons, and thus all cells would appear as repetitively firing neurons. Another possibility is wash out of chemical mediators of the oscillations in whole cell recordings. In fact, in the few cells that showed full accommodation in the cat and guinea pig LA, the oscillations were absent, suggesting that adaptation may reflect an inactivation of the oscillations when recorded in the whole cell mode (196). Finally, these differences may be species dependent, since microelectrode recordings in the LA in vivo have revealed that accommodating neurons can also be found in rats (35).

Two studies have examined the electrophysiological properties of neurons in the basal nucleus using intracellular recordings in rat brain slices and correlated them with their morphological properties (219, 283). As in the LA, these cells have been divided into pyramidal or projection neurons, comprising ~95% of the neuronal cell mass, and local circuit interneurons, which comprise the remaining 5%. Pyramidal neurons have been further classified into two electrophysiological groups based on their firing patterns, burst firing, and repetitive firing. Burst firing cells fired one or two spikes before ceasing firing, whereas repetitively firing cells fired throughout the current injection but showed little accommodation (219, 283, 297). A number of intermediate neurons have also been described (219, 283). Thus as with LA neurons, basal neurons form a continuum of firing patterns. The repetitive firing neurons described by Washburn and Moises (283) differ from those in the LA because they show a delay in firing when depolarized from more negative membrane potentials and have therefore been termed "late firing" neurons (Fig. 7C). This effect has been shown to be due to the presence of a low-threshold, slowly inactivating potassium current (I_D) in these neurons (283). Similar to LA projection neurons, action potentials in basal projection neurons are broad, and accommodating neurons have a significantly larger AHP than repetitively firing neurons. The difference in AHP is most likely the basis of the difference in two extremes of firing pattern (56, 243). The electrophysiological properties of pyramidal neurons in the LA and B are subject to modulation by ascending and local transmitter systems. Acetylcholine, norepinephrine, glutamate, serotonin, and opioids all modulate volt-

age- or calcium-dependent potassium currents leading to changes in spike frequency adaptation (57, 285) (E. Faber and P. Sah, unpublished observations).

Neurons in the basal nucleus have been examined in vivo in the cat (200, 201). In contrast to LA neurons, which are virtually silent, basal nucleus neurons were reported to fire in bursts at rest. The bursts of spikes were followed by a nonadapting train of spikes, due to activation of a slow afterdepolarization. These constituted 80% of basal nucleus neurons recorded from. The remaining 20% of neurons in the basal nucleus were nonbursting cells that accommodated and showed oscillations similar to those recorded in the LA. After reconstruction of these cells, they were all described as modified pyramids, and no consistent differences in morphology were noted. In recordings made in in vitro brain slices, Rainnie et al. (219) described the bursting cells to be spiny stellate, whereas Washburn and Moises (283) reported them to be spiny pyramidal. In contrast, a third study (297) reported the repetitively firing neurons to be stellate. The simplest explanation for these discrepancies is likely to be the large variation in the orientation of the apical dendrite which makes clear classification of cell morphology difficult (201). In summary, in contrast to the discrepancies in recordings from LA pyramidal cells, there is more consensus in the properties of neurons in the basal nucleus.

Recordings from interneurons in the basolateral complex have been made both in vitro and in vivo in both the lateral and basal nuclei. These neurons show a similar pattern of physiological properties. In all cases, they generate narrow action potentials (half width ~0.7 ms) and in response to a depolarizing current injection fire nonadapting trains of action potentials (109, 135, 201, 284). In contrast to pyramidal neurons, interneurons fire spontaneously in vivo at high frequencies (~10–15 Hz) (109, 201). As described above, interneurons can be divided into at least two classes based on their content of calcium binding proteins. However, no differences in physiological properties between interneurons have been reported.

C. Synaptic Properties

Pyramidal-like neurons in the basolateral complex show high levels of immunoreactivity for glutamate and aspartate (260) but not glutamic acid decarboxylase (28). Thus these cells are presumed to be glutamatergic and form the output cells of this structure. These neurons receive both cortical and thalamic inputs which form asymmetrical synapses (58). Consistent with their morphology, these inputs are glutamatergic and form synapses containing both α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors (59, 60). Three types of ionotropic

glutamate receptors, AMPA, NMDA, and kainate receptors, are recognized in the mammalian central nervous system (83). The presence of AMPA and NMDA receptors at excitatory synapses within the central nervous has been known for many years. Electrophysiological studies (Figs. 7D and 8) have confirmed that cortical and thalamic afferents to pyramidal neurons form dual-component glutamatergic synapses (32, 136, 220, 290). Analysis of spontaneous, miniature synaptic currents has shown that AMPA and NMDA receptors are present at individual synapses in these neurons (136). The properties of these two inputs are similar with regard to the type of AMPA receptors that they express. However, it has been suggested that NMDA receptors present at thalamic inputs might be different from those present at cortical inputs (291). At most synapses, NMDA receptors are not active at resting membrane potentials due to their voltage-dependent block by extracellular Mg^{2+} (146, 191). The suggestion is that NMDA receptors present at thalamic inputs have lower levels of Mg^{2+} block such that they are active at resting membrane potentials (127, 291, but see Ref. 136). This finding has not been further studied but has major implications for the interpretation of experiments in which NMDA receptors are blocked by specific antagonists (see below).

NMDA receptors are hetero-oligomers assembled from two types of subunits, NR1 and NR2. The NR1 subunit is a single gene product, whereas the NR2 subunit is encoded by four different genes: NR2A–NR2D (147). Native NMDA receptors are thought to be heteromultimers containing four or five subunits consisting of two NR1 subunits and two or three NR2 subunits (38). At most synapses throughout the central nervous system, NMDA receptors are composed of NR1 subunits in combination with either NR2A or NR2B subunits. NR2A and NR2B subunits are ubiquitously distributed through the central nervous system and have been shown to undergo a developmental switch in hippocampal and cortical neurons (179). At birth NMDA receptors are composed of NR1/NR2B subunits, and there is a switch from NR2B to NR2A subunits around P7. However, in the LA, a recent study has shown that application of the NR2B-selective antagonist ifenprodil blocks the induction of fear conditioning, suggesting that receptors containing NR2B subunits are present at synapses in the adult lateral amygdala where they are involved in initiating synaptic plasticity (227). While both NR2A and NR2B subunits are present in the lateral amygdala, the subunit composition of these receptors at synapses in the amygdala has not been determined.

Recently, the presence of kainate receptors at synapses has also been demonstrated (31, 280). It has been suggested that kainate receptors are also present at some glutamatergic inputs to pyramidal neurons in the basal nucleus, where they are proposed to be involved in basal synaptic transmission (126). All three types of ionotropic

glutamate receptor have been suggested to underlie different forms of synaptic plasticity in the amygdala (see below).

Glutamate also activates metabotropic receptors that are coupled via G proteins to phospholipase C or adenylyl cyclase (207). These receptors are found both presynaptically and postsynaptically in many regions of the central nervous system. However, only a few effects resulting from synaptically released glutamate have been described (206). Activation of metabotropic receptors by application of exogenous agonists in basal amygdala neurons has both presynaptic and postsynaptic actions (221, 222). However, effects of metabotropic glutamate receptors by synaptically released glutamate have only been described during the induction of synaptic plasticity (see below).

