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Abrupt pubertal elevation of DNase I gene expression in human pituitary glands of both sexes

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Abstract Deoxyribonuclease I (DNase I) was confirmed to be expressed in the human pituitary gland, particularly the anterior lobe, at levels comparable to those in the pancreas. The DNase I activity and the amount of gene transcript present in the pituitary glands of individuals aged from 1 month to 89 years was significantly age-dependent, with an abrupt elevation after the neonatal and prepubertal periods irrespective of gender, followed by a gradual age-dependent decline in males and a marked reduction in females in their postreproductive period. This DNase I age dependence in the pituitary gland was not present in the pancreas and serum. These observations suggest that tissue-specific up-regulation of DNase I gene expression in the pituitary gland occur, possibly at the onset of puberty.

Key words: Age-dependent alteration; Deoxyribonuclease I; Gene expression; Pituitary gland; Puberty; Human

1. Introduction

The primary role of deoxyribonuclease I (DNase I, EC 3.1.21.1) has been considered to be the digestion of DNA for nutritional purposes. However, a recent report [1] which showed that the absence of DNase I activity may be a critical factor in the initiation of systemic lupus erythematosus suggested that the enzyme has some other physiological function(s) in vivo. One of its proposed roles is DNA breakdown during apoptosis, leading to cell death in a gene-controlled manner [2,3]. Our comparative studies of lower to higher vertebrates with regard to tissue distribution of DNase I demonstrated that the enzyme also exists outside exocrine glands of the alimentary tract, such as in the pancreas and/or parotid gland [4–6]. Recently, we have found that somatostatin induces a transient down-regulation of DNase I in rat lower gut and serum through effects on its gene expression, but not in the parotid gland which exhibits the highest activity among rat tissues [7]. Somatostatin is known to inhibit endocrine secretion by the pituitary gland [8], reducing levels of DNase I activity by 50%. Also, up-regulation of DNase I activity in rat prostate has been observed following androgen withdrawal by castration [9]. From these findings we postulate that DNase I activity coupled to endocrine secretion could be controlled in a hormone-dependent manner. In this context, information on physiological changes in DNase I activity in the endocrine glands, such as the pancreas and the pituitary gland, in which a substantial DNase I activity could be observed in our preliminary survey [4–6], may be required for elucidation of potential hormonal regulation of the enzyme.

In this study, we confirmed the presence of DNase I in human pituitary gland and examined the age-related distribution of DNase I activity and the gene transcript present in paired samples of human pituitary gland and pancreas. The results lead us to conclude that the pituitary DNase I is regulated in an age-dependent manner, possibly through its gene expression.

2. Materials and methods

2.1. Biological samples and materials

Paired samples of human tissues including pituitary gland and pancreas were obtained at autopsy from individuals (aged from 1 month to 89 years) within 15 h after death and stored at −80°C until use. All the samples showed no pathological changes. A few samples of the pituitary gland were divided into two portions: from the anterior and posterior lobes. Also, serum samples were collected from healthy Japanese individuals. Specific antibodies against human DNase I were prepared according to the method described previously [10,11]. All the human samples were acquired and used in accordance with the guidelines for the scientific use of human materials by the Japanese Society of Legal Medicine.

2.2. Assay of DNase I and II activities and analytical methods

Enzyme activities of DNases I and II were determined by the single radial enzyme diffusion (SRED) method, and quantified as described elsewhere [4,10,12]. Briefly, the human tissues (about 25 mg) were homogenized in 2 ml Tris–HCl buffer (pH 7.5) containing 2 mM phenylmethylsulfonyl fluoride, and the supernatants obtained by centrifugation at $20\,000 \times g$ were used in the subsequent analysis. Immunological and enzymological properties of the enzymes present in each tissue sample were examined as described previously [6,10]. Isoelectric focusing in a thin layer of polyacrylamide gel (IEF–PAGE) was performed using Ampholine 3.5–5 (Amersham Pharmacia Biotech, Uppsala, Sweden) as a carrier ampholyte. The supernatants from the pituitary gland and pancreas, and serum that was simultaneously collected from the same individuals, were subjected to IEF–PAGE analysis following treatment with sialidase, after which the focused

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Abbreviations: DAFO, dried agarose film overlay; DNase I, deoxyribonuclease I; IEF–PAGE, isoelectric focusing in a thin layer of polyacrylamide gel; LH-RH, luteinizing hormone-releasing hormone; SRED, single radial enzyme diffusion

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DNase I was visualized by activity staining using a dried agarose film overlay (DAFO) method, as described previously [13].

