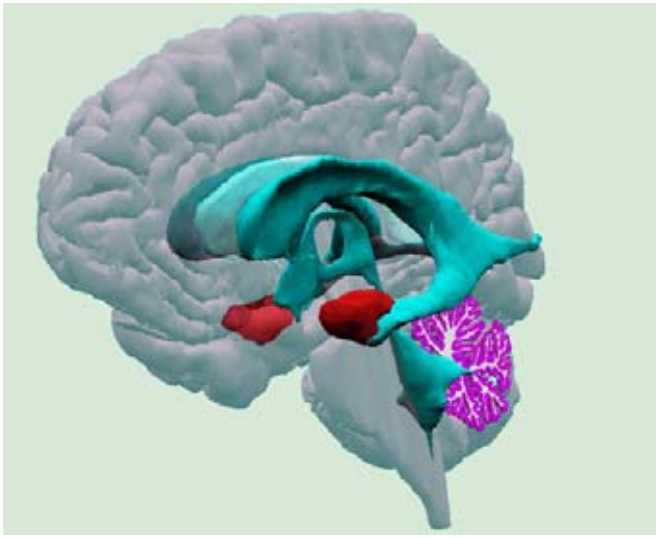
?á-Containing Nicotinic Acetylcholine Receptors on Interneurons of the Basolateral Amygdala and their Role in the Regulation of the Network Excitability



Maria F. Braga, DDS, PhD
Department of Anatomy, Physiology, and Genetics
Department of Psychiatry
F. Edward Hébert School of Medicine
Uniformed Services University of the Health Sciences

