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A Study on Serum Dopamine-ß-Hydroxylase Activity and Thermostability in a Randomly Selected Population of Adults[1].

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ABSTRACT

Distributions of serum dopamine-ß-hydroxylase(DBH) activity and thermostability in a randomly selected population of Korean adults were studied to investigate the genetic factor which could exert an influence on the serum DBH activity and thermostability.

The results were followings:

1. The mean serum DBH activity in a randomly selected population of adults was 18.3 ± 4.5 umol/min/l(mean ± SD;n = 327) which showed no age or sex variation.
2. The frequency distribution showed no isolated subgroup with very low serum DBH activity.
3. When the ratio of enzyme activity after heating 55 °C for 20 minutes to that before heating (heated-to-control or H/C ratio) was used as a measure of thermostability, the mean serum DBH H/C ratio in a randomly selected population of adults was 0.90 ± 0.17 (mean ± SD; n = 327) which showed no age or sex variation.
4. Serum DBH H/C ratio showed unimodal, homogeneous distribution.
5. There was significant negative correlation between serum DBH activity and H/C ratio ($r = -0.39$, $P < 0.01$).
6. Subjects with H/C ratio less than 0.7 had significantly higher basal enzyme activity (22.2 ± 4.5) (mean ± SD;n = 33) umol/min/l than those with H/C ratio more than 1.09 (15.5 ± 3.3) (mean ± SD;n = 32) umol/min/l.

This study shows that the distribution patterns of serum DBH activity and thermostability of Korean population are considerably different from those of Caucasian and it might be a line of evidence for the different inheritance pattern of plasma DBH enzyme between these racial groups.

Key Words: Serum dopamine-ß-hydroxylase activity, thermostability, normal adults, distribution

Abbreviation: DBH; dopamine-ß-hydroxylase, H/C; heated-to-control, CV; coefficient of variation

INTRODUCTION

Dopamine-ß-hydroxylase (DBH; E.C. 1.14.17.1) is the enzyme that catalyzes the conversion of 3,4-dihydroxyphenylethylamine(dopamine) to norepinephrine (Kaufman & Friedman, 1965). DBH is localized to catecholamine containing vesicles in the central nervous system, adrenal medulla and sym-

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pathetic nerves (Oka *et al.*, 1967; Stjarne & Lishajko, 1967), is released with catecholamines during stimulation of these structures (Viveros *et al.*, 1968; Smith *et al.*, 1970; Weinshilboum *et al.*, 1971), and is found circulating in the blood (Weinshilboum & Axelrod, 1971).

Plasma DBH has often been measured because of the possibility that it might reflect the extent of the exocytotic release of catecholamines (Axelrod, 1972). However, the results of a series of studies have demonstrated that serum DBH values in normal subjects are quite stable over long periods of time and there is a wide individual variation in serum DBH values (Ross *et al.*, 1973). Biochemical genetic studies of plasma DBH were initiated with experiments that demonstrated a significant familial aggregation of enzyme activity levels (Weinshilboum & Axelrod, 1971; Horowitz *et al.*, 1973). Sibling-sibling correlation coefficient was 0.57 ($p < 0.001$) (Weinshilboum, 1973) and the correlation coefficient for monozygotic twins was 0.96 whereas that for dizygotic twins was 0.75 (Ross *et al.*, 1973).

Weinshilboum *et al.* (1975) reported that when basal plasma DBH activity was measured in a large randomly selected population sample, the frequency distribution histogram was skewed and there was a subgroup of approximately 3-4% of subjects with a very low level of enzyme activity. The results of subsequent pedigree and segeration analyses performed with blood samples from first-degree relatives of probands with very low enzyme activity were compatible with the autosomal codominant inheritance of two alleles, one for low (DBH^L) and one for high (DBH^H) plasma DBH activity, and the gene frequency of DBH^L in a large randomly selected population was estimated to be approximately 0.2 with about one-third of a randomly selected population being heterozygous at the locus *DBH* (Dunnette & Weinshilboum, 1977; Elston *et al.*, 1979; Goldin *et al.*, 1982).

Variations in the thermal stability of an enzyme are often related to variations in protein structure (Paigen, 1971) and have proved useful in the study of many genetic polymorphisms (Langridge, 1968; Lehmann & Correll, 1969; Scanlon *et al.*, 1979).

