4-PBA improves lithium-induced diuresis by attenuating ER stress

The Kidney regulates body water and sodium balance. The kidney produces approximately 180L of primary glomerular filtrate per day in a healthy adult. The majority of this filtrate is reabsorbed in the segments of kidney through water channels and sodium transporters. As a result, the final urine volume of a healthy adult is about 2L per day. Recently, more than thirteen mammalian water channels have been identified, and among which the water channel aquaporin-2 is the most important one for water reabsorption. Aquaporin-2 (AQP2) is mainly localized at the kidney collecting duct, the most important renal tubular segment for regulating body water homeostasis and urine concentration. Water reabsorption in the collecting duct principal cells is controlled by arginine-vasopressin (AVP, also called antidiuretic hormone), a peptide hormone which induces the osmotic water transport across the collecting duct epithelia mainly via regulation of AQP2.

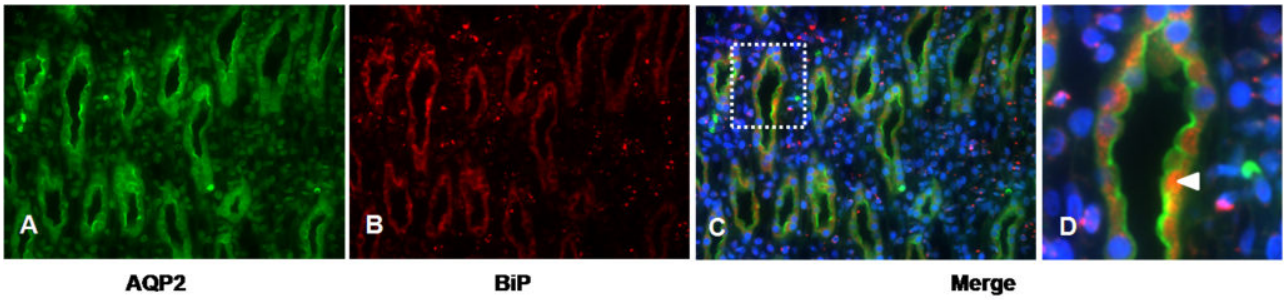

Fig. 1. Colocalization of BiP and AQP2 in rat inner medullary collecting duct principal cells. In the inner medulla, immunofluorescence showed that AQP2 (A) was labeled on the apical plasma membrane and intracellular domains (green), whereas immunolabeling of BiP (B) throughout the cytoplasm (red) was observed in the collecting duct principal cells. AQP2 and BiP are colocalized to collecting duct principal cells (C). At higher magnification (D), there is colocalization (arrowhead) of AQP2 and BiP and within the cytoplasm.

Abnormal regulation of AQP2 has been shown to be associated with some types of kidney diseases, one of which is called nephrogenic diabetes insipidus (NDI), due to inability of the kidneys to respond to vasopressin. Consequently, affected patients develop so-called polyuria, a phenomenon presenting constant, large volumes of dilute urine, and they always feel thirsty. Primary forms of NDI result from mutations in the AVP type-2 receptor or AQP2 genes, whereas secondary forms are usually associated with biochemical abnormalities, obstructive nephropathy or the use of certain medications, e.g lithium. Lithium is the classical and effective treatment in bipolar disorder and treatment-resistant depression.

Endoplasmic reticulum (ER) is an intracellular organelle where transmembrane, secretory, and ER

resident proteins are folded and matured. In many pathophysiological conditions, such as high blood glucose, abnormal blood fatty acid, disturbance of electrolytes etc, a lot of unfolded and misfolded proteins accumulate in the ER, which lead to protein toxicity and activate ER stress. During ER stress, the ER expands in size, synthesis of a certain type of protein attenuates, while degradation of these protein increases. This can lead to pathology as there is a decrease in essential proteins reaching the cell membrane and extracellular environment. To alleviate ER stress, the cell may synthesize some proteins acting as chaperons (e.g. BiP), which help protein folding and maturation. Some chemicals in nature such as 4-phenybutyric acid (4-PBA) are capable of attenuating ER stress. 4-PBA is a low molecular weight fatty acid which is reported to act as a molecular chaperone aiding in protein folding and trafficking, alleviating ER stress by reducing the load of misfolded proteins retained in the ER.

We recently found that lithium treatment resulted in increased urine output and decreased urinary osmolality, which was associated with reduced protein expression of AQP2 in inner medulla of kidneys from lithium-treated rats. All these were prevented by 4-PBA treatment. These findings suggested a potential occurrence of ER stress associated with lithium treatment in the kidney. Indeed, ER structure was damaged in inner medullary collecting duct principal cells in lithium treated rats with dilatation of cisternae and expansion of the ER, which indicates potential dysfunction of ER and thus reduced AQP2 synthesis. Interestingly, our imaging studies showed that increased protein expression of a molecular chaperone BiP colocalizes with reduced AQP2 expression in inner medullary principal cells of the kidneys from lithium-treated rats (Fig. 1).

We find that over-dose of lithium induces urinary concentration problems and reduced AQP2 protein expression, which is at least partially attributed to ER stress in renal inner medullary collecting duct principal cells. This finding may be helpful for understanding the cellular mechanisms and seeking a potential treatment strategy for NDI.

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