

Contextual Inhibitory Gating of Impulse Traffic in the Intra-amygdaloid Network

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ABSTRACT: New data on the organization of the intra-amygdaloid circuit is reviewed, beginning with the basolateral (BL) complex, the main input station of the amygdala for sensory afferents, and concluding with the central (CE) nucleus, an important source of projections to brain-stem structures mediating fear responses. The BL complex is endowed with a highly divergent system of intrinsic glutamatergic connections. Yet, BL projection cells have unusually low firing rates. This apparent contradiction is explained by the presence of powerful inhibitory pressures in the BL amygdala: (1) interneurons that generate large-amplitude inhibitory synaptic potentials and (2) projection cells that express a Ca^{2+} -dependent K^{+} current that can be activated by subthreshold synaptic inputs. Likewise, excitatory projections from the BL amygdala to the CE nucleus are controlled by clusters of GABAergic neurons, termed the intercalated (ITC) cell masses. In response to BL inputs, ITC cells generate feedforward inhibition in CE neurons. However, ITC neurons exhibit properties that allow them to modify the amount of inhibition they generate depending on the distribution of BL activity in space and time. Indeed, ITC cell masses can inhibit each other via lateromedial connections. Moreover, they express an unusual K^{+} conductance that modifies their response to BL inputs depending on their recent firing history. Thus, inhibitory mechanisms of the amygdala allow for flexible, context-dependent gating of BL impulses to the CE nucleus.

KEYWORDS: amygdala; perirhinal cortex; epilepsy; fear conditioning; freezing; anxiety; inhibition; gaba; interneurons.

INTRODUCTION

Despite recent advances in our knowledge of the functions of the amygdala,¹ we still lack a basic understanding of the type of computations it carries out. This chapter summarizes recent work that we performed to improve our grasp of intra-

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amygdaloid computations. A dominant theme in the recent literature has been the important role played by projections of the basolateral (BL) complex (consisting of the BL, basomedial [BM], and lateral [LA] nuclei) to the central (CE) nucleus and from there to a variety of brain structures involved in the generation of fear responses.^{2,3} The present chapter follows the logic of this functional scheme, beginning with the physiology of the BL complex and concluding with factors affecting impulse flow to the CE nucleus.

THE BASOLATERAL COMPLEX: A CORTICAL-LIKE STRUCTURE

Cell Types. Although BL neurons are oriented randomly, the cellular composition of the BL complex (reviewed in Ref. 4) is similar to that of the cerebral cortex. Like the cortex, the BL complex contains two main cell types: (1) spiny multipolar (often pyramidal-shaped) projection cells (P cells) with highly collateralized axons, and (2) a heterogeneous class of aspiny (or sparsely spiny) local-circuit neurons that use GABA as a transmitter (rat,⁵ cat,⁶ and monkey⁷). P cells account for most BL neurons,⁸ they use glutamate as a transmitter,⁹ and they are the source of most, if not all, of the internuclear projections within the amygdala^{9,10} (but see Ref. 11).

As in the cortex (reviewed in Refs. 12 and 13), local-circuit cells of the BL complex are morphologically and neurochemically heterogeneous.⁴ For example, subsets of GABAergic cells express somatostatin, neuropeptide Y, cholecystokinin, or vasoactive intestinal peptide.^{14,15} In addition, many GABAergic interneurons express Ca²⁺-binding proteins. For instance, parvalbumin (PV) colocalizes with GABA in as many as ~50% of local-circuit cells.^{16,17} By contrast, very few, if any, P cells express PV.¹⁸

As in the cortex, PV interneurons are believed to mediate feedback inhibition. Consistent with this view, BL P cells form asymmetric (presumably excitatory) synapses on PV interneurons, whereas cortical axons do not.¹⁹ On the output side, PV cells form numerous inhibitory synapses on the soma, initial axonal segment, and proximal dendrites of P cells.²⁰ The density of these inhibitory terminals is such that they delineate the soma and proximal processes of P cells.^{16–18}

Physiological Properties. Much less is known about the physiological properties of BL cells than of cortical neurons. However, the available data are consistent with findings in the cerebral cortex.^{21,22} The following is a summary of *in vitro*^{23–28} and *in vivo*^{29–32} studies that correlated the physiological and morphological properties of neurons of the BL complex.

