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Osmosensing mechanism of co-operation of Nax and TRPV4 channel

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Summary

TRPV4 is first reported to be a “hypoosmolality-sensing” cation channel. On the following studies with knockout mice (*Trpv4*$^{-/-}$), we have reported that response of vasopressin to hypertonicity was exaggerated but another group has reported that it was abolished in *Trpv4*$^{-/-}$. Although controversial in the response, both reports suggest that TRPV4 can be responsive to hypertonic stimuli. To elucidate “hyperosmolality- sensing” in TRPV4 activation, we designed to re-examine the response *in vivo* and investigate whether TRPV4 was sensitive to hyperosmolality in cultured neuronal cells. *Trpv4*$^{-/-}$ and *Trpv4*$^{+/+}$ mice were subjected to dehydration from 24 to 96 hrs. Then plasma osmolality and water intake were measured. There was not remarkable difference in plasma osmolality at any period of dehydration but a significant decrease in plasma osmolality of *Trpv4*$^{-/-}$ at 72 hrs dehydration. Water-crave behavior and amount of water intakes after the dehydrations were not changed. Thus TRPV4 channel may respond to hyperosmolality. Neuronal cell lines with and without TRPV4 and Nax expression were established from the N2A cell line. Hyperosmoliality (400 mOsm) induced robust Ca influx in the TRPV4 (+) cells, irrespective of the presence of Nax, while not in the TRPV4 (-) cells. The influx was not modified with indomethacin, partially blocked with genistein, miconazole, and completely blunted with pBPB, a blocker of PLA_2. Therefore, TRPV4 is hyperosmolality-sensng channel through activation of PLA_2 in neuronal cells.