Serum Growth Hormone and Insulin-Like Growth Factor-1 Concentrations in Japanese Black Cattle with Growth Retardation

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ABSTRACT. Serum concentrations of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) were determined in 5 calves in the same lineage with growth retardation. They had normal appetites, activities, body proportion, and laboratory test results. Calves with growth retardation had higher serum GH concentrations and lower serum IGF-1 concentrations. These findings suggested defects in the GH-IGF-1 axis, such as in the GH-receptor.

KEY WORDS: growth hormone, growth-retarded cattle, insulin-like growth factor-1.

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The growth of animals is regulated by many hormones and growth factors acting both in an endocrine (systemic) and autocrine/paracrine (local) manner, and requires the coordinated action of several hormones; growth hormone (GH, somatotropin), insulin-like growth factor-1 (IGF-1, somatomedin), thyroid hormone, insulin, leptin, glucocorticoid and sex steroids. Of these, the somatotrophic (GH to IGF-1) axis is the most important hormonal system for growth, primarily consisting of GH, IGF-1, their carrier proteins and receptors [3, 16].

Considerable numbers of cattle with growth retardation have been produced in populations of Japanese cattle [6]. Most of them are considered to result from infectious diseases such as pneumonia, diarrhea or parasitic diseases [9]. The cattle with hereditary diseases [17, 18] showed signs of prostration, anorexia and/or typical abnormal body shape in addition to growth retardation. We observed some Japanese Black cattle with marked growth retardation despite normal activity, appetite and proportional body shapes. In order to clarify the cause of growth retardation in these cattle, we determined the serum GH and IGF-1 concentrations in them.

Five Japanese Black calves with growth retardation were used. Their ages ranged from 3 to 13 months. Two calves were males and 3 were females. These calves were of the congenital strain (Fig. 1). Their father was in consensus, YIH, and the paternal grandfather was YF. The maternal grandfather was also YF in 4 calves (Nos. 4371, 4374, 4441 and 4451) and TM in 1 calf (No. 4315). DIZ was the maternal grandfather of YIH, and the father of TM. Nos. 4374 and 4451 were full sibs. Their dam delivered 2 affected calves at the 4th and 5th deliveries, consecutively, mating with YIH. Four dams of the calves with growth retardation had procreated 10 normal calves mating with other sires before mating with YIH. The sire YIH produced 100 calves during 2 years (1997 to 1998) by artificial inseminations in

the G region, and 9 calves (9.0%) were dwarfs. Gestations of all 5 calves were normal (288–295 days). They were delivered normally, and neonatal body weights (BW) were normal or slightly below (20 to 26 kg) [2]. These calves showed normal growth with no abnormal clinical signs until 3 or 4 months of age. At the first examinations, 3 calves (Nos. 4315 (160 kg in BW, 13 months of age), 4374 (144 kg in BW, 10 months of age) and 4441 (76 kg in BW, 5 months of age)) showed normal signs of appetite and activity, with no abnormal signs such as obesity, diarrhea, cough or nasal discharge. Two calves (Nos. 4371 (160 kg in BW, 11 months of age) and 4451 (44 kg in BW, 3 months of age)) had mild nasal discharges, but they recovered without treatment or after administration of an antibiotic for a few days. As controls, Japanese Black cattle of the same age with normal growth were used. The numbers of control cattle were shown in each table and figure.

Laboratory tests were performed by the standard procedures. Serum total thyroxine (tT₄) and total tri-iodothyronine (tT₃) concentrations were determined by radioimmunoassays (SPAC T₄ RIA Kit and SPAC T₃ RIA Kit, respectively, Daiichi Radio Isotope Lab., Ltd., Tokyo). As a thyrotrophin-releasing hormone (TRH) stimulating test, serum tT₄ concentrations were determined before and 6 hr after intravenous administration of bovine TRH (TRH Injection TANABE, Tanabe Pharmaceutical Co., Ltd., Osaka) at 0.5 mg/head [10]. The serum IGF-1 concentration was determined by immunoradiometric assay (Somatomedin C II Bayer, Yuka Medias Co., Ltd., Ibaraki, Japan). Serum concentrations of GH were measured by radioimmunoassay [11] every 15 min for 10 hr. A computer-assisted pulse analysis program (PULSAR) [15] was used to assess the pattern of GH secretion.

