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Mechanisms regulating GABAergic inhibitory transmission in the basolateral amygdala: implications for epilepsy and anxiety disorders

Minireview Article

V. Aroniadou-Anderjaska[1], **F. Qashu**[2], and **M. F. M. Braga**[1,2]

[1] Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, U.S.A.
[2] Neuroscience Program, Uniformed Services University of the Health Sciences, Bethesda, MD, U.S.A.

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Summary. The amygdala, a temporal lobe structure that is part of the limbic system, has long been recognized for its central role in emotions and emotional behavior. Pathophysiological alterations in neuronal excitability in the amygdala are characteristic features of certain psychiatric illnesses, such as anxiety disorders and depressive disorders. Furthermore, neuronal excitability in the amygdala, and, in particular, excitability of the basolateral nucleus of the amygdala (BLA) plays a pivotal role in the pathogenesis and symptomatology of temporal lobe epilepsy. Here, we describe two recently discovered mechanisms regulating neuronal excitability in the BLA, by modulating GABAergic inhibitory transmission. One of these mechanisms involves the regulation of GABA release via kainate receptors containing the GluR5 subunit (GluR5KRs). In the rat BLA, GluR5KRs are present on both somatodendritic regions and presynaptic terminals of GABAergic interneurons, and regulate GABA release in an agonist concentration-dependent, bidirectional manner. The relevance of the GluR5KR function to epilepsy is suggested by the findings that GluR5KR agonists can induce epileptic activity, whereas GluR5KR antagonists can prevent it. Further support for an important role of GluR5KRs in epilepsy comes from the findings that antagonism of GluR5KRs is a primary mechanism underlying the antiepileptic properties of the anticonvulsant topiramate. Another mechanism regulating neuronal excitability in the BLA by modulating GABAergic synaptic transmission is the facilitation of GABA release via presynaptic α_{1A} adrenergic receptors. This mechanism may significantly underlie the antiepileptic properties of norepinephrine. Notably, the α_{1A} adrenoceptor-mediated facilitation of GABA release is severely impaired by stress. This stress-induced impairment in the noradrenergic facilitation of GABA release in the BLA may underlie the hyperexcitability of the amygdala in certain stress-related affective disorders, and may explain the stress-induced exacerbation of seizure activity in epileptic patients.

Keywords: Amygdala – GABA release – Kainate receptors – α_1 adrenoceptors – Epilepsy – Anxiety disorders

Introduction

The amygdala is an almond-shaped structure – as its Greek name implies – consisting of at least 10 nuclei located in the midtemporal lobe (Sah et al., 2003; McDonald, 2003). Via reciprocal connections with the cerebral cortex, the thalamus, and other subcortical structures, the amygdala receives information from all sensory modalities, and plays a central role in assessing the emotional significance of this information, modulating memory formation, and orchestrating the behavioral response (LeDoux, 1992; Davis, 1994; Goldstein et al., 1996; Fanselow and Gale, 2003; McDonald, 2003; Sah et al., 2003). Via efferent pathways from the central nucleus of the amygdala to the hypothalamus and brain stem, the amygdala can also activate neuroendocrine and autonomic responses, as it occurs during stressful situations (Davis, 1992, 1994; Habib et al., 2001). Thus, the function of the amygdala is most intimately related to the neurobiological mechanisms that underlie emotional behavior. It is not surprising therefore that emotional disorders are often associated with pathophysiological changes in the amygdala (Abercrombie et al., 1998; Drevets, 1999; Rauch et al., 2000; Sheline et al., 2001; Villarreal and King, 2001; Chen et al., 2005). For example, a characteristic feature of anxiety disorders, such as Post-Traumatic Stress Disorder (PTSD), is an enhancement of neuronal excitability in the amygdala (Rauch et al., 2000; Villarreal and King, 2001).

In addition to its role in affective disorders, the amygdala also plays a central role in temporal lobe epilepsy (Gloor, 1992; Pitkanen et al., 1998). Temporal lobe epilepsy (TLE) is the most common form of epilepsy, and the most resistant to drug therapy (Pitkanen and Sutula, 2002). Both the amygdala and the hippocampus

display extensive neuropathology in TLE patients (Cendes et al., 1993a, b; Saukkonen et al., 1994; Pitkanen et al., 1998). The epileptic focus in TLE resides in the hippocampus, or the amygdala, or, most commonly, both (Dewar et al., 1996; Pitkanen et al., 1998; Morimoto et al., 2004).

The amygdala appears to be even more prone to generating seizure activity than the hippocampus. Kindling, which is the development of spontaneous, recurrent seizures after repeated electrical stimulation in laboratory animals, develops much faster by repeated electrical stimulation of the amygdala than the hippocampus (Goddard, 1967; McIntyre and Racine, 1986). In addition, the earliest onset of interictal discharge tends to appear in the amygdala/piriform cortex regardless of the site of kindling (Kairiss et al., 1984; Racine et al., 1988). The pivotal role of the amygdala in the spread of seizure activity may be significantly due to the extensive connections of the amygdala with temporal and extra-temporal regions; in this respect, it is noteworthy that the connections from the amygdala to the hippocampus are stronger than the connections from the hippocampus to the amygdala (Stefanacci et al., 1992), facilitating the spread of seizures from the amygdala to the hippocampus. The mechanisms, however, that underlie the proneness of the amygdala to generate epileptic activity are largely unknown (for reviews see Pitkanen et al., 1998; Rogawski et al., 2003).

