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GABAergic cell type diversity in the basolateral amygdala

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Here I review the diversity of GABAergic neurons in the rodent basolateral amygdala (BLA). In spite of the recent identification of the role played by certain neurons of BLA in learning and memory of fear, the diversity of GABAergic neurons has not been fully explored. I describe analogies and differences between GABAergic neurons in BLA and cerebral cortex. Emphasis is given to a comprehensive functional, neurochemical and anatomical classification of GABAergic neuron types.

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Understanding neuronal circuits of the basolateral amygdala

The amygdala is a brain region located in the temporal lobe composed by >10 nuclei that plays key roles in fear conditioning and emotional memory [1,2]. Two regions of the amygdala are intensively studied. First, the basolateral complex (BLA, comprising the lateral, basal and basomedial or accessory basal nuclei), a cortical-like structure containing glutamatergic principal cells (P-cells, majority of cells) with large somata, random oriented dendrites and projecting axon, and GABAergic neurons with smaller somata and highly heterogeneous dendritic and axonal patterns [3]. Second, the central amygdala (CeA) and the intercalated cell masses (ITC); they represent ventrocaudal extensions of the striatum and include both local and projecting GABAergic neurons [2]. The flow of information between the BLA (main inputs from cortex and thalamus) and the medial sector of CeA (CeM, main outputs to brainstem and hypothalamus) can be conceptualized as largely unidirectional and gated by multiple parallel pathways involving several types of GABAergic cells [4,5]. The aim of this article is to briefly review some recent progress characterizing GABAergic neurons of the rodents BLA and their role in the amygdala networks. For brevity, important differences amongst cells in lateral and basal nuclei will often be neglected, and data from the basomedial nucleus will not be discussed. Excellent, more detailed reviews on GABAergic neurons of amygdala and inhibitory circuits involved in fear encoding have recently been published [4–7].

The amygdala is one of the most powerful brain areas to address questions regarding the causal relationships between circuit function and behaviour. Remarkably, the physiological role of some specific neurons of the amygdala in fear and extinction behaviours has been defined [8,9,10••,11]. However, a comprehensive classification of GABAergic neuron types based on functional, neurochemical and anatomical features remains much less advanced in the amygdala than in cortical areas (hippocampus and isocortex) [12,13]. Several factors may be responsible for this gap including: the complex three-dimensional anatomical organization of BLA, the presence of inputs from multiple extrinsic brain areas, and the difficulty of a rigorous identification of interneurons that mediate feed-forward and/or feed-back inhibition of P-cells.

Key concepts for the definition of GABAergic neurons

Decades of research on GABAergic cells of cortical areas led to the discovery of several key principles useful for their classification. They include: firing patterns, neurochemical markers, axonal and dendritic aspects, definition of cell inputs and outputs including target specificity, cells' functional specialization, and pivotal role on network oscillations. First, GABAergic cells display heterogeneity in their morphological, molecular and functional aspects [12,13]. Combined information of dendritic and axonal patterns, molecular markers and functional activities of single neurons are needed to determine cell types [13]. Consistent with this, multiparametric methods have been endorsed to classify interneurons [14,15]. Second, GABAergic cells are eminently target specific, selectively innervating subcellular domains of certain postsynaptic cell types. Axo-axonic interneurons make synapses exclusively on the axon initial segment of cortical pyramidal cells [16]; basket cells target preferentially somata and proximal dendrites [17], Martinotti and neurogliaform cells target the dendrites of postsynaptic cells [18,19], some cortical interneurons target only other interneurons and not pyramidal cells [20]. Third, functional specialization of interneurons provides subtle regulation of cortical networks. For example, cortical neurogliaform cells provide feed-forward inhibition of distal dendrites of

Table 1

Salient features of GABAergic neurons in cortical areas (hippocampus and isocortex) and basolateral amygdala in rodents. For references see text.

