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Regulation of Body Fluid Volume by Kidney Macula Densa: Effect of Metabolic Acidosis on the Neuronal Nitric Oxide Synthase (nNOS)

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Summary

Nitric oxide (NO) generated by neuronal nitric oxide synthase (nNOS) in the macula densa blunts the tubuloglomerular feedback system. Experiments were performed in an established macula densa cell line with an nNOS-promoter-driven-EGFP (NE-MD) (Jpn J Physiol, 2005) to investigate whether metabolic acidosis may regulate the nNOS protein expression and/or activity. The previous study in our laboratory has demonstrated that the nNOS protein expression in NE-MD cells is time-dependently increased in the presence of 12 μ M furosemide, an inhibitor of the Na^+ - K^+ -2 Cl^- cotransporter. In the present study, NE-MD cells were incubated with furosemide for 2-5 hours with or without acidification. The nNOS protein expression was analysed by Western blotting. L-arginine (Arg)-induced NO generation was measured by using an NO-sensitive electrode (WPI, USA). Intracellular pH (pH_i) of NE-MD cells was monitored by the BCECF assay (unpublished). We found that L-Arg-induced NO generation and the nNOS protein expression was significantly lower at pH 7.1, compared with pH 7.4 (control). Further, L-Arg-induced NO generation was significantly higher when NE-MD cells were incubated with low (1/10) Cl^- solution, but not with low (1/10) Na^+ solution. These results indicate that the furosemide-induced nNOS protein expression and NO generation are significantly decreased in an acidic condition. In conclusion, low [NaCl] or acidic urine may modulate the tubuloglomerular feedback mechanism by decreasing NO generation in the macula densa probably due to low pH_i .