Recently, Dunnette and Weinshilboum (1979) reported that there is a wide individual variation in thermostability of serum DBH with 10% of randomly selected population having thermolabile serum DBH, and there is a significant familial aggregation of DBH thermostability, and there was no direct relation between DBH thermolability and the genetic locus *DBH* that plays a major role in the regulation of basal plasma DBH activity.

Because there are many lines of evidence that altered level of dopamine or norepinephrine may be involved in the pathophysiology of schizophrenia and there is a possibility that the altered level of the catecholamines may be caused by altered function of catecholamine biosynthetic and metabolic enzymes, studies on plasma DBH are being actively performed by many investigators. Recently, Markianos and Tripodianakis (1985) reported low plasma DBH activity in demented schizophrenics.

Because DBH activity has been shown to be reduced in some patients with affective disorder or schizophrenia where genetic factor is thought to be involved in the etiology (Shopsin *et al.*, 1972; Fujita *et al.*, 1978; Baron *et al.*, 1980; Hahn *et al.*, 1984; Kim *et al.*, 1985), it has been suggested that genetic variation in plasma DBH activity might be related to the pathophysiology of these disorders. The purpose of the present experiment was to study the enzyme activity and thermostability of plasma DBH in Koreans that are thought to be relatively homogeneous in genetic constitution.

MATERIALS AND METHODS

Subjects

Plasma samples were obtained from 327 randomly selected unrelated adult volunteers (male 127 : female 200) consisting of residents and employees in Seoul National University Hospital, and medical and nersing students in medical college, SNU. The following shows age distribution: 18-25 yrs old (135 individuals); 26-30 yrs old (116 individuals); 31-35 yrs old (26 individuals); 36-40 yrs old (28 individuals);

40-66 yrs old (23 individuals). Blood samples (5ml) were collected from antecubital vein in all subjects between 10 and 11 a.m. and immediately centrifuged (800xg, 10min) to obtain plasma, which was stored at -20 °C until assayed.

Materials

Tyramine hydrochloride, octopamine hydrochloride, pargyline hydrochloride, sodium periodate and catalase were obtained from Sigma Chemical Co., USA. Ascorbia acid, sodium thiosulfate, sodium fumarate, sodium hydroxide, trichloroacetic acid were purchased from Shinyo, Japan. Dowex-50 (H^+, 200-400 mesh) was purchased from Sigma Chemical Co., USA.

Plasma dopamine-ß-hydroxylase assay procedure

The serum DBH activity was assayed by the spectrophotometric procedure described by Nagatsu and Udenfriend (1972) using tyramine and octopamine as substrate and internal standard, respectively. The composition of reaction mixture (total volume, 1.0ml) was as follows: sodium acetate buffer (pH 5.0), 250mM; sodium fumarate, 10mM; ascorbic acid (freshly prepared), 10mM; catalase 1,500U; tyramine, 16mM; pargyline, 1mM; $CuSO_4$, 20uM; plasma, 50ul. A sample of boiled enzyme preparation was used as blank. A tube of the enzyme (diluted plasma) was placed in a boiling water bath so that the average temperature was 95 °C for 5min. The reaction mixture was preincubated at 37 °C for 3min and the incubation was started with the addition of plasma. The reaction mixture was incubated at 37 °C for 30min in a water bath with continual shaking; the reaction contents were exposed to air. The incubation was stopped by adding 200ul of 3M trichloroacetic acid, and the mixture was centrifuged at 800xg for 10min. The supernatant fluid was transferred to a small column of Dowex-50 (H^+, 200-400 mesh) (packed volumne, 0.2ml) that had been prepared in a disposable Pasteur pipette (0.5cm × 10cm). The tube and precipitate were washed with 1ml of water, and the washings were also transferred to the column. The column was washed two more times with 2ml of water and then the adsorbed amines were eluted with 1.0ml of 4M NH_4OH. Octopamine in the eluate was converted to *p*-hydroxybenzaldehyde by adding 0.1ml of $NaIO_4$ solution (20g/l). Excess periodate was then reduced by adding 0.1ml of $Na_2S_2O_5$ solution (100g/l). Absorbance was measured against water at 330nm in a microcuvet with a 1cm light path by use of a Pye Unicam model SP 1750 UV spectrophotometer. 20 nmol of octopamine in 1.0ml of 4M NH_4OH was carried through the oxydation procedure as standard and enzyme activity was expressed by umol/min/l.