P cells: Spiny multipolar neurons (i.e., presumed P cells) were reported to occur in two main varieties: (1) regular spiking neurons that generate spike trains displaying frequency accommodation (FIG. 1A2), and (2) burst firing cells reminiscent of the corresponding class of cortical neurons (generating high-frequency clusters of action potentials in response to threshold depolarizations). That at least some regular spiking and burst firing cells are P cells was confirmed *in vivo* by antidromically invading some of these cells from extra-amygdaloid sites.^{29–32} Some studies have reported a third class of spiny neurons (presumed P cells), termed late-firing cells because they exhibit a conspicuous delay to firing after the onset of depolarizing current pulses.^{23,26}

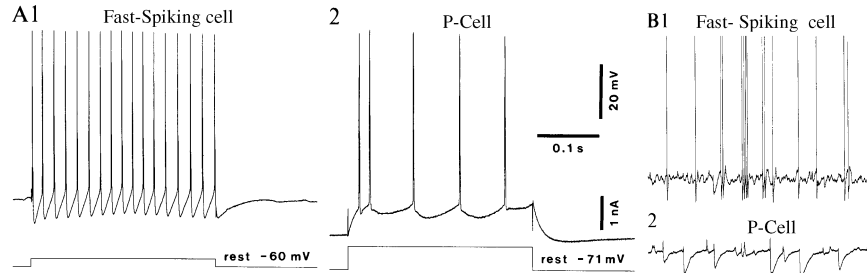


FIGURE 1. Current-evoked (A) and spontaneous activity (B) of fast-spiking (1) and P cells (2) at rest. Note lack of spike frequency adaptation in fast-spiking cell (A1) and the lower frequency, adapting discharge of the P cell (A2). Potassium acetate recordings. Also, note larger AHP amplitude in fast-spiking cell. In B, note that the interneuron trace shows many depolarizing events and spikes (B1), whereas the activity of the P cell is dominated by IPSPs (B2). Scale bar in B2: 1 second.

Local-circuit cells: Two physiological types of aspiny neurons (i.e., presumed inhibitory interneurons) have been described so far. The most frequent were termed fast-spiking cells by analogy with the corresponding class of PV cortical neurons.¹³ Like their cortical counterpart, these cells generate brief spikes and can sustain high firing rates with little frequency accommodation (FIG. 1A1). No such cells have been backfired from outside the amygdala.^{29,32} In addition, aspiny neurons generating spike bursts were described.²⁴ The peptide content of these two types of interneurons has not yet been investigated. However, fast-spiking cells most likely correspond to the PV interneurons that mediate feedback inhibition.^{19,20}

Finally, electrophysiological evidence for the existence of a class of fast-spiking inhibitory interneurons that would mediate feedforward inhibition was also obtained.³³ These cells exhibited excitatory responses to electrical stimuli applied in the external capsule and above the optic tract (putative cortical and thalamic inputs).

Inhibition As a Major Determinant of BL Activity. The foregoing indicates that the cellular composition of the BL complex is similar to that of the cerebral cortex in terms of physiological properties, morphology, and neurotransmitters. Yet, compared to the neocortex, neurons of the BL complex have extremely low firing rates. Indeed, physiological studies have emphasized the paucity of spontaneous activity (<1 Hz) of P cells in unanesthetized animals.^{34–36} This is in contrast to cortical pyramidal cells that fire at ~10 Hz during wakefulness (reviewed in Refs. 37 and 38).

This difference is especially puzzling because the LA is endowed with extremely divergent intrinsic connectivity. Indeed, the axon collaterals of P cells bear numerous varicosities that form en passant asymmetric synaptic contacts, typically with dendritic spines.⁹ For electron microscopists, these are code words for excitatory inputs to other excitatory neurons.³⁹ Moreover, these varicosities typically occur every 5–10 μm , suggesting that each P cell forms 100–200 excitatory synapses per millimeter of axon, most of which end on other P cells (88%⁹).

