Studies on the Neural Mechanisms for Salt Homeostasis in the Brain

Takeshi Y. Hiyama

National Institutes of Natural Sciences

Summary

Na\textsubscript{x} is a sodium-concentration ([Na\textsuperscript{+}])-sensitive Na channel with a gating threshold of \(~150\) mM for extracellular [Na\textsuperscript{+}] ([Na\textsuperscript{+}]\textsubscript{o}) in vitro. We previously reported that Na\textsubscript{x} was preferentially expressed in the glial cells of sensory circumventricular organs including the subfornical organ, and was involved in [Na\textsuperscript{+}] sensing for the control of salt-intake behavior. Although Na\textsubscript{x} was also suggested to be expressed in the neurons of some brain regions including the amygdala and cerebral cortex, the channel properties of Na\textsubscript{x} have not yet been adequately characterized in neurons. We herein verified that Na\textsubscript{x} was expressed in neurons in the lateral amygdala of mice using an antibody that was newly generated against mouse Na\textsubscript{x}. To investigate the channel properties of Na\textsubscript{x} expressed in neurons, we established an inducible cell line of Na\textsubscript{x} using the mouse neuroblastoma cell line, Neuro-2a, which is endogenously devoid of the expression of Na\textsubscript{x}. Functional analyses of this cell line revealed that the [Na\textsuperscript{+}]-sensitivity of Na\textsubscript{x} in neuronal cells was similar to that expressed in glial cells. The cation selectivity sequence of the Na\textsubscript{x} channel in cations was revealed to be Na\textsuperscript{+} ≈ Li\textsuperscript{+} > Rb\textsuperscript{+} > Cs\textsuperscript{+} for the first time. Furthermore, we demonstrated that Na\textsubscript{x} bound to postsynaptic density protein 95 (PSD95) through its PSD95/Disc-large/ZO-1 (PDZ)-binding motif at the C-terminus in neurons. The interaction between Na\textsubscript{x} and PSD95 may be involved in promoting the surface expression of Na\textsubscript{x} channels because the depletion of endogenous PSD95 resulted in a decrease in Na\textsubscript{x} at the plasma membrane. These results indicated, for the first time, that Na\textsubscript{x} functions as a [Na\textsuperscript{+}]-sensitive Na channel in neurons as well as in glial cells.