Thermal inactivation of plasma DBH

Thermal stability was determined as proposed by Dunnette and Weinshilboum (1979). Preincubation for the development of the characteristics of thermostability was performed by incubating samples exposed to air at 37 °C for 24 hrs. The thermal inactivation step necessary to bring about the expression of thermolability was performed by incubating samples at 55 °C for 10 min. The ratio of enzyme activity in a sample heated at 55 °C to the activity in the control sample, a so-called H/C ratio (heated divided by control), served as an index of thermal stability.

Statistics

We used *t*-test for evaluation of age & sex difference in DBH activity and thermostability. The distributions of enzyme activity and thermostability were examined for significant deviations from normality using chi-square test and estimated the skewness and kurtosis of each distribution curve.

RESULTS

Plasma DBH activity for normal adults

Table 1 shows plasma DBH activity for normal adults. The mean value for the entire population sample was 18.3 ± 4.5 (mean ± SD) umol/min/l. There was not a significant difference between male and female subjects in plasma DBH activity. The mean value for males was 18.9 ± 4.5 (mean ± SD), whereas that for female subjects was 17.9 ± 4.3 (mean ± SD).

Figure 1 shows the frequency distribution of plasma DBH activity for the entire population samples. The frequency distribution of plasma DBH activity shows right skewness (coefficient of skewness 0.59) with kurtosis being 3.64. It's range was 8.4-35.2 umol/min/l and coefficient of variation was 24.3%. While it showed slight departure from normal distribution by chi-square test ($p < 0.01$), it showed unimodal distribution without an isolated subgroup. After square-root transformations of plasma DBH activity, the distribution was compatible with normal distribution with skewness and kurtosis corrected.

Table 1. Human serum dopamine-B-hydroxylase (DBH) activity (umol/min/l) and thermostability measured by heated/control (H/C) ratios

	DBH activity Mean ± SD (C.V.)	H/C ratio Mean ± SD (C.V.)
Male (n = 127)	18.9 ± 4.5 (23.7%)	0.90 ± 0.17 (18.9%)
Female (n = 200)	17.9 ± 4.3 (24.2%)	0.90 ± 0.16 (18.0%)
Total (n = 327)	18.3 ± 4.5 (24.3%)	0.90 ± 0.17 (18.4%)

C.V. (Coefficient of variation) was calculated by mean/SD ratio.

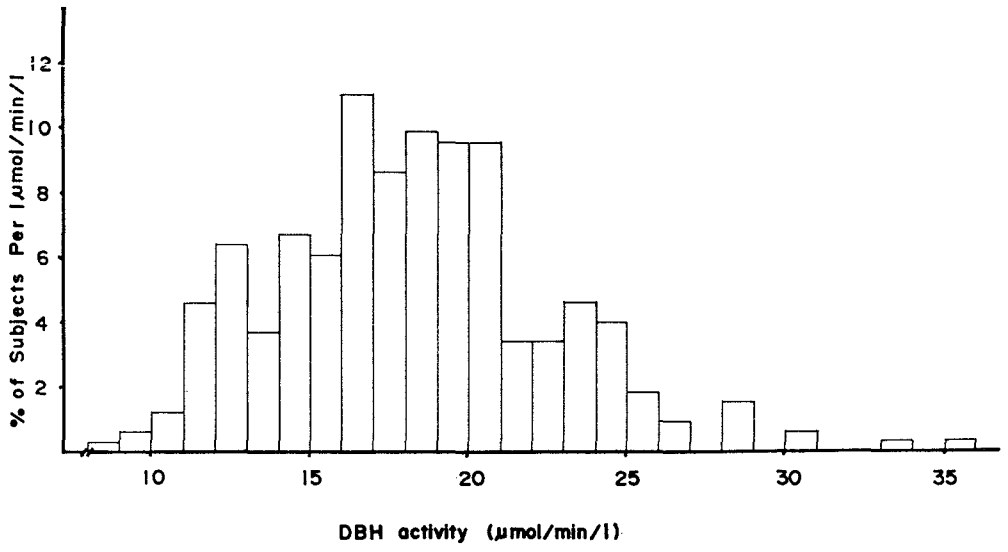

Fig. 1. Frequency distribution of human serum DBH activity from 327 randomly selected adult subjects.

