

Homocysteine augments BK channel activity and decreases exocytosis of secretory granules in rat GH3 cells

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In this study, we investigated the effects of L-homocysteine (Hey) on maxi calcium-activated potassium (BK) channels and on exocytosis of secretory granules in GH3 rat pituitary-derived cells. A major finding of our study indicates that short-term application of Hey increased the open probability of oxidized BK channels in inside-out recordings. Whole-cell recordings show that extracellular Hey also augmented BK currents during long-term application. Furthermore, Hey decreased the exocytosis of secretory granules. This decrease was partially prevented by the BK channel inhibitor paxilline and fully prevented by N-acetylcysteine, a reactive oxygen species scavenger. Taken together, our data show that elevation of cellular Hey level induces oxidative stress, increases BK channel activity, and decreases exocytosis of secretory granules. These findings may provide insight into some of the developmental impairments and neurotoxicity associated with Hyperhomocysteinemia (HHcy), a disease arising due to abnormally elevated levels of Hey in the plasma.

Keywords: BK channels; exocytosis; homocysteine; oxidative stress

Homocysteine (Hey) is a nonproteinogenic, sulfur-containing amino acid, biosynthesized via the methionine metabolism and is a homolog of cysteine. Hey may undergo remethylation to methionine by methylenetetrahydrofolate reductase (MTHFR) with vitamin B12 as a cofactor and folate as a promoter. Another metabolic pathway comprises transsulfuration of Hey to cysteine by cystathionine beta synthase (CBS) with production of hydrogen sulfide (H₂S) as an intermediate dependent on vitamin B6 as a cofactor [1]. Genetic mutations of the enzymes MTHFR and CBS as well as nutritional deficiencies of vitamin cofactors (folate, B12, and B6) are the primary causes of

hyperhomocysteinemia (HHcy)—a disease due to elevated Hey plasma levels [2]. HHcy is a well-known risk factor for cardio-vascular diseases, neurodegenerative disorders, common pregnancy complications [3,4] and induces proinflammatory and pro-oxidative conditions [2,4–6].

Maxi calcium-activated potassium (BK) channel are synergistically gated by both Ca²⁺ and membrane voltage. The channels are present in numerous cells being involved in controlling electrical activity, such as action- or synaptic potentials, in hormone secretion or vasoregulation [7,8]. The channels are modulated by a wide variety of factors, including protein kinases,

Abbreviations

BK channels, maxi-conductance calcium-activated potassium channels; CBS, cystathionine beta synthase; GH, growth hormone; Hey, L-homocysteine; HHcy, hyperhomocysteinemia; HX, hypoxanthine; MTHFR, methylenetetrahydrofolate reductase; NADH, β-nicotinamide adenine dinucleotide phosphate disodium salt; ROS, reactive oxygen species; XO, xanthine oxidase.