Cortical areas (hippocampus and isocortex)	Basolateral amygdala
Perisomatic inhibition	**Perisomatic inhibition**
For example, PV+ or CCK+ basket cells	For example, PV+ or CCK+ basket cells
Dendritic inhibition	**Dendritic inhibition**
For example, Martinotti cells, neurogliaform cells, O-LM cells	For example, some CB+ cells, neurogliaform cells
Feed-forward GABAergic inhibition	**Feed-forward GABAergic inhibition**
For example, interneurons of the stratum lacunosum moleculare in the hippocampal CA1 area	For example, CB+ cells
Feed-back GABAergic inhibition	**Feed-back GABAergic inhibition**
For example, hippocampal O-LM interneurons	For example, basket cells
Interneuron-selective interneurons	**Interneuron-selective interneurons**
For example, hippocampal CR+ and VIP+ interneurons	?
GABAergic long-range projecting neurons	**GABAergic long-range projecting neurons**
For example, hippocampal back-propagation cells, hippocampo-septal cells	SOM+ neurons projecting to basal forebrain

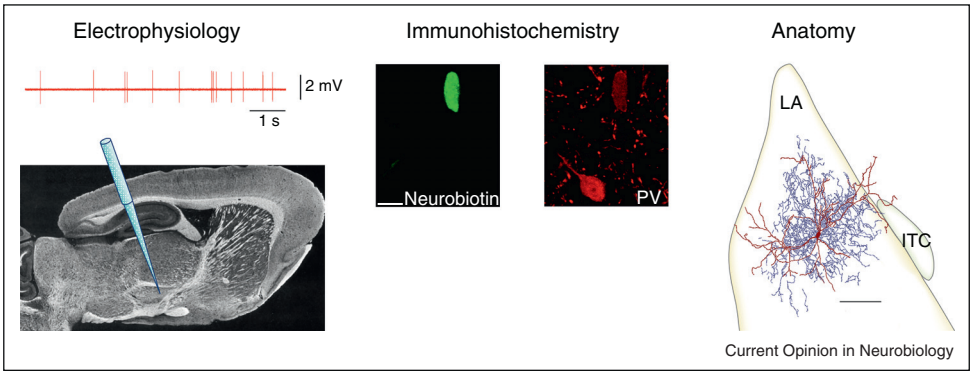
postsynaptic pyramidal neurons [19] and also elicit presynaptic inhibition of transmitter release [21]. Fourth, a division of labour amongst interneuron types in governing network activities is well known in cortical areas [13]. I suggest that these key principles emerged from studies on cortical GABAergic neurons are also useful to explain the operations of GABAergic neurons in BLA. However, I also propose that GABAergic neurons of BLA are not mere analogues of cortical cells but also display original features (Table 1). In the next sections I will briefly discuss some recent information available on GABAergic neurons of BLA using the key useful principles derived from cortical GABAergic neurons mentioned above.

GABAergic cell diversity in the BLA: functional, neurochemical and anatomical characterization

Classic studies by McDonald, Pitkänen and others have established the expression of neurochemical markers (calcium binding proteins or neuropeptides) in various GABAergic cells of BLA [7]. About 50% of neurons express calbindin (CB) and parvalbumin (PV) [22,23], their axons form preferentially perisomatic baskets or PV+ axo-axonic cells 'cartridges' onto postsynaptic neurons [23–25]. The PV neurons usually fire short duration non-adapting action potentials (half-width ~0.5 ms) [23,26], but a subset of them displays regular firing and accommodating phenotypes [23,26]. Another cell population that expresses cholecystokinin (CCK), often together with CB and type 1 cannabinoid (CB_1) receptors [27] makes synapses with somata [28], suggesting analogy with cortical CCK-expressing basket cells [29]. These interneurons fire broad action potentials and display firing adaptation [30]. Other interneurons express CB and somatostatin (SOM) [31], and some of them also express the neuropeptide Y (NPY) [32]. The SOM+ cell types selectively target dendrites [33], similar to SOM+ Martinotti cells in the cortex [34]. Interestingly, a recently described novel subpopulation of SOM+ (a third of these interneurons also express CB or NPY) have long range axons that project to the basal forebrain [35•], resembling hippocampal-septal neurons [36]. Another classical cell population expresses vasoactive intestinal peptide (VIP), calretinin (CR) and CCK [37], and targets somata and dendrites. This contrasts with the cortex, where CCK and CR are usually not co-localized [34]. A recent study classifies interneurons of the lateral nucleus of the amygdala (LA) based on a combination of electrophysiological and single-cell reverse transcription polymerase chain reaction (RT-PCR) methods [38]. Electrophysiological responses alone result into the separation of interneurons into five types (mostly expressing PV, CCK or CB). However, the same study did not find a striking correlation between mRNA levels of neurochemical markers and electrophysiological responses. In another recent paper, novel GABAergic neurons expressing neurokinin 1 (NK1), the preferred receptor of substance P, is reported in the LA connected through gap junctions [39]. This work also identifies the inputs to NK1-expressing neurons in LA and found that the majority of them originate from the neocortex, hippocampus, and/or amygdaloid pyramidal neurons, and the minority from subcortical areas.

