CLINICAL STUDY

Involvement of circulating interleukin-6 and its receptor in the development of euthyroid sick syndrome in patients with acute myocardial infarction

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Abstract

Objective: In patients with acute myocardial infarction (AMI), low triiodothyronine (T3) levels with normal or subnormal levels of thyrotropin (TSH), the euthyroid sick syndrome (ESS), have been reported, however, the mechanism of altered thyroid hormone metabolism is unknown. Recent reports have shown that interleukin-6 (IL-6) plays a key role in the pathogenesis of AMI and ESS. This preliminary study investigates the relationship between thyroid states and plasma levels of IL-6, the soluble IL-6 receptor (sIL-6R), and the soluble transducing 130 kDa glycoprotein (sgp130) in AMI.

Design and methods: We measured the concentration of TSH, free T3 (FT3), free thyroxine (FT4), IL-6, sIL-6R and sgp130 in plasma from 24 patients with AMI and 20 normal controls.

Results: All 24 AMI patients showed significantly lower concentrations of FT3 with normal or subnormal levels of TSH, and higher concentrations of IL-6 and sIL-6R than controls. IL-6 level was correlated with creatine phosphokinase (CPK) and FT3 levels but not with FT4 or TSH levels in patients with AMI. The time course of IL-6 and FT3 concentration seemed to be closely linked. sIL-6R level was correlated with CPK and sgp130 levels, but not with FT3, FT4 or TSH levels. FT4 level was correlated with sgp130 level.

Conclusion: Patients with AMI develop ESS through activation of IL-6 and its receptor system.

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Introduction

Alterations in thyroid hormone metabolism occur in patients with acute myocardial infarction (AMI) (1–5). This phenomenon, called euthyroid sick syndrome (ESS), is observed in patients with systemic diseases and may have a protective function (6, 7). It has recently been hypothesized that interleukin-6 (IL-6), a pleiotropic cytokine, has a causal role in the development of ESS in patients with systemic diseases (8–15). There is also increasing evidence to support IL-6 induction in AMI (16–19), and myocardial ischemia–reperfusion-induced IL-6. IL-6 receptor and gp130 expression in rats (20). These data suggest that the low triiodothyronine (T3) syndrome in AMI may partly be explained by an elevation of circulating IL-6. Binding of IL-6 to the soluble IL-6 receptor (sIL-6R) inhibits thyroid function, however, gene expression of IL-6 and gp130 but not IL-6R has been shown in human thyroid follicles (21). Thus, IL-6 may exert an inhibitory effect on thyroid function mainly through binding of the IL-6–sIL-6R complex to gp130. Recent data suggest that sIL-6R potentiates the antagonistic activity of soluble gp130 (sgp130) on IL-6 responses (22). In the case of ESS, there has so far been no investigation of the relationship between thyroid function, IL-6, and its receptor system, sIL-6R and sgp130. This preliminary study is the first report of close linking between thyroid function and the IL-6 binding system in patients with AMI.

Materials and methods

Patients and specimens

Twenty-four patients (20 men, 4 women; 45–79 years) admitted to Fujioka Hospital within 6 h of the onset of AMI symptoms and 20 healthy controls (16 men, 4 women; 45–55 years) were enrolled after informed consent was obtained. In patients with AMI, informed consent was obtained on admission and percutaneous transluminal coronary angioplasty (PTCA) was performed immediately. Subjects were free of collagen diseases, liver disease, renal failure, malignancy,
infection, thyroid disease, antithyroglobulin antibodies, antithyroidperoxidase antibodies, or antithyrotropin receptor antibodies. The diagnosis of AMI was based on chest pain resistant to nitroglycerin, electrocardiographic ST-segment elevations in >2 leads with or without Q-wave formation, and significant increases in plasma creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels. The MB isozyme of CPK, a relatively specific indicator of myocardial damage, was elevated by >5% in all 24 patients. Blood specimens were drawn from the femoral vein on admission and every 12 h until 120 h after admission. Plasma was centrifuged for 15 min at 3000 c.p.m. at 4 °C and stored at −80 °C until assayed.

Measurement of plasma contents

IL-6 concentration was measured by a chemiluminescent enzyme immunoassay kit (Fujirebio, Tokyo, Japan). Soluble IL-6 receptor concentration was measured by an enzyme-linked immunosorbent assay (Bender Medsystems, Vienna, Austria). Soluble gp130 concentration was measured by an immunoenzymometric assay (Medgenix Diagnostics S.A., Fleurus, Belgium). Normal ranges were as follows: IL-6, <1.5 pg/ml; sIL-6R, 25–91 ng/ml; and sgp130, 280–620 ng/ml. Thryrotropin (TSH), free T₃ (FT₃), and free thyroxine (FT₄) concentrations were measured by enzyme immunoassays (Sanyokasei, Kyoto, Japan). CPK and LDH concentrations were measured by autoanalyzer.