The basolateral nucleus of the amygdala (BLA) plays a key role in the functions – and dysfunctions – of the amygdala. The BLA receives sensory information via direct as well as indirect thalamic and cortical inputs (McDonald, 1998; Pitkanen et al., 2000). Via extensive reciprocal connections with the prefrontal/frontal cortex and the hippocampus, the BLA modulates cognitive and memory processes. In fact, studies have suggested that modulation of memory consolidation by the amygdala is mediated selectively by the BLA (Cahill and McGaugh, 1998; Ferry et al., 1999; McGaugh, 2002, 2004). In addition, the BLA is interconnected with the other nuclei of the amygdaloid complex, and has a direct output to the central nucleus which in turn can activate the neuroendocrine and autonomic systems (Pitkanen et al., 1997). Furthermore, the BLA is particularly important for the spread of seizure activity. Thus, activation of the BLA is primarily responsible for the generation of widespread status epilepticus, even in animal models where seizures are evoked in extra-amygdalar regions (White and Price, 1993a, b). In addition, prolonged electrical stimulation triggers status epilepticus more readily when the stimulation is applied to the BLA than to the central and medial amygdala, or to the adjacent piriform cortex (Mohapel et al., 1996). Why the BLA is exceptionally prone to generating seizure activity is largely unknown. Below, we will describe mechanisms regulating neuronal excitability in the BLA that may provide part of the answer.

Regulation of GABAergic synaptic transmission by GluR5KRs in the BLA

Although for the past two to three decades the NMDA and AMPA subtypes of ionotropic glutamate receptors have been at the center of scientific interest, recently, there has also been an explosion of information in regard to the role of kainate receptors. The kainate subtype of glutamate receptors have been shown to participate in mediating glutamatergic synaptic transmission in some brain regions (Castillo et al., 1997; Vignes and Collingridge, 1997; Cossart et al., 1998), modulate the presynaptic release of glutamate (Chittajallu et al., 1996) and GABA (Cunha et al., 1997; Jiang et al., 2001; Huettner, 2003; Lerma, 2003), and be involved in synaptic plasticity (Li et al., 1998, 2001; Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2001), as well as epilepsy (Smolders et al., 2002; Rogawski et al., 2003; Kaminski et al., 2004). Kainate receptors consist of five different subunits, namely GluR5, GluR6, GluR7, KA1 and KA2 (Chittajallu et al., 1999). The GluR5, GluR6 and GluR7 subunits form homomeric and heteromeric functional channels when expressed in heterologous systems (Bettler et al., 1990; Sommer et al., 1992; Egebjerg and Heinemann, 1993). The KA1 and KA2 subunits do not form functional homomers in the same systems, but generate functional receptors with distinct physiological properties when combined with GluR5, GluR6, or GluR7 subunits (Herb et al., 1992; Schiffer et al., 1997). In addition, kainate receptor subunits are subjected to both alternative splicing and RNA editing, which significantly increase the number of subunit isoforms (Bettler et al., 1990; Sommer et al., 1991, 1992; Herb et al., 1992; Schiffer et al., 1997). Consequently, a large number of distinct kainate receptor subtypes could be assembled based on the combinative possibilities of the different subunits. The composition and stoichiometry of native kainate receptors are not known at present.

The amygdala expresses high levels of mRNA coding for the GluR5, GluR6 and KA2 subunits, as determined by in situ hybridization (Li et al., 2001; Braga et al., 2003, 2004a). The GluR5 mRNA, in particular, is markedly high in the amygdala, higher than in the hippocampus, and is concentrated in the BLA and medial nuclei (Li et al.,

2001; Braga et al., 2003). What is the function of GluR5-containing kainate receptors (GluR5KRs) in the BLA? Rogawski's team demonstrated that GluR5KRs participate in synaptic transmission between principal BLA neurons (Li and Rogawski, 1998; Gryder and Rogawski, 2003). Thus, using selective pharmacological receptor antagonists, this group showed that a component of the excitatory postsynaptic potentials (EPSPs) or currents (EPSCs) recorded from BLA principal neurons in response to stimulation of the external capsule is mediated by GluR5KRs (Li and Rogawski, 1998; Gryder and Rogawski, 2003). Subsequently, we observed that a specific GluR5KR agonist, ATPA (Clarke et al., 1997) enhances the frequency and amplitude of action potential-dependent, spontaneous GABAergic currents (IPSCs) recorded from BLA pyramidal cells (Braga et al., 2003). This finding suggested that GluR5KR activation depolarizes inhibitory interneurons. Indeed, the presence

