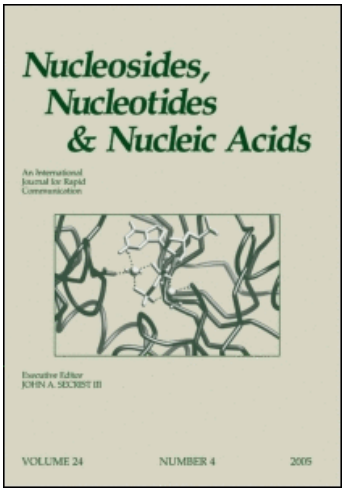

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P_1-Purinergic Receptor-Mediated Modulation of TSH Actions on FRTL-5 Thyroid Cells: Possible Switching From cAMP Pathway to Inositol Phosphate-Ca System

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P_1-PURINERGIC RECEPTOR-MEDIATED MODULATION OF TSH ACTIONS ON FRTL-5 THYROID CELLS: POSSIBLE SWITCHING FROM CAMP PATHWAY TO INOSITOL PHOSPHATE-CA SYSTEM.

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Abstract In thyroid cells, a P_1-agonist, via G_i like protein, enhanced a TSH-induced I^--efflux by intensifying a TSH-dependent inositol polyphosphate production followed by a Ca^{2+} mobilization, but diminished a TSH-dependent DNA synthesis by attenuating a TSH-dependent cAMP accumulation.

In FRTL-5 cells, a cell line derived from normal rat thyroid, TSH stimulates ^{131}I-efflux as a process of thyroid hormone synthesis, which is mediated by intracellular Ca^{2+} mobilization [1], and increase ^3H-thymidine incorporation into DNA as a process of growth promotion, which involves a stimulation of cAMP production [2]. Recently, we found that P_1-purinergic receptor agonists such as adenosine phenylisopropyladenosine (PIA) prevented an forskolin-dependent adenylate cyclase activation[3], but enhanced an α_1-adrenergic agonist-induced Ca^{2+} mobilization[4]. Both PIA actions were sensitive to an islet-activating protein (IAP), pertussis toxin treatment of the cells. This led us to examine the modulation of the TSH signal transduction by P_1-purinergic agonists.

One tenth μM PIA remarkable enhanced TSH-dependent ^{131}iodide efflux for 1 min from previously labeled FRTL-5 cells, whereas the P_1-agonist significantly reduced ^3H-thymidine incorporation into DNA for 24 hr. Both PIA effect completely disappeared after the treatment of the cells with IAP. To identify the action site of PIA in the signal transduction pathways for TSH, PIA modulations of the cAMP and Ca responses of to TSH were investigated. In the presence of 0.1 μM PIA, ^3H-inositol polyphosphate production induced by 10^{-8}M TSH and the intracellular Ca^{2+} increase

by graded doses of TSH were remarkably enhanced and the dose-response curve of Ca response shifted 1 to 2 orders to the left. The minimum effective dose of TSH was 10^{-10}M. Prior treatment of the cells with 50 ng/ml IAP abolished this PIA effect, indicating the participation of G_i or an IAP-sensitive G-protein(s). The Ca^{2+} response to TSH increased with PIA doses from 10^{-11} to 10^{-5}M, and its EC_{50} was around 10^{-8}M. On the contrary, PIA dose-dependently inhibited the TSH-induced cAMP accumulation in FRTL-5 cells. EC_{50} of PIA for the cAMP response was about one order lower than that for the Ca response. When 0.5 U/ml of adenosine deaminase was added to the reaction medium, as for at least one TSH action, the induction of cAMP accumulation was significantly enhanced. In IAP-treated cells, the level of TSH-induced cAMP accumulation reached that obtained by deaminase treatment of control cells, but no further increase was observed even when adenosine deaminase was added. These deaminase effects proved that endogenous as well as exogenous adenosine acts on FRTL-5 cells as an autocrine agent. When we consider a possible neuronal supply of adenosine in addition to the autocrine one, the present findings suggest that, in the thyroid, under certain conditions, an adenosine signal mediated by G_i-like protein switches a TSH signal from the cAMP pathway to the Ca^{2+} pathway (Fig. 1).

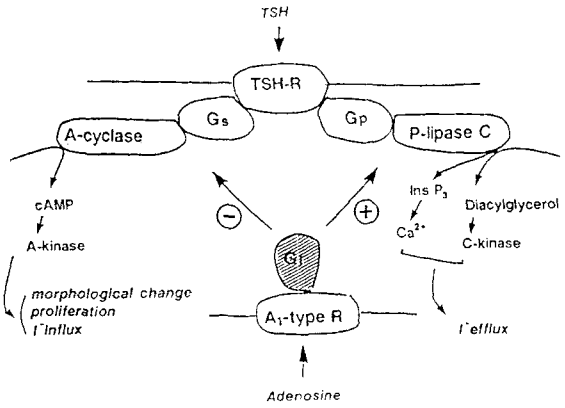

Fig. 1 Adenosine modulation of TSH actions

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