Figure 2(a)(b) show the frequency distribution of plasma DBH activity for male and female subjects, respectively. Coefficient of skewness of the frequency distribution curve for male subjects is 0.07 with kurtosis being 5.13. It's range was 10.7-35.2 umol/min/l and coefficient of variation was 23.7% and it was compatible with normal distribution by chi-square test. The frequency distribution of plasma DBH activity for 200 female subjects shows right skewness (coefficient of skewness 0.39) with kurtosis being 0.39. It's range was 8.4-32.1 umol/min/l and coefficient of variation was 24.2%. It showed slight departure from normal distribution by chi-square test($0.5 < P < 0.1$), but after square root transformation it was compatible with normal distribution.

Thermostability of plasma DBH for normal adults

Table 1 shows the thermostability (H/C ratio) of plasma DBH for normal adults. The mean value for the entire population sample was 0.90 ± 0.17 (mean $\pm$ SD). There was not a significant difference between male and female subjects in H/C ratios. The mean value for males was 0.90 ± 0.17 (mean $\pm$ SD), whereas that for female subjects was 0.90 ± 0.16 (mean $\pm$ SD).
Figure 3 shows the frequency distribution of H/C ratios for the entire population sample. The frequency distribution of H/C ratios shows right skewness (coefficient of skewness 0.61) with kurtosis being

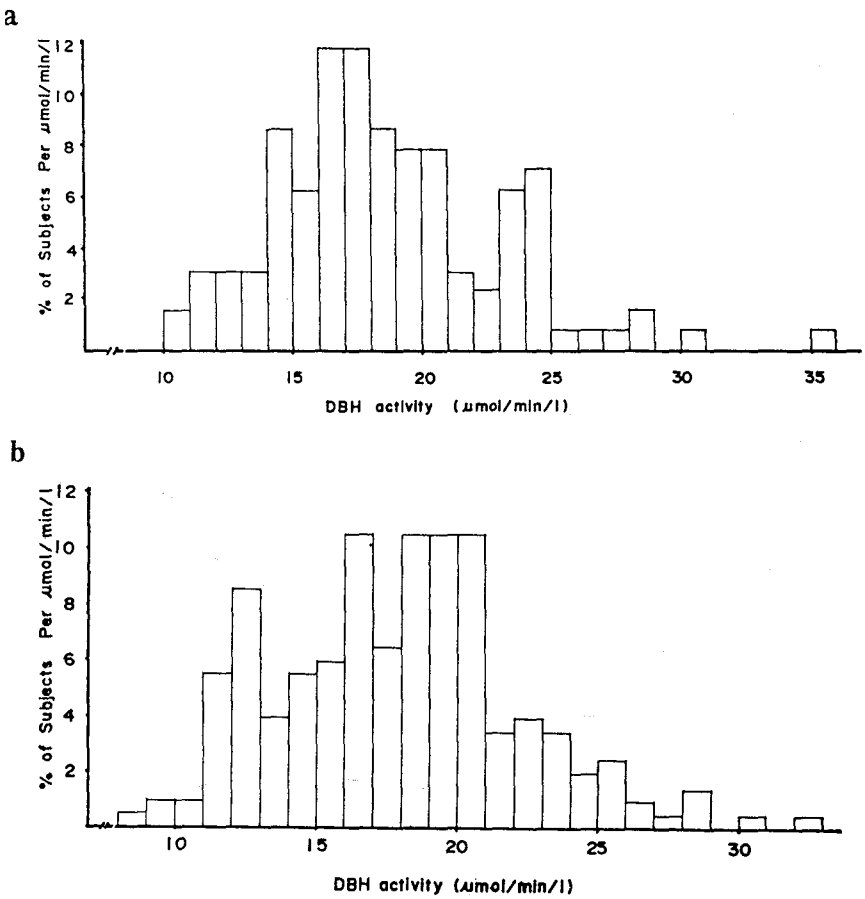

Fig. 2. Frequency distribution of human serum DBH activity from randomly selected (a) 127 male and (b) 200 female adult subjects.