2.3. Detection and sequencing of DNase I gene transcripts in human tissues

RNA was extracted from human pituitary gland and pancreas samples by the acid guanidinium thiocyanate–phenol–chloroform method [14]. The DNase I gene transcript was amplified by reverse transcriptase-PCR and analyzed as described previously [6]. Amplification of portions of the total RNA derived from the pituitary gland and pancreas collected from a 21-year-old male (obtained at autopsy 12 h after death caused by loss of blood) using sets of the primers 5′-CTCTGAGGACATCACCATCA-3′ and 5′-AGTTCAACTGGTGTGGGGAG-3′, corresponding to the 5′-upstream and 3′-downstream untranslated regions of the human DNase I cDNA [15], respectively, was performed by reverse transcriptase-PCR. The amplified products were subcloned into the pCR II vector (Invitrogen, San Diego, CA, USA), and sequenced using a Dye Terminator Cycle Sequencing kit (FS; Applied Biosystems, Urayasu, Japan). The sequencing run was carried out on an Applied Biosystems Genetic Analyzer (model 310), and all DNA sequences were confirmed by reading both DNA strands.

2.4. Semi-quantification of DNase I gene transcript levels expressed in human tissue samples

In order to semi-quantify levels of DNase I gene transcript in the pituitary gland and pancreas, a competitive PCR method based on a non-homologous internal standard approach [16] was employed. A non-homologous DNA fragment with a primer template corresponding to sets of primers 5′-CTGAAGATCGCAGCCTTCAAC-3′ (primer 1) and 5′-CTTCAGCATCACCTCCACTGG-3′ (primer 2), corresponding to the N- and C-terminal portions of the mature human DNase I [15], tentatively named PCR-MIMIC, was used as a competitive internal standard during PCR amplification, and was prepared using a PCR-MIMIC construction kit (Clontech, Palo Alto, CA, USA) according to the manufacturer's instructions. A 5–10-fold dilution series (from 100 to 10^{-5} amol/μl) of the PCR-MIMIC was prepared for use in a competitive PCR. A constant amount of the first-strand cDNA derived from the total RNA of each human pituitary gland and pancreas was subjected to PCR amplification along with each of the PCR-MIMIC dilutions. Series of competitive PCRs using the primer 1/primer 2 set in the copresence of PCR-MIMIC at different concentrations were performed separately, and analyzed as described previously [5,17].

3. Results

3.1. Highest DNase I activity present in human pituitary gland and pancreas

Similar high levels of DNase I activity were detected in the human pituitary gland and pancreas derived from the same individuals (mean ± S.D.: 0.92 ± 1.3 and 1.0 ± 0.73 U/g wet weight, respectively; $n = 80$). The human pituitary gland is composed of two main lobes (anterior and posterior), and the DNase I activity was only detected in the anterior lobe in both sexes ($n = 4$; anterior lobe: 0.48–0.55 U/g wet weight; posterior lobe: not detected). All the enzyme activity detectable in each pituitary extract was completely inhibited by 1 mM EGTA, 1 mM EDTA, or 0.1 nM G-actin which is known to be a potent inhibitor of human DNase I [10]. Notably, the activity was completely abolished by anti-human DNase I antibody. These findings indicate that the activity detected in the human pituitary gland was indeed derived from authentic DNase I. Mammalian DNase I is classified into three types: pancreatic, parotid, and pancreatic–parotid (mixed) [6]. Human DNase I is of the pancreatic type, being more sensitive to acidic conditions than the other types; the DNase I activity present in the pituitary extracts was labile under acidic conditions in the same manner as urinary purified DNase I. On the other hand, in rat the DNase I (parotid type) activity present in the pituitary glands ($3.5 \pm 0.58 \times 10^{-2}$ U/g wet weight; $n = 10$) was extremely low compared to that in the parotid ($84 \pm 22 \times 10^{3}$ U/g); similar results were seen in mouse (parotid type). Furthermore, the DNase I (mixed type) activity in the rabbit pituitary gland was below the detection limit of our assay (about 0.01 U/g). Therefore, the high levels of DNase I activity observed in the pituitary gland allowed the human type to be distinguished from the others.

