Paraoxonase1 Phenotype Distribution in Thais

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Objective: *To determine the PON1 activity and phenotype distribution in a Thai population.*
Study design: *Prospective Descriptive study.*
Material and Method: *Between October 2001 and April 2002, 160 healthy Thai individuals aged 20-74 years were assessed for PON1 activity and the phenotype distribution by using dual substrate method.*
Results: *The means ± SD of basal, salt-stimulated paraoxonase and arylesterase activities were 239.7 ± 83.9 nmol/min/mL 555.2 ± 222.2 nmol/min/mL and 147.6 ± 33.8 μmol/min/mL respectively. The authors observed a wide interindividual variability up to 6.9-fold for paraoxonase activity and 4.6-fold for arylesterase activity. The authors found a range of ssPON/ARE ratio from 1.04 to 7.05 and three distinctive phenotype modals of AA (1.04-2.25), AB (2.44-4.29), and BB (4.53-7.05) with frequencies of 14.4% (AA), 51.9% (AB), and 33.7% (BB). The authors also observed the association of sex with lipid parameters and PON1 activity.*
Conclusion: *The distribution of PON1 phenotype in Thais is clearly trimodal with high frequency in BB phenotype.*

Keywords: *Aryldialkylphosphatase, Demography, Paraoxon, Phenotype*

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Paraoxonase1 or PON1 (aryldialkylphosphatase [EC 3.1.8.1]) has long been known in the field of toxicology because in the liver it hydrolyzes paraoxon, a toxic catabolite of organophosphates parathion[1]. In this decade, PON1 has been extensively investigated in the field of atherosclerosis due to its inherent physical and biological properties. PON1 is synthesized in the liver and secreted into blood stream by association with high-density lipoprotein (HDL) and Apolipoprotein AI (Apo AI) where it exhibits an important function[2]. PON1 has been found to play a role in the antioxidant system by preventing the oxidation of low-density lipoprotein (LDL) and high density lipoprotein (HDL) via hydrolyzed lipid peroxide and hydrogen peroxide[3-5]. There is growing evidence from human studies and mouse models demonstrating that PON1 is anti-atherosclerotic. The over-expression of PON1 gene decreased atherosclerotic lesion while PON1-deficit mouse increased atherosclerotic lesion[6-8].

PON1 is a calcium-dependent glycoprotein of 43-45 kDa. Its gene is located on the long arm of chromosome 7q21-22[9]. PON1 activity increases from birth to 15-25 months of age and reaches a plateau in adults. It is sex-independent[10]. Between individuals, there is an approximately 10 to 40 folds variation in PON1 activity[11]. PON1 exhibits genetic polymorphism, which later has been found to influence the PON1 activity and concentration and response for the substrate dependent as well as cause marked inter-individual variation[9,12]. The two major polymorphisms found in coding region of PON1 are due to amino acid substitution of leucine (L) to methionine (M) at position 55 and of glutamine (Q) to arginine (R) at position 192[13]. However, subsequent studies have found a wide range of activities of up to 13-30 folds in PON1 concentrations and activities for individuals even within the same genotypes group[9,14]. Numerous

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evidences revealed that in addition to genetic factors, other factors such as drugs, environmental, chemicals, physiological and pathological states, diet, and lifestyle also influenced PON1 expressions and activities. More recently, evidences are emerging to support the fact that PON1 phenotype rather than genotype is a closer association and hence a better predictor for coronary heart disease (CHD). Many studies including a large meta-analysis demonstrated that PON1 genotype is not significantly associated with CHD[15-20]. Jarvik et al had demonstrated that the PON1 activity phenotypes associated to the CHD better than PON1 genotypes[21,22]. Moreover, different ethnic groups around the world demonstrated differences distribution of PON1 phenotypes. In the present study, the authors assessed the PON1 activity and phenotype distribution in a healthy Thai population by using dual substrate[23].