Neurons in the LA have also been suggested to have a fast excitatory inputs mediated by 5-hydroxytryptamine (5-HT) receptors (264). However, since this initial report, subsequent experiments have been unable to reproduce these results as all inputs to these neurons can be blocked with a combination of glutamatergic and GABAergic antagonists (136, 259, 290). Instead, 5-HT₃ receptors in this nucleus have been proposed to be present presynaptically on interneuron terminals (103, 104).

Interestingly, although heterogeneity in firing properties has been described in pyramidal neurons, there have been no reports of differences in synaptic properties between cells, suggesting that the properties of exogenous inputs to all pyramidal neurons are similar. As discussed above, the axons of pyramidal neurons have substantial local collaterals (150, 260). Many of the local targets of these collateral are interneurons (262), but they are also likely to contact nearby pyramidal neurons (150). The properties of any of these local connections are not known.

Interneurons in the basolateral complex receive excitatory inputs from local, cortical, and thalamic sources (109, 135, 270). In addition, these neurons are connected in local networks such that interneurons have synaptic connections with each other (109). In contrast to pyramidal-like neurons, glutamatergic inputs to interneurons activate synapses that express few or no NMDA receptors in the postsynaptic membrane (135). Furthermore, the AMPA receptors present at these inputs show marked inward rectification and appear to be calcium permeable (135). AMPA receptors are heteromultimers assembled from four genes, GluR1–GluR4. Receptors that lack GluR2 subunits have strong inward rectification (Fig. 8) and a high calcium permeability (93, 286). Consistent with the marked inward rectification reported at these synapses (135), GABAergic cells in the basolateral complex have been shown to express low levels of GluR2 subunits (157). As described above, interneurons in the basolateral complex are a heterogeneous population of neurons that can be separated on morphological grounds and their

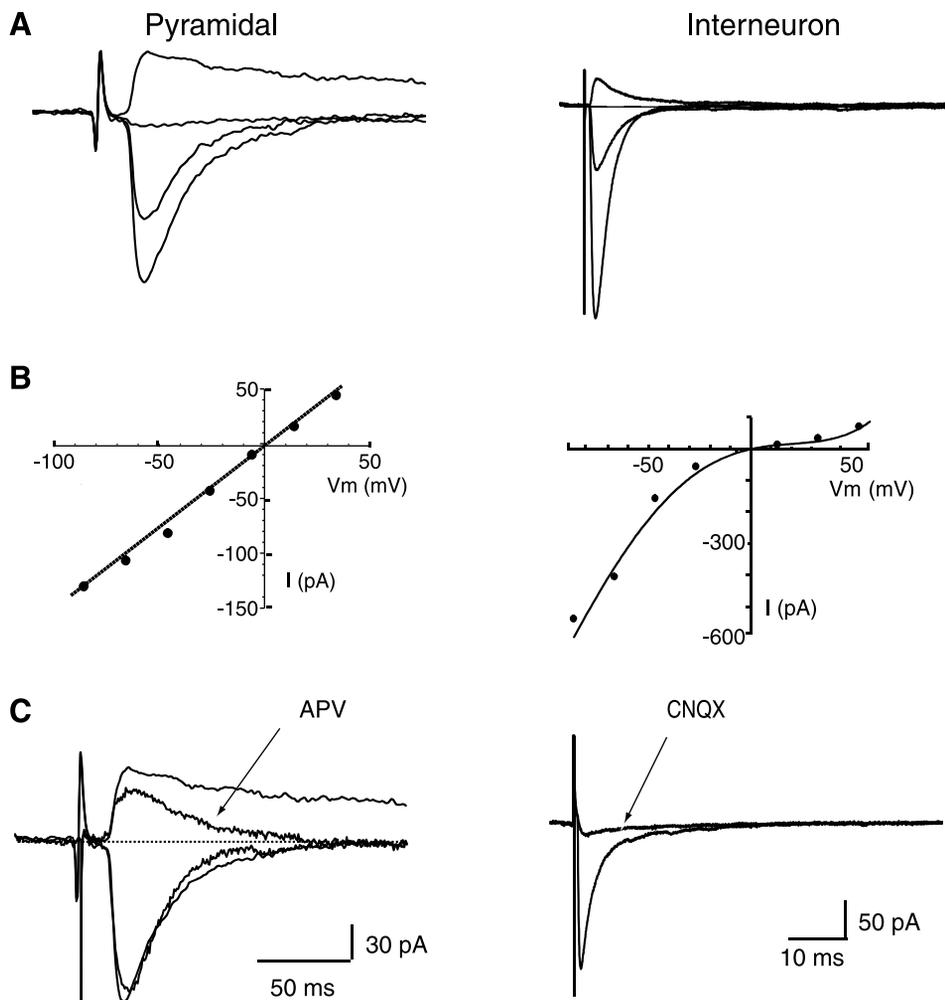


FIG. 8. Pyramidal cell and interneurons in the basolateral complex have different types of excitatory inputs. Recordings are shown from a pyramidal-like neuron (*left panels*) and interneuron (*right right*) in the lateral amygdala. *A*: excitatory synaptic currents recorded at the indicated holding potentials following stimulation of the external capsule. In pyramidal cell, a slower current can be seen with membrane depolarization, which is absent in interneurons. Inhibitory synaptic currents have been blocked with picrotoxin (100 μM). *B*: peak current (I)-voltage (V_m) relationships are shown for the fast inward current in pyramidal neurons and interneurons. Note that the I - V is linear in pyramidal cells but shows marked outward rectification in interneurons, indicating the presence of AMPA receptors which lack GluR2 subunits. *C*: excitatory synaptic currents in a pyramidal cell recorded at -80 mV and $+40$ mV (*left traces*). Application of the NMDA receptor antagonist D-APV (30 μM) blocks the slow component. Records on the *right* are synaptic currents recorded from an interneuron at -80 mV before and after application of CNQX (10 μM), showing that the current is mediated by AMPA receptors.

content of calcium binding proteins. Physiological studies of these neurons have not thus far reported differences in synaptic properties between different cells. However, recent results from our laboratory suggest that some interneurons in the basolateral complex do express synaptic NMDA receptors (A. Woodruff and P. Sah, unpublished observations).

As in most other parts of the central nervous system, the fast spiking cells are GABAergic and constitute local circuit interneurons (160, 189, 202, 209). Activation of these cells in the basolateral complex generates inhibitory synaptic potentials that have fast and slow components (Fig. 7D) (108, 218, 284). As originally described in the hippocampus (52), the fast component is mediated by GABA_A receptors while the slow component is mediated by activation of GABA_B receptors (135, 218, 284). Measurements of spontaneously occurring miniature inhibitory synaptic currents have suggested that different interneurons in the basolateral complex are responsible for generating the GABA_A and GABA_B receptor-mediated component of inhibitory synaptic current (263). Direct evidence for this proposal, for example, by paired inter-

neuron/pyramidal cell recordings, is currently lacking. However, stimulation of different afferents indicates that these different interneurons cannot be independently stimulated by extrinsic inputs *in vivo* (107). In contrast to most other cells, the slow component of the inhibitory synaptic potential in LA pyramidal neurons is in part generated by a calcium-activated potassium conductance that is activated by calcium influx via NMDA receptors (39, 108). This observation raises the possibility that, as recently described in the olfactory bulb (85), NMDA receptors in lateral amygdala neurons might be coupled to calcium-activated potassium channels.