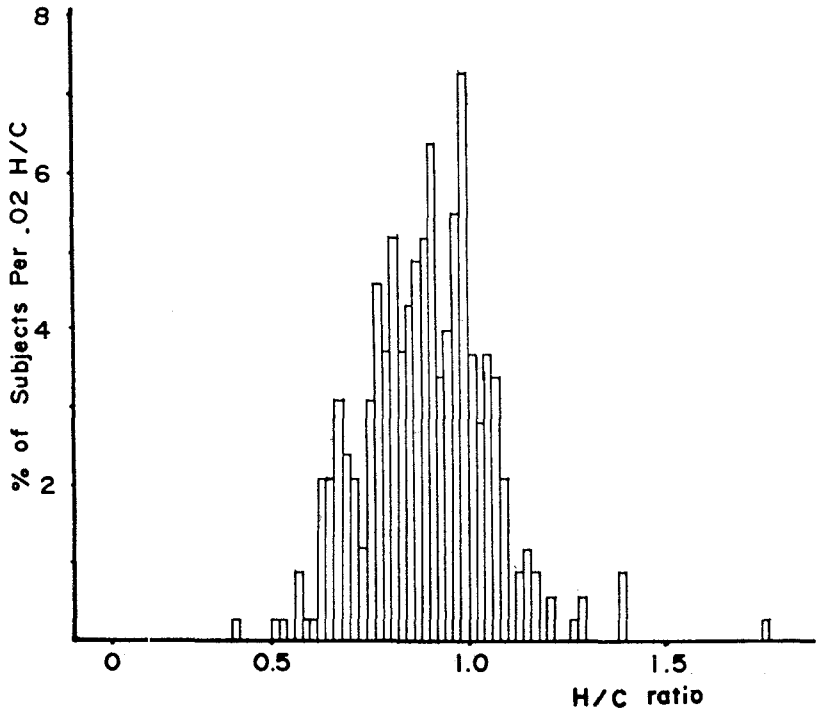

Fig. 3. Frequency distribution of human serum DBH thermostability
Serum samples from 327 randomly selected adult subjects were incubated for 20 minutes at 55 °C, and the fraction of baseline activity remaining, or H/C ratio, was calculated for each sample.

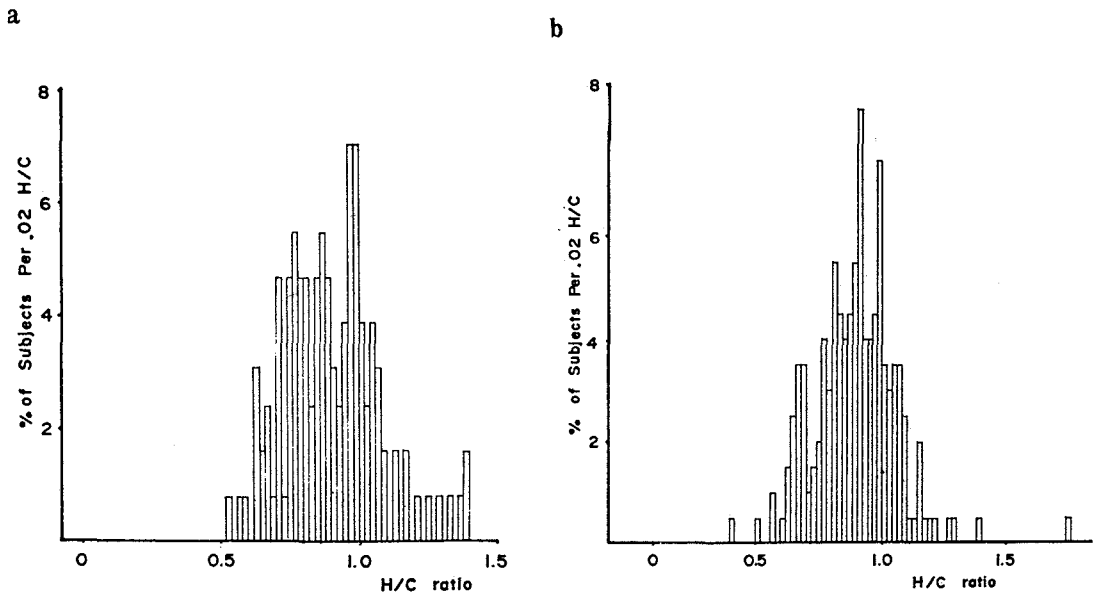

Fig. 4. Frequency distribution and human serum DBH thermostability from randomly selected (a) 127 male and (b) 200 female adult subjects.