Material and Method

Serum sampling

Serum samples were collected from the left-over frozen serum (-20°C) that were previously obtained from routine health check-ups of the Mobile Unit of the Faculty of Medical Technology, Mahidol University, Thailand, between October 2001 and April 2002 and were correspondingly assay within one month. Eligible serum samples were selected from healthy subjects who were defined by physical examination, laboratory examination, and historical questionnaires without consideration of occupation or hometown origin. Subjects with hypertension, diabetes mellitus, cardiovascular diseases, renal or hepatic diseases, who smoked or alcohol or drug abusers were excluded from the present study. The blood chemistry was analyzed using an auto-analyzer (Hitachi 917) and manufacture's reagent kits for glucose, total cholesterol, triglycerides, and HDL cholesterol. LDL cholesterol was calculated by using Friedewald formula.

Paraoxonase and arylesterase activities

Paraoxonase activities were determined by using two substrates; paraoxon and phenyl acetate. Paraoxonase activity was measured using paraoxon as substrate either without added sodium chloride (basal activity, bPON), or with 1 M sodium chloride (salt-stimulated activity, ssPON) as previously described by Eckerson[23]. In brief, the assay was performed by adding 20 ml of serum to 1 mL Tris-HCl buffer (100 mM, pH 8.0) containing 2 mM calcium chloride and 1.1 mM paraoxon. The hydrolysis rate of paraoxon was followed by measuring the liberation of p-nitrophenol at 405 nm, at 37°C over 90 seconds after a 20-second lag time with a SEAC Ch100 spectophotometer. The reaction was linear for at least 5 minutes. The enzyme activity was calculated from the molar extinction coefficient of 18,700 $M^{-1}.cm^{-1}$. Intra-assay CV was 2.2% and the inter-assay CV was 3.5% for bPON, while intra-assay CV was 0.7% and the inter-assay CV was 1.3% for ssPON.

Arylesterase (ARE) activity was assayed by using phenyl acetate as substrate as previously described by Eckerson[23]. The reaction mixture contained 1 mM phenyl acetate and 0.9 mM calcium chloride in 9 mM Tris-HCl buffer (pH8.0). The reaction was initiated by adding 20 ml 1:20 prediluted serum with 10 mM Tris-HCl buffer (pH7.4) to the reaction mixture. The increased in absorbance of phenol was followed at 270 nm, at 25°C using a Hitachi U-3210 spectrophotometer. The molar extinction coefficient of 1,310 $M^{-1}.cm^{-1}$ was used to calculate ARE activity. The intra-assay and inter-assay coefficients of variation were 2.2% and 2.8%, respectively.

Paraoxonase to arylesterase activities ratio (PON/ARE ratio)

The phenotype distribution of PON1 was determined by using the dual substrate method of Eckerson[23]. The ratio of the hydrolysis of paraoxon in 1 M sodium chloride (ssPON) to the hydrolysis of phenyl acetate (ssPON/ARE ratio) was used to assign an individual specimen to one of the three phenotypes: AA (homozygous with low activity), AB (heterozygous with moderate activity), or BB (homozygous with high activity).

Statistical analysis

All values were presented as means $\pm$ SD. The distribution normality of parameters was assessed by using Kolmgorov-Smirnov. Differences between means were assessed with Students' t-test, Mann-Whitney test, and Anova. The chi-square test was used to determine the observed phenotype frequencies deviated from Hardy-Weinberg equilibrium expectations. A p-value level of < 0.05 was considered as statistically significant. Statistical analyses were performed using the SPSS 10.0 software.

Results

Table 1 shows the demographic data of the study population. It consisted of 74 males and

Table 1. General and biochemical characteristics of subjects and paraoxonase activities

Parameters	Total (n = 160)	Male (n = 74)	Female (n = 86)	p-value
Age (years)	45.1 ± 10.0	46.2 ± 9.9	44.2 ± 10.1	0.600
Systolic pressure (mmHg)	114.5 ± 9.6	116.0 ± 9.4	113.3 ± 9.7	0.084
Diastolic pressure (mmHg)	76.4 ± 7.4	77.6 ± 7.4	75.5 ± 7.3	0.072
Glucose (mg/dL)	95.5 ± 8.5	96.3 ± 8.3	94.7 ± 8.6	0.230
Total cholesterol (mg/dL)	203.1 ± 19.3	206.6 ± 17.5*	200.1 ± 20.4	0.034
Triglycerides (mg/dL)	123.4 ± 42.0	116.6 ± 39.0	129.2 ± 43.9	0.058
HDL (mg/dL)	58.9 ± 12.7	60.4 ± 13.6	57.6 ± 11.8	0.161
LDL (mg/dL)	119.5 ± 16.0	122.8 ± 13.6*	116.6 ± 17.4	0.013
bPON (nmol/min/mL)	239.7 ± 83.9	248.6 ± 87.1	232.1 ± 80.8	0.216
ssPON(nmol/min/mL)	555.9 ± 222.2	609.2 ± 234.3*	510.1 ± 201.5	0.044
ARE (μmol/min/mL)	147.6 ± 33.8	160.0 ± 37.9*	137.0 ± 25.7	0.000

