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ZINK BINDING SITE MAPPED ON THE CRYSTAL STRUCTURE OF THE REGULATORY DOMAIN OF THE HUMAN SODIUM-DRIVEN CHLORIDE/ BICARBONATE EXCHANGER

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The sodium-driven chloride/bicarbonate exchanger (NDCBE) is a member of the sodium-bicarbonate co-transporters (NBCs) within the solute carrier 4 (SLC4) gene family and mainly expressed in the brain, especially in the choroid plexus. NDCBE is primarily associated with the presynaptic vesicles of glutamatergic and GABAergic neurons; Zn has been shown to accumulate in presynaptic vesicles of glutamatergic neurons and efflux from the cytoplasm to the vesicle is facilitated by the membrane exporter ZnT-3. The glutamatergic neurons are found cerebral cortex and may be critical for cognitive and emotional functioning. The trace element Zn is vital for life and involved in several functional and catalytic binding sites in enzymes and proteins regulating physiological processes. In the brain, zinc dependent processes include central nervous system development, and neuronal modulation. The crystal structure at 2.8 Å resolution of the regulatory N-terminal domain of human NDCBE represents the first crystal structure of an electroneutral sodium-bicarbonate co-transporter. A novel conserved Zn-binding motif present in the N-terminal domain of NDCBE is identified and characterized *in vitro*. The Zn site is mapped to a cluster of histidines close to the conserved ETARWLKFEE motif and is likely involved with regulation of this important motif. The combined structural and bioinformatics analysis provides a model that predicts, with additional confidence, the physiologically relevant interface between the cytoplasmic domain and the transmembrane domain. As even small variations in concentration of the intracellular Zn would affect the equilibrium between the histidine binding sites and free Zn ions, we hypothesize that this site would consequently act as a pH sensor.

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