A recent study attempts an unprecedented definition of GABAergic neuron types of the rodent BLA using multiple functional, anatomical and neurochemical parameters providing a comprehensive definition of neurons types [40••]. In this study, neurons of the BLA were recorded and subsequently labelled in anesthetized rats and post hoc identified (Figure 1). By using such a multidisciplinary approach four distinct GABAergic cell types are identified. First, PV-expressing interneurons constitute the most numerous cell populations, as in cortical areas. Amongst these neurons, basket cells target with dense axonal arborizations somata and proximal dendrites of P-cells, and axo-axonic neurons innervate almost exclusively the axon initial segment of P-cells forming cartridges. Dendrite-targeting interneuron types are also found, but their similarity to dendrite-targeting

Figure 1



Functional, neurochemical and anatomical identification of GABAergic neuron types of BLA. Left, sagittal rodent brain and single unit juxtacellular recording of firing from a single cell of BLA. Middle and right, immunofluorescence positive for PV (scale bar = 10 μm) and anatomical reconstruction (soma and dendrites are shown in red, axon in blue, scale bar = 100 μm) of the recorded cell (labelled by Neurobiotin). LA, lateral amygdala; ITC, intercalated nucleus. Further electrophysiological, immunohistochemical and electron microscopic analyses allowed the identification of this neuron as axo-axonic cell [40••]. Middle and right panels are taken from [40••].

interneurons of the cortex is more difficult to assess. One cell type expresses CB and targets dendrites of small-medium diameter, presumably distally located. Another neuron type is termed AStria-projecting, since its axon makes dense ramification in the BLA but also projects to the amygdalo-striatal transition area (AStria), and contacts not only middle-sized dendrites but also somata. Overall, CB+ (and to a lesser extent AStria-projecting) dendrite-targeting GABAergic cell type fires preferentially in phase with hippocampal theta oscillations. By contrast, the firing of perisomatic PV+ basket and axo-axonic neurons is not tightly synchronized with theta oscillations in the majority of cases. Furthermore, responses of neurons to noxious stimuli, such as hindpaw pinches and footshocks, are also found to be cell type-specific. In particular, AStria-projecting cells and axo-axonic cells, but not basket or CB+ interneurons, are strongly modulated by the noxious stimuli. Overall, this study suggests that distinct types of BLA interneuron contribute to the integration of hippocampal theta oscillations and salient stimuli in a cell type-specific manner.