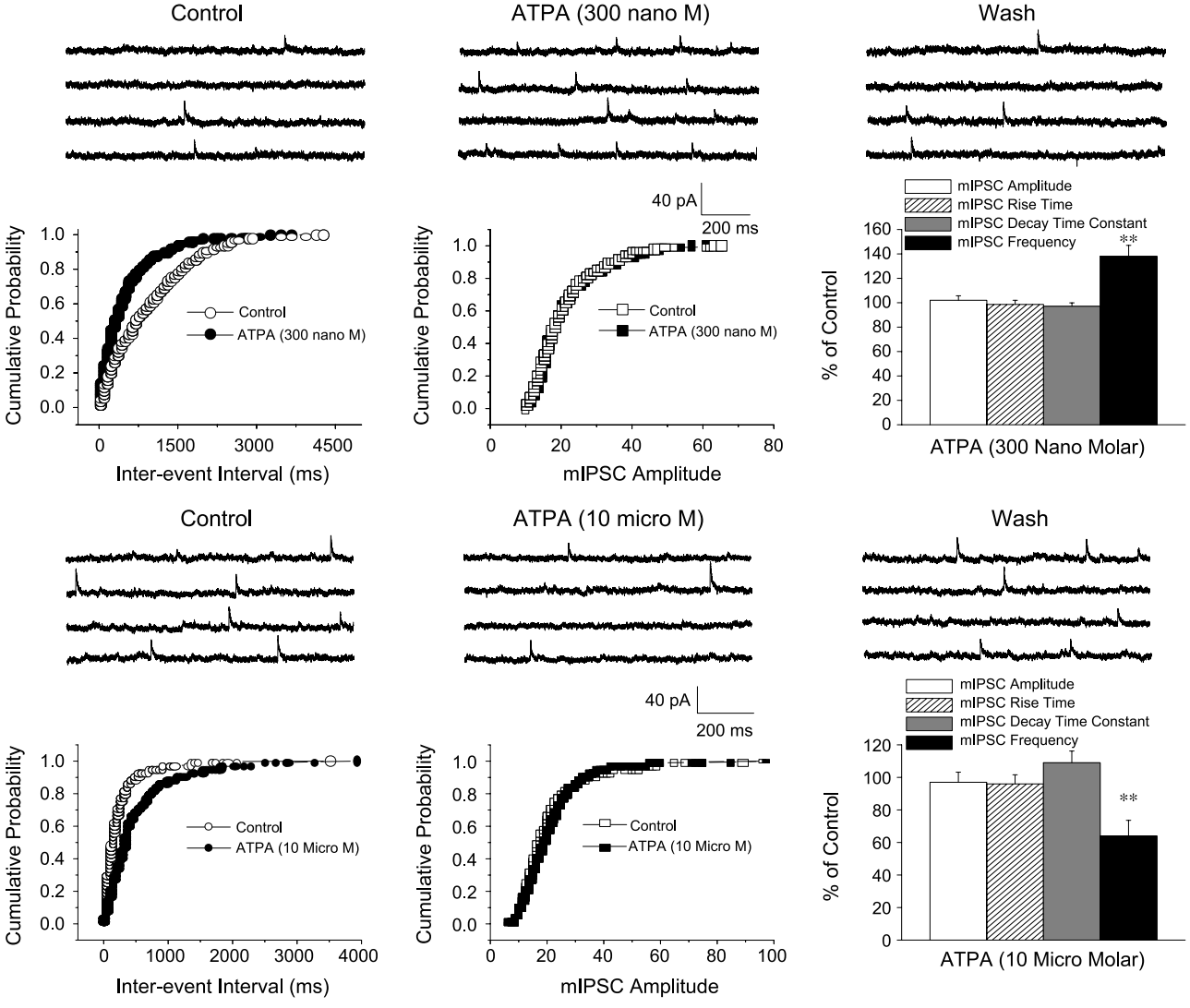

Fig. 1. Activation of GluR5KRs alters the frequency of miniature inhibitory postsynaptic currents (mIPSCs) in an agonist concentration-dependent, bidirectional manner, in the rat basolateral amygdala (BLA). Traces show samples of mIPSCs recorded from two different BLA pyramidal neurons, in in vitro amygdala slices, before, during, and after application of the GluR5 agonist ATPA, at a 300 nM or 10 μM concentration. Recordings were obtained in the presence of TTX (1 μM), GYKI 53655 (50 μM), D-APV (50 μM), and SCH50911 (20 μM), at a holding potential of +10 mV. The plots show the corresponding cumulative probability of inter-event intervals and amplitudes of mIPSCs in control conditions and during the application of ATPA. Bar graphs show pooled data (means ± SEM) on the effects of ATPA on mIPSCs. At 300 nm, ATPA increased the frequency of mIPSCs ($n = 9$, $^{**}p < 0.01$). In contrast, at 10 μM, ATPA caused a marked reduction in the frequency of mIPSCs ($n = 7$, $^{**}p < 0.01$). The peak amplitude, rise time, and decay time constant were not significantly affected by either of the concentrations of ATPA. Perfusion of the slices with ATPA-free ACSF completely reversed the effects of the agonist

of GluR5KRs on postsynaptic (somatodendritic) regions of interneurons was confirmed with the demonstration that an EPSC which was blocked by a GluR5KR antagonist could be synaptically evoked in BLA interneurons (Braga et al., 2003). Recordings of miniature IPSCs, as well as monitoring the failure rate of IPSCs evoked in pyramidal cells by minimal synaptic stimulation revealed that GluR5KRs are also present on the terminals of GABAergic neurons, in interneuron to pyramidal cell synapses in the BLA. These presynaptic GluR5KRs were found to modulate the release of GABA in an agonist concentration-dependent, bidirectional manner (Braga et al., 2003). Low concentrations of GluR5KR agonists (ATPA or glutamate), as well as basal concentrations of extracellular, endogenous glutamate facilitated GABA release, whereas high concentrations of GluR5KR agonists suppressed GABA release, in interneuron to pyramidal cell BLA synapses (Figs. 1 and 2). These findings suggested that the terminals of GABAergic neurons in the BLA carry two subtypes of GluR5-containing kainate receptors, which have different agonist affinities, and activate opposing mechanisms of action.