Fig. 1. IEF–PAGE (pH 3.5–5) patterns of desialylated DNase I from pituitary gland (lanes 1–3), pancreas (lanes 4–6), and serum (lanes 7–9) samples detected by activity staining using the DAFO method. Paired samples were obtained from the same individuals. Details of the analytical conditions are described elsewhere [13]. In genetic polymorphism of human DNase I, three common phenotypes (1, 1–2, and 2) have been classified on the basis of differences in electrophoretic patterns revealed by IEF–PAGE [18]: lanes 1, 4, and 7 (type 1); lanes 2, 5, and 8 (type 1–2); lanes 3, 6, and 9 (type 2). The anode is at the top.

Genetic polymorphism of human DNase I in body fluids and the pancreas has been demonstrated by differences in p*I* values of phenotype-specific enzymes [18,19]. The IEF–PAGE patterns of DNase I in the pituitary samples closely resembled those of the paired samples of pancreas and serum from the same individuals in each phenotype (Fig. 1). The phenotypes determined from the pituitary samples were completely consistent with those from the pancreas or serum samples of the corresponding individuals. Since DNase I present in the pituitary gland exhibited the same genetic polymorphism as that in the pancreas, the enzyme in the former was obviously derived from the same DNase I gene expressed in the latter.

3.2. DNase I-specific gene transcript present in the pituitary gland

A unique fragment corresponding to DNase I-specific mRNA could be amplified by reverse transcriptase-PCR from the total RNA in all the pituitary gland samples with a detectable DNase I activity, whereas the cerebrum, in which DNase I activity could not be detected, gave no amplified product. Furthermore, the fragment covering the entire region of the open reading frame in its cDNA, which was amplified from each of the pituitary gland and pancreas samples from the same individual, was subcloned and sequenced. The sequence of the pituitary gland-derived clone (DDBJ/EMBL/GenBank accession number AB004858) was identical to that from the corresponding pancreas. We could therefore rule out the possibility that the DNase I activity observed in the pituitary gland originated from the other source organs and/or was merely stored. Therefore, from these observations we concluded that the human pituitary gland is the first endocrine gland in which the DNase I gene has been shown to be expressed to a substantial extent.

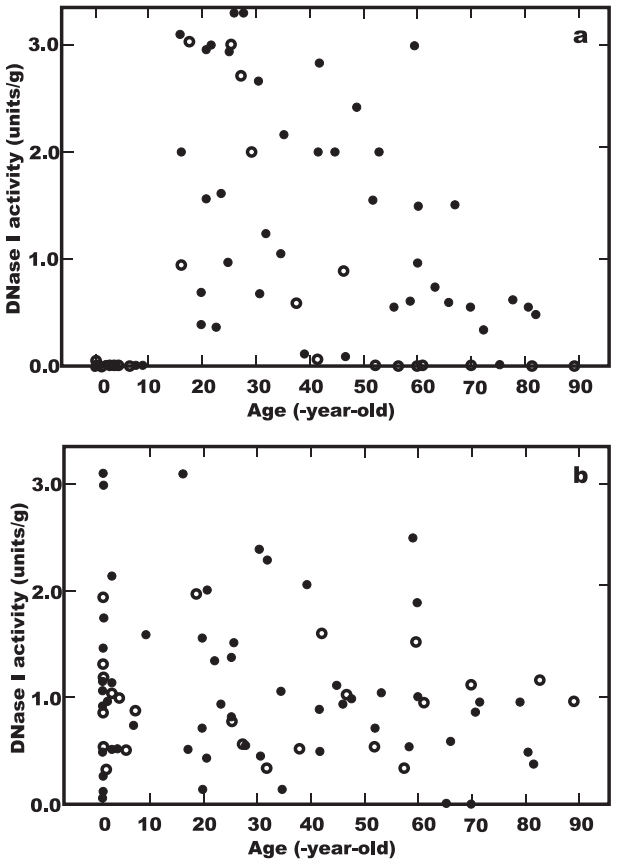

Fig. 2. Age-dependent distributions of DNase I activity in (a) human pituitary gland and (b) pancreas (●, males; ○, females). Eighty-five samples of human pituitary gland, together with pancreas samples that were collected simultaneously, were used to determine the levels of DNase I activity by the SRED method.