Given this astonishing potential for divergence in the intra-BL network, the silence of P cells is remarkable. Considering that the BL complex and cortex are subjected to the same neuromodulatory inputs⁴⁰ and exhibit similar responses to these neurotransmitters,^{41–43} this peculiar situation suggests that inhibition is a major

determinant of BL activity. Consistent with this, *in vitro* and *in vivo* intracellular studies have reported that afferent stimulation elicits an initial EPSP that is truncated by a large amplitude prolonged hyperpolarizing potential in P cells of the BL complex.^{28,30–32,44,45} Moreover, *in vivo* intracellular recordings of P cells have revealed that their spontaneous activity is dominated by similarly large hyperpolarizing potentials (FIG. 1B2).^{30–32}

Inhibitory Mechanisms in the BL Complex

The large hyperpolarizations that dominate the spontaneous (FIG. 1B2) and stimulus-evoked (FIG. 2A) synaptic responses of P cells in the BL complex are generated by the combined action of synaptic conductances (IPSPs) and synaptically activated intrinsic membrane conductances.

IPSPs. *In vitro* studies have demonstrated the presence of GABAergic IPSPs in P cells of the BL complex.^{28,44–46} *In vitro*, electrical stimuli evoke an initial EPSP that is followed by distinct “early” GABA-A and “late” GABA-B mediated IPSPs. Local interneurons are primarily responsible for these GABAergic IPSPs, as deafferentation of the amygdala produces only slight reductions in the concentration of glutamic acid decarboxylase.⁴⁷ Consistent with the idea that the IPSPs have a local origin, a close parallel exists between the amount of excitation evoked by perirhinal stimulation in interneurons and the appearance and growth of IPSPs in P cells (FIG. 2).³²

Similar to *in vitro* studies, *in vivo* experiments have also indicated the presence of large IPSPs that truncate stimulus-evoked or spontaneously occurring EPSPs; however, only a single monophasic hyperpolarization is observed in contrast to the

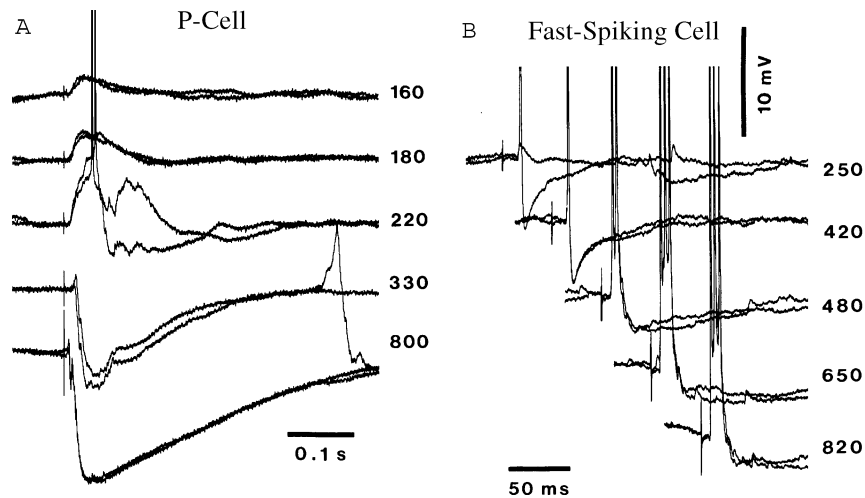


FIGURE 2. Contrasting response profile of P-cell (A, rest = -70 mV) and fast-spiking neuron (B, rest = -62 mV) to perirhinal stimuli of gradually increasing intensity (numbers to the right, μA). Both neurons were recorded intracellularly *in vivo*. Potassium acetate recordings. Note that the P cell is progressively more inhibited as stimulation intensity is increased, whereas the fast-spiking cell shows the opposite behavior. Tests were carried out at -62 mV. Spikes are truncated.

biphasic GABA-A GABA-B sequence that is observed *in vitro* (FIG. 2A).³⁰ Several factors account for the different synaptic response profiles obtained *in vivo* and *in vitro*. In particular, the cortical and amygdaloid circuits, which are largely lost in slice preparations, remain intact under *in vivo* conditions and allow for widespread divergence and convergence of activity. This results in a temporally distributed activation of interneurons and an overlap of the GABA-A and GABA-B IPSPs from different interneurons.³⁰ In addition, the amplitude of the GABA-B IPSP appears to be relatively small under *in vivo* conditions compared to those *in vitro*.³¹