In summary, what we know so far is that GluR5KRs, in the BLA, are present on somatodendritic regions of both pyramidal cells and interneurons, where they mediate a component of the evoked EPSCs, as well as on the presynaptic terminals of GABAergic interneurons, in interneuron to pyramidal cell synapses, where they modulate GABA release, in an agonist concentration-dependent, bidirectional manner.

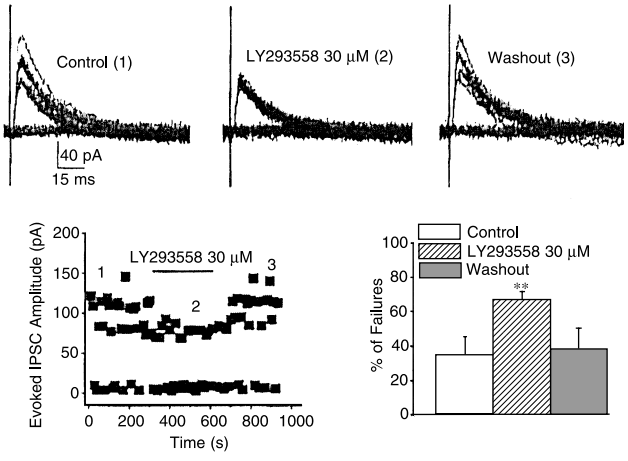

Fig. 2. Endogenous glutamate tonically activates GluR5 kainate receptors, facilitating GABAergic synaptic transmission, in the rat BLA. Top panel: superimposed traces of evoked IPSCs recorded from a BLA pyramidal neuron, in rat amygdala slices, before, during, and after application of LY293558 (30 μM). Recordings were obtained in the presence of GYKI 53655 (50 μM), D-APV (50 μM), and SCH50911 (20 μM), at a holding potential of +10 mV. The effects of LY293558 (30 μM) were not accompanied by changes in the kinetics of the IPSCs. Bottom panel: the plot shows the time course of the effects of LY293558 (30 μM) on the amplitude and number of failures of evoked IPSCs (same cell as in top panel). The bar graph shows pooled data (means ± SEM) illustrating a marked increase in the percentage of failures of evoked IPSCs induced by bath application of LY293558 ($n = 8$, $^{**}p < 0.01$)

GluR5KRs and temporal lobe epilepsy

Several lines of evidence point to the importance of GluR5KRs in temporal lobe epilepsy: 1) GluR5KR antagonists prevent hippocampal seizures induced by pilocarpine or electrical stimulation, in rats, both in vitro and in vivo (Smolders et al., 2002). 2) The selective GluR5KR agonist ATPA induces spontaneous epileptiform bursting in rat amygdala slices (Li et al., 2001), and limbic status epilepticus when infused intravenously, or directly into the rat amygdala (Rogawski et al., 2003; Kaminski et al., 2004). These effects of ATPA are blocked by the GluR5KR antagonist LY293558. 3) GluR5KRs are a primary target of the structurally novel anticonvulsant topiramate. Thus, in vivo, topiramate protects against seizures induced by intravenous infusion of the selective GluR5KR agonist ATPA, but not against seizures induced by AMPA or NMDA (Kaminski et al., 2004). In amygdala slices, topiramate blocks the GluR5KR-mediated excitation of principal BLA neurons (Gryder and Rogawski, 2003), as well as the GluR5KR-mediated inhibition of GABA release from the presynaptic terminals of BLA interneurons (Li et al., 2004), at clinically relevant concentrations. At the same low concentrations, topiramate has no apparent effect on AMPA receptors, or on voltage-gated calcium and sodium channels (Li et al., 2004). These results suggest that blockade of GluR5KRs is one of the primary mechanisms responsible for the antiepileptic properties of topiramate. 4) Expression of GluR5KRs is elevated in epileptic temporal lobe regions, in both humans and rats (Palma et al., 2002; Ullal et al., 2005).