5.12. It's range was 0.42-1.76 and coefficient of variation was 18.4%. While it showed slight departure from normal distribution by chi-square test ($0.01 < P < 0.05$), it showed unimodal distribution without an isolated subgroup. There was no H/C value less than 0.39 which value is 3 SD below peak value. Figure 4(a) shows the frequency distribution of H/C ratios for 127 male subjects. It shows right skewness (coefficient of skewness 0.54) with kurtosis being 5.12 and it was compatible with normal distribution by chi-square test. Figure 4(b) shows the frequency distribution of H/C ratios for 200 female subjects. It shows right skewness (coefficient of skewness 0.66) with kurtosis being 6.42. It's range was 0.42-1.76 and coefficient of variation was 18.0%. It was compatible with normal distribution by chi-square test.

Relationship of basal DBH activity to H/C ratio

Figure 5 shows the relationship of DBH activity to H/C ratio. There was a slight negative correlation

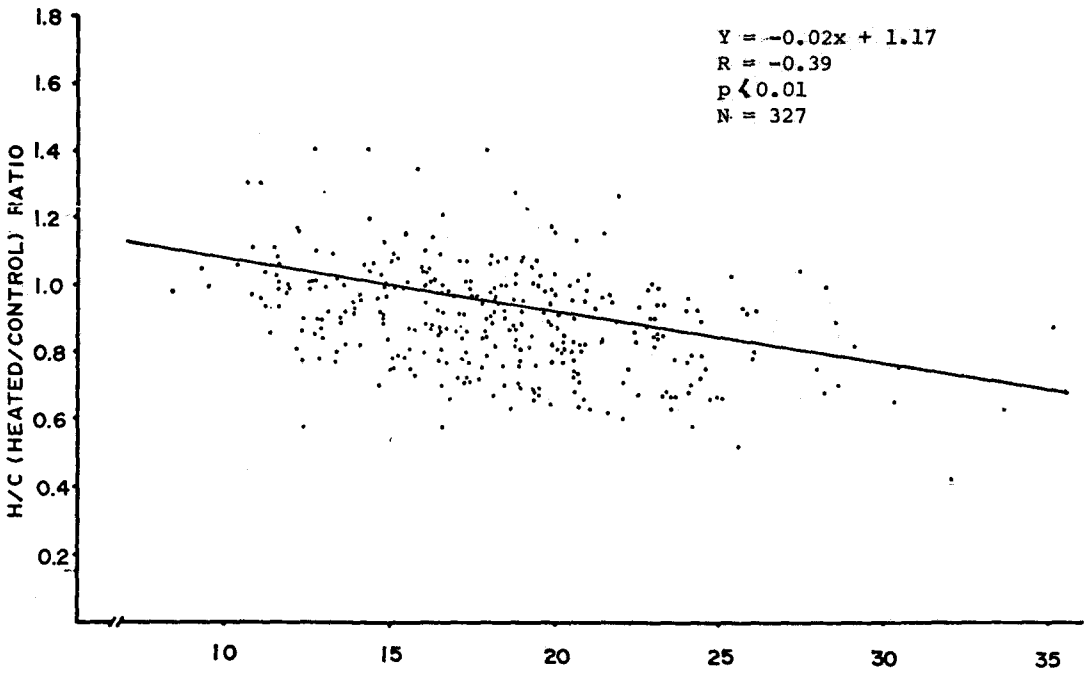

Fig. 5. Correlation of human serum DBH activity with thermostability
Thermal stability of serum DBH measured by heated/control (H/C) ratios plotted against basal enzyme activity for 327 randomly selected adult subjects.