Following a similar approach, a comprehensive definition of a novel GABAergic cell type of BLA expressing NPY (and SOM) has recently been provided [41•]. This neuron, termed neurogliaform cell (NGFC), has short sparsely spiny dendrites arranged in a stellate fashion around the soma. The axon branches profusely mostly around the soma, displaying frequent, small en passant varicosities. These aspects resemble what observed in cortical NGFCs [19]. Unique from other interneurons studied so far, NGFCs tend to form non-synaptic apposition to postsynaptic membranes, that in the BLA are not only postsynaptic dendrites or axon terminals, as in the cortex [21], but also somata. Consistent with such 'loose' connectivity promoting volume transmission of transmitter and broad spatiotemporal profile of extracellular GABA [42], inhibitory synaptic responses evoked by NGFC last longer than those evoked by any other BLA interneuron type known [26]. This duration matches that of the inhibitory synaptic potential evoked by cortical NGFCs [19,43], and it is close to a single theta cycle. Interestingly, the firing of NGFC of BLA is phase-locked to hippocampal theta oscillations, further suggesting a key contribution in shaping hippocampo-amygdala theta activities [44].

Functional specialization, target specificity and synaptic plasticity

Few studies have clarified the inputs to BLA GABAergic cells as well as their specialized roles within the network. The PV+ interneurons receive strong excitatory inputs from P-cells of BLA but weak inputs from the cerebral cortex [45] suggesting a main role in feedback inhibition. On the other hand, large inhibitory synaptic events underlie spontaneous and cortically-evoked membrane potential fluctuations of BLA P-cells [46,47]. Since BLA interneurons fire robustly during oscillatory activity, inhibition of P-cells may also originate from feed-forward action of local GABAergic neurons [48]. An interesting recent study sheds light on this issue showing that CB+ interneurons mediate cortically-evoked feedforward inhibition in the BLA [49•]. Selective feed-forward and feedback inhibition onto P-cells has been suggested to be mediated by different types of PV+ interneurons of BLA [26,50].

Limited quantitative information is available on the relative innervation by BLA interneurons of excitatory or inhibitory cells [7]. It is clear from both functional and anatomical data that PV expressing cells powerfully inhibit both P-cells as well as other interneurons [26,51]. A recent study demonstrates an interesting target-specific

effect induced by dopamine acting at PV expressing-P-cells or PV-expressing-interneuron synapses [52•]. Specifically, dopamine selectively inhibits the release of GABA from PV+ interneurons to P-cells, but not to other interneurons. This target-specific neurochemical modulation enables a sharp disinhibition of P-cells not accompanied by a concomitant alteration of the inhibitory inputs. Such a decrease of the inhibitory tone on BLA P-cells by dopamine may facilitate the induction of long-term potentiation at sensory afferents [53] and the formation of fear memories [54]. There is no specific information on the target specificity of dendrite-targeting interneurons of the BLA, as whether, for example, NGFCs also inhibit other interneurons and not only P-cells, as in the hippocampus [55]. It is also unknown whether interneuron-specific interneuron exists in the BLA, as reported for some CR and/or VIP in the hippocampus [20].

Functional selectivity mediated by interneurons is also achieved through synaptic plasticity [2]. In BLA, classic work has documented plasticity of inhibitory synaptic transmission [56], as well as of excitatory synaptic transmission impinging onto interneurons [57]. Furthermore, the suppression of GABAergic transmission facilitates the induction of long term potentiation of thalamic inputs to the LA [53]. Recent data indicate that theta-burst stimulation induces heterosynaptic potentiation of synaptic inhibition onto P-cells via nitric oxide (NO) signalling [58•]. However, the identity of the interneuron types involved in this synaptic plasticity is unknown. A recent study documents remarkable behaviour-induced target-specific plasticity of perisomatic inhibitory synapses in the basal amygdala [59•]. Specifically, using *c-fos*-based transgenic mice, the authors have identified a population of fear neurons in the basal amygdala that is no longer active after contextual fear extinction. These 'silent fear neurons' are subjected to increased perisomatic inhibition from PV neurons, whereas fear neurons that remain activated after extinction training receive increased CB_1 receptor-mediated disinhibition.

