Continuous intravenous infusion of prostaglandin I2 (PGI2) analog, epoprostenol, has improved the survival rate for severe pulmonary hypertension, but longer treatment with PGI2 sometimes occurs hyperthyroidism. For the hyperthyroidism during PGI2 treatment, two molecular mechanisms are speculated; the direct effect of PGI2 on thyroid follicular cells via PGI2 receptor which is coupled with G-protein alpha subunit like TSH receptor, and the indirect effect of PGI2 on activated T helper 17 cells which are associated with autoimmune disease (1). Here, we experienced three different cases of hyperthyroidism during PGI2 treatment in pulmonary hypertension. In case 1, epoprostenol had been administered intravenously for about ten months before the onset of hyperthyroidism. TSAb became positive (591%) and technetium uptake was elevated (4.7%), which were similar to the typical observations in Grave’s disease. Total thyroidectomy was needed to control the thyroid function in case 1. In case 2, no thyroid antibody was detected and technetium uptake was almost vanished, as in the destructive thyroiditis. The thyroid function eventually normalized without any intervention. In case 3, hyperthyroidism occurred during oral PGI2 analog selexipag administration, but no evidence of Grave’s disease or destructive thyroiditis was observed. Hyperthyroidism was declined when the dose of selexipag was reduced. To investigate the molecular mechanism underlying each case, we added the drugs which were used in each case on a thyroid follicular cell line, FRTL5. The thyroid tissue which was resected in case 1 and FRTL5 cells expressed PGI2 receptors in immunohistochemistry and immunofluorescence study. Human thyrotropin alpha (TSH) and epoprostenol elevated the intracellular cyclic AMP (cAMP) in FRTL5 (1.33 fold and 1.20 fold each, P<0.05, n=3), but the other PGI2 analogs and the other drugs for pulmonary hypertension didn’t change the cAMP in FRTL5. The gene expression level of Na/I symporter was up-regulated only by TSH (2.39 fold, P<0.02, n=3), but not by PGI2 analogs in qPCR study. It is suggested that PGI2 increases the intracellular cAMP in thyroid follicular cells, but does not cause the same genetic changes as TSH. In conclusion, PGI2 analog may not directly affect the thyroid hormone synthesis in follicular cells, but further analysis is needed to elucidate the molecular mechanism underlying hyperthyroidism during PGI2 analog treatment. Reference: (1) Satoh et al., Endocrine Journal 2017,64(12),1173-1180

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