What are the mechanisms by which GluR5KR activation can induce epileptic activity in the amygdala? As discussed above, so far we know that GluR5KRs are present on somatodendritic sites of both pyramidal cells (Gryder and Rogawski, 2003) and interneurons (Braga et al., 2003) in the BLA, as well as on presynaptic terminals of GABAergic interneurons (Braga et al., 2003). Activation of somatodendritic GluR5KRs on pyramidal cells will enhance amygdalar excitability due to pyramidal cell depolarization and enhanced glutamate release. Activation of somatodendritic GluR5KRs on interneurons will suppress amygdalar excitability due to interneuronal

depolarization and enhanced GABA release. GluR5KRs on GABAergic terminals, in interneuron to pyramidal cell synapses, will facilitate GABA release if they are activated by low concentrations of glutamate, suppressing pyramidal cell excitability. However, when glutamate concentrations are high, as during seizure activity, activation of presynaptic GluR5KRs will inhibit GABA release (Braga et al., 2003), further exaggerating seizure activity. Indeed, field potential and intracellular recordings have revealed that the net effect of GluR5KR activation by high agonist concentrations (5–10 μM ATPA) is a dramatic enhancement in neuronal excitability in the BLA, and generation of spontaneous epileptiform activity. These effects of ATPA are blocked by the GluR5KR antagonist LY293558, and are absent in GluR5 knock-out mice. Thus, the high expression of GluR5KRs in the BLA may significantly underlie the proneness of this amygdala region for generating epileptic activity.

A role for GluR5KRs in anxiety disorders?

Considering that anxiety disorders are associated with pathophysiological changes in amygdalar excitability (Pitman et al., 2001; Stein et al., 2002; Nutt and Malizia, 2004; Straube et al., 2005), any mechanism that plays an important role in the regulation of neuronal excitability in the amygdala should be viewed as a potential therapeutic target. GluR5KRs, if their pharmacological manipulation proves to be clinically useful, would be an ideal therapeutic target. This is because, in contrast to AMPA and NMDA receptors, GluR5KRs have more of a modulatory role in synaptic transmission, rather than a primary role in mediating excitatory synaptic transmission. In addition, GluR5KRs are not widely distributed in the brain. Therefore, drugs targeting GluR5KRs are unlikely to produce significant side effects.

In anxiety disorders, the amygdala is usually hyperactive and hyper-responsive (Pitman et al., 2001; Stein et al., 2002; Nutt and Malizia, 2004; Straube et al., 2005). Whether changes in the expression or function of GluR5KRs are involved in the hyperexcitability of the amygdala in anxiety disorders is not known. Nevertheless, pharmacological manipulation of GluR5KRs could potentially alter the abnormal excitability of the amygdala in these disorders. Consistent with the agonist concentration-dependent, bidirectional effect of GluR5KR activation on GABA release (Fig. 1; Braga et al., 2003), field potential and intracellular recordings in rat amygdala slices have shown that the overall, net effect of weak activation of GluR5KRs (1 μM ATPA in the slice medium) is a suppression in neuronal excitability, whereas the net effect of strong activation of GluR5KRs (10 μM ATPA) is an enhancement in neuronal excitability. Therefore, in an anxiety state, when the amygdala is hyperactive, and GluR5KRs are likely to be strongly activated by glutamate, a selective GluR5KR antagonist could suppress neuronal excitability. However, the same antagonist would have the opposite effect (increase neuronal excitability) when the amygdala is at a resting state, or overinhibited (as it appears to be the case in certain psychiatric illnesses, Abercrombie et al., 1998; Schneider et al., 1998; Drevets, 1999). This is because, in these conditions, GluR5KRs would be weakly activated, facilitating GABA release, and therefore a GluR5KR antagonist would prevent this facilitation. Thus, pharmacological antagonism of GluR5KRs has the potential of altering neuronal excitability in the amygdala in either direction (enhance or suppress) depending on the excitability state of the amygdala before the administration of the antagonist. These mechanisms could, potentially, be exploited for the pharmacological treatment of different psychiatric illnesses.

Regulation of GABAergic synaptic transmission in the BLA by α_{1A} adrenoceptors

The noradrenergic system modulates brain activity in such a way as to increase alertness, and facilitate memory formation, selective attention, as well as exploratory behavior and responsiveness to novelty (Selden et al., 1990; Sara et al., 1995; Usher et al., 1999; Berridge and Waterhouse, 2003). Most of the noradrenergic innervation of the brain arises from the locus coeruleus (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). The amygdala receives extensive noradrenergic innervation from the locus coeruleus (Pitkanen, 2000), as well as from the nucleus of the solitary tract (Clayton and Williams, 2000; Pitkanen, 2000; Williams et al., 2000). A lot of knowledge has been gained in regard to the role of norepinephrine (NE) in the physiology and function of the amygdala. For example, it is well established that activation of β adrenergic receptors in the BLA is critical for the role of the amygdala in encoding emotional memory (Cahill and van Stegeren, 2003; Miranda et al., 2003; Strange and Dolan, 2004). In contrast, activation of α_2 adrenoceptors appears to impair the memory functions of the amygdala (Schulz et al., 2002), and inhibits the induction of both Long-Term Potentiation and Long-Term Depression in the BLA (DeBock et al., 2003). How NE affects different cell types, via different adrenoceptor subtypes, and modifies the activity of neuronal networks in

the amygdala, so as to facilitate (or impede) the involvement of the amygdala in cognitive or emotion-related functions is far from clear.