Values are represented as mean ± SD
* Indicates the significant difference between male and female

86 females. There was no significant difference in mean age, blood pressure, glucose, triglycerides, and HDL between male and female. However, a significant difference between male and female in mean of total cholesterol and LDL were observed in the present study. The mean ± SD of bPON activity, ssPON activity, and ARE activity were 239.7 ± 83.9 (range from 65.4 to 449.9) nmol/min/mL, 555.2 ± 222.2 (range from 130.8 to 1153.0) nmol/min/mL, and 147.6 ± 33.8 (range from 68.7 to 319.8) μmol/min/mL, respectively (Table 1). These results revealed the variation in bPON, ssPON, and ARE activities among population with up to 6.9, 8.8, and 4.6 times, respectively. Salt increased the PON activities approximately 2.3 fold. There were significant differences between male and female in means ssPON and ARE (Table 1). The distribution by using histogram demonstrated that only ARE activity was unimodally distributed (Fig. 1).

The ratio of ssPON to ARE revealed a trimodal PON1 frequency distribution in the present study population (Fig. 2). This trimodal distribution distinctively grouped the PON1 phenotypes into AA: 1.04-2.25, AB: 2.44-4.29, and BB: 4.53-7.05, corresponding to low-, intermediate-, and high-activity towards paraoxon. The frequency distribution of AA, AB, and BB phenotypes was 14.4, 51.9, and 33.7, respectively. No significant deviation of PON1 phenotype frequencies from Hardy-Weinberg equilibrium was found in the present study population. Table 2 shows the PON1 activities accordingly to phenotypes. Significant differences were found in means of bPON1 and ssPON1 activities and ratio of ssPON to ARE among phenotypes. Moreover, no significant difference in mean of ARE was found between phenotype AA and AB. Significant differences in means of triglycerides and HDL between phenotype AB and BB were noted.

Table 3 shows the differences between male and female in mean of PON1 activities and lipid parameters accordingly to PON1 phenotypes. The AB phenotype showed the significant differences between male and female in mean of LDL, ssPON, and ARE, whereas, the significant difference between male and female in mean of ARE within phenotype AA was also found. Only phenotype BB did not show significant differences in all parameters, except triglycerides, between male and female.

Discussion

Paraoxonase1 plays a major role in the metabolism and detoxification of insecticides processes and is involved in the metabolism of oxidized lipids. There is a large inter-individual variation in the amount of PON1 protein and activity. Moreover, in recent investigations, PON1 activity has been found to have marked variation within its genotypes, which indicate that factors other than genetic inheritance also influence its activity[14,24]. Growing evidence revealed the significance of PON1 phenotypes over its genotypes on its association to atherosclerosis related diseases such as coronary heart disease (CHD). Hence, the PON1 activity or status is becoming prominent in the epidemiology of toxicology and atherosclerosis. In our study, we found a wide variation in PON1 activities towards paraoxon for both basal (bPON) and salt-stimulation (ssPON) and towards phenyl acetate (ARE), which have been previously observed in other