The Amygdala

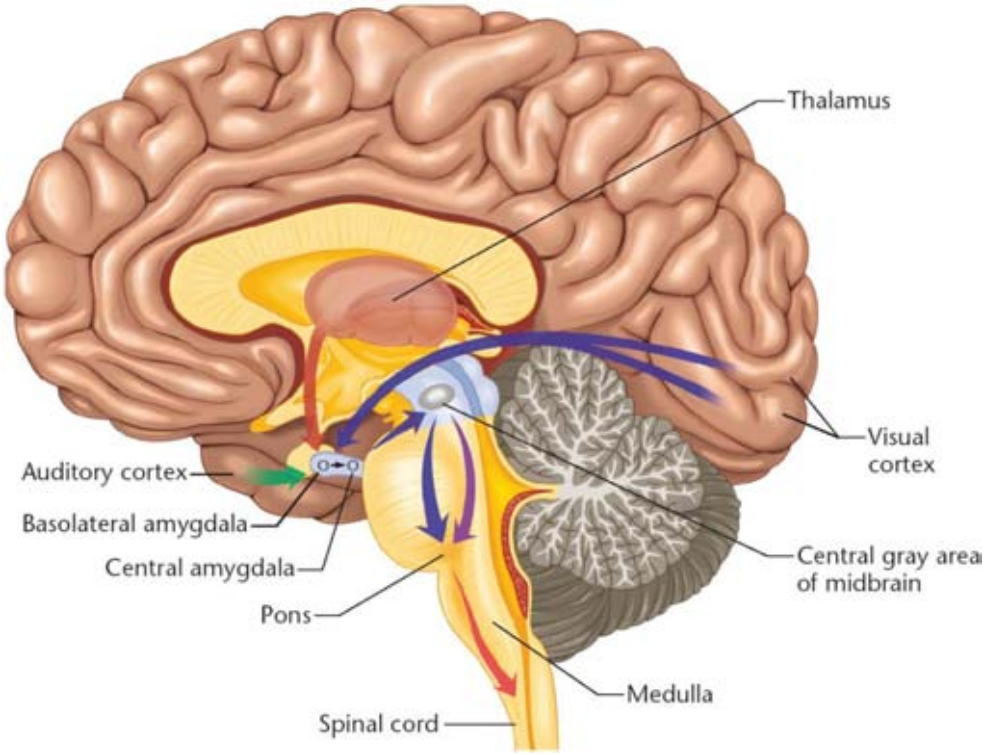
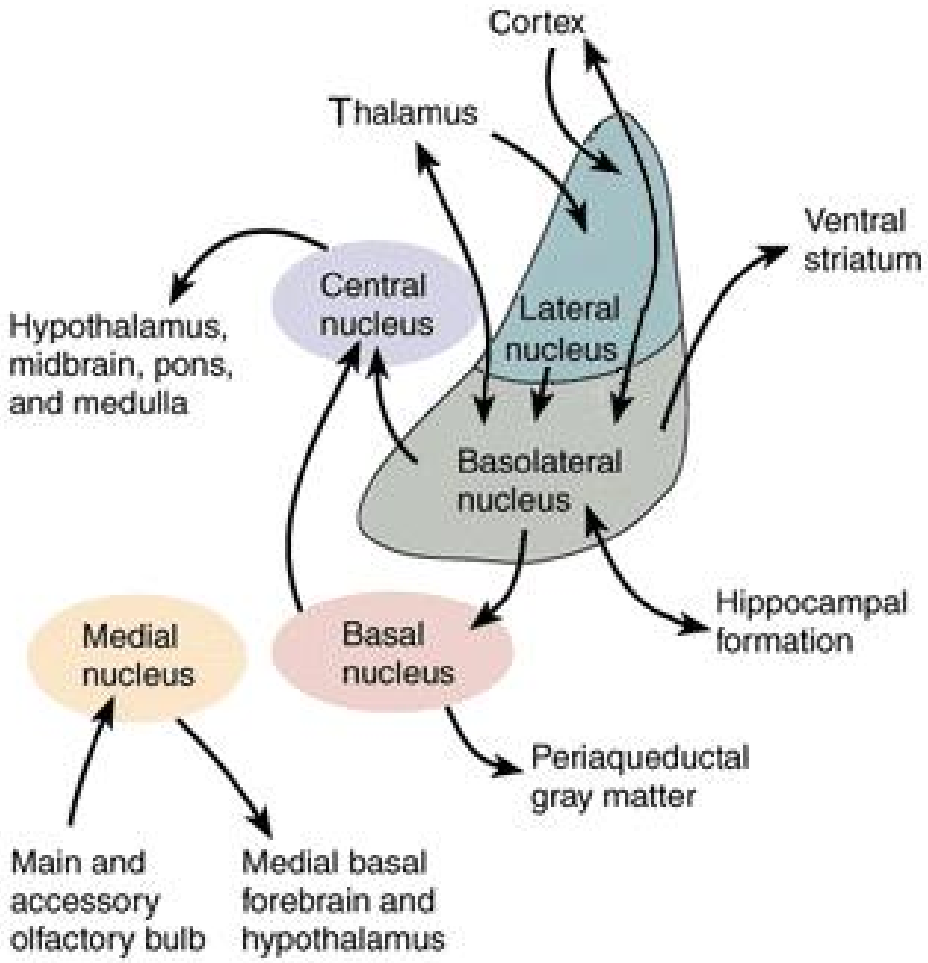
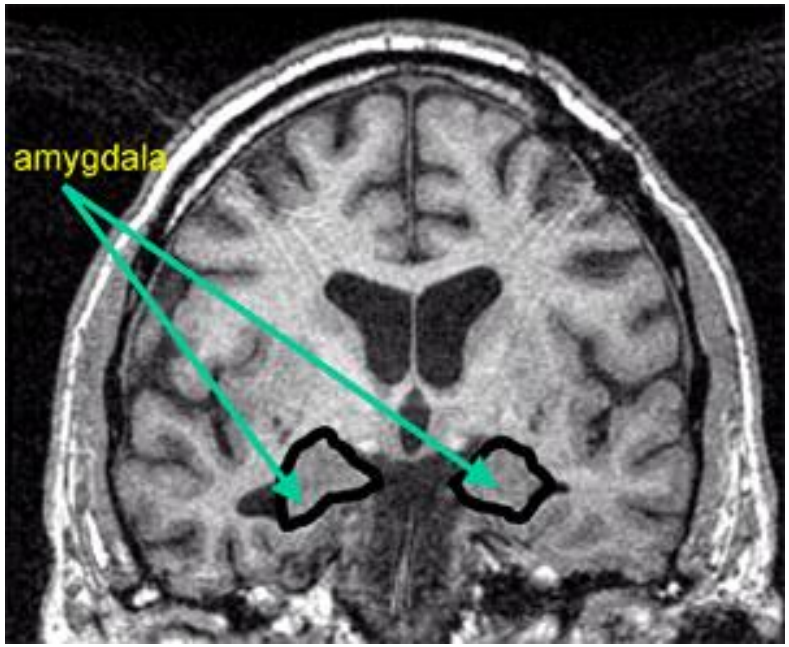


Diagram of the Major Divisions and Connections of the Amygdala



The Role of the Amygdala in the Pathogenesis and Symptomatology of Temporal Lobe Epilepsy

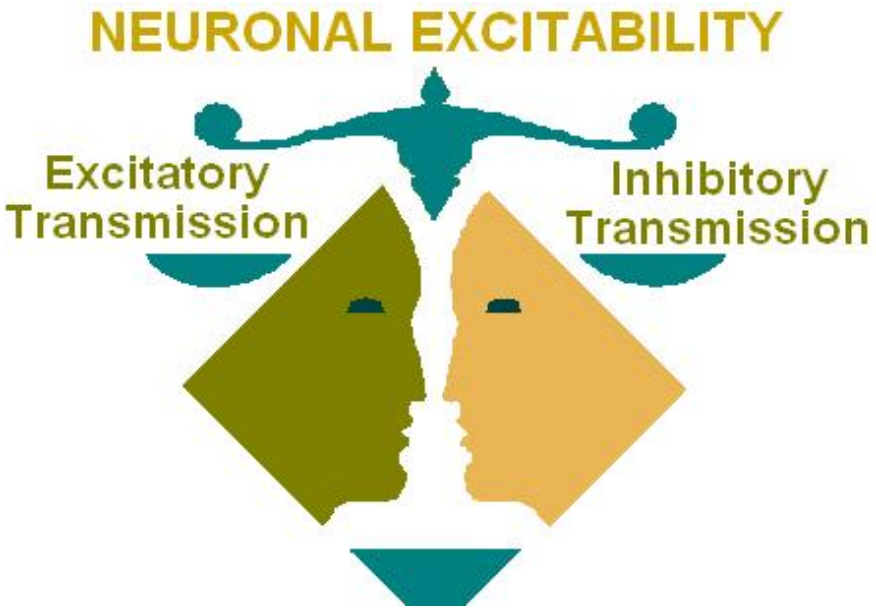


The amygdala is a critical part of the temporal lobe structures mediating limbic seizures