Studies performed in cortical areas indicate a division of labour between perisomatic-targeting and dendrite-targeting interneurons: the former control the output firing of pyramidal cells, the latter regulate the dendritic integration of glutamatergic inputs terminating on the dendritic domain [29]. It has not yet been experimentally proven that a similar functional specialization also applies to perisomatic-targeting and dendrite-targeting interneurons of BLA. Furthermore, it is also not known whether, as in the hippocampus [29], PV+ and CCK+ basket cells operate respectively as oscillators and fine-tuning device encoding information about motivation, emotions, and the autonomic state of the animal, that represent a crucial part of amygdala processing. It has been shown that CCK+ basket cells mediate depolarization induced suppression of inhibition via CB_1 receptor [60], as in the hippocampus [29]. Putative axo-axonic cells of BLA have been suggested to be excitatory and to drive P-cells to fire [50], as originally proposed in cortex [61], but future investigation will be needed to test this issue directly and to assess under which physiological conditions this may occur in situ. Future work will hopefully clarify whether NGFCs of BLA mediate only feed-forward inhibition, as in cortical areas [55], or also feedback inhibition onto P-cells.

Key role in network oscillations

The identity of GABAergic neurons controlling oscillatory activity in the BLA starts to emerge as cell-type specific roles in coordinating hippocampal theta rhythm and in response to salient stimuli has recently been reported, as mentioned above [40]. Classic work has shown that ~60% of putative GABAergic interneurons display firing modulation with entorhinal theta oscillations during paradoxical sleep [62]. Fear extinction deficits observed in GAD-65 knock-out mice correlate with sustained synchrony at theta frequency between BLA and prefrontal cortex [63]. Moreover, phasic GABAergic transmission appears to mediate the electrical foot-shock-induced transitions from down to up states in BLA P-cells [64]. In a recent study, spontaneous, large inhibitory postsynaptic potentials (IPSPs) from PV+ interneurons have been shown to increase spike-timing precision both within and across BLA P-cells [65•]. This effect could promote action potentials synchronization in P-cells. Moreover, the same study reports that large IPSPs entrain membrane potential oscillation at high delta/low theta frequency. This effect could synchronize firing activity promoting network oscillations within the BLA, and could also strengthen coherent oscillations between the BLA and other brain regions involved in fear processing. Characteristically, PV+ neurons of BLA make electrical synaptic junctions with each other [26,51], thereby promoting synchronization of BLA activities, as in cortical areas [66].

Conclusion and future directions

In the last few years remarkable progress has been made in the definition of various GABAergic neuron types of BLA (and in other areas of amygdala too). Some speculations on BLA interneurons functional specialization can be drawn. From one hand, certain interneurons of the BLA (such as CB+) receive strong and direct excitation from extra-amygdaloid areas (such as the cerebral cortex), fire phase-locked to the peak of network oscillations when external excitation arrives, and mediate feedforward inhibition of the dendritic domain of postsynaptic P-cells. Conversely, other interneuron populations (such as PV+) receive strong and direct excitation from BLA P-cells, fire less synchronized to network oscillations, and mediate feedback inhibition of the somatic domain of P-cells. It is also likely that, as in the hippocampus [29], PV+ and CCK+ basket interneurons of BLA have complementary

and cooperative roles, namely they are being specialized to regulate fast rhythm and mood, respectively, but this hypothesis needs to be experimentally challenged. Much work is still needed to close the gap between the knowledge of GABAergic neuron types in BLA and in cortical areas. Several future research approaches may be potentially fruitful; I will mention two of them. First, standard electrophysiological techniques used to record from non-anesthetized, freely moving animals do not allow the identification of neuron types. Even when these recordings are combined with Cre-line-based optogenetics, cell identification remains limited to broad categories expressing a molecular marker such as PV or SOM common to different types of interneurons [67]. An alternative approach would be to characterize the physiological role of GABAergic cell types of BLA in non-anaesthetized, awake and behaving animals using the comprehensive functional, neurochemical and anatomical approach delineated above [68,69]. Second, genetic approaches that permit rapid and reversible manipulation of neuronal function are rapidly developing [70]. Silencing methods based on chemical genetics have been already used to elucidate the role of GABAergic cell types of the lateral subdivision of the central amygdala in fear conditioning [9]. It is likely that this promising approach will be more extensively adopted in the near future to assign specific roles to neuron types of BLA.

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