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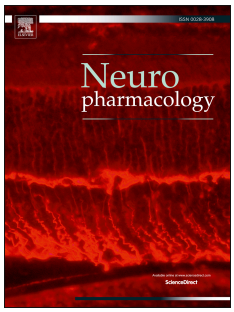

Selective ligands for Na^+/K^+-ATPase α isoforms differentially and cooperatively regulate excitability of pyramidal neurons in distinct brain regions

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Brief Running Title: Selective NaKA α isoform inhibition in adult mouse brain

ABSTRACT

Sodium-potassium ATPase (NaKA) is a plasma membrane enzyme responsible for influencing membrane physiology by direct electrogenic activity. It determines cellular excitability and synaptic neurotransmission, thus affecting learning and memory processes. A principle catalytic α subunit of NaKA has development-specific expression pattern. There are two α isoforms, α1 and α3, in adult brain neurons. Although NaKA is a housekeeping enzyme, the physiological differences between these two α isoforms in different brain regions have not been well explored. Endogenous cardiotonic steroids, including Marinobufagenin and Ouabain, control the cell homeostasis and cell functions via inhibiting NaKA. Here we employed selective inhibition of α1 and α3 NaKA isoforms by Marinobufagenin and Ouabain respectively, to measure the contribution of α subunits in cellular physiology of three distinct mouse brain regions. The results of the whole cell recording demonstrated that α1 isoform predominated in layer-5 pyramidal cells at rostral motor cortex, while α3 isoform governed the pyramidal neurons at hippocampal CA1 region and to a lesser extent the layer-5 pyramidal neurons of parietal cortex. Furthermore, selective α isoform inhibition induced differential effects on distinct physiological properties even within the same brain region. In addition, our results supported the existence of synergism between two NaKA α isoforms. To conclude, this systematic study of NaKA α isoforms demonstrated their broader roles in neuronal functioning in a region-specific manner.

KEYWORDS

Marinobufagenin; Ouabain; Synergistic effect; Rodent Brain Na+/K+-ATPase α1 and α3 isoforms; Whole cell recording/ Patch clamp; Action potential properties; Synaptic Properties.