3.3. Age-dependent alteration of DNase I activity in the human pituitary gland

In order to examine potential effects of age on the DNase I activity, the activities of DNases I and II were determined in paired samples of the pituitary gland and pancreas (together with the serum samples) obtained from different individuals aged from 1 month to 89 years. As shown in Fig. 2a, all the pituitary gland samples from the individuals aged from 1 month to 9 years in both sexes in the neonatal and prepubertal periods exhibited low or undetectable levels of activity. In contrast, a marked age-dependent increase of the DNase I activity in the pituitary samples from individuals over 16 years old was observed in the reproductive period irrespective of their gender, followed by a gradual age-dependent decline in males and a low level in females in their postreproductive period. The DNase I activity in the pituitary gland was age-dependent regardless of gender. However, there were no such age-related alterations in the activity levels of the enzyme in the pancreas samples from the same individuals (Fig. 2b). Similarly, the age of the subjects did not affect the levels of serum DNase I activity significantly (Table 1). Although expressed from the same gene, the activity levels of DNase I in the pituitary gland exhibits a significant age-related alteration, whereas this is not the case in the pancreas and serum.

DNase II (EC 3.1.22.1) is known to be another major type

Table 1
Age-dependent DNase I activity in human pituitary gland, pancreas, and serum

Life stage	DNase I activity (U/g tissue)				DNase I activity (10^{-3} U/ml serum)		DNase II activity (U/g tissue)	
	Pituitary gland		Pancreas		Serum		Pituitary gland	
	Male	Female	Male	Female	Male	Female	Male	Female
Neonatal and prepubertal	0.0086 ± 0.018* (18)	0.033 ± 0.035* (10)	1.2 ± 0.92 (18)	1.0 ± 0.52 (10)	8.5 ± 4.7 (18)	7.2 ± 4.1 (32)	43 ± 24 (18)	51 ± 22 (10)
Reproductive	2.0 ± 1.6 (25)	1.6 ± 1.1 (8)	1.2 ± 0.78 (24)	0.84 ± 0.44 (7)	4.6 ± 1.2 (25)	4.2 ± 1.8 (24)	63 ± 33 (25)	55 ± 32 (8)
Postreproductive	0.94 ± 0.75** (16)	0.061 ± 0.034* (8)	0.95 ± 0.61 (14)	0.91 ± 0.41 (7)	5.4 ± 2.8 (31)	4.8 ± 3.2 (19)	41 ± 30 (16)	52 ± 22 (8)

DNase I and II activities in each tissue and serum were determined by the SRED method [12]. The results for the pituitary gland and pancreas (Fig. 2) were analyzed and are presented tentatively as three groups representing different life stages: neonatal and prepubertal (0–15 years old), reproductive (16–50 years old), and postreproductive (51–89 years old). Values are mean ± S.D. of triplicate determinations in each tissue and serum sample. The figures in parentheses represent the number of samples tested. Statistical significance was evaluated by two-sample *t*-test, separately relative to levels of DNase I activity in male and female samples of reproductive stage (* $P < 0.005$; ** $P < 0.05$).

of DNase present in mammalian tissues, including in the pituitary gland [20]. In contrast to DNase I, no age-related changes in the levels of DNase II activity were observed in the pituitary gland (Table 1). Thus, among the two major types of DNase in the pituitary gland, only DNase I activity was confirmed to be significantly age-dependent.