We initiated our efforts to determine how NE modulates neuronal excitability in the BLA by studying the effects of NE on inhibitory BLA neurons (Braga et al., 2004b). NE, from 1 to 100 μM, facilitated the spontaneous release of GABA, as determined by recording spontaneous inhibitory postsynaptic potentials (IPSCs) from BLA pyramidal cells. These results suggested that NE depolarizes inhibitory neurons, and/or acts directly at the presynaptic terminals of GABAergic interneurons to facilitate GABA release. In another series of experiments, we found that NE also facilitates evoked GABAergic synaptic transmission, in interneuron to pyramidal cell synapses, when $GABA_B$ receptors – which inhibit the presynaptic release of GABA – are blocked. Finally, to conclusively determine whether NE acts on GABAergic presynaptic terminals we recorded miniature IPSCs from pyramidal cells. NE (10 μM) facilitated the quantal release of GABA, as evidenced by the significant increase in the frequency of mIPSCs. All of the effects of NE took place in the presence of β and α_2 adrenoceptor antagonists, were not blocked by α_{1D} and α_{1B} adrenoceptor antagonists, and were mimicked by the α_{1A} adrenoceptor agonist A61603 (Figs. 3A and 4A). These studies indicate that NE, acting via α_{1A} adrenoceptors present on GABAergic presynaptic terminals, facilitates GABAergic synaptic transmission in the BLA. Whether or not α_{1A} adrenoceptors are also present on somatodendritic regions of GABAergic interneurons in the BLA and contribute to the facilitation of GABA release remains to be determined.

What might be the physiological significance of these findings? At a resting (unstimulated) state of the amygdala, basal levels of NE, acting via α_{1A} adrenoceptors, may contribute to tonic inhibition of BLA pyramidal neurons, by facilitating both action potential-dependent and