As shown in Table 1, No. 4451 had an increase in the WBC count and a slightly lower phosphorus concentration. No. 4374 had slightly lower serum sodium and chloride con-

Table 2. Serum thyroid hormone concentrations

Group	Cattle No.	Basal serum tT_3 concentration (ng/dl)	Serum tT_4 concentration (μ g/dl)	
			Basal	After TRH stimulation
Control (n=15)	Mean	136	4.9	8.2
	SD	34	1.5	2.1
Growth retardation	4315	50	<1	5.3
	4371	60	2.5	6.2
	4374	50	2.6	5.8
	4441	130	5.8	7.5
	4451	<10	<1	2.9

tT_3 : Total tri-iodothyronine, tT_4 : total thyroxine, TRH: thyrotrophin-releasing hormone.

Age: age at the determination, SD: standard deviation.

tT_4 after TRH stimulation: 6 hr after administration of TRH (TRH stimulation test).

TRH stimulation test was carried out in 3 control cattle. Mean $\pm$ SD of tT_4 before stimulation in 3 control cattle was 4.6 ± 1.9 (μ g/dl).

ease. A low IGF-1 concentration despite a high GH level suggests a low expression or defect in GH receptors, or abnormality of post-receptor mechanisms, as well as molecular defects in GH. There are many possible reasons for this phenomenon. In human patients with Laron syndrome [13], a noncontiguous loss of exons 3, 5 and 6 [5] or a series of mutations in the extracellular domain of the GH receptor [19, 21] were revealed. Miniature Bos Indicus cattle, which had characteristics similar to human Laron type dwarfism, had reduced expressions of mRNAs of GH receptor 1A in the liver [13]. Molecular abnormalities in GH, which had low biological activity despite an immunological determination system recognizing them as normal, were reported in dwarf humans [20]. Moreover, regulatory mechanisms for expressions of GH receptors [1] may be abnormal. Although the real reason for dwarfism in the calves in the

present study was not determined, it is possible that the abnormality may be limited to the growth stages. Even if the abnormality is transient, however, growth retardation is a serious defect in beef cattle. The growth promoting effects of GH are actually due to IGF-1 acting on its target organs, bones and muscles. It has been considered that the plasma IGF-1 concentration is directly related to growth in mammals [3, 16]. In any case, the retardation may be due to a low serum IGF-1 concentration in the cattle in the present study.

The data on pedigree suggested the role of heredity in growth retardation, but the sire YF and his offspring were used intensively in the region, and only 9 calves were produced as dwarfs by matings between sire YIH and different dams that were daughters of YF, so that we could not ascertain whether the disease was hereditary.

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Fig. 2. Serum IGF-1 concentrations in control and growth-retarded cattle.

Fig. 3. Serum growth hormone concentrations determined every 15 min for 10 hr.

Table 3. Analysis of serum growth hormone concentrations sampled every 15 min for 10 hr by PULSAR

Group	Cattle No.	Baseline concentration (ng/ml)	Maximum concentration (ng/ml)	AUC (ng/min/ml)	Peak number (/10 hr)	Peak amplitude (ng/ml)	Peak duration (min)	Peak frequency (number/min)	Peak interval (min)
Control (n=4)	Mean	3.25	8.88	2811	8.5	3.64	40.73	0.014	76.21
	SD	0.65	3.40	1275	0.6	1.17	27.92	0.001	50.31
Growth retardation	4315	10.26	54.63	9637	9	15.68	40.00	0.015	73.13
	4371	7.67	13.25	5021	5	5.20	18.00	0.010	86.25
	4441	24.07	46.93	18226	3	26.24	70.00	0.005	270.00
	4451	8.04	48.63	9352	7	20.66	62.14	0.012	92.50

PULSAR: Computer-assisted pulse analysis program.

AUC: Area under concentration curve, SD: standard deviation.

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