A major factor contributing to the suppression of P-cell activity is the relatively low level of inhibition directed towards interneurons (FIG. 2B). Several factors underlie this relatively weak inhibitory control of interneurons. First, inhibitory responses in interneurons appear to be comprised simply of GABA-A IPSPs and not GABA-B IPSPs or the synaptically activated Ca^{2+} -dependent K^+ (K_{Ca}) conductance found in P cells.^{28,31,32} Second, the reversal potential of GABA-A IPSPs in interneurons is depolarized with respect to that in P cells. This difference arises from cell type-specific chloride homeostatic mechanisms whereby the prevalent regulators of intracellular Cl^- are cation-chloride cotransporters that accumulate chloride in fast-spiking interneurons and extrude chloride in P cells.²⁸ Third, GABAergic interneurons (at least the parvalbumin-positive subset) receive a significantly lower proportion of GABAergic synapses than do P cells.²⁰ These factors conspire to keep interneurons in a relatively excitable state, which is reflected in intracellular recordings in which these cells display depolarized resting potentials that are punctuated by numerous spontaneous EPSPs and spikes but relatively few IPSPs (FIG. 1B1).³²

K_{Ca} Conductances. In addition to IPSPs, both *in vivo* and *in vitro* studies in the LA nucleus have demonstrated that a synaptically activated K_{Ca} conductance is a major inhibitory component of P-cell responses to afferent activity.^{30,31,46,48} Activation of this K_{Ca} conductance appears to be linked to Ca^{2+} influx via NMDA receptors.⁴⁶ Under *in vivo* conditions, this K_{Ca} conductance is active throughout the synaptic response and opposes the initial EPSP in addition to contributing throughout the subsequent prolonged hyperpolarization.^{31,48} The importance of this conductance for controlling LA activity is indicated by the fact that paroxysmal depolarizations that underlie epileptic discharges do not occur in P cells after blocking GABA-A and GABA-B IPSPs unless K_{Ca} conductances are also reduced by intracellular injection of the calcium chelator BAPTA.⁴⁶ It should be mentioned that K_{Ca} conductances are also largely responsible for the pronounced spike adaptation observed in LA P cells, which limits their spike activity to sustained excitatory input.^{27,48}

To summarize, considerable resources are devoted to control the activity of BL P cells, particularly those of the LA nucleus, where both synaptic and synaptically activated intrinsic conductances contribute to limit their orthodromic responsiveness. This powerful inhibitory control may be essential for preserving the associative potential of a divergent intrinsic circuitry, while preventing the genesis of epileptic events.

PROJECTION OF THE BASOLATERAL COMPLEX TO THE CENTRAL NUCLEUS

The LA nucleus is an important input station of the amygdala for thalamic and cortical sensory afferents. By contrast, the CE nucleus is currently conceived of a

major output of the amygdala for conditioned fear responses.^{3,49} Indeed, CE lesions abolish a variety of conditioned fear responses.^{2,50,51} However, it is important to keep in mind that different parts of the CE nucleus have distinct projection sites. Freezing, for instance, is mediated by projections of the CE nucleus to the periaqueductal grey (PAG).⁵² In fact, most CE projections to the PAG and other brain-stem structures originate from the medial sector of the CE nucleus (CE_M).⁵³ Thus, accounts of classically conditioned fear responses must explain how sensory inputs that mainly reach the amygdala by way of the LA nucleus ultimately influence the CE_M.

The LA Has Little, If Any, Direct Links to Brain-Stem–Projecting CE Neurons

To address this issue, we now turn to anatomical data regarding LA projections to the CE. Tract-tracing studies have shown that different nuclei of the BL complex project to different parts of the CE nucleus. For instance, the LA nucleus projects to the capsular or lateral sectors of the CE nucleus (CE_L),^{9,11,54,55} but has little, if any, projections to the CE_M. In contrast, the basal nuclei have projections to the different subdivisions of the CE nucleus.^{10,54}

These results were confirmed in a study in which the responses of CE neurons to electrical stimuli delivered in the BL complex were recorded in brain slices kept *in vitro*.⁵⁶ In this study, it was found that LA stimuli do not elicit responses in the CE_M but only in more lateral sectors of the CE. By contrast, stimulation of basal nuclei evoked responses throughout the CE.

