α-Lipoic Acid and Insulin Autoimmune Syndrome

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Insulin autoimmune syndrome, a relatively rare cause of hypoglycemia, is characterized by the production of autoantibodies to insulin in individuals who have not previously been injected with this hormone (1). Drug-induced autoimmunity appears to be important in the pathogenesis of this syndrome, given that ~50% of affected individuals have taken certain drugs, most of which (such as methimazole, α-mercaptopropionyl glycine, or glutathione) contain the sulfydryl group, before its onset (1). We now report a case of insulin autoimmune syndrome likely induced by α-lipoic acid (ALA), a reduced form of which contains the sulfydryl group (2).

RESEARCH DESIGN AND METHODS

— A 32-year-old Japanese woman visited Ishida Clinic on 1 June 2005 because of a feeling of weariness before lunch and dinner. This symptom, which first occurred on 23 May 2005, was relieved by ingestion of the meal. The patient had been well until the onset of the preprandial weariness, had never been injected with insulin, and had no family history of metabolic, hormonal, or autoimmune diseases. Her weight was 60 kg and height 155.4 cm.

The patient's plasma glucose levels during a 75-g oral glucose tolerance test (OGTT) (59, 154, 207, and 227 mg/dl at 0, 30, 60, and 120 min after glucose ingestion, respectively) performed on 3 June 2005 were consistent with a diagnosis of diabetes, whereas her A1C level was low (4.5%). Serum concentrations of insulin during the test were high (2,390, 2,580, 3,730, and 5,680 μU/ml, respectively) (see online appendix [available at http://dx.doi.org/10.2337/dc07-0689]). The subject manifested the feeling of weariness at the clinic on 8 June at 11:00 A.M., and it disappeared rapidly after intravenous injection of glucose. Plasma glucose, serum insulin, and serum C-peptide immunoreactivity levels immediately before the glucose injection were 44 mg/dl, 2,180 μU/ml, and 8.6 ng/ml, respectively. Before symptom onset, the patient had not regularly taken any medication or supplement with the exception of ALA (200 mg/day), which she had started to take at the beginning of April 2005. She was instructed to discontinue ALA, and the symptom disappeared by the end of June 2005. She was referred and admitted to Kobe University Hospital on 5 July 2005 for a checkup because of her increased plasma glucose and serum insulin concentrations.

RESULTS

— A 75-g OGTT performed after admission revealed that her glucose tolerance was impaired (plasma glucose of 69, 74, 160, 196, and 146 mg/dl at 0, 30, 60, 120, and 180 min, respectively) and that her serum insulin levels were greatly decreased compared with those of a month ago but were still relatively high (664, 594, 991, 1,650, and 1,580 μU/ml, respectively). Antibodies to insulin were detected (insulin binding ratio 81.8% and free insulin 10 μU/ml at 0 min of the OGTT), and Scatchard plot analysis revealed that the affinity of the antibodies was low and their binding activity high (Table 1), which are common characteristics of anti-insulin autoantibodies observed in insulin autoimmune syndrome (3–5). HLA typing revealed the patient to have the DRB1 *0406 allele, which confers a high level of susceptibility to this syndrome (6,7). Antibodies to the insulin receptor or to DNA were not detected, whereas immunofluorescence analysis revealed a low level of anti-nuclear antibodies. Serum levels of thyroid hormone, glucocorticoid, and catecholamine were normal. Computed tomography revealed no abnormalities of the abdomen or pelvis. The patient did not manifest hypoglycemia after admission, even after fasting for 48 h, and was discharged on 9 July 2005. A 75-g OGTT performed on 15 December 2005 indicated that she was normoglycemic (plasma glucose of 90, 123, 110, and 109 mg/dl at 0, 30, 60, and 120 min, respectively) and that her serum levels of insulin were within the normal range (9 μU/ml at 0 min of the OGTT). Antibodies to insulin were still present, but the titer was greatly decreased (binding ratio 32.0% and free insulin 8 μU/ml).

CONCLUSIONS

— The subject developed spontaneous hypoglycemia and was found to have antibodies to insulin after the regular intake of ALA, which contains a disulfide binding in its molecule and, when reduced in vivo, produces a sulfydryl group (2) (online appendix). After cessation of intake of the supplement, the hypoglycemia disappeared, and the titer of the anti-insulin antibodies was markedly decreased. The patient possesses an HLA genotype that confers susceptibility to insulin autoimmune syndrome, and the kinetic properties of her anti-insulin antibodies were consistent with those of such antibodies in individuals with this syndrome. Although the major presenting manifestation of insulin autoimmune syndrome is spontaneous hypoglycemia, the concomitance of glucose intolerance,

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Abbreviations: ALA, α-lipoic acid; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Three cases of insulin autoimmune syndrome thought to be related to intake of ALA*

	Subjects		
	44 years old, female	55 years old, male	32 years old, female
Onset	August 2005	November 2005	May 2005
Duration of intake before onset	3 months	1 week	2 months
Peak IRI (μU/ml)	538	2,531	5,860
Kinetics of antibodies			
Affinity (K1, 10^8 M^{-1})	0.089	ND	0.0894
Binding (B1, 10^{-8} M)	10.0	ND	10.9
DRB1 *0406	+	+	+
Purpose of intake	Health supplement	Weight loss	Cosmetic
Reference no.	5	9	Present case

IRI, immunoreactive insulin; ND, not determined.

as observed in the present case, has been described (8).

Two additional cases of insulin autoimmune syndrome possibly related to the ingestion of ALA in Japan were recently reported (5,9) (Table 1). In these cases, antibodies to insulin and hypoglycemia manifested after the ingestion of ALA and disappeared rapidly after cessation of its intake. Since insulin autoimmune syndrome was first described in 1970 (10), no case of the syndrome associated with the ingestion of ALA was reported until 2006. In Japan, ALA had been sold only as a medicine until June 2004, when the Ministry of Health, Labor, and Welfare of Japan reclassified it as a food. The increased availability of ALA thus likely explains the recent appearance of insulin autoimmune syndrome associated with its ingestion.

ALA is a potent antioxidant and is thought to have therapeutic potential for the treatment of several conditions including atherosclerosis, diabetes complications, and inflammation (11–15). Moreover, it appears to exert an anorectic effect, at least in rodents, by modulating AMP-activated protein kinase in the hypothalamus (16). Indeed, in the case of insulin autoimmune syndrome reported by Takeuchi et al. (9), the subject took ALA for such an effect. Although ALA has potential applications in both alternative and conventional medicine (as well as in cosmetics), it is important to be aware that the ingestion of this compound may trigger insulin autoimmune syndrome in East Asians and in some North American natives, among whom the prevalence of HLA alleles that confer predisposition to this syndrome is relatively high (17).

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