Interneurons can mediate both feed-forward or feedback inhibition (3). In the basolateral complex, whether interneurons mediate feed-forward inhibition or feedback inhibition (or both) has not been fully determined. Electrophysiological studies in acute slices in the rat have shown that these cells receive both cortical and thalamic excitatory inputs, consistent with a role of these cells in feed-forward inhibition (109, 135, 270). However, it is possible that the excitatory inputs to interneurons are due to activation of axon collaterals of pyramidal cells, which

indicates a feedback role for interneurons. Tract tracing studies in the cat and monkey found that cortical afferents form few if any synapses with parvalbumin positive neurons, while local afferents do make synapses onto them (262). In contrast, a similar study in the rat has described thalamic inputs to interneurons in the LA (295). These findings are consistent with the proposal that different populations of interneurons can have a feed-forward and/or a feedback role in the basolateral complex.

In summary, pyramidal neurons and local circuit interneurons in the basolateral nuclei can be separated on electrophysiological grounds. As in the cortex, pyramidal neurons have a range of firing properties. However, unlike in the cortex, these different repetitive firing properties are not accompanied by clear morphological differences. Among the interneurons, several classes of cell can be identified based on the presence of different calcium binding proteins. The roles of these cells with different firing properties are not currently understood. However, it seems likely that neurons with differing electrophysiological properties will involve different local circuits and have distinct afferent/efferent connections.

VI. MORPHOLOGY AND PHYSIOLOGY: CENTRAL NUCLEUS

A. Morphology

The morphology of neurons in the central nucleus has been studied using Golgi techniques as well as reconstruction after recording physiological properties in acute brain slices (144, 252). As with the basolateral complex, the different subdivisions of the central nucleus (30, 105, 149, 208) cannot be easily identified in acute slices maintained *in vitro* (Fig. 5). Thus, while Golgi studies have described neurons in the different subdivisions, results from cell fills in slices have either not discussed subdivisions (252) or divided cells into those in the lateral and medial sectors (144, 251). Here we will therefore concentrate on cells in the lateral and medial sectors of the central nucleus. There is general agreement that in both subdivisions there is one predominant cell type that has been called "medium spiny neurons" in the CeL by comparison with neurons in the nearby striatum (73, 149). These cells have an ovoid or fusiform soma and three to five nonspiny primary dendrites from which moderately spiny, sparsely branching secondary and tertiary dendrites arise (144, 149, 252). Axons give off several local collaterals before leaving the nucleus. A second type of neuron has also been described that has a somewhat larger soma and a thick primary aspiny dendrite that tapers into sparsely spiny secondary dendrites (29, 149, 252). In addition, a small number of aspiny neurons have also been described (29). These three cell types are dis-

tributed homogeneously throughout the CeA. Immunohistochemical studies have demonstrated the presence of a wide variety of peptides in cells in the CeA as well as in the afferents innervating these neurons (29, 30, 177). One study has shown that the peptides enkephalin, neurotensin and corticotropin releasing hormone (CRH) is found in GABAergic neurons. There appear to be two populations of these cells: one contains enkephalin and the other CRH (44). Both populations have a partial overlap with neurotensin containing neurons (44, 258). Interestingly, intraperitoneal administration of the cytokine interleukin-1 β preferentially activated GABAergic neurons containing enkephalin (44), suggesting that neurons with different peptide content have different functional roles. Thus neurons in the central nucleus are morphologically very different from those found in the basolateral complex with basolateral neurons having similar morphology to cortical structures and the central nucleus being more striatal-like (73, 149). This finding is consistent with the different embryological origins of the two nuclei (214, 269). Finally, as with the majority of cells in the striatum, projections from the central nuclei are predominantly GABAergic while the basolateral nuclei have glutamatergic projections (42, 244, 269).

B. Physiological Properties

Only a small number of studies have examined the electrophysiological properties of cells in the central nucleus (144, 190, 251, 252). These recordings have been performed *in vitro* in coronal slices from rat and guinea pig using either whole cell or microelectrode recordings. As discussed above, cells have only been described in the lateral and medial subdivisions as the boundaries for the intermediate and capsular divisions are not apparent in acute slices. At least three types of cells have been described that can be separated by their firing properties (Fig. 9). Using intracellular recordings with sharp microelectrodes, Schiess and co-workers (251, 252) described two types of cells that they called type A and B cells. Type A (~75%) cells fired throughout a prolonged current injection, showing little spike frequency adaptation, and action potentials were followed by a medium-duration AHP (243) in response to short depolarizing current injections. Type B cells (~25%) accommodated and exhibited both a medium and slow AHP. The two cell types had similar passive membrane properties other than the resting membrane potential, which was more depolarized in type B cells. Using whole cell recordings in guinea pig slices *in vitro*, Martina et al. (144) divided cells into three types. The most common type was described as "late firing" (95% in CeM and 56% in CeL; Fig. 9C). These cells displayed a pronounced outward rectification in the depolarizing direction (144). In addition to the late-firing

