GABA$_A$ receptor-mediated tonic currents are reduced in cortical neurons in GABA$_A$ receptor α4 subunit knockout mice

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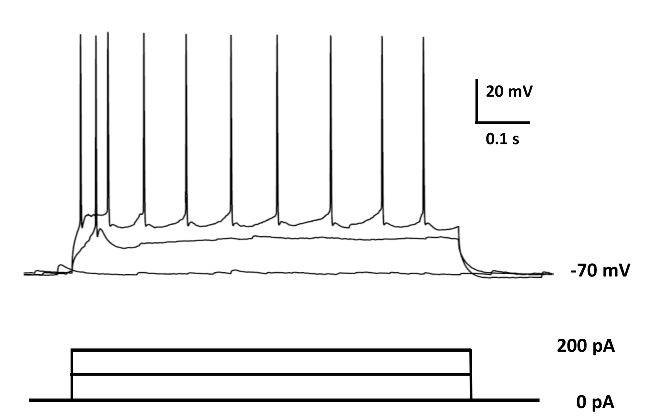
Background GABA$_A$ receptor (GABA$_A$-R) mediated tonic currents are an important source of inhibition in the cortex. GABA$_A$-Rs that contain α4, α5, or α6 subunits contribute to formation of GABA$_A$-Rs that are located at extra-synaptic sites along the plasma membrane, and are activated by ambient GABA that results from "spillover" from the synaptic cleft and possibly other sources. Neocortical α4 subunit-containing GABA$_A$-Rs are predominantly located in the superficial layers of somatosensory cortex in mice, but the extent to which this receptor is responsible for mediating the tonic current is unknown.

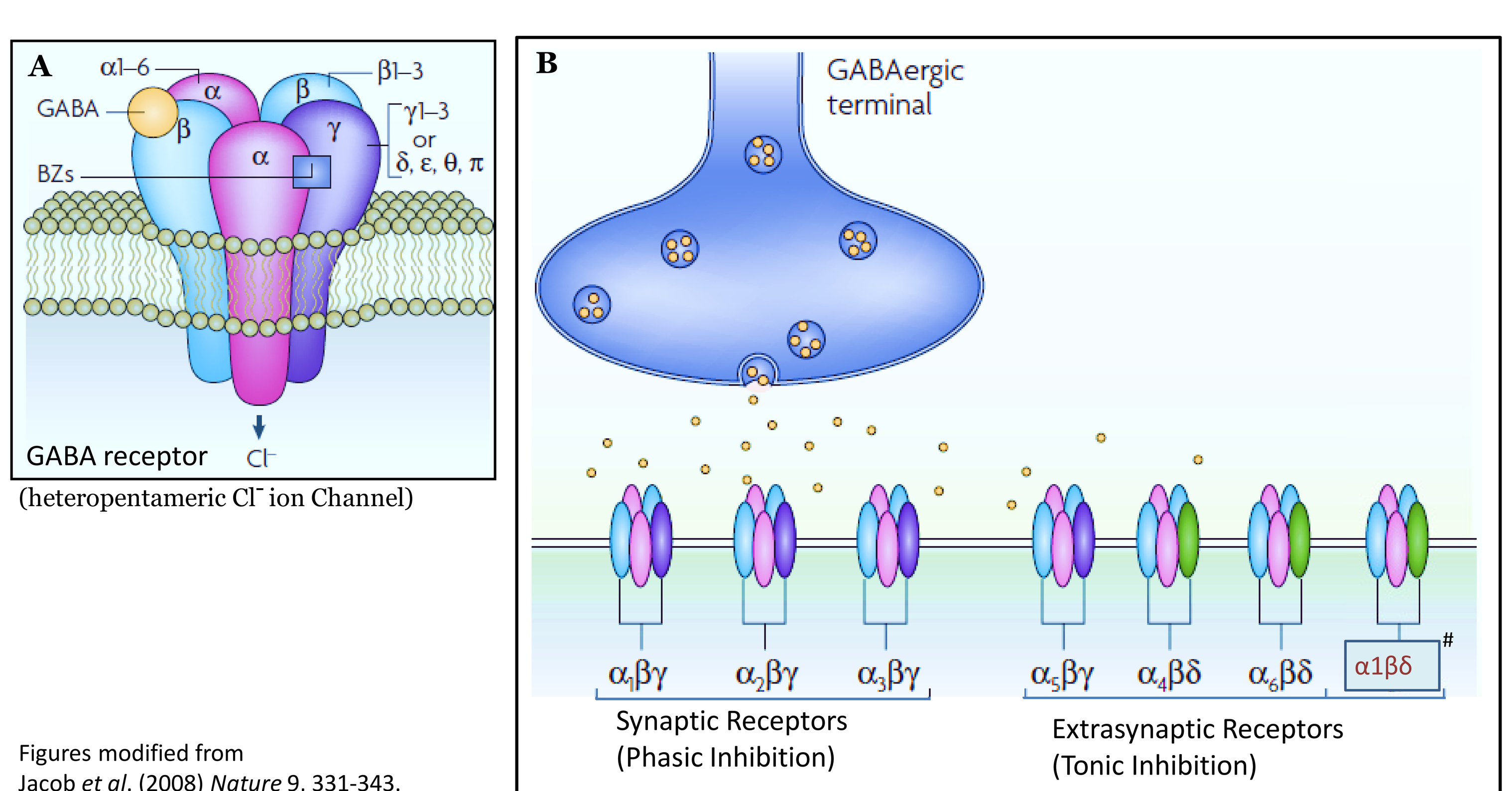
In this study, our objective was to define the contribution of the GABA$_A$ α4 subunit to bicuculline-sensitive tonic currents in layer II/III pyramidal cells in somatosensory cortex.

