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The choroid plexus sodium-bicarbonate cotransporter NBCe2 regulates mouse cerebrospinal fluid pH

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Abstract:
The coroid plexus epithelium (CPE) is located in the brain ventricles where it produces the majority of the cerebrospinal fluid (CSF). The hypothesis that normal brain function is sustained by CPE-mediated CSF pH regulation by extrusion of acid-base equivalents was tested by determining the contribution of the electrogenic Na^+-HCO_3^- cotransporter NBCe2 to CSF pH regulation. A novel strain of NBCe2 (*Slc4a5*) knockout (KO) mice was generated and validated. The base extrusion rate after intracellular alkalization was reduced by 77 % in NBCe2 KO mouse CPE cells compared to control mice. NBCe2 KO mice and mice with CPE-targeted NBCe2 siRNA knockdown displayed a reduction in CSF pH recovery during hypercapnia-induced acidosis of approximately 85 % and 90 % respectively, compared to control mice. NBCe2 KO did not affect baseline respiration rate or tidal volume, and the NBCe2 KO and wild-type (WT) mice displayed similar ventilatory responses to 5 % CO_2 exposure. NBCe2 KO mice were not protected against pharmacological or heating-induced seizure development. In conclusion, we establish the concept that the CPE is involved in the regulation of CSF pH by demonstrating that NBCe2 is necessary for proper CSF pH recovery after hypercapnia-induced acidosis.

Keywords: choroid plexus epithelium (CPE), cerebrospinal fluid (CSF), pH regulation, NBCe2, extrusion rate, pH recovery