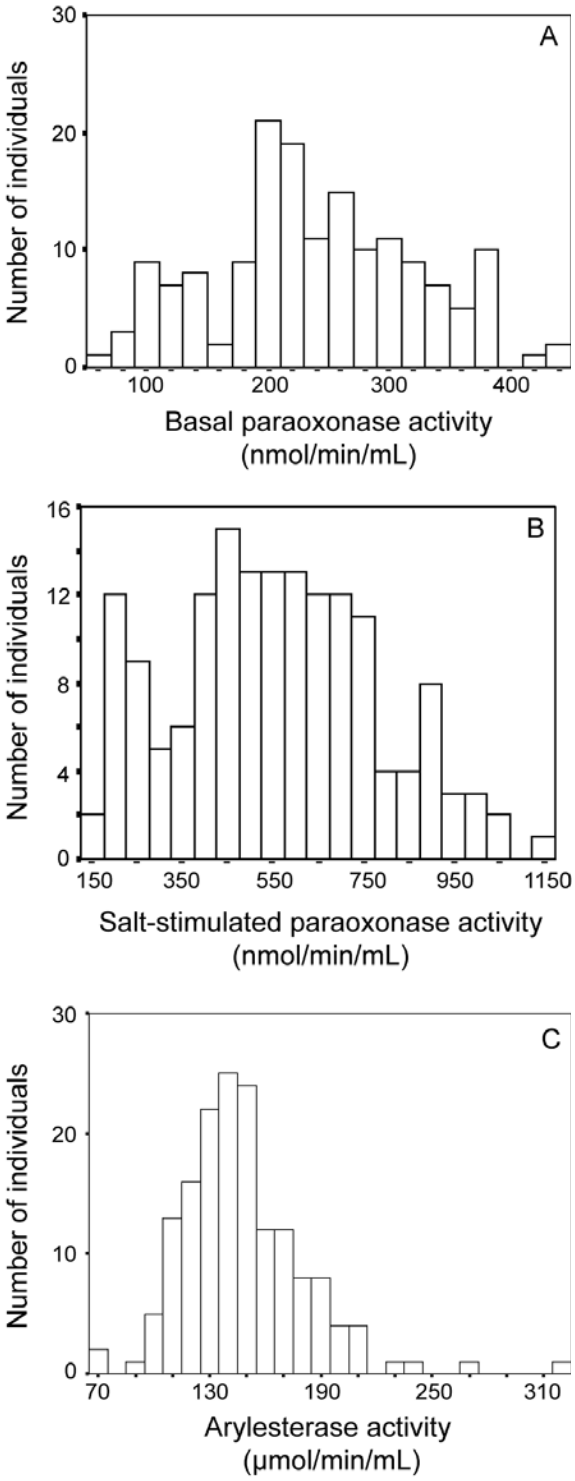

Fig. 1 Histogram of distribution of paraoxonase and arylesterase activities in subjects. (A) Frequency of basal paraoxonase activities, (B) Salt-stimulated paraoxonase activities, and (C) arylesterase

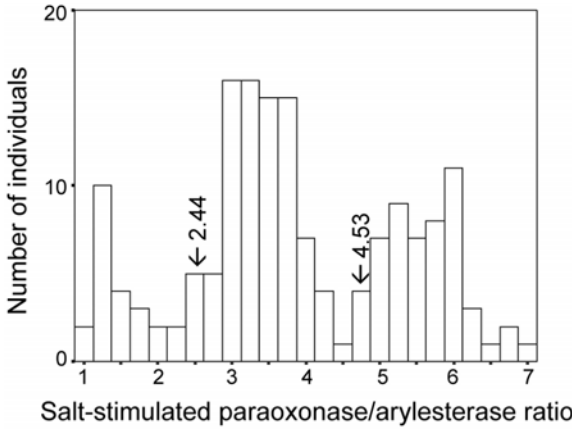

Fig. 2 The PON1 phenotype was determined by the ratio of ssPON1/ARE

ethnic groups around the world[25]. The phenotype is grouped according to the ratio of ssPON/ARE[23]. The presented frequency distribution analysis revealed a trimodal mode for PON1 phenotype with a low-activity homozygotes (phenotype AA), an intermediate-activity heterozygotes (phenotype AB), and a high-activity allele homozygotes (phenotype BB) towards paraoxon. This trimodal distribution with values (ratios) for the first mode approximately 1.46, for the second of around 3.37, and for the third about 5.61. This finding is in agreement with other studies that PON1 phenotype is a trimodal by using dual substrate[23]. In the presented study population, the distribution of PON1 phenotypes did not deviate from Hardy-Weinberg equilibrium. Phenotype frequencies of PON1 in this study population were 14.4% AA, 51.9% AB, and 33.7% BB, which was comparable to findings from Central Africa, some aboriginal or isolated regions, and Chinese with estimated frequencies of 14% AA, 50% AB, and 36% BB[26]. However, this phenotype distribution was totally different from those reported in Caucasian populations from European countries and North America with estimated frequencies of 47%AA, 43% AB, and 10%BB[23]. Based on the capacity of paraoxon hydrolysis, the authors found the majority of the present study population had intermediate to high paraoxonase activity as seen in the other study in Thai population[27] but in disagreement with the report of Phuntuwate et al[28].

