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Effects of hormone replacement therapy on serum amyloid P component in postmenopausal women

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Abstract

The pentraxin serum amyloid P component (SAP) is a 9.5Sα1-glycoprotein and it has recently been found to be deposited in atherosclerotic lesions or neurofibrillary tangles, which are related to the aging process and Alzheimer's disease. The level of SAP was measured by micro single radial-immunodiffusion. Sample sera were obtained from 420 healthy humans, from newborn to 86 years old. The changes in SAP during the menstrual cycle were investigated in 6 women that were 20–21 years. Fifty of the postmenopausal women, suffering from climacteric symptoms, were administered either conjugated estrogen (E), or dehydroepiandrosterone (DHEA). The SAP levels increased with age, being 1.12 ± 0.82 mg/dl (means $\pm$ S.D.) in neonates, and 6.15 ± 0.92 mg/dl in persons over 80 years. The SAP level in the females between 15 and 49 years (3.32 ± 0.95 mg/dl) was significantly ($P < 0.001$) lower than that in the males in the same age group (5.19 ± 1.25 mg/dl). The SAP level in the follicular phase was significantly ($P < 0.01$) lower than that in menstrual phase (menstrual: 4.36 ± 0.90 mg/dl versus follicular: 2.61 ± 0.99 mg/dl). In the postmenopausal women that were administered E (1.25 mg/day), the SAP decreased significantly ($P < 0.001$) from the prelevel of 5.64 ± 1.40 mg/dl to 4.26 ± 0.98 mg/dl on the 14th day. In the postmenopausal women that were administered DHEA (60 mg/day), the SAP increased rapidly from the prelevel of 4.97 ± 0.76 mg/dl to 6.17 ± 1.20 mg/dl on the 21st day. SAP seems to be a marker that can monitor the effect of hormone replacement therapy. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Serum amyloid P component (SAP) has an important immunological role in the activation of

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complement [1–3]. SAP was first described as a 9.5Sα1-glycoprotein by Haupt et al. [4]. It was later identified as one of the proteins that can be extracted from amyloid tissues, and it was shown to have a pentameric structure. Another pentamer protein is CRP, a typical acute phase protein in the human [1]. SAP and CRP have a 70% homology in their primary structure, and both genes are located on chromosome 1 [5]. Tissue damage will liberate interleukin (IL)-1 and IL-6, both of which mediate the rapid synthesis of SAP in the liver as acute phase proteins [6,7]. In vitro studies, using primary hepatocyte cultures, show that SAP mRNA and protein levels increase in response to stimulation with a variety of cytokines such as IL-1, IL-6, tumor necrosis factor α, and transforming growth factor β [8].

SAP levels were previously reported to be increased in aged human subjects [9]. Serum concentrations of SAP are regulated by the balance between production, catabolism and excretion. In man,both catabolism and excretion of SAP may become hindered with age, and consequently the serum level of SAP may increase. Furthermore, as the concentration of IL-6 in the serum from aged subjects is high [10], the production of SAP may also become stimulated in elderly humans. However, a high concentration of SAP has recently been found to be related to the aging process and arteriosclerosis [11], and the deposition of SAP in the brain has been reported to induce Alzheimer's disease [12–14]. Some investigators have suggested that the increased incidence of Alzheimer's disease in postmenopausal women may be due to estrogen deficiency and that estrogen replacement therapy may be useful for preventing or delaying the onset of this disease [15,16]. Although the normal concentration of SAP in human females has been preliminarily reported to be lower than that in males [9,17], the age-dependent changes in SAP level and the effects of sex hormones on SAP have not been clarified. We investigated the relationship between age and SAP and the effects of sex steroids on SAP concentration.

2. Materials and methods

2.1. Subjects

The study population consisted of 420 subjects, 223 females and 197 males, ranging in age from neonates to 86 years old. The changes in SAP level during the menstrual cycle were investigated in six women aged 20–21 years, who had a normal basal body temperature (BBT) chart. Blood (4 ml) was obtained in the menstrual, early follicular, late follicular, early luteal, and late luteal phases.

Thirty-four women (45–64 years) suffering from climacteric symptoms such as hot flushes and headaches were treated with conjugated estrogen (E), Premarin® (Asahikasei, Osaka) at 1.25 mg/day for 21 days. The level of SAP was measured before administration of E and on the 7th, 14th, and 21st days of administration. Sixteen women (45–55 years) with climacteric symptoms were treated with dehydroepiandrosterone (DHEA) acetate (Teikoku Hormone MFG, Co., Japan) 60 mg/day, oral therapeutic system for 21 days. Written consent was obtained from all subjects. The replacement dose of DHEA in postmenopausal women is usually about 60 mg/day [18,19]. The level of SAP was measured before administration of DHEA, and on the 7th, 14th, and 21st days of administration. Twelve women (37–50 years) suffering from hypermenorrhea were given an intramuscular injection of testosterone enanthate (T), Testoviron Depot® (Nihon Schering, Osaka) 250 mg. The level of SAP was measured before the injection of T, and on the 14th day after injection. All the sera was stored at −80°C until assay.