The Role of the Amygdala in the Pathogenesis and Symptomatology of Temporal Lobe Epilepsy

- Magnetic resonance imaging in patients with TLE has shown that the volume of the amygdala is reduced by ~57%
- In the human amygdala, neuronal loss and gliosis have been reported in the basolateral and lateral nuclei of TLE patients
- The amygdala is the limbic area typically stimulated to generate kindling (the most widely used model of TLE)
- The amygdala is among the structures of the temporal lobe whose surgical removal can lead to the elimination of seizures

Affective Disorders, Epilepsy and Neuronal Excitability

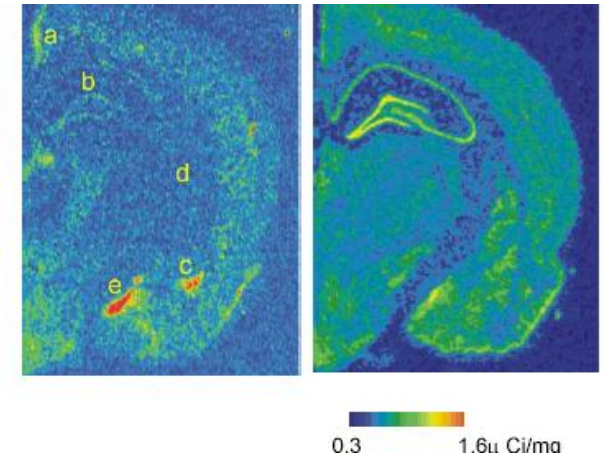


GABAergic Synaptic Transmission in the BLA

GABAergic inhibition plays a primary role in the regulation of the excitability of neuronal networks.

Although GABAergic interneurons in the BLA make up only a small proportion (about 20%) of the total neuronal population they tightly regulate principal cell excitability.

Neuromodulatory systems participate in the regulation of GABAergic Synaptic transmission in the BLA

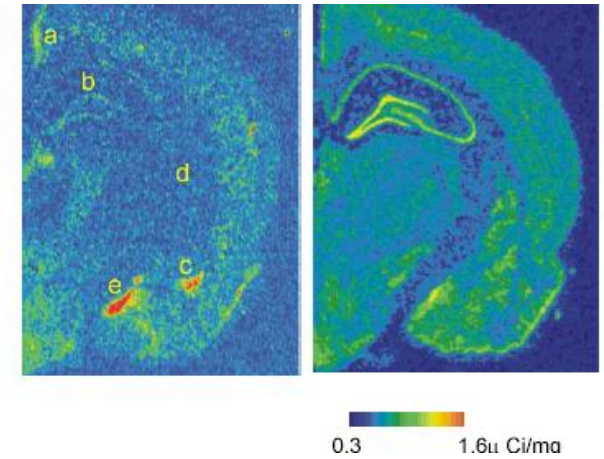


The cholinergic system is prominently present in the BLA but its involvement in the regulation of GABAergic synaptic transmission is not well understood.

The cholinergic projections to the BLA arise primarily from the nucleus basalis magnocellularis, a collection of neurons in the substantia innominata of the basal forebrain.

Afferents from these neurons synapse on both pyramidal cells and interneurons targeting nicotinic and/or muscarinic acetylcholine receptors, which are abundantly present in the BLA

Neuromodulatory systems participate in the regulation of GABAergic Synaptic transmission in the BLA



Neuronal nicotinic acetylcholine receptors (nAChRs) are pentameric and are composed, in different subunit combinations, of ?2-?10 and ß2-ß4 subunits.

The homomeric ?7 and heteromeric ?4ß2 are the two major subtypes of nAChRs found in the mammalian brain.

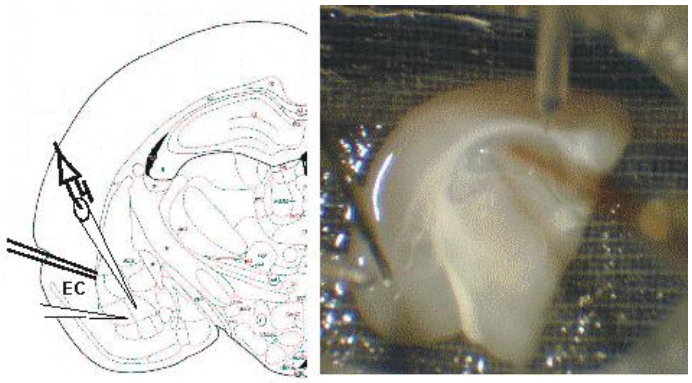
?7-nAChRs play an important role in the regulation of neuronal excitability in different brain regions but little is known about the role of ?7-nAChRs in the BLA.