In the present study population, the authors observed the differences in mean of total cholesterol, LDL, ssPON, and ARE between male and female. The analysis of correlation of PON1 phenotype and sex

Table 2. Paraoxonase activities and lipid profile according to phenotypes

Parameter	Phenotype		
	AA (n = 23)	AB (n = 83)	BB (n = 54)
Total cholesterol (mg/dL)	201.5 ± 21.2	202.6 ± 17.8	204.6 ± 20.9
Triglycerides (mg/dL)	124.8 ± 39.3	131.1 ± 39.7[c]	110.8 ± 44.2
HDL (mg/dL)	56.4 ± 10.5	57.1 ± 11.0[c]	62.6 ± 15.2
LDL (mg/dL)	120.1 ± 16.7	119.1 ± 15.6	119.9 ± 16.6
bPON (nmol/min/mL)	113.3 ± 26.9[a,b]	223.4 ± 53.6[c]	318.6 ± 51.9
ssPON (nmol/min/mL)	227.7 ± 48.4[a,b]	506.7 ± 140.0[c]	771.4 ± 137.4
ARE (μmol/min/mL)	159.4 ± 35.6[b]	150.9 ± 38.2	137.6 ± 21.6
ssPON/ARE ratio	1.46 ± 0.34[a,b]	3.37 ± 0.45[c]	5.61 ± 0.56

Values are represented as mean ± SD
[a] Indicates the significant difference between phenotype AA and AB with p-value < 0.05
[b] Indicates the significant difference between phenotype AA and BB with p-value < 0.05
[c] Indicates the significant difference between phenotype AB and BB with p-value < 0.05

Table 3. Activities and lipid profile according to phenotypes and sex

Parameter	Phenotype	Male	Female	p-value
Total cholesterol (mg/dL)	AA	206.8 ± 16.5.3	197.4 ± 24.1	0.376
	AB	207.1 ± 17.8	199.5 ± 17.3	0.796
	BB	206.0 ± 18.0	203.0 ± 24.4	0.083
Triglycerides (mg/dL)	AA	131.3 ± 43.3	119.8 ± 36.9	0.483
	AB	127.1 ± 37.6	133.9 ± 41.3	0.497
	BB	99.8 ± 33.7*	124.6 ± 52.1	0.003
HDL (mg/dL)	AA	57.9 ± 12.7	55.3 ± 8.9	0.879
	AB	57.4 ± 10.1	56.9 ± 11.6	0.231
	BB	64.6 ± 16.3	60.1 ±13.6	0.316
LDL (mg/dL)	AA	122.6 ± 12.4	118.1 ± 19.6	0.079
	AB	124.2 ± 13.4*	115.6 ± 16.2	0.012
	BB	121.4 ± 14.6	117.9 ± 19.0	0.069
bPON (nmol/min/mL)	AA	108.2 ± 37.4	117.3 ± 15.6	0.077
	AB	232.0 ± 59.5	217.5 ± 48.8	0.239
	BB	314.2 ± 55.4	324.1 ± 47.7	0.201
ssPON (nmol/min/mL)	AA	231.5 ± 64.9	224.8 ± 33.5	0.832
	AB	560.5 ± 157.5*	469.4 ± 113.8	0.003
	BB	790.2 ± 150.8	747.9 ± 117.6	0.072
ARE (μmol/min/mL)	AA	176.2 ± 41.3*	146.4 ± 25.0	0.044
	AB	171.8 ± 41.1*	136.4 ± 28.4	0.045
	BB	141.1 ± 23.2	133.2 ± 19.0	0.234
ssPON/ARE ratio	AA	1.33 ± 0.35	1.57 ± 0.30	0.094
	AB	3.26 ± 0.46	3.44 ± 0.43	0.589
	BB	5.60 ± 0.51	5.63 ± 0.63	0.300