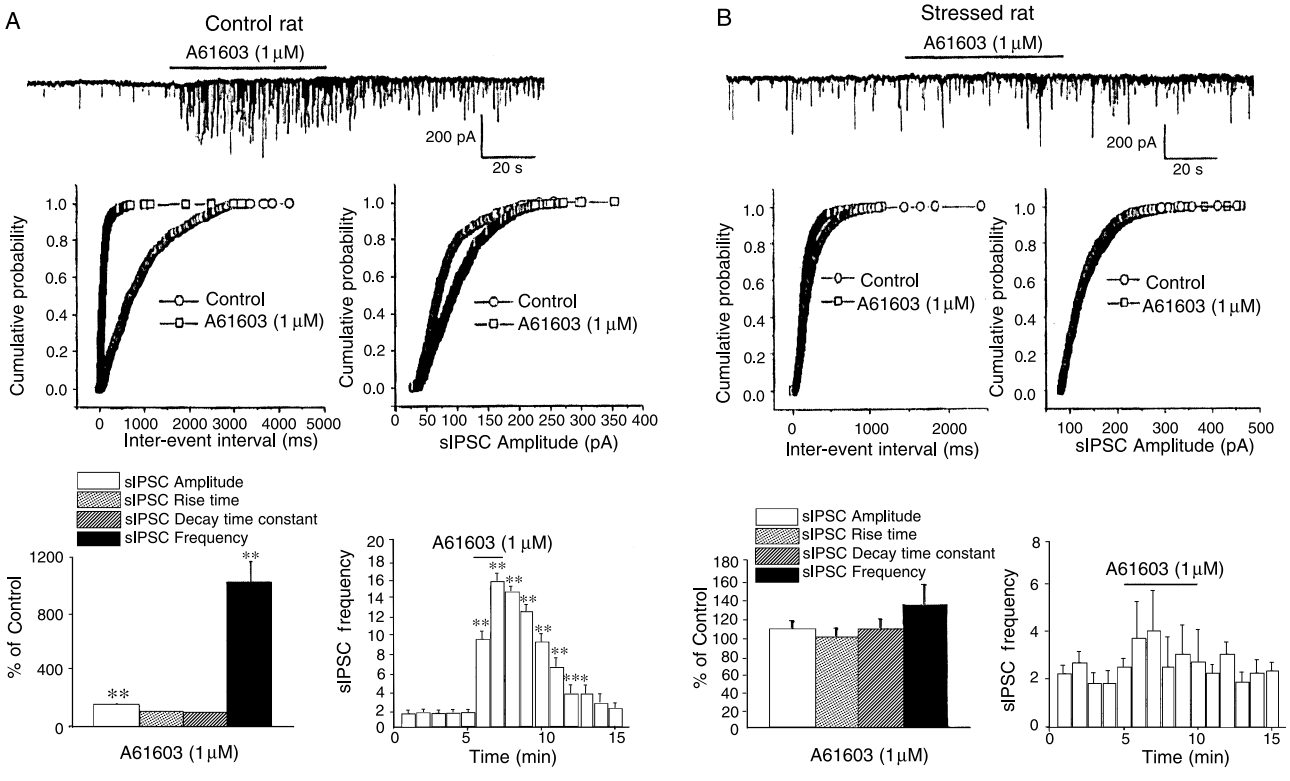

Fig. 3. Activation of α_{1A} adrenoceptors increases tonic inhibition of BLA pyramidal neurons in control rats, but not in stressed rats. **A** Spontaneous IPSCs (sIPSCs) recorded from a BLA pyramidal cell of a control rat (holding potential is −70 mV). Bath application of A61603 (1 μM), a specific α_{1A} adrenoreceptor agonist, reversibly increased the frequency and amplitude of sIPSCs. The slice medium contains D-AP5 (50 μM), CNQX (10 μM), propranolol (10 μM) and yohimbine (20 μM). Middle graphs: Cumulative probability plots of sIPSC inter-event intervals and amplitude in control conditions and during A61603 perfusion (same cell as in the top trace). Bottom graphs: Bar graphs show pooled data (mean ± SEM) from 16 neurons. **B** sIPSCs recorded from a BLA pyramidal cell of a stressed rat (holding potential is −70 mV). Bath application of A61603 (1 μM) caused no significant change in the frequency or amplitude of sIPSCs. Middle graphs: Cumulative probability plots of sIPSCs inter-event intervals and amplitude in control conditions and during A61603 (1 μM) perfusion (same cell as in the top trace). Bottom graphs: Bar graph shows pooled data (mean ± SEM) from 18 neurons

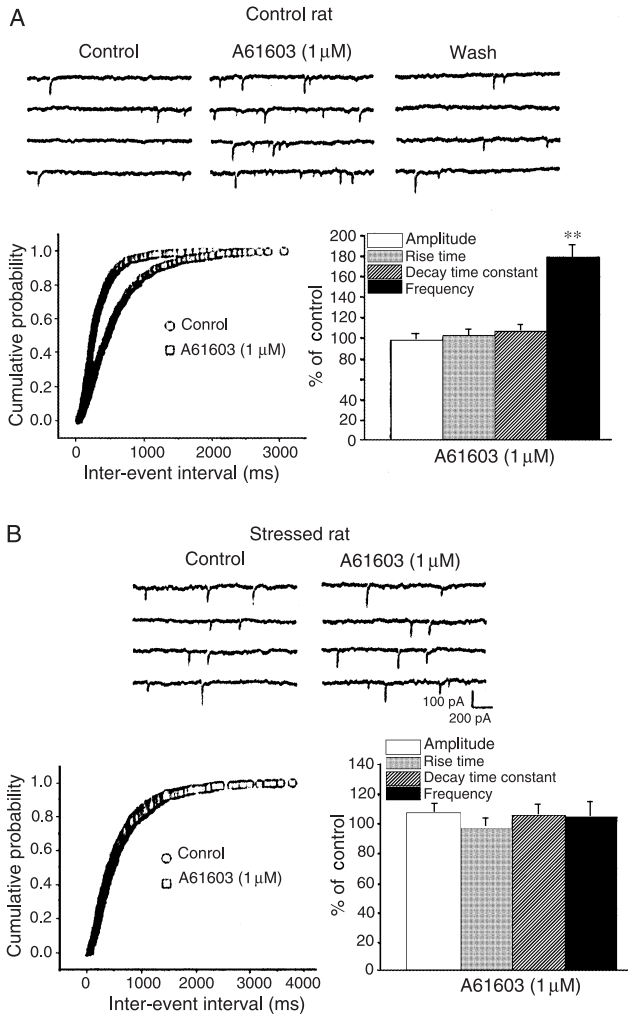

Fig. 4. Activation of α_{1A} adrenoceptors increases the frequency of mIPSCs recorded from BLA pyramidal neurons in control rats, but not in stressed rats. Miniature IPSCs (mIPSCs) were recorded in the presence of TTX (1 μM), D-AP5 (50 μM), CNQX (10 μM), propranolol (10 μM) and yohimbine (20 μM). **A** Traces show mIPSCs recorded from a BLA pyramidal neuron of a control rat. The α_{1A} agonist A61603 (1 μM) increased the frequency of mIPSCs. The plot shows the cumulative probability of inter-event intervals of mIPSCs in control conditions and during application of A61603 (same cell as in the traces). The bar graph shows the effect of A61603 on the amplitude, kinetics, and frequency of mIPSCs. Pooled data from 9 neurons ($^{**}p < 0.01$) **B** Similar data to those shown in **A**, but from stressed rats. A61603 (1 μM) had no significant effect on mIPSCs. Bar graph shows pooled data from 8 neurons

independent spontaneous GABA release. Such an effect would serve to increase the threshold of activation of the amygdala, and prevent or dampen amygdala's excitation in response to stimuli that have only mild emotional significance. During stressful situations, when the amygdala is strongly activated, there is an excessive release of NE in the amygdala (Stanford, 1995; Galvez et al., 1996; Quirarte et al., 1998; Tanaka et al., 2000). By facilitating GABAergic inhibitory transmission in the BLA, NE may help prevent excessive excitation of the amygdala, and may help shape and sharpen the flow of excitatory activity, so that the emotional stimulus is processed and interpreted appropriately. In addition, enhancement of GABAergic inhibition by NE might suppress memory formation, or, perhaps, by optimizing the activity level of the amygdala, NE might facilitate optimal registration of the memory trace representing the emotional event.

It should be considered that when NE is released it will not act selectively on α_{1A} adrenoceptors, and that opposing effects may result when different types of adrenergic receptors are activated simultaneously. However, we have observed, in field potential recordings, that the net effect of NE when no adrenergic receptor blockers are present is a suppression of excitatory synaptic transmission and overall neuronal excitability in the BLA.