Methods Experiments were performed in accordance with institutional and federal guidelines. Whole-cell patch clamp recordings were obtained in voltage clamp mode at -70 mV from layer 2/3 pyramidal cells in acutely prepared brain slices from both wild-type (α4$^{+/+}$) and GABA$_A$-R α4 subunit deletion (α4$^{-/-}$) mice in the presence of glutamate and GABA$_B$ receptor antagonists using a KCl-based internal solution. The tonic current was measured as a shift in the holding current after application of bicuculline (50 μM).



Representative trace of firing pattern from a Layer III pyramidal neuron

Fig. 1 Schematic diagram of synaptic and extrasynaptic GABA$_A$ receptors



Figures modified from Jacob *et al.* (2008) *Nature* 9, 331-343.

Glykys *et al.* (2007) *Nat. Neurosc.* 10, 40-48 .

Fig. 2 GABA$_A$-R α4 subunit expression is necessary for the generation of the tonic current in LII/III pyramidal cells

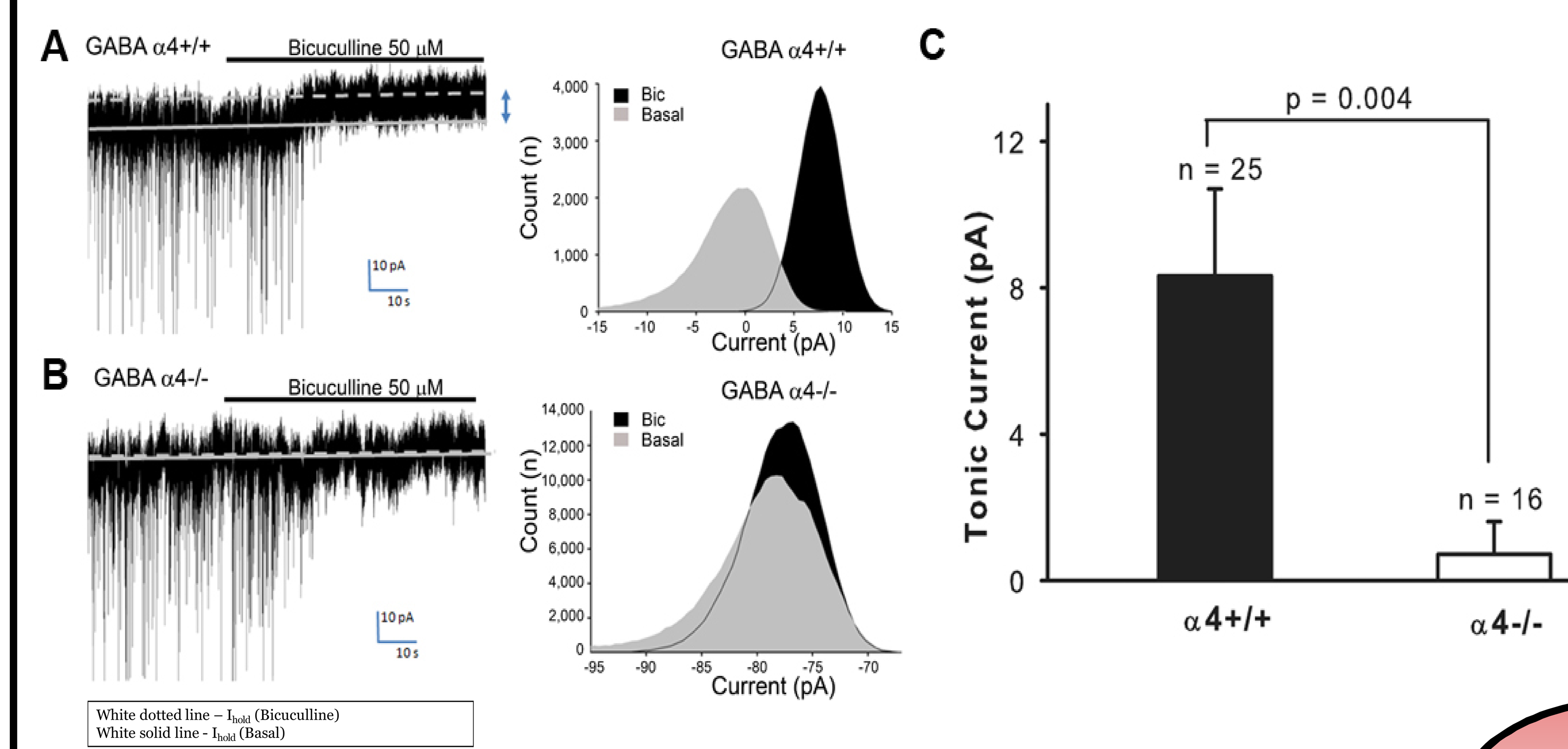
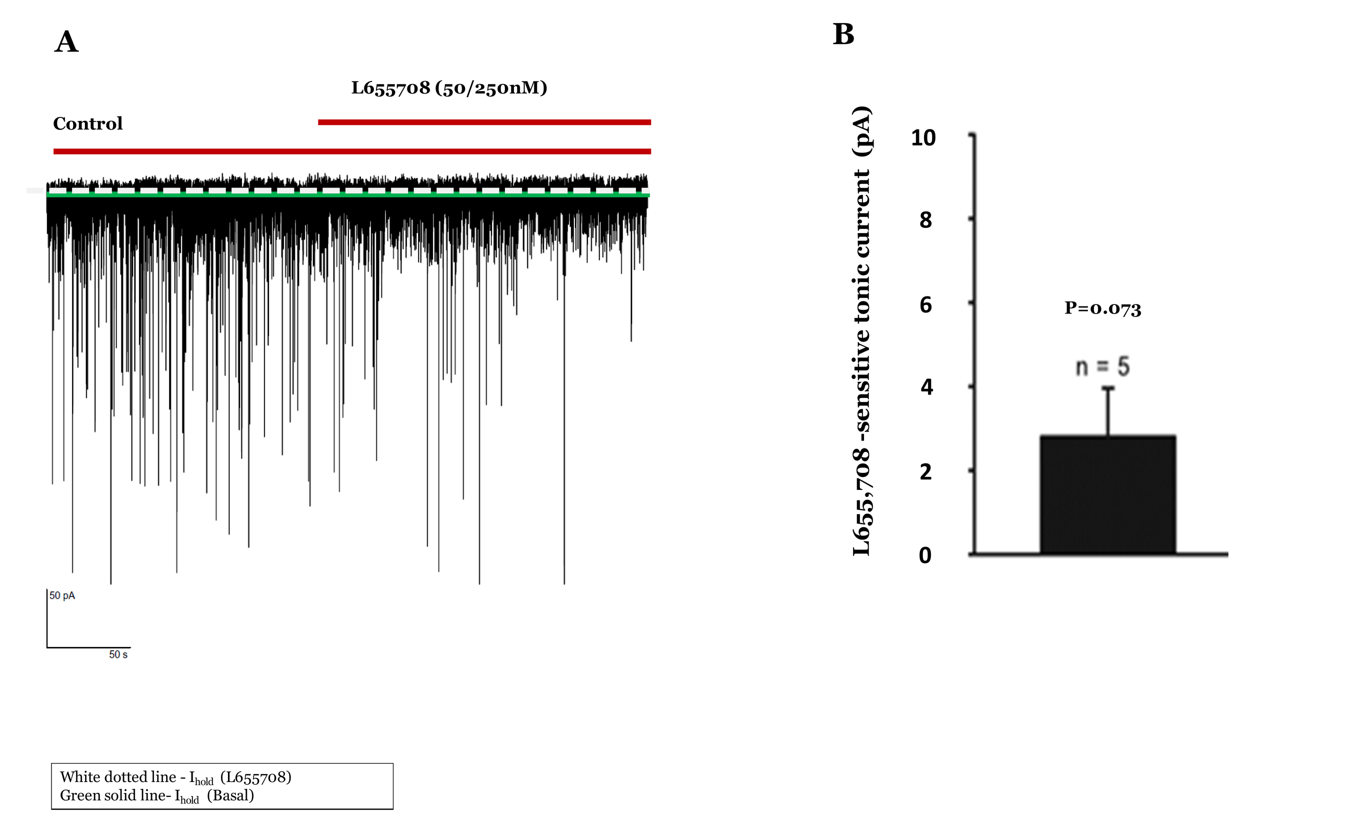