However, such data can be criticized on the grounds that brain slices do not preserve long pathways. Fortunately, cross-correlation studies of simultaneously recorded neurons of the BL complex and CE nucleus *in vivo* support the foregoing *in vitro* results. Indeed, a positive correlation was found between the firing of simultaneously recorded neurons in the CE and basal nuclei. Surprisingly, an inverse relation was found between the auditory-evoked and spontaneous activity of LA and CE_M neurons in unanesthetized animals.⁵⁷

Since P cells of the LA nucleus use glutamate as a transmitter and exclusively form asymmetric synaptic contacts,^{9,10} the fact that the firing of LA cells coincides with inhibition of CE_M neurons is surprising. Moreover, this finding is inconsistent with the prevailing model of pavlovian fear conditioning,³ which predicts that the increased responsiveness of LA neurons to the conditioned stimulus produces an augmented depolarization of brain-stem projecting CE neurons, leading to conditioned fear responses. To explain how the increased firing of LA neurons generates inhibition in CE_M neurons, we now turn to a poorly understood structure of the amygdala, intercalated (ITC) cell masses (FIG. 3).

INTERCALATED NEURONS AS A CONDITIONAL GATE BETWEEN THE BASOLATERAL COMPLEX AND CENTRAL NUCLEUS

ITC Neurons Generate Feedforward Inhibition in CE Neurons

The ITC cell masses are interconnected clusters of GABAergic neurons^{6,7,58} located between the BL complex, from which they receive much glutamatergic

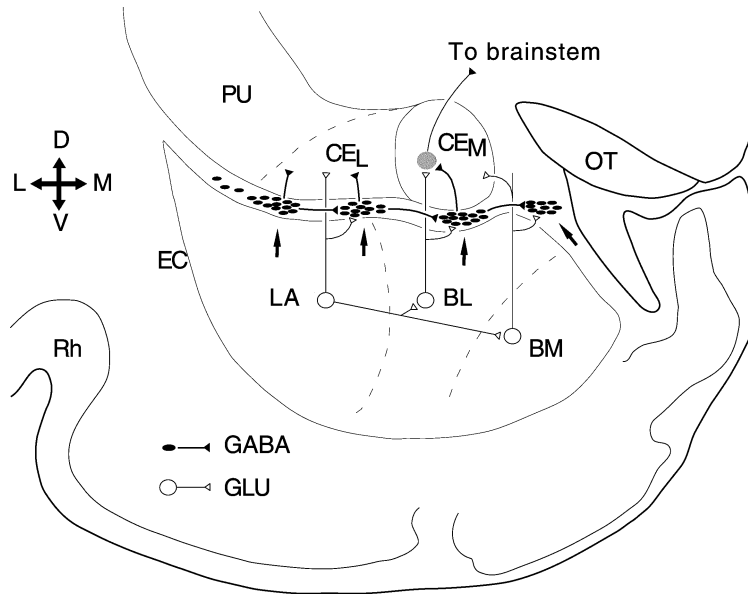


FIGURE 3. Connectivity of ITC cell masses. Scheme of a coronal section through the amygdaloid complex of the guinea pig. ITC cell masses (*arrows*) receive glutamatergic inputs from components of the basolateral complex (namely, lateral [LA], basolateral [BL], and basomedial [BM] nuclei) and contribute a GABAergic projection to lateral and medial sectors of the central nucleus (CE_L and CE_M, respectively). ITC cell masses are interconnected by lateromedial connections. Abbreviations: EC, external capsule; OT, optic tract; PU, putamen; Rh, rhinal sulcus.

inputs⁵⁶ (FIG. 3), and the CE nucleus (FIG. 3), their main projection site.^{59,60} Our recent work revealed that the connections and intrinsic membrane properties of ITC cells enable them to act as a context-dependent gate that can dampen or enhance the impact of BL impulses on CE neurons.

To analyze how ITC neurons affect impulse traffic between the BL complex and the CE nucleus, we studied the responses of ITC cells to electrical stimuli delivered in the BL complex. ITC neurons were morphologically identified by intracellular injection of neurobiotin and recorded in brain slices kept *in vitro*.^{56,61} We found that a lateromedial correspondence exists between the position of ITC cells, their projection site in the CE nucleus, and the source of their afferents in the BL complex⁵⁶ (FIG. 3). In addition, we noted that ITC cells are interconnected, but only in a lateromedial direction⁶¹ (FIG. 3).

