

Fundamental Research of WNK-NKCC1 Signaling Activity in Pregnant Mice

Koichi Inoue, Tomonori Furukawa, Atsuo Fukuda

Department of Neurophysiology, Hamamatsu University School of Medicine

Summary

Pregnancy-induced hypertension (PIH) is condition with high blood pressure related to pregnancy, and can affect 5-8% in pregnancy. The severe cases, regarded as eclampsia, further have brain swelling and subsequent convulsions. Although the exact mechanism by which PIH develops remains uncovered, we hypothesized that Cl⁻ transporter, NKCCs and KCCs are associated with the pathophysiology of the disorders because high blood pressure and brain edema are involved in the main symptoms. NKCCs make an influx of Na⁺, K⁺ and Cl⁻ into cells while KCCs extrude K⁺ and Cl⁻ out of cells. Our preliminary experiments indicated that β-estradiol activates NKCC activity in rat neuronal cells by means of whole-cell patch-clamp recordings. Therefore, to examine the relation between NKCC/KCC and pregnancy, expression and phosphorylation of Cl⁻ transporter-related proteins were investigated in brain and kidney in the absence or presence of pregnancy. Immunoblot analysis revealed that NKCC1/2 protein decreased in kidney, but not in brain, in mice on gestational day 17. Indeed, KCC2, a counterpart of NKCC1, did not change in brain. On the other hand, the phosphorylation of SAPK, an upstream kinase of NKCC/KCC, decreased in brain, but not in kidney, in pregnant mice. These results may suggest that in both brain and kidney Cl⁻ transporter activity shifts not to import salt and the resultant passive water intake. To study the possibility, brain slices were prepared, and gramicidin-perforated patch-clamp recordings were carried out on cortical neurons in the absence or presence of pregnancy. Reversal potential of GABA in pregnant mice was likely to be more hyperpolarized than that of non-pregnant ones, suggesting the reduction of NKCC activity. This is consistent with that biochemical data in which NKCC activity decreased in pregnancy. Taken together, ion balance may forward to export Cl⁻ outside cells and body in normal pregnancy. The system could play a role in maintenance of systemic ion and water circulation. Elucidation of the mechanism and the effect on PIH would be expected in future.