Statistical analysis

Data are presented as means ± s.d. Statistical analysis was performed using Student’s unpaired t-test or linear regression. A level of P < 0.05 was accepted as significant.

Results

In all 24 patients with AMI the mean overall plasma levels of CPK, IL-6 and sIL-6R were significantly increased, while the FT₃ level was significantly decreased compared with controls (Table 1). TSH and FT₄ levels were decreased after onset of AMI, and both subsequently recovered to the normal range. In patients with AMI, the minimum levels of TSH were significantly decreased (P < 0.05, 0.64 ± 0.15 μU/ml; 25 ± 11 h after onset of AMI) compared with controls. Circulating levels of IL-6 were already elevated at admission, then increased to the maximum level. The time course of IL-6 and FT₃ concentration seemed to be closely linked (Fig. 1A). IL-6 concentration had increased maximally (50 ± 24 pg/ml) 75 ± 46 h after onset of AMI, while FT₃ concentration had decreased minimally (1.4 ± 0.4 pg/ml) 76 ± 43 h after onset of AMI. Two patients showed subnormal levels of FT₄, but no overall significant decline was observed compared with controls. The plasma levels of sIL-6R and sgp130 gradually decreased from admission to the end of the study. In AMI patients, the FT₃ level was subnormal, but both TSH and FT₄ levels were within the normal or subnormal range (Table 1). This hormonal state was characteristic of ESS.

The CPK level was positively correlated with IL-6 (Fig. 2A) and sIL-6R (Fig. 2D) levels. IL-6 concentration was inversely related to FT₃ concentration (Fig. 2B) and FT₄/FT₃ ratio (Fig. 2C), but not to FT₄ or TSH levels in AMI. The sIL-6R level was negatively correlated with FT₃ (Fig. 2B) and sgp130 level (Fig. 2E), but not with TSH, FT₃, or FT₄ levels in AMI. Plasma levels of sgp130 were the same as control levels (Table 1), and a significant relationship was detected between sgp130 and FT₄ levels in AMI (Fig. 2F). These significant relationships were obtained by analysis of overall data from admission to 120 h after onset of AMI. Then we analyzed these data according to the time after onset of AMI (group 1: 12 h and 24 h after onset of AMI; group 2: 36 h and 48 h after onset of AMI; group 3: 60 h and 72 h after onset of AMI; group 4: 84 h after onset of AMI). The IL-6 level was negatively related to TSH level (Fig. 1B) in group 1, but no significant relationship was detected between IL-6 and TSH levels in other groups. On the other hand, the IL-6 level was negatively correlated to FT₃ level and FT₄/FT₃ ratio in all groups (P < 0.05, respectively). Total data are shown in Fig. 2B and C. Similarly significant relationships between sIL-6R and sgp130 levels, and between sgp130 and FT₄ levels were detected in all groups (P < 0.05, respectively). Total data are shown in Fig. 2E and F.

Discussion

This preliminary study indicates that IL-6 and sIL-6R may be pathogenic factors in the development of ESS in AMI.
Recent reports have shown a negative correlation between T₃ and T₄ levels and the level of IL-6 (8, 13–15). IL-6 given to cancer patients decreases serum T₃ and TSH levels, but not T₄ level (23). Production of IL-6 is induced by IL-1 or tumor necrosis factor α (TNFα) (24), and a direct effect of IL-1 and TNFα on thyroid function has been reported (25–30). Administration of IL-1 and TNF to rodents or humans causes ESS (25, 26, 31). These cytokines may assist in the onset of ESS in AMI, although we did not determine plasma levels of them. IL-6 is produced by many cell types, including monocyte/macrophages, fibroblasts, endothelial cells, mast cells, neutrophils, keratinocytes, and osteoblasts (32). Expression of IL-6 mRNA has been confirmed in cultured thyroid follicles (21) and ventricular myocytes (19). Recently, induction of IL-6, IL-6R, and gp130 expression in rats cardiomyocytes after reperfusion from brief ischemia has been shown (20). In patients with AMI significant correlation between levels of CPK and both IL-6 and sIL-6R suggest that both IL-6 and sIL-6R in AMI patients are released from both inflammatory cells and cardiomyocytes. In addition, the time course of IL-6 and FT₃ seemed to be closely linked and a strong relationship between IL-6 and FT₃ was detected in AMI. These findings suggest involvement of IL-6 and its receptor system in the pathogenesis of ESS in patients with AMI. Thus acute cardiac damage may affect thyroid states through activating IL-6 and its receptor system in AMI.