Relation to anxiety disorders

Is there a clinical significance of the facilitation of GABAergic inhibition by NE, in the BLA? We have found that following exposure to restrain/tail-shock stress the α_{1A} adrenoceptor-mediated facilitation of GABA release in the rat BLA is severely impaired (Figs. 3 and 4; Braga et al., 2004b). Adrenergic receptors desensitize or undergo downregulation following prolonged exposure to the agonist (Yang et al., 1999; Chalothorn et al., 2002), and this is also true for the α_{1A} adrenoceptors (Rankin et al., 2005). Thus, excessive NE release in the amygdala during stress (Galvez et al., 1996; Quirarte et al., 1998; Tanaka et al., 2000) may be responsible for the impairment of α_{1A} adrenoreceptor function. An alternative, or additional possibility is that corticosterone released during exposure to restrain/tail-shock stress (Servatius et al., 1995) downregulates α_{1A} adrenoceptors, since glucocorticoid receptors co-localize with α_1 adrenoceptors (Fuxe et al., 1985; Williams et al., 1997), and corticosterone is known to downregulate α adrenoceptors (Stone et al., 1986, 1987; Joels and de Kloet, 1989). The functional implications of a stress-induced impairment in the noradrenergic facilitation of inhibitory synaptic transmission in the BLA may be hyperactivity of the amygdala at the resting state, a lower threshold of activation of the amygdala, as well as over-responsiveness to an emotional stimulus, which could be accompanied by impairment in the processing and interpretation of the stimulus. In a hyper-responsive amygdala, events of little emotional significance may be registered as significant, and memories of emotionally significant events may be ''over-consolidated''.

Our results provide the first direct evidence of a stress-induced impairment in inhibitory transmission in the amygdala, and suggest that a reduction in the $GABA_A$ receptor-mediated inhibitory transmission due to the loss of the α_{1A} adrenoceptor-mediated facilitation of GABA release may be one of the mechanisms responsible for the hyperexcitability of the amygdala in stress-related anxiety disorders, such as PTSD.

Relation to epilepsy

The facilitation of GABA release via α_{1A} adrenoceptors in the BLA is consistent with the well-documented antiepileptic properties of NE (Weinshenker and Szot, 2002; Weinshenker et al., 2002; Giorgi et al., 2004). Early studies demonstrated that NE delayed the onset of amygdala kindling in rats (Corcoran and Mason, 1980; McIntyre, 1981; McIntyre and Wong, 1986), while damage to the locus coeruleus accelerated the rate of amygdala kindling (McIntyre, 1980; Corcoran, 1988). The antiepileptic activity of endogenous NE is also revealed by studies demonstrating that an intact noradrenergic system is necessary for the action of multiple anticonvulsant drugs (Quattrone and Samanin, 1977; Quattrone et al., 1978; Crunelli, 1981; Waller and Buterbaugh, 1985), as well as for the efficacy of alternative anticonvulsant therapies, such as vagal nerve stimulation and ketogenic diet (Krahl et al., 1998; Szot et al., 2001). The mechanisms underlying the neuroprotective, antiepileptic effects of NE are not completely understood, and different adrenoreceptor subtypes may be involved in different brain regions (Weinshenker and Szot, 2002; Giorgi et al., 2004). Our studies suggest that facilitation of GABA release by NE via α_{1A} adrenoceptors may be an important mechanism underlying the antiepileptic effects of NE in the amygdala. Furthermore, our findings suggest that the stress-induced increased frequency of seizures in patients with temporal lobe epilepsy (Temkin and Davis, 1984; Frucht et al., 2000) could be due to an impairment in α_{1A} adrenoceptor function in the BLA.

Concluding remarks

Knowledge of the mechanisms regulating neuronal excitability in the amygdala is crucial for understanding the pathophysiology of epileptogenesis and epilepsy in the temporal lobe, as well as the pathophysiology of affective illnesses, and particularly anxiety disorders. GABAergic inhibitory synaptic transmission is a primary regulator of neuronal excitability in the brain. In this article, we described a glutamatergic and a noradrenergic mechanism involved in the regulation of neuronal excitability in the amygdala, by modulating the synaptic release of GABA in the BLA, which is a nucleus that plays a central role in the function and dysfunction of the amygdala. The markedly high expression of GluR5KRs in the BLA may be a clue that these receptors play a prominent role in the physiology and pathophysiology of the amygdala. The information obtained so far suggests that the high expression of these receptors in the BLA may in part underlie the exceptionally high proneness of this amygdala nucleus to generating epileptic activity. The functional role of GluR5KRs at all types of neuronal synapses in the BLA should be delineated, as these receptors may prove to be a useful pharmacological target for the treatment of epilepsy and certain types of affective disorders; drugs targeting GluR5KRs can be expected to have few side effects, due to the primarily modulatory rather than mediatory role of these receptors, and their relatively limited distribution in the brain (in comparison to the other types of glutamate receptors). In addition, the apparent susceptibility of α_{1A} adrenoceptors in the BLA to conditions that produce excessive NE release, as evident in the stress-induced impairment of their function, may in part underlie the vulnerability – and the resulting neuropathology – of the amygdala to stress exposure.

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Authors' address: Maria F. M. Braga, DDS, PhD, Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, U.S.A.,

Fax: +1-301-295-3524, E-mail: mbraga@usuhs.mil