Table 2. Serum DBH activity (umol/min/l) was compared between subjects with H/C greater than 1.09 and subjects with H/C ratio less than 0.7

	DBH activity of subjects with H/C ratio		
	H/C < 0.7	H/C > 1.09	*P* Value
Male	21.6 ± 4.6 (n = 12)	15.9 ± 3.4 (n = 14)	$P < 0.01$
Female	22.5 ± 4.6 (n = 21)	15.3 ± 3.5 (n = 18)	$P < 0.01$
Total	22.2 ± 4.5 (n = 33)	15.5 ± 3.3 (n = 32)	$P < 0.01$

of DBH activity with H/C ratio. The average plasma DBH activity for the subjects who had relatively thermolabile plasma DBH expressing H/C ratios below 0.7 (lowermost 10% of total samples) was significantly higher than that of those who had relatively thermostable plasma DBH with H/C values above 1.09 (uppermost 10% of total samples); 22.2 ± 4.5 (mean $\pm$ SD) vs 15.5 ± 3.3 (mean $\pm$ SD) ($p < 0.01$)(Table 2).

DISCUSSION

Serum DBH activities of the normal population reported by other investigators were 42.6 ± 27.0 (mean $\pm$ SD; n = 54) (range 3-100) umol/min/l by spectrophotometric assay using tyramine as a substrate (Nagatsu & Udenfriend, 1972), 622 ± 422 (mean $\pm$ SD;n $\pm$ 227) (range 0-2450) nmol/hr/ml by coupled radioenzymatic assay using phenylethylamine as a substrate (Weinshilboum *et al.*, 1975). In this study using modified Nagatsu & Udenfriend spectrophotometric method, it was 18.3 ± 4.5 (mean $\pm$ SD; n = 327) (range 8.4-35.2) umol/min/l. Direct comparisons of the results of independent studies are often difficult because various assay methods, substrates and methods for the expression of enzyme activity have been used. About the racial difference in serum DBH values, whereas several studies have shown that serum DBH activity is slightly lower in black than in white subjects (Horowitz *et al.*, 1973), one population survey of many black and white subjects in the United States failed to demonstrate a significant racial difference in serum enzyme values. (McGuffin *et al.*, 1976). It is uncertain that Koreans should show different serum DBH value compared with other racial groups.

However, the coefficient of variation of serum DBH activity in this study was 25%, which was quite small compared with those reported by others, i.e. 63% (Nagatsu & Udenfriend, 1972), 62% (Weinshilboum *et al.*, 1975). The range of serum DBH activity in this study was 8.4-35.2 umol/min/l, which is considerably narrow compared with those reported by others, i.e. 3-100 umol/min/l (Nagatsu & Udenfriend, 1972), 0-2450 nmol/hr/ml (Weinshilboum, 1975). As to the general distribution pattern of plasma DBH activity, these data show serum DBH activity 18.3 ± 4.5 (mean $\pm$ SD) umol/min/l, coefficient of skewness 0.59 which is considerably low, kurtosis 3.64 which is a little high compared with the values reported by Goldin *et al.* (1980) (mean $\pm$ SD 612.2 ± 458.8 nmol/hr/ml; coefficient of skewness 1.38; kurtosis 2.80). Weinshilboum *et al.* (1975) reported that 3-4% of sample population as an isolated subgroup showed very low serum DBH activity (less than 50 nmol/hr/ml which is approximately 7% of mean serum DBH activity, i.e. 682 nmol/hr/ml). Our sample shows no subjects with serum DBH activity lower than 1.3 umol/min/l, which is 7% of mean serum DBH activity (18.3 umol/min/l) and shows unimodal distribution pattern without an isolated subgroup from main distribution, in contrast to the report by Weinshilboum *et al.* (1975). These findings may be related to the fact that Korean population maintains racial homogeneity compared with the United States population. As previously reported (Goldin *et al.*, 1982), no age or sex effect on the DBH activity was found in this study. By the way, in the study of genetic regulation of enzymes, electrophoretic mobility and thermostability can be used in addition to the total enzyme activity (Paigen, 1971). Dunnette and Weinshilboum (1979, 1982) obtained the ratio between the enzyme activity after treatment at 55 °C for 20 min and the control value at 4 °C for the same period (H/C ratio) and used it as an index of thermostability. They reported that mean H/C ratio of 114 men was 0.925 ± 0.197 (SD) (C.V. 21.3%) with median 0.963, that of 116 women was 0.920 ± 0.152(SD) (C.V. 16.5%) with median 0.937. Our results show that mean H/C ratio of 127 male subjects was 0.91 ± 0.17 (SD) (C.V. 18.9%) with median 0.9, and that of 200 female subjects was 0.90 ± 0.16 (SD) (C.V. 18.0%) with median 0.91. Dunnette and Weinshilboum (1979) were unable to seperate clearly subjects with thermolabile DBH from those with thermostable enzyme, though H/C frequency distribution curve showed marked asymmetry with range 0.1-1.28. So a normal curve was modeled to the downslopes of H/C ratios with values above the peak of the distribution and a standard deviation was computed and an H/C ratio which is 3 SD below the peak value was selected as a cutoff line seperating subjects with thermolabile DBH from those with thermostable enzyme. 10% of the