Yamazaki et al. (1996) could not detect IL-6 receptor mRNA in cultured human thyroid follicles, and they indicated that sIL-6R exerted the inhibitory effects of
IL-6 on thyroid cells (21). All of our patients with AMI showed elevated levels of sIL-6R, yet no significant correlation between sIL-6R and TSH, FT₃, or FT₄ was detected. In this regard, elevated sIL-6R levels may be necessary but insufficient alone to exert the inhibitory effects of IL-6. Further study is required to determine the role of sIL-6R in the pathogenesis of ESS.

The IL-6–sIL-6R complex affects thyroid function in cultured human thyroid follicles through binding to gp130 (21). Muller-Newen et al. (1998) reported that sgp130 antagonizes the effect of the IL-6–sIL-6R complex and that this antagonistic effect is enhanced by sIL-6R in cells lacking membrane-bound IL-6R (22). Thus sgp130 may antagonize the inhibitory effects of IL-6 binding to sIL-6R on thyroid function in thyroid follicles that lack IL-6R (21). This hypothesis is supported by the result that elevation of IL-6 and sIL-6R and normal levels of sgp130 were detected in AMI. The negative relationship between sIL-6R and sgp130 also supports the hypothesis. In this regard, the positive relationship between sgp130 and FT₄ might be caused by an inhibitory action of sgp130 on the IL-6–sIL-6R complex. Two questions remain unanswered. Does sgp130 antagonize the inhibitory effects of the IL-6/sIL-6R complex? And does sIL-6R enhance the antagonistic effects of sgp130 on thyroid cells?

Administration of IL-6 briefly but significantly decreased TSH levels in cancer patients (23). In our study, the plasma level of TSH was significantly decreased after the onset of AMI and then recovered, similar to the findings of Stouthard et al. (1994). Additionally, TSH level was negatively correlated to IL-6 level in the first 24 h after onset of AMI. These facts suggest that the decline in plasma TSH was also associated with an elevated IL-6 level. The gradual recovery of plasma TSH, however, occurred whilst plasma IL-6 was still elevated. This may suggest that circulating TSH is affected by IL-6 and other factor(s) in AMI. TSH is a key factor which stimulates thyroid hormone production and release by thyroid cells. The low circulating level of FT₃ cannot be explained by
changes in TSH alone in patients with AMI. Thus, IL-6 may affect thyroid metabolism at both pituitary and thyroid levels.

Patients with a decrease in serum T3 alone, representing the mildest form of ESS, do not show clinical signs of hypothyroidism (7). IL-6 inhibits thyroid hormone conversion of T4 to T3 by blocking 5'-deiodinase activity or mRNA expression (9, 33, 34), suggesting that the development of ESS in AMI is induced by an effect of IL-6 on both the pituitary–thyroid axis and peripheral conversion of thyroid hormone. Altered thyroid hormone homeostasis in ESS is related to an increase in reverse T3 (rT3) levels (7, 8, 23). We did not determine circulating levels of rT3, however, fact that FT3, but not FT4, decreased significantly might suggest an increase in rT3 levels in AMI. In this regard, the negative relationship between IL-6 level and FT3/FT4 ratio represents the mildest form of ESS in AMI. In some conditions, there is a gradual progression from a low T3 level to an advanced illness with extremely low T3 and T4 levels, which can be associated with high mortality (7). Similarly excessive decreases of T4 are linked with increasing mortality in AMI (4, 35). In this study two patients with subnormal levels of FT4 were graded Killip IV (Killip’s classification). Circulating levels of FT3 and FT4 in patients with AMI classified Killip IV were significantly lower than those of Killip I (Table 2), and those patients received catecholamine treatment. These findings support the idea that excessive decreases of T4 are linked with seriousness of AMI. In this regard, catecholamine administration might affect circulating levels of FT4 in AMI, similar to findings of former investigations (36, 37). Previous reports have not defined a role for IL-6 in progression to low circulating levels of T4. In this regard, the positive relationship between sgp130 and FT4 levels may reflect a self-protective action for providing progression of low FT4 in AMI. This raises the question of whether circulating levels of FT4 relate to sgp130 in severe cases of AMI.

In conclusion, our results suggest that acute cardiac damage leads to development of ESS through activation of IL-6 and its receptor system.

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