Objective of Study

The focus of the present study was to delineate the role of ?7-nAChRs in the regulation of GABAergic activity in the BLA, and determine the net effect of ?7-nAChR activation on the excitability of the BLA network.

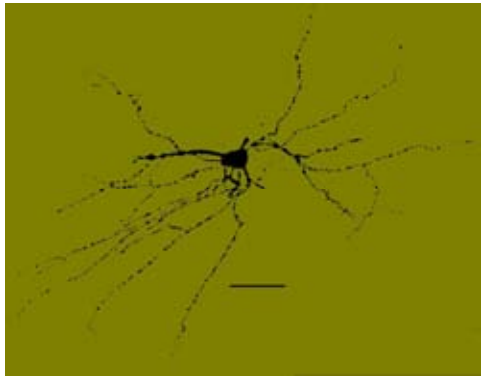
Methods

Whole Cell Recordings are Obtained from Identified Interneurons or Pyramidal Cells in Amygdala Slices

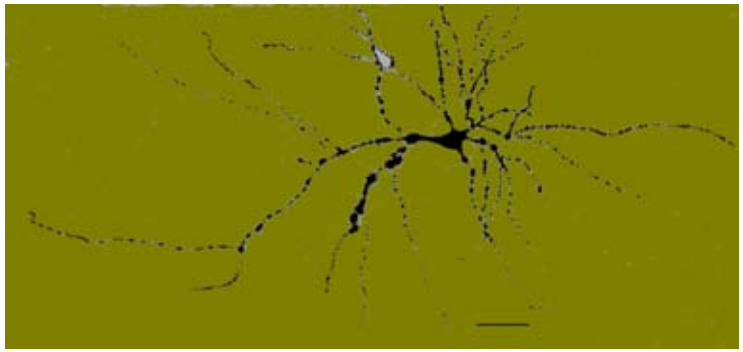


Post hoc Morphological Identification of Neurons

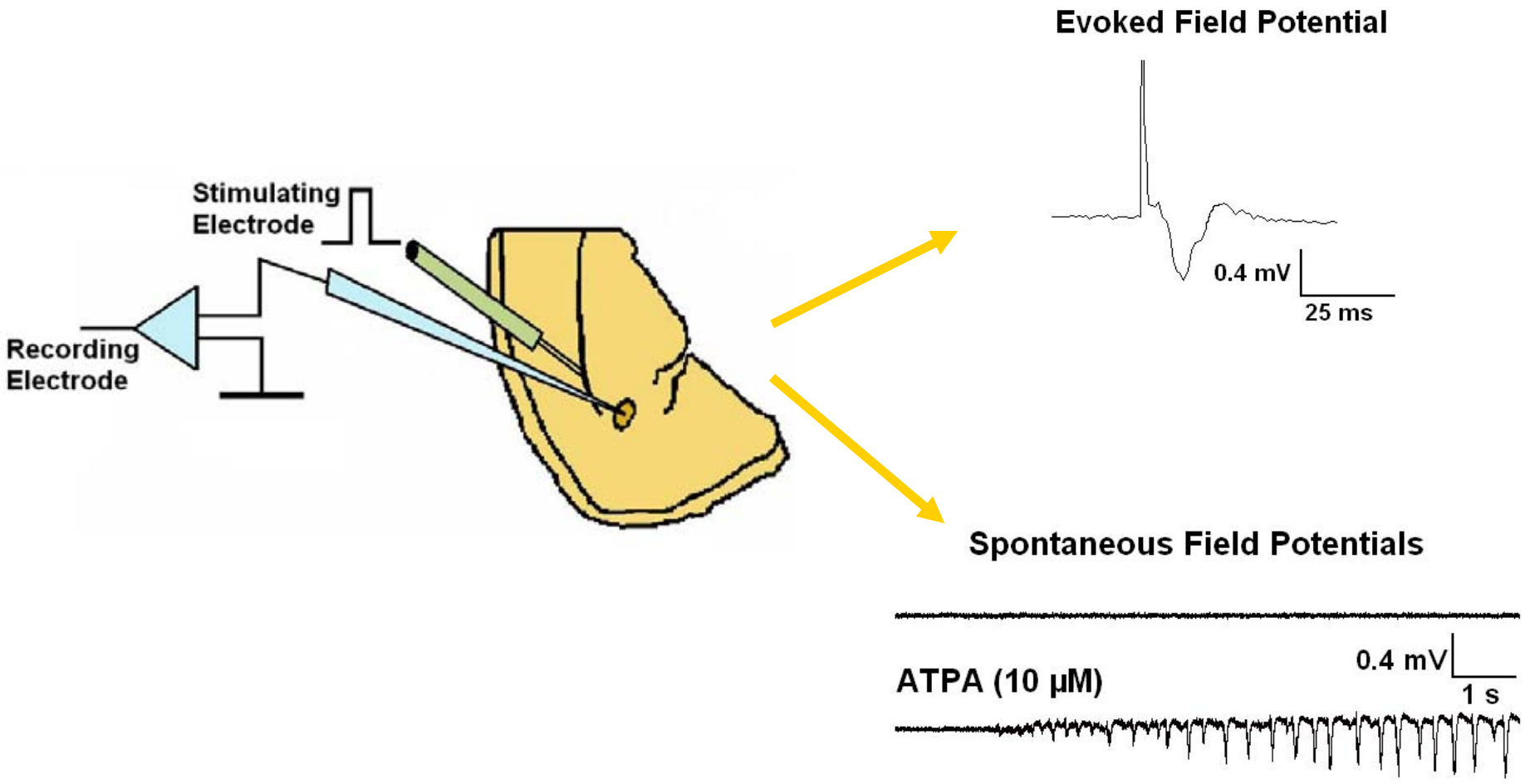
