Interaction between Endocrine and Immune System
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Close communication between endocrine system and immune system has been increasingly recognized. Firstly, as demonstrated for glucocorticoids which inhibit most of immune responses, many hormones modify immune reactions. Secondly, a number of cytokines produced by immunocompetent cells has been shown to modulate growth and functions of endocrine cells. Furthermore, it has been shown that immunocompetent cells are able to secrete classical hormones and express their receptors, suggesting that these hormones may have autocrine/paracrine roles in regulating growth and functions of these cells. Finally, endocrine cells are frequently sites of autoimmune reaction, causing a number of autoimmune diseases such as Graves' disease, Hashimoto thyroiditis or insulin-dependent diabetes mellitus (IDDM).

Thyroid and cytokines
Graves' disease or Hashimoto disease is a typical autoimmune disease and a number of autoantibodies such as anti-thyroglobulin antibody, anti-thyroid peroxidase antibody and antibody to TSH receptors called TRAb can be detected in sera of these patients. It is very likely that a number of cytokines are involved in these autoimmune thyroid diseases. Interferon α or γ has been frequently used for treatment of C-type hepatitis. However, many undesired side-effects have been recognized, including autoimmune thyroid disease, IDDM, depressive state and so on. In our experience, 9 patients out of 109 hepatitis patients treated INF-α developed autoimmune thyroid diseases (Graves' disease 2, painless thyroiditis 3, primary hypothyroidism 4). Six patients were positive for autoantibody
to thyroid antigens before treatment with IFN-α, and the titers increased significantly in association with development of autoimmune thyroid diseases. INF-γ has been shown to induce HLA-DR antigen in thyroid epithelial cells, which may trigger immunologic responses in the cells. However, the mechanism that IFN-α induces autoimmune thyroid disease is not clear, because IFN-α lacks the ability to induce DR antigen. We have shown that both IFN-α and IFN-γ transiently inhibit iodine metabolism stimulated by TSH in vitro. It is not clear whether this direct inhibitory effect of IFNs is related to development of autoimmune thyroid diseases.

Another cytokines, specially interleukin (IL)-1 as well as IL-6 have potent effects on thyroid functions. When given in rats or mice intravenously, serum TSH levels transiently decreased and serum T3 and T4 remained low over 24 h. On molecular basis, IL-1 was much more potent compared to IL-6. Expression of mRNA of hypothalamic TRH pituitary TSH-β were not affected by IL-1 or IL-6. There was no change in hypothalamic somatostatin content in IL-1 or IL-6 treated rats. TSH responses to TRH in pituitary cells cultured in monolayers were also not attenuated in the presence of these cytokines. Presumably, inhibition of TSH secretion by these cytokines is mediated by production of corticosterone which was stimulated by CRH-ACTH system. Both IL-1 and IL-6 inhibit TSH-induced iodide uptake, its organification and expression of mRNA of thyroid peroxidase in vitro in a non-cAMP dependent manner. Furthermore, IL-1 modified activity of 5'-deiodinase activity. Thus, both IL-1 and IL-6 affected thyroid functions by acting on multiple sites of TRH-TSH-thyroid axis. These results may account for the abnormality of thyroid functions frequently seen in patients with infection, malnutrition, stress and
other chronic diseases (euthyroid sick syndrome).

**Adrenal gland and cytokines**

CRH-ACTH-Adrenal axis is also very sensitive to various exogenous and endogenous cytokines. The major cytokines involved in the stimulation of the axis are IL-1, IL-6 and tumor necrosis factor (TNF)-α. Administration of these cytokines in human produces a marked elevation of plasma ACTH and cortisol levels. Animal studies have suggested that the cytokines-mediated secretion of ACTH is mediated by stimulation of hypothalamic CRH. There is no direct effect of the cytokine on secretion of ACTH from pituitary cells. Glucocorticoids stimulated by cytokines may, in turn, act on immunoregulatory cells and inhibit overresponses to cytokines. It, thus, appears that there is a kind of negative feedback mechanism between CRH-ACTH-Adrenal axis and immune system. Recent studies have demonstrated that IL-1 or IL-6 is produced by central nervous system including hypothalamus and pituitary, but physiological significance is not known. In addition, immunocompetent cells can produce CRH and ACTH, which is stimulated by endotoxins and is suppressed by cortisol, indicating that there is a regulation system similar to that seen in pituitary-adrenal axis.

In summary, a number of cytokines directly or indirectly modify functions of endocrine tissues and could induce transient or permanent endocrine disorders. These side effects should be kept in mind in the use of cytokines or antagonists for treatment.