3.4. Age-dependent expression of the DNase I gene transcript in human pituitary glands

Higher amounts of the DNase I gene transcript were expressed in the pituitary gland samples (5×10^{-2}–5×10^{-3} amol/μg total RNA; $n=8$), with more than 0.4 U/g of the DNase I activity of the subjects from the reproductive stages. On the other hand, expression levels of the DNase I gene ($n=5$) from the neonatal and prepubertal stages were found to be below the detection limit (10^{-5} amol/μg total RNA) of our method. Furthermore, the amounts of gene transcript in the pituitary gland samples ($n=5$) with less than 0.05 U/g of the activity from the postreproductive stage were less than one tenth of those from the pubertal and reproductive stages. These levels of DNase I-specific mRNA expressed in each pituitary gland sample correlated well with those of DNase I activity measured in the corresponding tissue extraction, and are consistent with previous findings [5,7,21]. On the other hand, no significant difference in the expression levels of the DNase II-specific mRNA in corresponding pituitary gland samples from individuals of different ages could be observed (data not shown), indicating that the mRNA might not be degraded particularly rapidly in samples from neonates and prepubertal individuals. Therefore, elevation of pituitary gland DNase I activity after the prepubertal stage appears to be due to up-regulation of the DNase I gene expression rather than to recruitment of potential inhibitors such as G-actin and/or to breakdown of DNase I protein molecules during the neonatal and prepubertal stages. No significant age-related differences in the levels of the gene transcript among the corresponding pancreas samples were observed. These findings provide strong evidence that expression of DNase I gene in the pituitary gland is regulated in an age-dependent manner.

4. Discussion

To our knowledge, the finding of an age-related alteration of DNase I activity in the human pituitary gland is the first to demonstrate that physiological factors such as aging could affect DNase I gene expression in vivo. The abrupt elevation of DNase I activity coincided with the onset of puberty in both sexes (Fig. 2a). The onset of puberty is controlled by the reactivation (disinhibition) of the human hypothalamic luteinizing hormone-releasing hormone (LH-RH) pulse generator, leading to increased amplitude and frequency of LH-RH secretion and an increase in sensitivity of the pituitary gland to LH-RH [22,23]. With regard to the effects of LH-RH on gonadotropin subunit synthesis within the gonadotrope cells of the pituitary gland, it is well documented that the primary interaction of LH-RH with the membrane receptor initiates multiple events inside the cells, including Ca^{2+} mobilization, inositol phospholipid hydrolysis, and cAMP accumulation [24]. The human DNase I gene contains two sites corresponding to a unique sequence of the *cis*-element that confers cAMP responsiveness on the gene through a cAMP-responsive element-binding protein [15]. Previously we suggested that down-regulation of the DNase I gene by somatostatin might result from a decrease of cAMP concentration through a G protein-coupled signaling pathway [7]. In fact, a significant elevation of the DNase I activity in rat pituitary glands was observed in response to administration of LH-RH (Yasuda et al., unpublished data). Therefore, since LH-RH is capable of increasing both diacylglycerol and cAMP production within gonadotrope cells [25], it seems plausible that LH-RH is involved in up-regulation of the DNase I gene through the two intracellular pathways implicated in the successive activation of protein kinase C and then A in the same manner as the expression of the gonadotropin genes. Several cardinal hormonal characteristics of puberty such as increased gonadal steroids, growth hormone, and insulin-like growth factor I secretions have been confirmed; an abrupt elevation of DNase I gene expression in the pituitary gland might be regarded as one of the characteristics of puberty.

Over about 50 years of age, the male pituitary gland DNase I activity decreased slowly with age, whereas in females the decrease was much more rapid (Fig. 2a). However, the levels of DNase I activity in pancreas and serum were approximately constant (Table 1). The menopausal cessation of ovarian function (follicular development) leads to decreased secretion of estradiol and inhibin, with consequent loss of negative feedback to the hypothalamus and pituitary gland in the hypothalamic–pituitary–ovarian axis: the serum levels of gonadotropins, follicle-stimulating hormone, and LH increase [26]. In contrast, men do not experience an analogous rapid total cessation of Leydig cell or seminiferous tubule function with old age, and the decline in male sexual function with age does not appear to be endocrine-mediated: the decline in the function of hypothalamic–pituitary–testicular axis is gradual [27]. Although the role and mechanism underlying DNase I gene expression is still to be elucidated in the pituitary gland, the differences in the reduction of responses between the sexes suggest that the enzyme activity coincides with hormonal changes or old age. Also, age-related differences in both the DNase I activity and amount of gene transcript between the pituitary gland and pancreas revealed that DNase I gene expression in these tissues is regulated in a tissue-specific manner. Previously, based on the differences in response to somatostatin, tissues containing DNase I could be classified into two types: somatostatin-sensitive and somatostatin-resistant [7]. Elucidation of tissue-specific hormonal regulation of DNase I is currently under way in our laboratory.

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