Interneuron



Pyramidal Cell

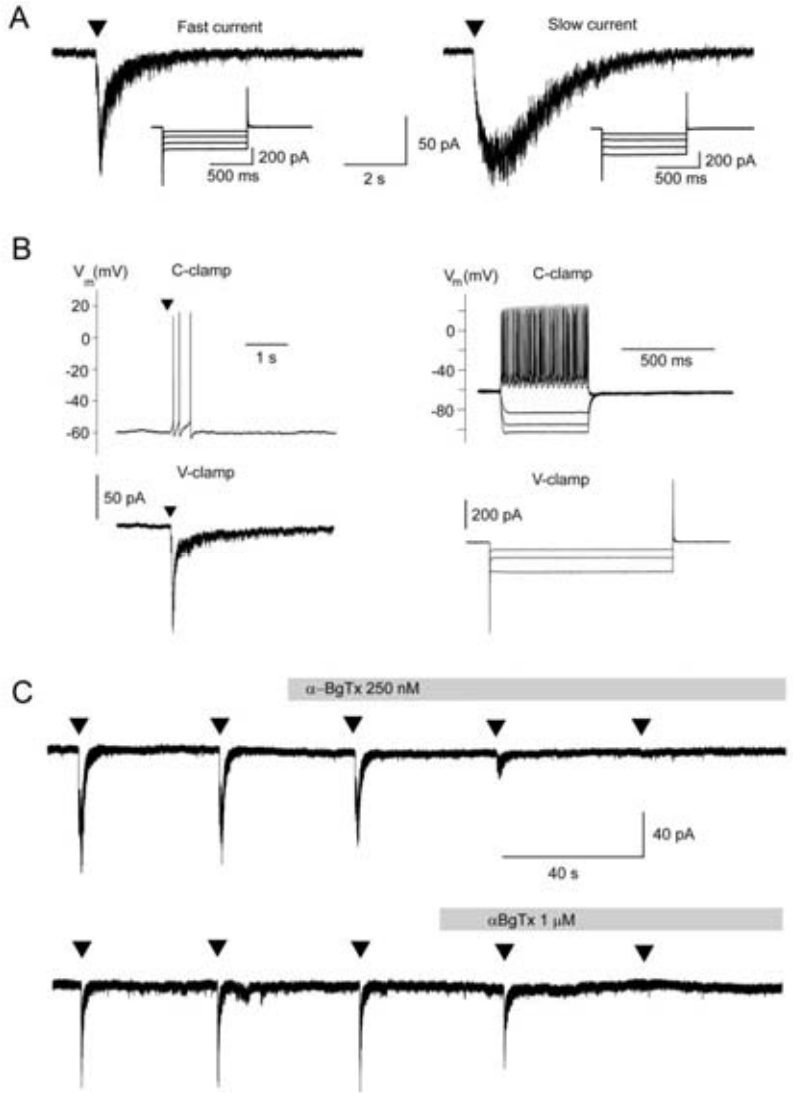


Field Potentials Recordings in the Basolateral Amygdala

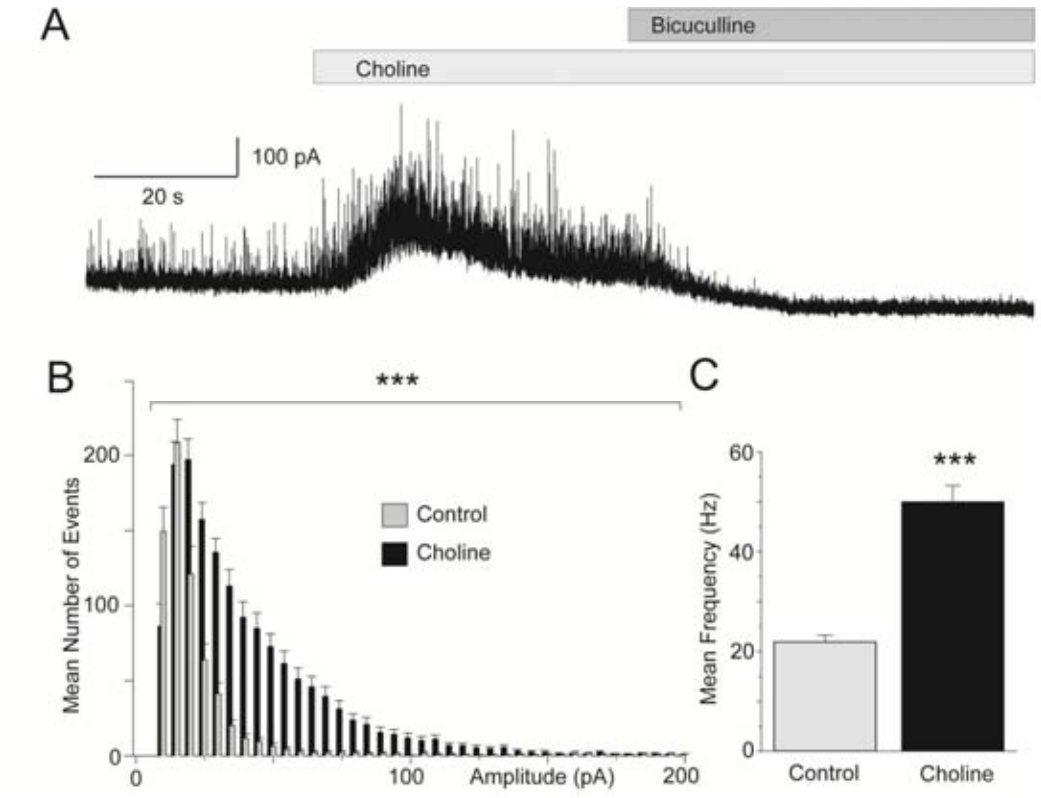


Results

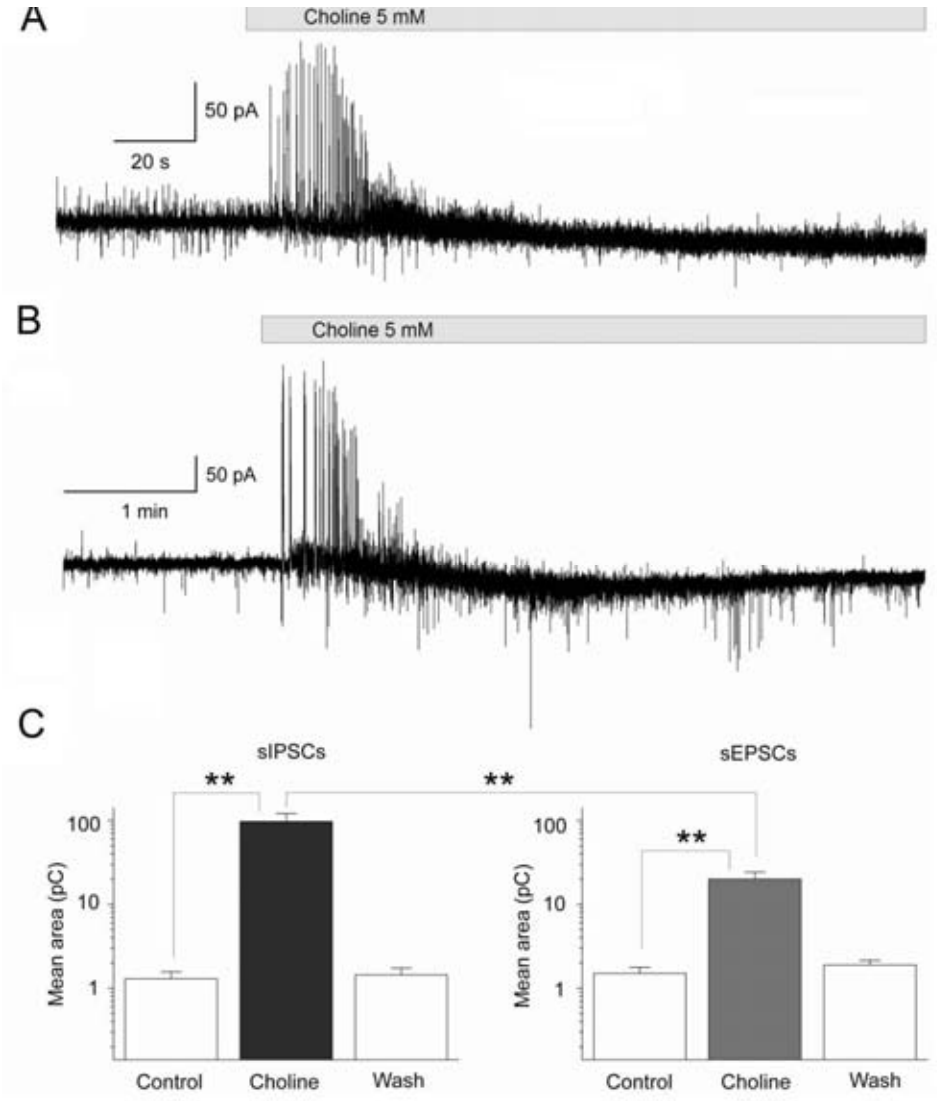
?ã-nAChRs are present on BLA interneurons



