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Studies on the Neural Mechanisms for Salt Homeostasis in the Brain

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Summary

Na_x is a sodium-concentration ($[Na^+]$)-sensitive Na channel with a gating threshold of ~150 mM for extracellular $[Na^+]$ ($[Na^+]_o$) in vitro. We previously reported that Na_x was preferentially expressed in the glial cells of sensory circumventricular organs including the subfornical organ, and was involved in $[Na^+]$ sensing for the control of salt-intake behavior. Although Na_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_x have not yet been adequately characterized in neurons. We herein verified that Na_x was expressed in neurons in the lateral amygdala of mice using an antibody that was newly generated against mouse Na_x. To investigate the channel properties of Na_x expressed in neurons, we established an inducible cell line of Na_x using the mouse neuroblastoma cell line, Neuro-2a, which is endogenously devoid of the expression of Na_x. Functional analyses of this cell line revealed that the $[Na^+]$-sensitivity of Na_x in neuronal cells was similar to that expressed in glial cells. The cation selectivity sequence of the Na_x channel in cations was revealed to be $Na^+ \approx Li^+ > Rb^+ > Cs^+$ for the first time. Furthermore, we demonstrated that Na_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_x and PSD95 may be involved in promoting the surface expression of Na_x channels because the depletion of endogenous PSD95 resulted in a decrease in Na_x at the plasma membrane. These results indicated, for the first time, that Na_x functions as a $[Na^+]$-sensitive Na channel in neurons as well as in glial cells.