Even though BL projections to the CE nucleus are glutamatergic, BL stimuli evoke a biphasic EPSP-IPSP sequence in CE neurons (FIG. 4A)^{56,62,63} mediated by GABA-A and GABA-C receptors.⁶⁴ To determine whether ITC cells take part in generating this inhibition, we investigated the effect of local pressure application of NBQX, a non-NMDA receptor antagonist, on BL-evoked inhibition in CE cells (FIG. 4A). CE cells were dialyzed with QX-314 and depolarized to -50 mV. Local application of NBQX in ITC cell masses below the CE greatly reduced the inhibitory

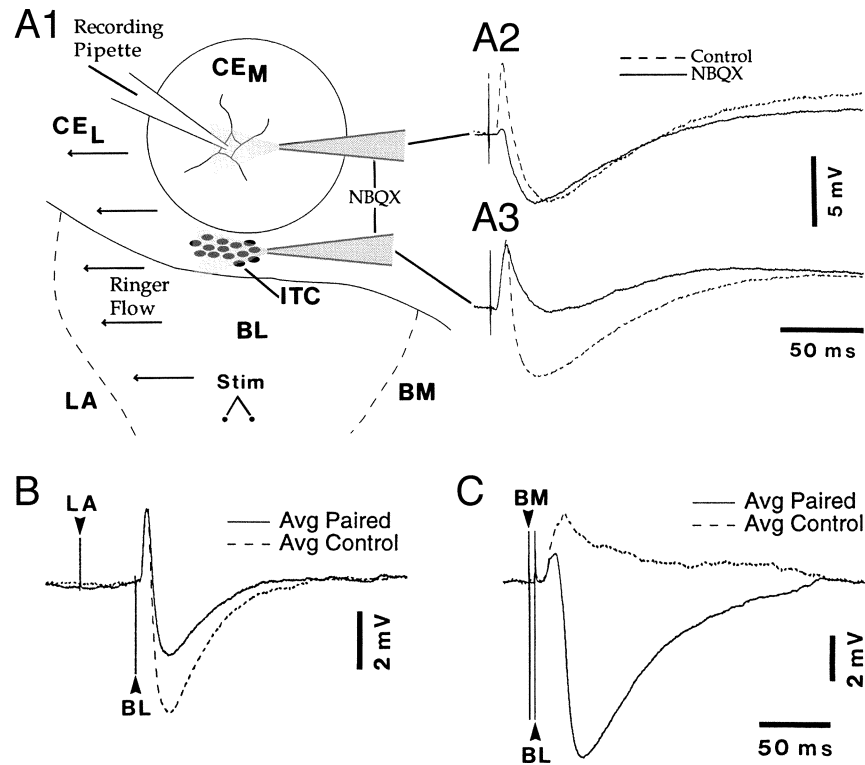


FIGURE 4. ITC neurons generate feedforward IPSPs in CE_M cells. (**A1**) Scheme illustrating the approach used to test the effect of local pressure application of NBQX on CE_M responses to BL stimuli (dots). Horizontal arrows on the left indicate the direction of Ringer flow. The ejection pipette was first positioned in the CE_M and, after a period of recovery (10 minutes), close to ITC cells. The effect of NBQX pulses (1 second, 10 PSI) in the CE_M and the ITC cell mass is shown in **A2** and **A3**, respectively. Each trace is the average response to four BL stimuli delivered at 0.1 Hz in control conditions (dashed line) or preceded by an NBQX pulse (dashed line; pulse-shock interval of 100 ms). (**B, C**) Stimuli having no direct effects on CE_M neurons can reduce or enhance BL-evoked CE_M responses by modulating ITC neurons. (**B**) BL-evoked IPSPs of CE_M neurons (Control) are reduced when BL stimuli are preceded by a LA shock (Paired). To carry out these tests, the cell was depolarized to -49 mV (with 0.06 nA) and the pipette contained QX-314 to prevent spiking. Averages of four paired and unpaired (Control) responses. (**C**) BM stimulation enhances IPSPs evoked by BL stimuli. CE_M neuron depolarized to -51 mV (0.05 nA). Intensity of BL stimuli was gradually reduced to minimize the amplitude of evoked IPSP in control conditions and then paired with BM stimuli. The recording pipette contained QX-314. Averages of four paired and unpaired (Control) responses.

phase of the response with little effect on the early excitation (FIG. 4A3). By contrast, NBQX application in the CE abolished or greatly reduced the BL-evoked EPSPs without interfering with the BL-evoked IPSPs (FIG. 4A2). Thus, BL stimulation provokes a feedforward inhibition of CE cells in part via the glutamatergic activation of ITC neurons.