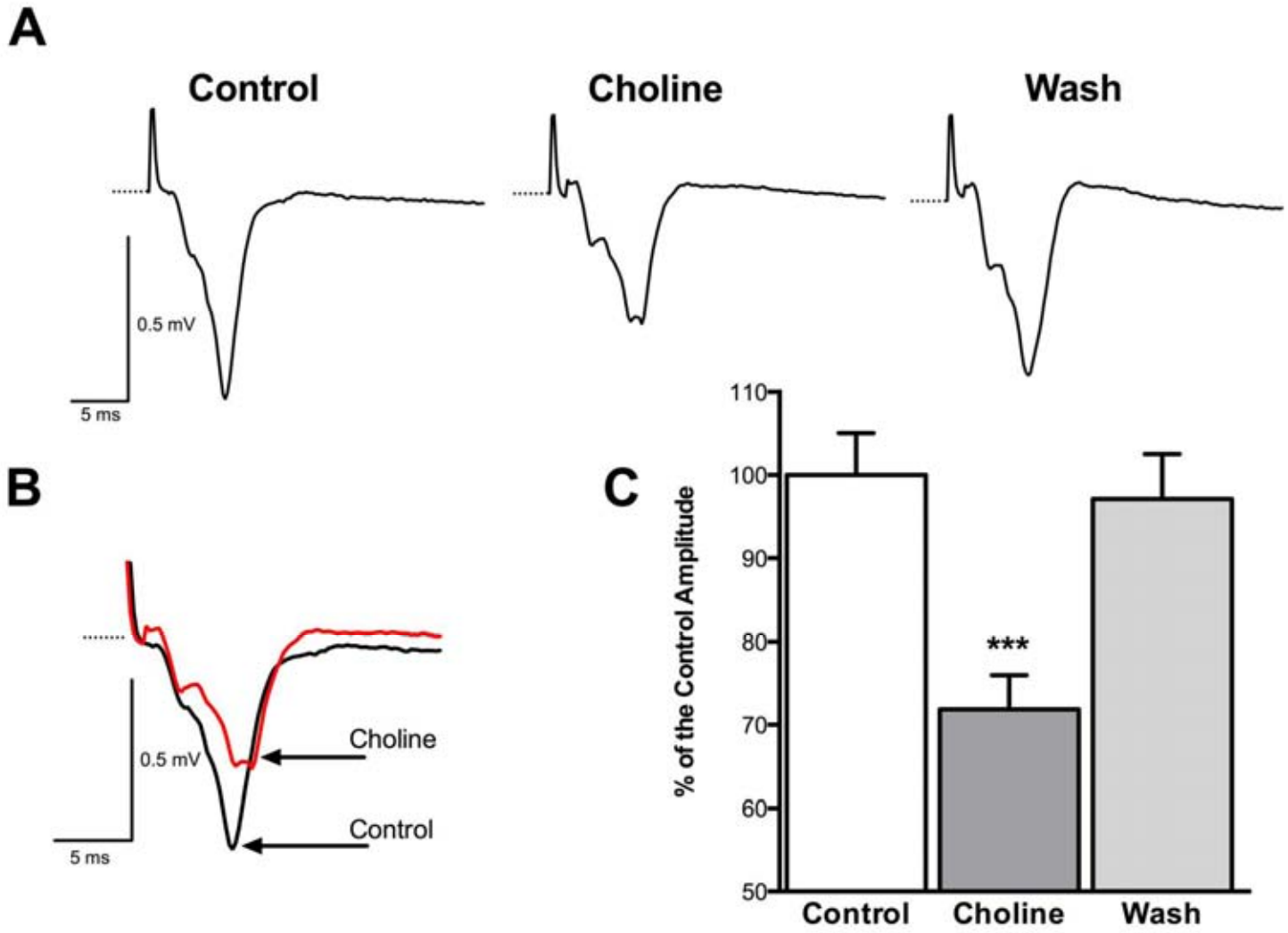
Activation of ?¢-nAChRs enhances spontaneous $GABA_A$ receptor-mediated IPSCs



