The molecular mechanism of ouabain-evoked inhibition of synthesis of melatonin, a biological rhythm-producing hormone, in mammalian pineal glands.

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Summary

The mammalian pineal gland is a photoneuroendocrine transducer that rhythmically synthesizes and secrete melatonin at night in response to photoperiodic stimuli from endogenous circadian oscillators. In the rat, this process is positively regulated through sympathetic neurons projecting into the gland: norepinephrine secreted from nerve ending stimulates serotonin-N-acetyltransferase (NAT), a key enzyme for melatonin synthesis, resulting in the increased melatonin output. We have found that very low concentration of ouabain (50 nM), a specific inhibitor for Na^+/K^+-ATPase, strongly inhibits the NE-evoked melatonin synthesis. In the present study, we investigated the molecular mechanism of ouabain-evoked inhibition. At first, we have observed that degrees of ousbain-evoked inhibition of NAT and Na^+/K^+-ATPase are correlated to each other. Upon treatment of 50 nM ouabain, the NAT activity is strongly inhibited without affecting the level of mRNA of NAT gene, and of NAT protein. Thus, ouabain may inhibit NAT through posttranslational modification of the enzyme. It is possible that perturbation of membrane potential inhibits the expression of one tupe of 14-3-3 protein, resulting in inhibition of NAT through decreased its binding. Durinf the study, we have also noticed that NAT is controlled under redox switch. Amino acid residures involving in the redox switch and changes of 3D structures of NAT during conversion from active and inactive state will be presented.