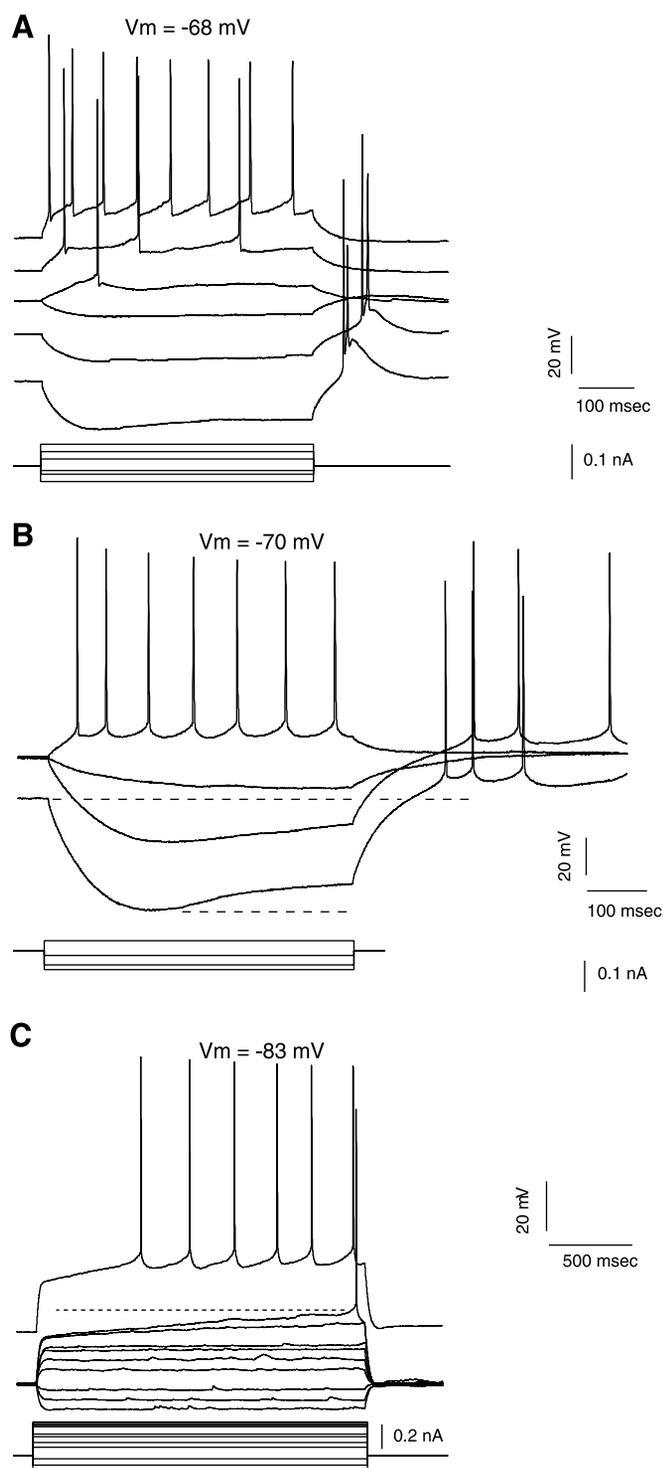


FIG. 9. Physiological properties of three types of neuron in the central nucleus. Recordings are from the rat central nucleus showing the three most prominent types of neurons. *A*: low-threshold spiking neuron. *B*: regular spiking neuron. *C*: late firing neuron. In each case, whole cell recordings were made from neurons in the central nucleus and depolarizing and hyperpolarizing currents injected as shown.

neurons, the CeL also contained neurons that fired spikes repetitively in response to a prolonged current injection and were termed “regular spiking” cells (~40%, Fig. 9*B*). The regular firing cells of Martina et al. (144) likely correspond to type A cells described in the rat (251).

Two further cell types were described in the guinea pig that were called fast-spiking cells and “burst-firing” cells (144). Fast-spiking cells were typical of interneurons and fired fast action potentials at high frequency, showing no accommodation. In contrast, burst-firing cells fired repetitively, showing some accommodation, in response to a prolonged current injection and fired rebound bursts of action potentials, riding on a depolarizing potential (Fig. 9*A*). These cells therefore are similar to the type B cells described in the rat (251). However, after a hyperpolarizing current step, low-threshold bursting neurons in the guinea pig show a clear rebound depolarization, similar to that reported by Scheiss et al. (251) in type A cells. It should be noted that the whole cell recordings of Martina et al. (144) were made with potassium gluconate-containing internal solutions, which makes comparison with microelectrode recordings difficult since the slow AHP is very sensitive to the anion present in the internal solution (299). Thus some of the discrepancies in the findings of Schiess and co-workers (251, 252) and Martina et al. (144) may be due to the different recording techniques used. In addition, it is notable that these studies were done in different species, and it has recently been suggested that there are differences in the distribution of cells with distinct properties between rat, cat, and guinea pig (50). Thus, for example, while late-firing neurons constituted >90% of the cell population in the CeM in guinea pigs, they accounted for only 2 and 6% of neurons in the rat and cat CeM, respectively (50).

After recovery of physiologically identified neurons, cells in the CeL were found to have generally smaller cell bodies than cells in the CeM (144). However, while in the rat Scheiss et al. (251) suggested that the two cell types they found had different cell morphologies, Martina et al. (144) did not find any systematic correlation between cell firing properties and their morphology. In both studies, the major physiological cell type recovered corresponded to the medium spiny neurons described in Golgi studies.

C. Synaptic Properties

Consistent with tract tracing studies, experiments in acute slices from rats and guinea pig have shown that neurons in both the CeM and CeL receive glutamatergic inputs from the lateral and basal nucleus which activate both AMPA and NMDA receptors (130, 239). In the guinea pig, CeL neurons largely receive inputs from the lateral nucleus while neurons in the medial subdivision receive inputs from the basal nucleus (239). It should be noted,

however, that when recording from CeL neurons in acute brain slices, cells are difficult to separate from those in the capsular subdivision unless they are filled, recovered, and divisional boundaries visualized histologically.

Excitatory inputs to CeL neurons also express presynaptic metabotropic glutamate receptors (186). As in many other regions of the central nervous system (132, 207), activation of these receptors leads to depression of the synaptic input. The activity of these receptors is modulated following kindling and chronic cocaine treatment (186). The central amygdala is particularly sensitive to a kindling stimulus (123a) and has been implicated in the reinforcing ability of repeated cocaine exposure (170). These findings suggest that alterations in synaptic efficacy at inputs to the CeA may be involved in the changes seen in epilepsy and behavioral sensitization to cocaine.

In the lateral subdivision of the central nucleus, two distinct types of ionotropic GABA receptors have been demonstrated. One type is similar to typical GABA_A receptors and is blocked by low concentrations of bicuculline and positively modulated by benzodiazepines and barbiturates (293). In addition, these cells express a second type of GABA receptor that is markedly less sensitive to bicuculline. This bicuculline-resistant component was initially suggested to be due to activation of nicotinic acetylcholine receptors (190). However, recent experiments have shown that it is blocked by the specific GABA_C receptor antagonist 1,2,5,6-tetrahydropyridine-(4-yl)methylphosphinic acid (TPMPA) (46). These receptors have been called GABA_C-like receptors due to their pharmacological similarity to retinal GABA_C receptors (89, 217). Bicuculline-insensitive receptors have also been shown to be present in the medial subdivision (239), indicating these receptors are present throughout the central nucleus. Although bicuculline-insensitive ionotropic GABA receptors have been described in other regions of the central nervous system (90), the presence of these receptors at synapses has not been shown outside the central amygdala. The two GABA receptor types appear to be localized to different GABAergic inputs onto CeL neurons. Thus inputs from the intercalated neurons that form synapses onto the dendrites of CeL neurons express both GABA_A- and GABA_C-like receptors. In contrast, a different input that enters the central nucleus from a dorsomedial source activates synapses located on the soma. These somatic synapses express only GABA_A receptors (47). The initial segment of CeL neuron axons is spiny (149). It is therefore tempting to speculate that if the somatic GABAergic synapses were made onto these spines, their activity would constitute a powerful means to inhibit the output of CeL neurons. These results suggest that the different GABA receptors may play distinct roles in the local circuitry of the central amygdala (47). Interestingly, the GABA_C-like receptor is negatively modulated by benzodiazepines such as diazepam (47). The

amygdaloid complex has long been known to have a high density of benzodiazepine binding sites (188), and the actions of these agents may reflect their action at sites in the amygdala. Benzodiazepines are thought to produce their anxiolytic actions by enhancing the activity of GABA_A receptor-mediated inhibitory synaptic potentials (192). The presence of a GABA receptor in the central amygdala with a novel benzodiazepine pharmacology suggests an alternative mechanism for the anxiolytic actions of benzodiazepines.

