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_A 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).

Results  

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_A 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.

Fig. 1 Schematic diagram of synaptic and extrasynaptic GABA_A receptors

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

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

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

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