Studies on Na^+-dependent Glutamate transporter as a Regulatory Mechanism for Melatonin Synthesis

Yoshinori Moriyama
Department of Biochemistry, Faculty of Pharmaceutical Sciences, Okayama University, Okayama 700-8530, JAPAN
Tel and Fax: (81)-86-251-7933; E. mail: moriyama@pheasant.pharm.okayama-u.ac.jp

Melatonin is a hydrophobic hormone that affects many physiological functions, such as the circadian rhythm and seasonal reproduction. In mammals, melatonin synthesis is under photoperiodic control by way of the suprachiasmatic nucleus (SCN) of the hypothalamus. At night, the SCN sends stimulatory signals to the pineal gland through sympathetic neurons. Norepinephrine released from nerve endings binds to the adrenergic receptors on the plasma membranes of pinealocytes and activates adenylate cyclase through a heterotrimeric guanine-nucleotide-binding protein. The resultant increase in the concentration of cAMP stimulates the transcription of the serotonin *N*-acetyltransferase gene, causing stimulation of melatonin output. Thus, melatonin synthesis is positively controlled by sympathetic neurons. In contrast, exogenous L-glutamate inhibits synthesis and secretion of melatonin, suggesting a negative regulatory role of L-glutamate. We found that pinealocytes equip endogenous glutaminergic systems and use L-glutamate as a negative modulator for melatonin synthesis. The glutaminergic system is composed of machineries for glutamate signal output (exocytosis of glutamate), input (metabotropic glutamate receptor type 3-mediated inhibitory cAMP cascade), and termination. A plasma-membrane-type Na^+-dependent glutamate transporter is responsible for glutamate signal termination. Although several isoforms has been identfied so far, the pinealocytes Na^+-dependent glutamate transporter was found to be novel isoform. Although the pineal gland contains several cell species, no other cell types, including glial-like cells, express these transporters. The Na^+-dependent glutamate transporter seems to be involved in the regulation of melatonin synthesis.