The subdivisions of the central nucleus have extensive intradivisional connections (see above) (92). Many of the neurons in the central nuclei are thought to be GABAergic (160, 189, 209). Both morphological (265) and electrophysiological (190) studies have indicated the presence of abundant local GABAergic connections within the central nucleus. However, direct functional evidence for this is not currently available.

VII. MORPHOLOGY AND PHYSIOLOGY: OTHER NUCLEI

In comparison with the large number of studies that have examined properties of cells in the basolateral complex and central nucleus, there are very few detailed studies of cells in the remaining amygdaloid nuclei.

A. Intercalated Cell Masses

The GABAergic intercalated cells (202) that lie in the fiber bundles between the basolateral complex (173) and the central nucleus act as feed-forward interneurons to cells in the CeA, leading to the generation of a disynaptic inhibitory synaptic potential in these neurons following stimulation in the basolateral complex (47, 203, 239). There are two main types of neuron found in the intercalated cell masses. The first, which accounts for the vast majority of cells, has medium (~10–15 μm) ovoid cell bodies with spiny, largely bipolar dendritic trees and axons that send collaterals into the lateral, basal, and central nuclei (173). The other type are very large cells (~50 μm) with very long thick spiny or aspiny dendrites that travel in parallel to the borders of the basal, lateral, and central nuclei (173, 203). These two cell types are very similar to striatal neurons. Although detailed electrophysiological studies of these neurons have not been reported, trains of action potentials in these neurons are followed by an afterdepolarization (ADP) lasting several seconds (240). Activation of this ADP imparts a heightened excitability to these cells. As the intercalated cells inhibit neurons in the CeA, modulation of the activity of these neurons will have a significant impact on the output of the CeA. In addition, intercalated neurons are connected in local networks oriented in the lateral to medial direction such that activa-

tion of intercalated cells preferentially inhibits neurons in the medial direction (241). This organization within the intercalated cell masses leads to a very specific control of inhibition in the central nucleus as information passing through the basolateral complex activates different populations of intercalated cells (241).

B. Medial Nucleus

The medial nucleus contains just one cell type that resembles the main neurons located in the CeM. They are small to medium-sized ovoid cells with two to four moderately spiny primary dendrites (156). There do not appear to be any local circuit neurons in this structure. Neurons in the bed nucleus of the stria terminalis, which are similar to the main cell types found in the medial and intermediate subdivisions of the central nucleus, have medium-sized somata and multipolar spiny dendrites (151). The anterior amygdaloid area contains cells that have ovoid somata and three to four primary dendrites that branch sparingly and have few spines (73). Thus they resemble the second class of neuron found in the CeM. The cell types observed in the nucleus of the lateral olfactory tract, the amygdalohippocampal area, and the cortical nuclei are similar to those in the basolateral complex. The majority of the cells are pyramidal-like with smaller stellate cells (which resemble the local circuit neurons), spiny stellate cells, and neurogliaform cells also present to lesser degrees (156, 152). Orientation of neurons in the olfactory areas is more cortical-like with apical dendrites oriented parallel to each other. To our knowledge there have been no detailed studies of the electrophysiological properties of neurons in these other nuclei.

VIII. ROLE OF THE AMYGDALOID COMPLEX

It has been known for over a century that the temporal lobe, including the amygdala, is involved in emotion. In 1888, Brown and Schafer (21) described taming in monkeys affect associated with temporal lobe retraction. Klüver and Bucy (102) elaborated on this finding by characterizing a collection of emotional disturbances caused by temporal lobe damage, which became known as Klüver-Bucy syndrome. Monkeys with temporal lobe lesions exhibited an absence of anger and fear, increased exploration, visual agnosia, hyperorality, hypersexuality, and loss of social interactions. Subsequent work has shown that lesions restricted to the amygdala produced many of these effects including a loss of fear and anger, increased exploration, and hyperorality (288, 300). The reduced fear and anger, "taming" effect, of amygdalar lesions is seen in many animal species (71). While amygdala damage in humans rarely results in full-blown Klüver-Bucy syn-

drome, it is associated with some emotional deficits (2) including loss of the recognition of fear in others (1).

Our understanding of the amygdala and its role in emotion is hampered by the abstract nature of emotion itself. In humans, bilateral damage restricted to the amygdala is extremely rare. Animal studies are limited by their inability to tell us how they "feel." Thus much of our understanding of the role of the amygdala in emotion comes from the animal studies on fear (115). Fear, conditioned and unconditioned, elicits a constellation of autonomic and hormonal responses that include cardiac effects (increased blood pressure, changes in heart rate), hormonal effects (release of stress hormones, adrenaline), defecation, vocalization, freezing, and a potentiated startle response (20, 115, 116, 141). These fear response patterns are similar in animals and humans (110). Electrical stimulation of the amygdala elicits fear and anxiety responses in both humans (34, 70) and animals (94), and lesions of the amygdala block the expression of certain, but not all, types of unconditioned fear. For example, rats with amygdala lesions show reduced freezing in response to cats (17) or cat hair (276), attenuated analgesia and heart rate responses to a loud noise (14, 298), and have reduced taste neophobia (182). However, amygdala lesions do not affect other measures of fear such as open arm avoidance in an elevated plus maze (271, 272) or analgesia to shock (287).

The amygdala is also necessary for many types of fear-motivated learning. Amygdala lesions disrupt the acquisition, but not the retention, of both active avoidance (escape from fear) (212) and passive avoidance (124, 235, 271) conditioned responses. Moreover, emotional processing in the amygdala is not limited to fear and aversive stimuli. The amygdala is also involved in conditioning using appetitive stimuli such as food, sex, and drugs. Amygdalar lesions disrupt appetitive Pavlovian conditioning (66, 266), conditioned place preference (54, 55, 166), and conditioned taste aversion (180, 182, 230, 292) and reduce gustatory neophobia (51, 266). Finally, in addition to the direct role of the amygdala in learning and memory, activation of the amygdala also has a modulatory effect on the acquisition and consolidation of memories that evoke an emotional response (168, 169, 195). Although it is well recognized that the amygdala is involved in a myriad of memory- and learning-related tasks, the best studied is its role in Pavlovian fear conditioning and fear-motivated operant conditioning. The remainder of this review will therefore focus on the neural substrates of classical fear conditioning.

IX. THE AMYGDALA AND FEAR CONDITIONING

The neural circuitry of fear conditioning has been extensively studied and recently reviewed (63, 116, 141).

In Pavlovian fear conditioning, a neutral conditioned stimulus (CS) is paired with an aversive unconditioned stimulus (US), such as a mild foot-shock. CS-US pairings result in an association of the CS and US, whereby presentation of the CS subsequently elicits a conditioned fear response (CR), such as freezing. The CS can be a discrete presentation of auditory, visual, olfactory, or tactile stimuli or the CS can be contextual, a collection of numerous environmental features. Foot-shocks or loud noises are typically used as unconditioned stimuli. In rats, lesions to the amygdala disrupt Pavlovian fear conditioning regardless of stimulus modality or response measures (17). Likewise, amygdalar lesions disrupt fear conditioning in non-human primates and humans (11, 106). Studies over many years have clearly established that within the amygdala,

the basolateral complex and CeA play key roles in the acquisition and expression of fear-related behaviors. One prevailing view is that during fear conditioning sensory input reaches the basolateral complex via the LA, which is the site for CS-US association. The basolateral complex then controls the outputs of the CeA to evoke the behavioral and autonomic responses. The pathways involved in this model of fear conditioning are outlined in Figure 10.