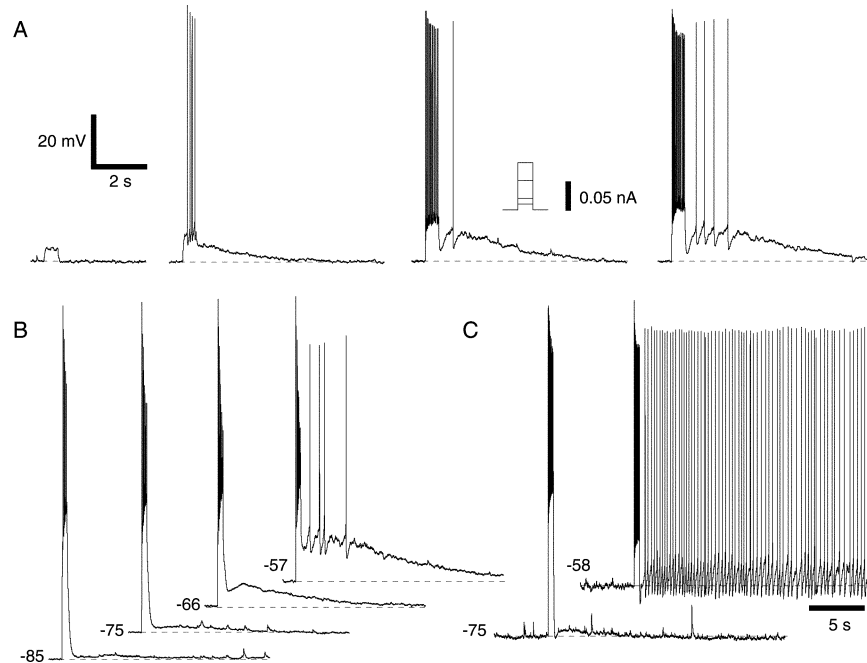


FIGURE 5. Suprathreshold depolarizations elicit ADPs in ITC cells. (A) Depolarizing current pulses of gradually increasing amplitude (*left to right*) applied at -60 mV. (B) Depolarizing current pulses adjusted to elicit approximately the same number of spikes were delivered from different membrane potentials (numbers on *left*). (C) Spike trains elicited from a depolarized potential lead to tonic firing. Voltage scale is the same for A-C. Same time scale for A and B.

Importantly, because ITC neurons inhibit each other in a lateromedial direction, the feedforward inhibition they generate in CE neurons and, indirectly, the amplitude of BL-evoked EPSPs depends on which combination of BL nuclei is activated and in what sequence (FIG. 4B-C). For instance, when subthreshold BL stimuli are preceded by LA stimuli, the BL-evoked response becomes suprathreshold, provided that the interstimulus interval ranges between ~ 5 and 80 ms. This effect results from a reduction of the hyperpolarizing component evoked by BL stimuli, as evidenced in tests carried out in CE_M cells dialyzed with QX-314 and maintained at a more depolarized V_m (FIG. 4B). In contrast with LA shocks, BM stimuli could enhance the hyperpolarizing component of the BL-evoked response (FIG. 4C).

ITC neurons are endowed with another property that allows them to modify the amount of feedforward inhibition they generate in the CE nucleus in a context-dependent manner. Indeed, ITC cells express an unusual K^+ current (termed I_{SD} for slowly deinactivating) that activates in the subthreshold range of V_m , inactivates in response to suprathreshold depolarizations (FIG. 5) in a Ca^{2+} - and Na^+ -independent manner, and deinactivates very slowly upon return to rest.⁶⁵

As a result, after episodes of suprathreshold activity, these cells enter a self-sustaining state of heightened excitability associated with increased input resistance