Values are represented as mean ± SD
* Indicates the significant difference between male and female

demonstrated that the differences in mean of ssPON, ARE, and LDL between male and female were found only in AB phenotype. Whereas, AA phenotype showed significant difference between male and female in the mean of ARE. This indicates that sex may have an influence over the lipid parameters and PON1 activity related to PON1 phenotype. However, there were still some arguments on relation of PON1

phenotype to lipid parameters until now[29,30]. These may be due to the complication of lipid metabolism due to genetic variations and environmental factors such as lifestyle and diet. Further investigations are needed to clarify the actual influence of PON1 activity and phenotype on lipid parameters.

Evidences have demonstrated that the capability of PON1 to hydrolyze organophosphates is associated with PON1 phenotype. The BB and AB phenotypes are more resistant to the organophosphates than the AA phenotype[12,23]. From the present finding on phenotype distribution, it may be hypothesized that most Thais may have resistance to organophosphates. This may in part be due to the adaptive nature of this populace who is living in an agriculture country that widely uses pesticides and herbicides. On the other hand, from phenotype and CHD association studies, it was found that AA phenotypes individuals are more resistant to atherosclerosis development[31]. The authors hypothesize that most of this population may be prone to develop atherosclerosis. In conclusion, the finding of the present study may facilitate further epidemiological studies in Thai populations involving the influence of PON1 activity variability on the development of pesticides toxicity and cardiovascular disease.

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การกระจายตัวของเอนไซม์ paraoxonase1 phenotype ในกลุ่มตัวอย่างคนไทย

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วัตถุประสงค์: *ศึกษาการกระจายตัวของเอนไซม์ PON1 ในกลุ่มตัวอย่างคนไทย*

การออกแบบการศึกษา: *เป็นการศึกษาเชิงพรรณาแบบไปข้างหน้า*

วัสดุและวิธีการ: *ตรวจวัดระดับการทำงานและวิเคราะห์การกระจายตัวของของเอนไซม์ PON1 จากตัวอย่างตรวจที่ได้มาจากคนปกติ ในช่วงเดือน ตุลาคม พ.ศ. 2544 ถึง เมษายน พ.ศ. 2545 จำนวน 160 คน อายุระหว่าง 20-74 ปี ด้วยการใช้ substrate 2 ตัว*

ผลการศึกษา: *ในกลุ่มตัวอย่างของประชากรไทยมีค่าเฉลี่ย (means $\pm$ SD) ระดับการทำงานของ PON1 แบบ basal และ salt-stimulated paraoxonase และ arylesterase เท่ากับ 239.7 $\pm$ 83.9 nmol/min/mL, 555.2 $\pm$ 222.2 nmol/min/mL และ 147.6 $\pm$ 33.8 nmol/min/mL ตามลำดับ จากการศึกษาพบว่าระดับการทำงานของ PON1 มีค่าแตกต่างกันถึง 6.9 เท่า และ 4.6 เท่า เมื่อใช้ paraoxon และ phenyl acetate เป็น substrate จากการวิเคราะห์ โดยอาศัยอัตราส่วนของ ssPON/ARE ในการจัดแบ่งการกระจายตัวของ PON1 พบว่าค่าการกระจายของ อัตราส่วนอยู่ระหว่าง 1.04-7.05 และได้ phenotype 3 แบบ คือ AA (1.04-2.25), AB (2.44-4.29), และ BB (4.53-7.05) ด้วยความถี่ 14.4% (AA), 51.9% (AB), และ 33.7% (BB) นอกจากนี้ยังพบความสัมพันธ์ของระดับไขมัน ระดับการทำงาน และการกระจายตัวของเอนไซม์ PON1 กับเพศ*

สรุป: *ในกลุ่มตัวอย่างคนไทยมีการกระจายตัวของเอนไซม์ PON1 เป็น 3 แบบ โดยแบบ BB มีค่าความถี่มากที่สุด*