

New Genetic Approaches to Study Regulatory Mechanisms of Sodium·Water Balance

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Summary

A neurohypophysial hormone, arginine vasopressin (AVP) as well as oxytocin is known to an anti-diuretic hormone because AVP acts on V2 receptor in the kidney and reabsorb water in the systemic circulation. AVP is main regulatory system to maintain water balance via the central nervous system. The magnocellular neurosecretory cells (MNCs)-synthesizing AVP locate in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus, terminate their axon terminals to the posterior pituitary, and secrete AVP into the systemic circulation with depending on the firing rate of MNCs.

Recent development of chemogenetic techniques as well as optogenetic techniques have made a progress to understand the neural circuits in the central nervous system. In particular, these techniques have been widely used to understand the linkage between neuronal activity and diverse behaviors. Designer receptors exclusively activated by designer drugs (DREADDs) are the most common G-protein coupled receptors (GPCRs) used in chemogenetic approaches. Human muscarinic acetylcholine receptor (hM3Dq), of which ligand is Clozapine-N-oxide (CNO), is one of the pharmacologically modulated GPCRs which enables us to exploit Gq signaling pathway.

We generated a novel transgenic rat line which expresses both hM3Dq and mCherry fluorescence specifically in AVP-synthesizing neurons. The mCherry neurons that indicate the expression of the hM3Dq gene were observed in the PVN and the SON. The hM3Dq-mCherry fluorescence was localized mainly in the membrane of the neurons. The mCherry neurons were co-localized with AVP-like immunoreactive (LI) neurons, but not with oxytocin-LI neurons. The induction of Fos, which is the indicator for neuronal activity, was observed in approximately 90% of the AVP-LI neurons in the PVN and the SON 90 min^[11]_{SEP} after intraperitoneal (i.p.) administration of CNO. Plasma AVP was significantly increased and food intake, water intake, and urine volume were significantly attenuated after i.p. administration of CNO.

This novel DREADDs transgenic rat line that expresses the AVP-hM3Dq-mCherry fusion gene promise the future to provide new insights into the neuronal mechanism regarding AVP system responsible for the central regulation of sodium and water balance in whole body.