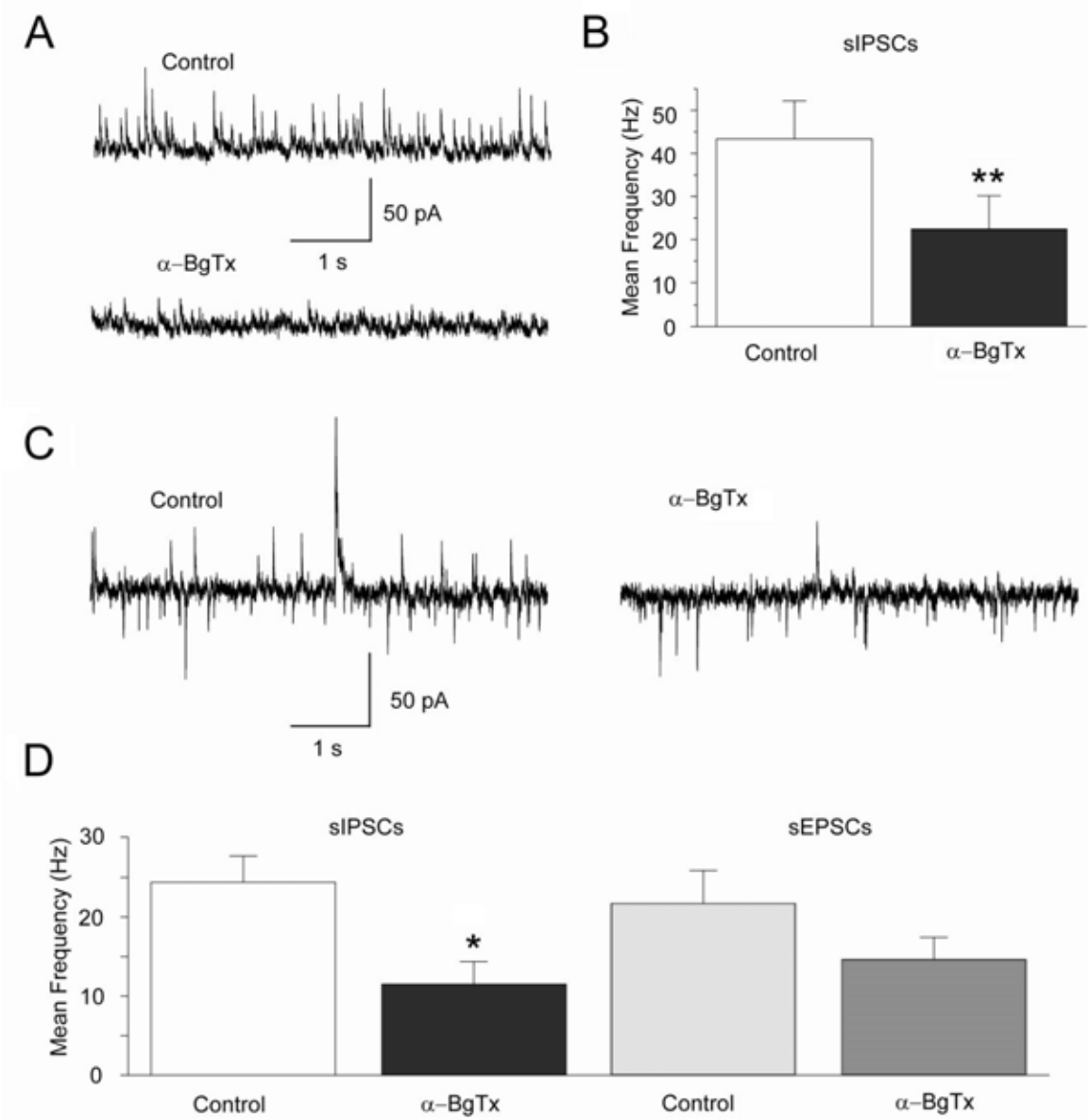
Effects of ?É-nAChR activation on simultaneously recorded sIPSCs and sEPSCs.



Activation of ?É-nAChRs reduces evoked field potentials in the BLA



Blockade of ?É-nAChRs in the basal state decreases the frequency of sIPSCs



SUMMARY

- ?ā-nAChRs are present on somatic or somatodendritic regions of BLA interneurons.

- These receptors are active in the basal state enhancing GABAergic inhibition, and their further – exogenous – activation produces a transient but dramatic increase of spontaneous inhibitory postsynaptic currents (sIPSCs) in principal BLA neurons.

- In the absence of AMPA/kainate receptor antagonists, activation of ?ī-nAChRs in the BLA network, increases both GABAergic and glutamatergic spontaneous currents in BLA principal cells, but the inhibitory currents are enhanced significantly more than the excitatory currents, reducing overall excitability.

SUMMARY I

- The ?7-nAChR-mediated increase in GABAergic activity in the BLA may be one of the mechanisms by which nicotine suppresses BLA excitability, thereby reducing anxiety and alleviating depression.
- Considering that the amygdala is a seizure-prone structure with an important role in certain forms of epilepsy, the question arises as to whether ?4-nAChRs, by regulating both GABAergic and glutamatergic activity in the BLA, play a significant role in seizure generation and/or suppression.
- An involvement of the ?7-nAChR in epilepsy is suggested by the association of juvenile myoclonic epilepsy with a mutation in the gene coding for the ?7 subunit.
- In addition, systemic administration of an ?7-nAChR agonist, in mice, showed anticonvulsant potential in the audiogenic seizure paradigm which is known to involve the amygdala.
- The present data showing a preferential increase of inhibitory activity in the BLA by ?7-nAChR activation, suggest that in the amygdala these receptors contribute to the suppression of seizures.

Acknowledgements

Uniformed Services University

Vassiliki Aroniadou-Anderjaska, PhD
Volodymyr I. Pidoplichko, Ph.D.
Eric M. Prager, M.S.

NIH – NINDS

Michael Rogawski, MD, PhD
Felicia Rankin, PhD

This work was funded by the National Institutes of Health through the National Institute of Neurological Disorders and Stroke (award # U01 NS058162-01), by the Defense Threat Reduction Agency (award # 1.E0021_07_US_C), and by the Defense Brain and Spinal Cord Injury Program (award # TRP-2005-02).