A. Basolateral Complex

A converging body of literature has implicated the basolateral complex in assigning affective value to stimuli (27, 43, 82, 116). Anatomically, the basolateral complex is

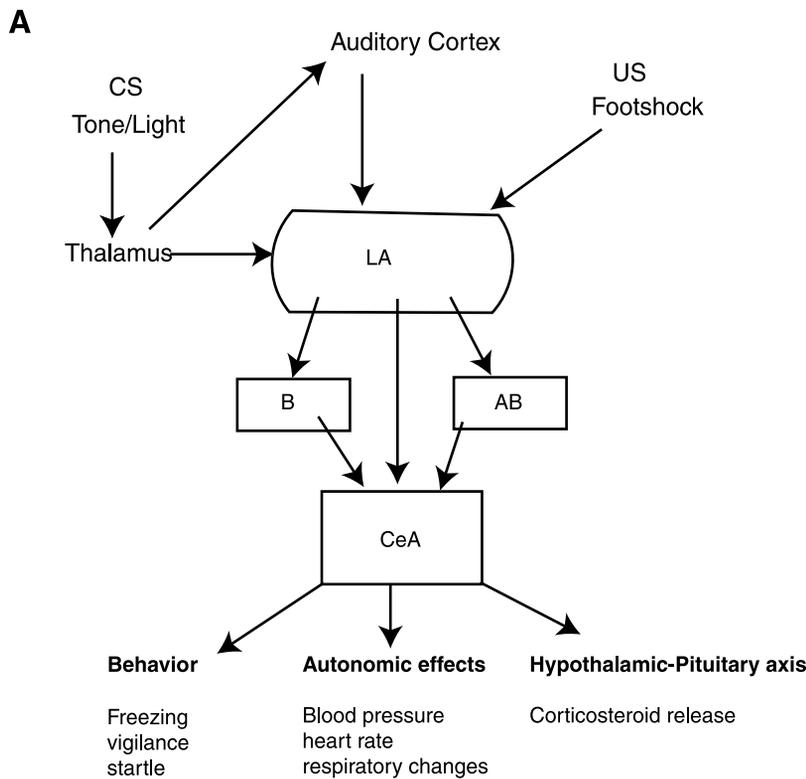
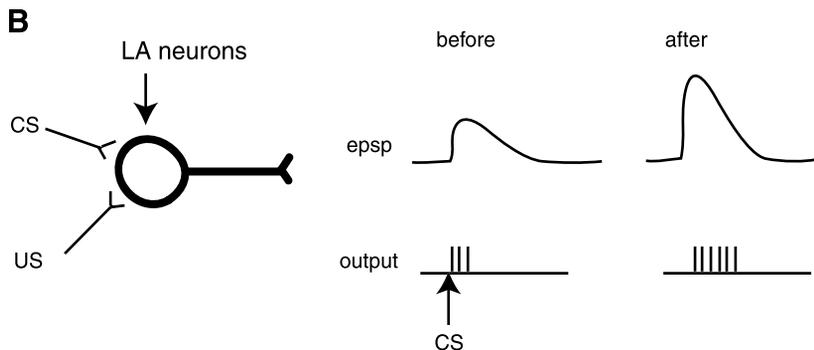


FIG. 10. Functional model of the basic pathways and synaptic plasticity proposed to underlie fear conditioning. Sensory stimuli about the conditioned stimulus (CS) and the unconditioned stimulus (US) converge on the lateral nucleus of the amygdala. During fear conditioning, convergence of inputs to single neurons results in enhancement (long-term potentiation) of excitatory postsynaptic potentials (EPSP) evoked by the CS (B). This synaptic plasticity enhances the response of LA projection neurons in response to the CS. CS-evoked information reaches the CeA directly and via the B and AB nucleus. Projections from the central nucleus control the physiological responses, which include behavioral, autonomic nervous system, and hypothalamic-pituitary axis responses. As shown in B, the convergence of the conditioned and unconditioned input to neurons in the LA has been suggested to result in a larger output in response to the CS. All projections, except those from the CeA, are thought to be glutamatergic.



well positioned for associative learning. Afferents conveying conditioned and unconditioned stimulus information from the neocortex, thalamus, and hippocampus converge on the basolateral complex (232). Lesions of the basolateral complex block acquisition and expression of fear conditioning (24, 117, 142). Functional inactivation of the basolateral complex by infusion of muscimol, a GABA_A agonist, into the basolateral complex disrupts fear conditioning when applied immediately before conditioning or during testing, but not when applied immediately after conditioning (77, 181, 294).

Different CS modalities are mediated by different amygdala afferents. Thalamic medial geniculate and auditory cortical afferents are essential for conditioning to an auditory CS (24, 122, 233), while projections from the perirhinal cortex are essential for conditioning to a visual CS (24, 236, 253). Foot-shock unconditioned information is conveyed to the basolateral complex by projections from the posterior parietal insula (IC) and the posterior intralaminar nuclei of the thalamus (PoT/PIL) (253, 257). Combined, but not separate, lesions of the IC and PoT/PIL disrupt fear conditioning (234, 253, 257).

B. Central Nucleus

As described above, the basolateral complex receives both direct and highly processed sensory information. This information is processed locally and then transmitted to the central nucleus which projects to hypothalamic and brain stem areas that mediate the autonomic and behavioral signs of fear. Lesions of the CeA block the expression of fear conditioned response using visual or auditory CS (24, 72, 76, 78, 79, 99, 298). Furthermore, stimulation of the CeA produces the constellation of conditioned fear responses even in the absence of prior fear conditioning (86, 97). These findings indicate that the complex behavioral pattern of the fear response is probably hard wired. In fear conditioning, it is only necessary for the conditioned stimulus to activate the CeA; the CS-US association occurs in or before the CeA. While the CeA is often considered essential only for expression of the conditioned fear response (116), this view of the CeA is probably an oversimplification. There are no studies involving selective reversible inactivation of the CeA during conditioning. There is considerable evidence showing that CeA is not simply an output pathway of the basolateral complex. Data from other learning paradigms implicate the CeA in the modulation of attention, arousal, and vigilance during conditioning (43, 82). These effects are mediated by the CeA via striatal and basal forebrain connections (27, 74, 80, 81). Finally, CeA activation of the cholinergic system modulates neuronal processing in sensory and learning systems including the basolateral complex, which is highly enriched in cholinergic receptors.