population were thus defined as thermolabile and the thermolabile subjects had a significantly lower average DBH activity than those with the thermostable enzymes, and this trait was shown to have familial aggregation. To investigate the heritability of DBH thermostability, Dunnette and Weinshilboum (1982) divided the sample into thermolabile and thermostable by the same way and found that 8.01% of randomly selected children and 5.46% of randomly selected adults have thermolabile DBH and that pattern was compatible with the autosomal recessive inheritance pattern. Baron *et al.* (1982) also divided normal adult subjects (140 individuals) into thermolabile and thermostable by the same way and reported that 10% of sample subjects have thermolabile DBH whose mean serum DBH activity was 49.4% of that of total sample subjects. In contrast to the above reports, we could not divide sample subjects into thermolabile and thermostable by the same way as other investigators have used, because there was no H/C value less than 0.39 which is 3 SD below peak value. Moreover, mean serum DBH activity of subjects showing lowermost 10% H/C ratio (H/C less than 0.7) was significantly higher (121%) than that of total sample subjects and mean serum DBH activity of subjects showing uppermost 10% H/C ratio (H/C more than 1.09) was 85% of that of total sample subjects. In other words, this finding may be interpreted as subjects with the higher serum DBH activity showed the more thermal liability and *vice versa*. In conclusion, this study shows that the distribution patterns of serum DBH activity and thermostability of Korean population are considerably different from those of Caucasian and it might be a line of evidence for the different inheritance pattern of plasma DBH enzyme between these racial groups. And family study as well as molecular biologic study is thought to be needed to investigate the genetic mechanism and the difference of genetic pattern.

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=국문초록=

정상인 혈청 Dopamine-β-Hydroxylase 활성도 및 Thermostability에 관한 검토

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한국인에 있어서 혈청 dopamine-β-hydroxylase(DBH)에 대한 유전적 양상을 알아보기 위해 정상성인 327명에서 혈청 DBH 활성도 및 thermostability를 측정한 결과 다음과 같은 결과를 얻었다.

1. 정상성인 327명의 평균혈청 DBH 활성도는 18.3±4.5(SD)umol/min/l였으며 연령 및 성별에 따른 차이는 없었다.

2. 혈청 DBH 활성도의 분포는 unimodol한 분포를 보였으며 매우 낮은 효소활성도는 관찰할 수 없었다.

3. 정상성인 327명의 평균 thermostability index(H/C : heated-to-control)는 0.90±0.17(SD) 이었으며 연령 및 성별에 따른 차이는 없었다.

4. H/C비의 분포는 unimodal한 homogenous분포를 보였다.

5. 혈청 DBH 활성도와 thermostability 사이에는 유의한 역상관 관계가 있었다 ($r=-0.39$, $p<0.01$).

6. H/C 0.7 미만인 군의 평균 혈청 DBH 활성도는 22.2±4.5(SD)umol/min/l 였으며 H/C 1.09이상인 군의 평균 혈청 DBH 활성도는 15.5±33(SD)umol/min/l로서 유의한 차이가 있었다($p<0.01$).

이상의 결과에서 정상 한국인에 있어서 혈청 DBH 활성도 및 thermostability의 분포양상이 Caucasian과는 상당히 다른 점을 알 수 있었다.