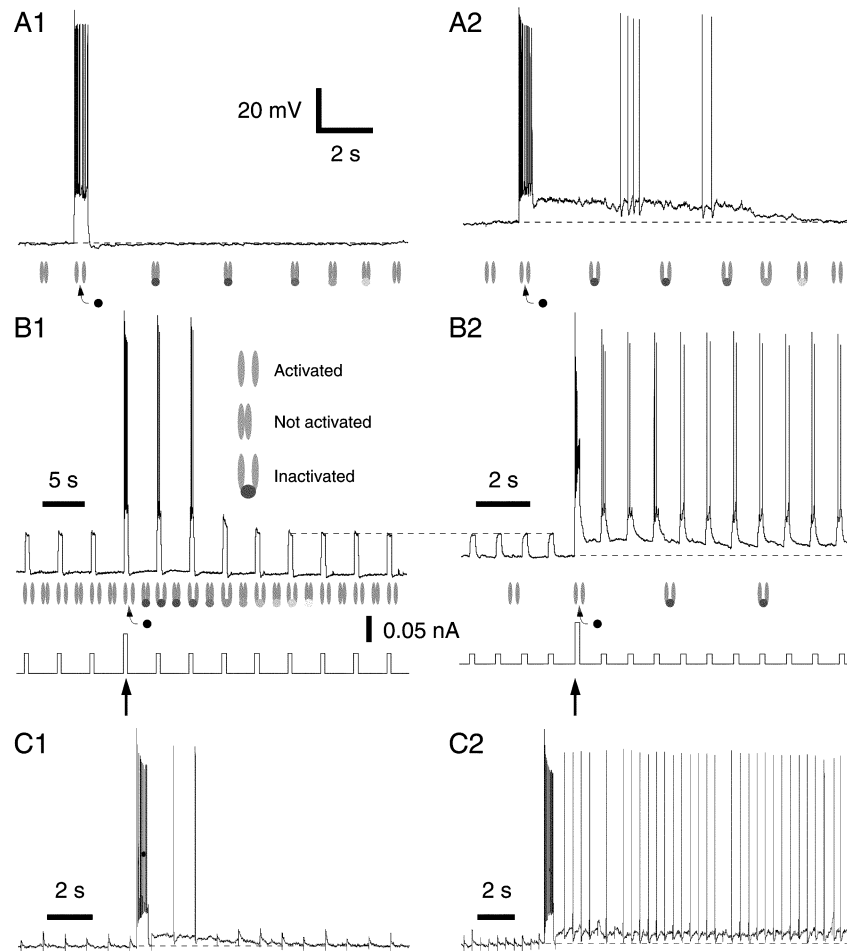


FIGURE 6. Impact of I_{SD} on responsiveness of ITC neurons. **(A)** Changes in degree of activation of I_{SD} when suprathreshold current pulses are applied from -75 (A1) or -62 mV (A2). Symbols below traces indicate the hypothesized state of the channels. **(B)** Voltage response (*top trace*) to repetitive current pulses (*lower trace*) applied from a V_m of -74 (B1) or -66 (B2) mV. **(C)** Response to repetitive electrical stimuli in basolateral complex delivered at two different frequencies before versus after a suprathreshold current pulse from -60 mV. Voltage scale is the same for A-C.

and membrane depolarization (FIG. 5C). In turn, these changes increase the likelihood that ongoing synaptic activity will trigger orthodromic action potentials. However, because each orthodromic spike “renews” the inactivation of I_{SD} , ITC cells can remain hyperexcitable for a long time (FIG. 6). The intrinsic properties of ITC neurons enable them to “remember” their recent firing history and modify their activity accordingly.

This property takes on particular significance in ITC cells, because they control impulse traffic between the BL complex and CE nucleus. Indeed, increases in the responsiveness of particular ITC clusters (via inactivation of I_{SD}) can bias ITC cells to dampen excitatory inputs to specific populations of CE neurons and enhance the responses of others via lateromedial inhibitory ITC connections (FIG. 3). Such modal shifts in the excitability of ITC cells could profoundly alter emotional reactivity, because CE neurons, via their projections to the brain stem and hypothalamus, play a critical role in fear expression.²

CONCLUSION

This short review of our recent work illustrates that the intra-amygdaloid circuit is complex and multipotential. The highly divergent excitatory intrinsic connectivity of the BL complex is kept under control by powerful inhibitory mechanisms. Considerable resources are also devoted to control impulse traffic from the BL complex to the CE nucleus. We feel that this makes perfect sense, given that most sensory events should not evoke fear responses. At the same time, the bistable behavior of ITC neurons and their intricate interconnections allow for flexible, context-dependent gating of BL impulses to the CE nucleus. ITC cells thus represent a likely site of experience-dependent plasticity.

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