C. Where Is the Memory Stored?

Although there is general agreement about the circuitry that participates in fear and fear conditioning, the exact role played by the different amygdala regions has been questioned. One issue that has been at the forefront of discussion is whether the amygdala is involved in the acquisition and/or storage of fear-related memories or is its role largely in the expression of fear responses. There is a large amount of literature showing that the amygdala plays a role in memory formation in other neural systems (168); however, it has been suggested that the same is also true for fear learning. Thus it has been argued that although the amygdala has a key role in the analysis of emotional content, it largely modulates plasticity in other brain regions that are the substrates for memory storage (23, 167). It has been shown that fear conditioning can cause synaptic changes in regions outside the amygdala. Furthermore, rats can be fear conditioned even following complete lesions of the basolateral complex (22, 277).

There is abundant evidence that synaptic plasticity occurs in the basolateral complex during fear conditioning (see below). However, the issue of whether these changes are necessary and sufficient for fear conditioning remains to be resolved. The basolateral complex, rather than simply controlling the CeA, has extensive projections to the striatum and prefrontal cortex (27, 53, 54), allowing it to influence complex behaviors. Studies demonstrating that inactivation of the basolateral complex (by infusion of lidocaine or tetrodotoxin) many hours after the conditioning can interfere with consolidation of the fear memory (242, 278) is consistent with the proposal that while plasticity within the amygdala is associated with fear conditioning, changes in other brain regions, which require amygdala activation, are also involved.

Apart from fear conditioning, the amygdala is involved in a range of memory tasks. It is well known that the amygdala is necessary for fear-motivated operant conditioning. Unlike Pavlovian fear conditioning, in the instrumental-avoidance task animals are able to avoid the aversive stimulus by making the appropriate behavioral response. Amygdala lesions disrupt the acquisition, but not the retention, of both active avoidance (escape from fear) (64, 212) and passive avoidance (124, 235, 271) conditioned responses. These different learning tasks related to fear can be double dissociated within the amygdala (99). In this study, one measure was a classical fear response measured as a reduction in ongoing behavior during CS presentation and was dependent on the CeA. This result is consistent with previous findings with CeA lesions and agrees with the idea that CeA outputs mediate behavioral responses. The other behavior, measured concurrently with the first, involved an operant choice dependent on the predictive value of the CS. This behavior was independent of the CeA but required the basolateral com-

plex (LA and B). It was notable that the classical fear responses were unaffected by basolateral lesions, a finding that suggests that information about the CS need not require activity within the basolateral complex. Although the exact interpretation of these conclusions has been debated (183), it seems clear that while the outputs of the CeA are involved in one type of emotional learning, the outputs of the basolateral complex need to be considered in other types of learning that involve the amygdala (168). Despite these caveats, simple Pavlovian fear conditioning remains the single most tractable model in which to address the cellular substrates that might underlie these learned behaviors.

X. SYNAPTIC PLASTICITY AND FEAR CONDITIONING

How does the amygdala mediate memory storage in fear conditioning? As described above, there is considerable evidence suggesting that the CS-US association occurs in the basolateral complex. Inputs to the basolateral complex use glutamate as the transmitter and activate synapses expressing both AMPA and NMDA receptors. Results from several laboratories have shown that infusion of the NMDA receptor antagonist D,L-2-amino-5-phosphonovaleric acid (AP5) into the basolateral complex blocks the acquisition of amygdala-dependent conditioning (24, 68, 100, 176). Within the basolateral complex, selective lesions of the lateral amygdala disrupt fear conditioning (9, 72, 117, 184, 281). Recordings of single units with the LA in vivo have shown that these neurons respond to both auditory (tone; CS) and somatosensory (shock; US) stimulation (199, 232). Auditory fear conditioning enhances short latency CS firing in LA neurons (216). The enhanced neuronal firing to the CS observed in the LA precedes behavioral expression of the conditioned response (225). Conditioning-associated increases in firing to the CS are also observed in the auditory cortex, but this change is subsequent to the firing rate changes in the LA (215). Furthermore, animals can undergo auditory fear conditioning following lesions to either the thalamo-amygdala or cortico-amygdala pathways, but not both (24, 233). Finally, the auditory evoked potentials recorded in the LA are enhanced in conditioned rats, but not in pseudoconditioned controls that receive unpaired CS and US presentations (229).

Most recently, a study by Rosenkrantz and Grace (238) provides compelling evidence suggesting that the LA is indeed a site of plasticity during fear conditioning. Using intracellular recordings in vivo, these authors show that pairing an odor (CS) with a foot-shock (US) enhanced the amplitude of the response to the paired odor. Simultaneously they also showed that the response to an unpaired odor is unaffected. The potentiation of the

paired response could be blocked by hyperpolarizing the postsynaptic cell during pairing, indicating that the plasticity required the postsynaptic neuron.

Together, these studies have led to the suggestion that NMDA receptor-mediated synaptic plasticity (long-term potentiation, LTP) within the basolateral complex underlies the acquisition and storage of memory related to fear conditioning (140). Moreover, it has been suggested that these changes occur in projection neurons in the LA (116, 117). In agreement with this suggestion, in vivo recordings have shown that tetanic stimulation of thalamic inputs to the LA enhance both electrically evoked as well as auditory evoked responses in the LA (228). Unfortunately, whether the changes in synaptically evoked responses were sensitive to NMDA receptor blockade was not tested. In a different set of experiments, McKernan et al. (171) have shown that the amplitude of AMPA evoked currents at thalamic inputs to neurons in the LA were larger in animals that had undergone auditory fear conditioning. With the use of paired pulse facilitation as an index of release probability (301), it has been suggested that the site of plasticity during fear conditioning is presynaptic (171). Finally, if fear conditioning results from LTP at inputs to neurons in the basolateral complex, one might expect that the induction of LTP at synapses that have participated in fear conditioning would be occluded. This has recently been demonstrated at inputs to pyramidal neurons in the LA (273). In summary, there is convincing evidence that the response of neurons in the LA to CS stimulation is enhanced after fear conditioning.

The basic properties of LTP, input specificity, cooperativity, and associativity, have made it an attractive cellular model of associative learning (18). While LTP has been studied at many other synapses, the most extensively studied form occurs at excitatory synapses between Schaffer collaterals and CA1 pyramidal neurons in the hippocampus (133, 137). These studies have shown that the induction of LTP requires a rise in postsynaptic calcium (138). In the classical model of LTP, depolarization of the postsynaptic neuron relieves the Mg^{2+} blockade of NMDA receptors (191), allowing Ca^{2+} to enter via NMDA receptor channels to trigger signal transduction cascades that initiate the molecular changes that underlie LTP (18, 139). The depolarization required to activate NMDA receptors is provided either by AMPA receptors (during tetanically induced LTP) or by backpropagating action potentials (134). While the postsynaptic induction of this LTP is certain, the final locus of the change that underlies LTP, whether it is presynaptic or postsynaptic, has been much debated (139). NMDA receptor-independent forms of LTP have also been described. In NMDA-independent induction of LTP, postsynaptic calcium comes from voltage-gated calcium channels (VGCCs) (296) or calcium-permeable AMPA receptors (135). Finally, at some synapses, a presynaptic form of LTP, which

does not require NMDA receptors, has also been described (187).