Fig. 4 GABA$_A$-R α5 subunit does not contribute appreciably to native tonic current in GABA α4 +/+ mice



Results

Fig. 3 Magnitude of tonic current unmasked by blocking GABA reuptake was significantly reduced in mice lacking the GABA α4 subunit.

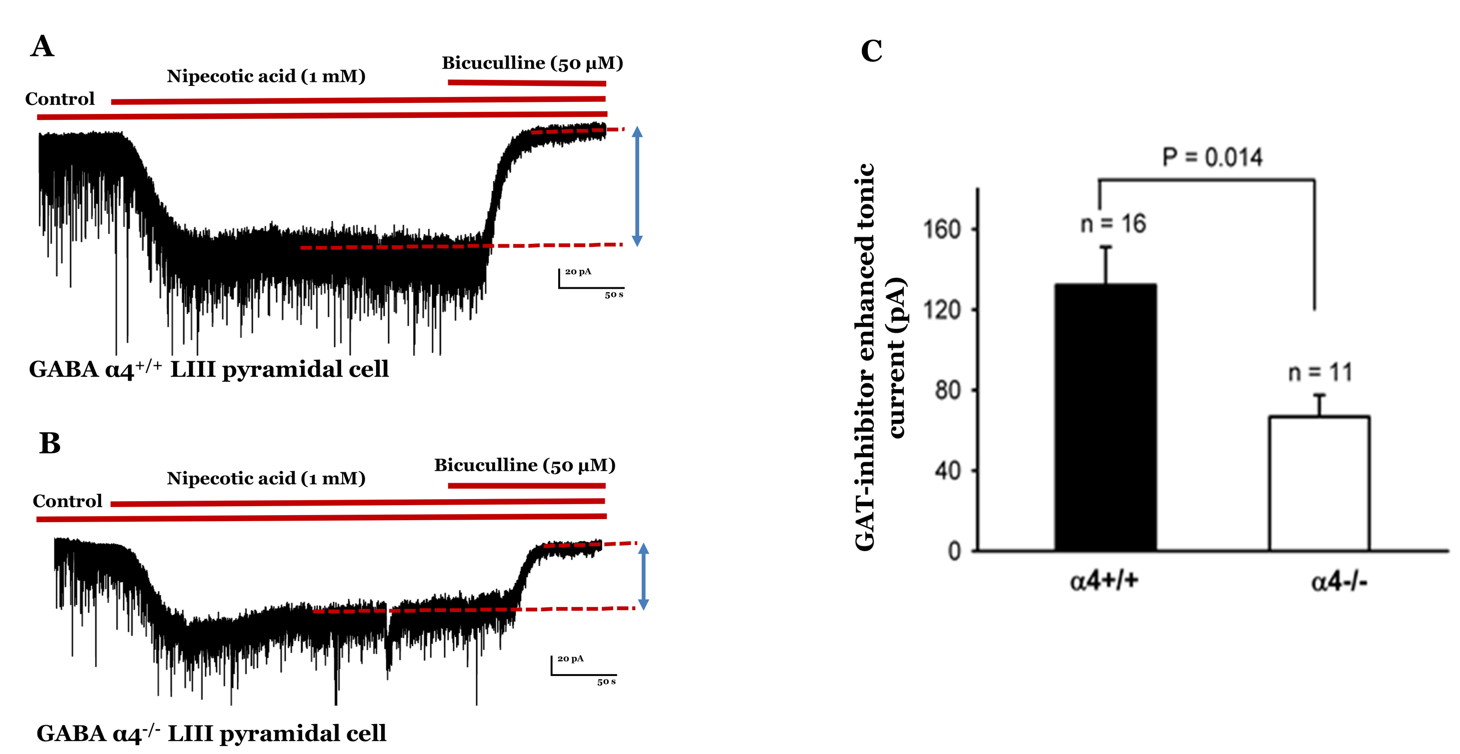
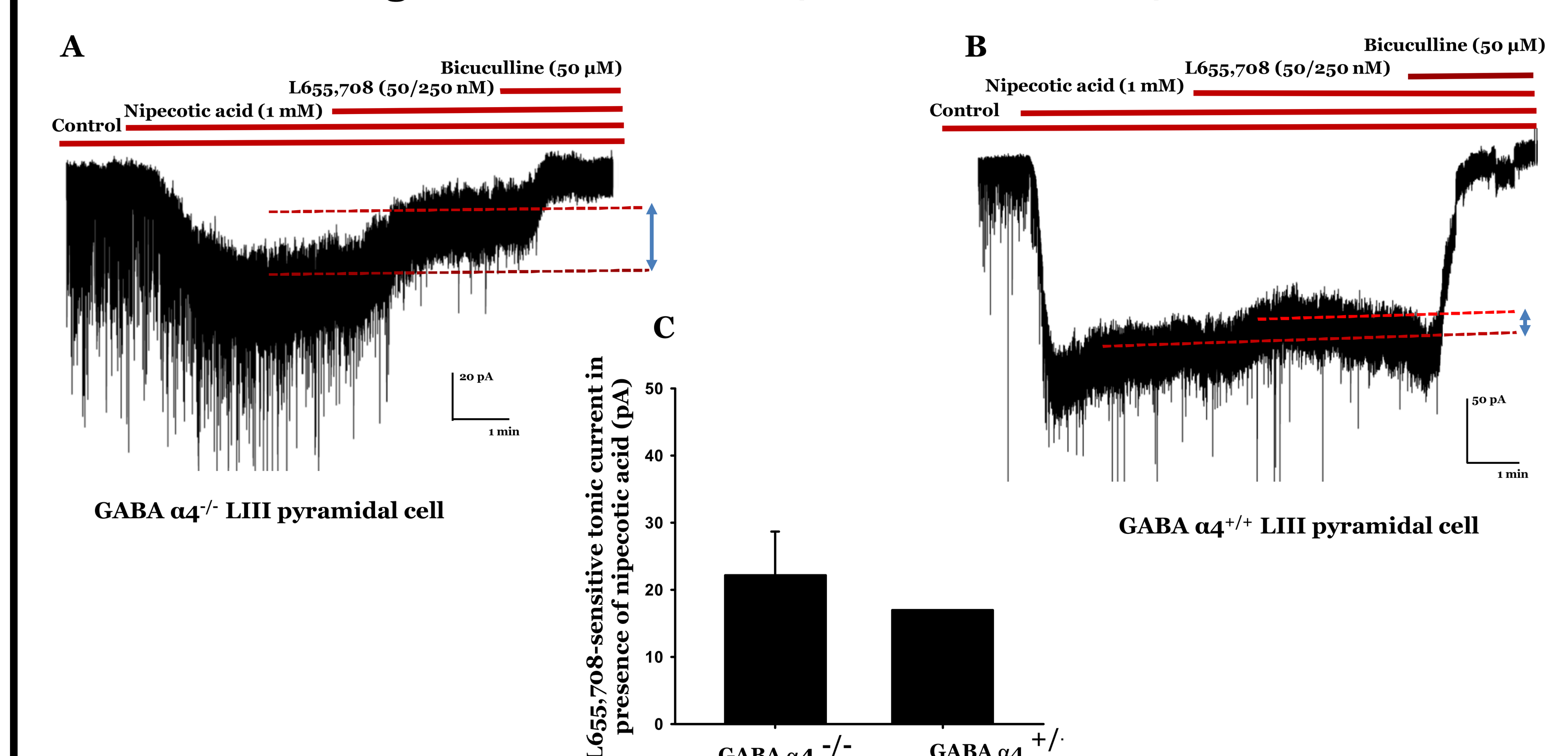


Fig. 5 The L655,708 –sensitive, GAT-inhibitor augmented tonic current is similar in magnitude in GABA α4$^{-/-}$ and GABA α4$^{+/+}$ mice.



Conclusions

- Under baseline conditions, the GABA$_A$-R α4 subunit is responsible for mediating the tonic current in superficial cortical pyramidal cells.
- Neurons lacking the GABA$_A$ α4 subunit retain the capacity to generate a tonic current in the presence of elevated [GABA], possibly due to activation of GABA$_A$-Rs containing α1 or α5 subunits.
- A compensatory increase in α5 GABA$_A$-R subunit expression in GABA α4$^{-/-}$ mice does not appear likely, consistent with published results (Suryanarayanan *et al.* 2011).

Significance

Extrasynaptic GABA$_A$-Rs are involved in a variety of physiological and pathological states including sleep, learning and memory, and seizures.

Determining the contribution of the various GABA$_A$ subunits underlying the tonic current in specific neuronal populations will facilitate the development of more targeted therapeutic modalities in relevant pathological conditions.