Both cortical and thalamic afferents to the LA are capable of long-term plasticity after tetanic stimulation. Tetanic stimulation of afferents to the basolateral complex has been shown to result in LTP both in vivo (36, 143, 228) and in vitro (10, 32, 33, 84, 289). All studies are in agreement that a rise in postsynaptic calcium is required for the induction of LTP at both cortical and thalamic inputs to basolateral neurons. The site of plasticity has been proposed to be presynaptic with an increase in the probability of transmitter release (84, 143, 273). However, whether induction of LTP at synapses to LA neurons requires activation of NMDA receptors is not clear. Although some groups have shown NMDA-dependent LTP in vitro (84), others have found that tetanically induced LTP does not require activation of NMDA receptors (32). Furthermore, a recent study found that tetanic stimulation alone was ineffective in inducing LTP, but pairing action potentials with thalamic excitatory postsynaptic potentials did lead to a form of LTP that required activation of L-type VGCCs for induction (273, 289). As mentioned above, NMDA receptors have also been suggested to contribute to basal transmission at thalamic inputs to the lateral amygdala (127, 291). In agreement with this finding, behavioral evidence has suggested that AP5 may block the acquisition of fear conditioning by disrupting normal synaptic transmission in the amygdala (62, 123). These results challenge the notion that NMDA receptor-mediated plasticity within the amygdala is the mechanism underlying the acquisition and storage of fear-related memories (23).

One potential problem has been that all the in vivo studies (and some in vitro studies) have relied on field potential measurements of inputs to the amygdaloid complex. However, unlike in clearly layered structures like the hippocampus or cerebellum, there is little organization to the architecture of the neurons and where they receive their synaptic inputs. Thus, because there are no clear sources and sinks when inputs are stimulated, it is difficult to separate field potentials associated with synaptic currents and those associated with action potentials (143). Thus changes in field potentials are difficult to interpret with regard to the locus of change that is being measured. Neurons in the lateral amygdala have extensive local connections (153). Following fear conditioning, an increase in the correlated firing of neurons in the lateral amygdala have been reported (199, 215), suggesting that there might also be changes in the local connections or cell properties following conditioning. Thus it is possible that the changes in field potential measurements following fear conditioning may result from changes in the strength of connections between neurons rather than of excitatory inputs to these cells. Only in a few studies have

changes in field potentials been correlated with changes in synaptic potentials (84).

Recent in vitro studies have also demonstrated several other forms of plasticity in the basolateral amygdala. First, glutamatergic inputs to interneurons in the basolateral complex activate synapses that do not express NMDA receptors. LTP at these inputs is triggered by a rise in calcium by influx via AMPA receptors (135). Because interneurons are the only source of inhibitory potentials in the basolateral complex, potentiation of excitatory afferents to interneurons leads to an increase in the amplitude of the disynaptic inhibitory potentials (135). Second, as in the hippocampus, low-frequency stimulation of inputs to the basal nucleus leads to long-term depression (LTD) (75, 282). This LTD is input specific and requires activation of metabotropic receptors and a rise in postsynaptic calcium levels (75, 128, 223). Lastly, low-frequency stimulation of inputs to the basal nucleus evokes a slow onset of facilitation of these inputs (125). Its induction was shown to result from activation of kainate receptors present in the basal nucleus (125). This is a novel form of synaptic plasticity that has not been previously described, and its relationship to LTD described by others, is not clear. The possible roles of these phenomena in amygdala-mediated learning are not known at present. In summary, although the role of the basolateral complex in the induction of fear conditioning is clear, there is considerable debate as to the nature of the changes that occur during the conditioning.

If the underlying mechanism for the acquisition and storage of fear-related memories is LTP within the amygdala, it is useful to consider how this might operate mechanistically. As originally formulated, LTP results from the coincident activation of two different inputs to single cells. One of these is considered the "weak" input and represents the CS. The other input is a "strong" input and represents the US. The "strong" input is capable of activating postsynaptic cells causing a strong depolarization and/or evoking repetitive action potential firing. The weak input, however, is not as effective as the strong input in driving the postsynaptic cell. During conjunctive stimulation, these two inputs undergo a pairing in which the weak input is potentiated, that is, undergoes LTP and becomes capable of driving the postsynaptic cell. This is the principle of associativity. Neurons in the basolateral complex have been shown to respond to both the CS and US. While the response to the CS is perhaps not as strong as to that of the US (215), it is currently unclear how CS-US association during fear conditioning would lead to LTP of the CS inputs. Interestingly, in a recent study, intracellular recordings maintained during the CS-US pairing revealed that plasticity of the CS occurs despite the lack of significant postsynaptic depolarization during the conjunctive stimulation (238). This result suggests that alternate mechanisms to classical LTP may be oper-

ating in the LA during fear conditioning. Conditioning to different modalities has been shown to require activation of basolateral neurons. Fear conditioning to one modality preserves the response to a different modality showing that the associated plasticity is restricted to the input that has undergone conditioning (24). In vitro recordings in acute brain slices prepared from fear-conditioned animals show enhanced responses when inputs to LA neurons are stimulated (171). These results suggest that different modalities must converge on all neurons and does not resolve how input specificity of conditioning is generated. These considerations show that a simple model involving plasticity of synapses made by a given input in one structure cannot entirely account for the complexity of the phenomenon of learning.

XI. CONCLUSIONS

Studies performed over the last 50 years have clearly established the role of the amygdala in a range of related learning and memory tasks. The anatomy of the amygdaloid complex, its local connectivity, and afferent and efferent systems that interact with the amygdaloid complex are now known in great detail. However, there is a paucity of knowledge of information transfer through this structure. In addition, although much is known anatomically about cell types present in most areas of the amygdala, the physiology of cell types has been examined in detail in only a few nuclei. Furthermore, an analysis of the physiology of local connections within the amygdaloid nuclei has largely been ignored. An analysis of the physiology of the local circuitry is essential to elucidate the nature of information processing within the amygdala.

Studies of fear conditioning have provided the most detailed understanding of the role of the amygdala and its afferent and efferent connections in this simple learning paradigm. Long-term synaptic plasticity, involving activation of glutamate receptors within the LA, has been proposed as the mechanism underlying the acquisition and storage of fear conditioning. However, the types of plasticity that are present and their underlying mechanism are just beginning to be studied and in general are not always in good agreement with the behavioral data. The modulation of processing within the amygdala by neuromodulators and hormones that are known to play key roles in memory formation (168, 169) has been largely ignored. A recent report examining the changes in synaptic input to neurons in the LA following odor-induced fear conditioning has found that the plasticity induced during conditioning required activation of dopaminergic systems in vivo (238). It is therefore tempting to speculate that some of the differences between results obtained in vivo and those seen in vitro might result from changes in the availability of some of these modulatory influences.

The major challenge for the future is in the study of the local physiology and types and properties of receptors and ion channels present in the amygdala. Fear conditioning is a relatively simple learning paradigm, and the involvement of the amygdala in its induction is clear. An analysis of the physiological properties of the circuits underlying fear conditioning will provide a deeper understanding of the neural mechanisms underlying the acquisition and storage of emotionally related memories. These studies will set the foundations for understanding the neurological basis of fear and nervous disorders related to fear.

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