2.2. Assay of SAP

The level of SAP was measured by micro single radial-immunodiffusion according to the previous report [9,20]. SAP was purified from human sera by affinity chromatography on a phosphorylcholine conjugated Sepharose 6B and AcA54 Ultragel (LKB, Sweden) column. Antisera against purified SAP was obtained from injections into rabbits (Sankyo Lab.). Another aliquot of anti-

SAP sera was presented by Dr. M.B. Pepys of the Immunological Medicine Unit, Royal Postgraduate Medical School, London. The specificity of both of the anti-SAP antisera was confirmed to be the same by the Ouchterlony test. Antibody-containing agarose gel plates were made by pouring agarose into a mold $65 \times 100 \times 1$ mm. The agarose (GP36, Nakarai Chemical) gel concentration was adjusted to 2% w/v in 5 ml of veronal buffer (pH 8.6) ionic strength 0.05, and the antiserum (0.05 ml) was mixed in at 57°C. Circular holes were punched out in the antibody agar plate, using a syringe needle that was 1 mm in diameter. Each hole received 0.4 μl of the sample, which was delivered by a needle mounted on a 10 μl Hamilton microsyringe with a repeating dispenser (Dispenser PB600, Hamilton Co.). For the standard serum, lyophilized pooled serum was used by adding the prescribed quantity of distilled water at 100% and 200% of the standard serum concentration. The plate was kept in a moist chamber for 2 days, and then soaked in 0.02 M borate-buffered saline for 2 days. After drying, the plate was stained with Coomassie Brilliant Blue G-250 (Nakarai Chemical, Co.). The diameters of the precipitate rings were enlarged ten times, and measured with a Profile Projector (Model 6C, Nikon Co., Japan) equipped with a Scale Counter (Beldx type BS-105). The interassay and intra-assay coefficients of variation were 3.0–4.4% and 2.5–4.2%, respectively.

2.3. Assay of estradiol (E2) and DHEA level

Serum E2 and DHEA levels were determined by radioimmunoassay using an E2 assay kit (Daiichi Isotope Laboratory, Tokyo, Japan) and a DHEA assay kit (Diagnostic Products Corporation, Los Angeles, USA), respectively. The interassay and intra-assay coefficients of variation for E2 were 4.6–5.5% and 5.7–6.9%, respectively. Those for DHEA were 6.8–9.9% and 4.8–6.4%, respectively.

2.4. Analysis of data

Statistical analyses were performed using Student's t-test, but if variances were unequal then Welch's test was employed. Data are presented as means $\pm$ standard deviation (S.D.). Spearman's correlation coefficient was calculated and a regression line was plotted. Statistical significance was assumed at $P < 0.05$.

3. Results

3.1. SAP levels in normal female and male subjects

The levels of SAP in the sera of both sexes by age are shown in Fig. 1. In females, the mean ($\pm$S.D.) SAP level was 1.11 ± 0.80 mg/dl in neonates, which gradually increased to 3.20 ± 1.09 mg/dl by 10–14 years. Serum SAP level in males was 1.13 ± 0.83 mg/dl in neonates, which also increased to 3.92 ± 0.53 mg/dl at 10–14 years. No differences were noted in the serum SAP levels between the sexes from birth up to the age of 14 years. The average SAP level in the 14 sera samples obtained from 15–19 year females was 3.10 ± 1.19 mg/dl, and those in the 16 sera obtained from 15–19 year males was 4.25 ± 1.11 mg/dl. This difference was significant ($P < 0.01$). The average level of SAP in the 69 females between 15 and 49 years (3.32 ± 0.95 mg/dl) was significantly ($P < 0.001$) lower than that in the 77 males of the corresponding age group (5.19 ± 1.25

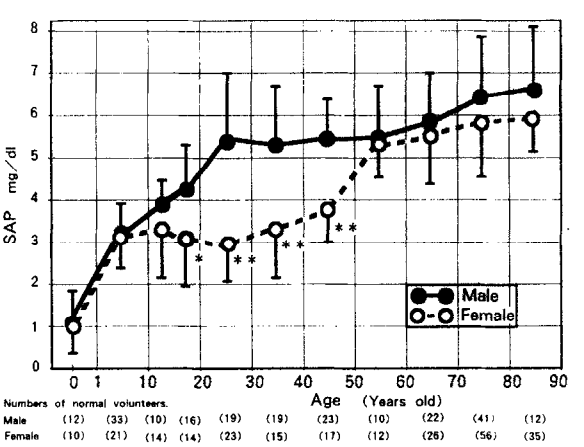

Fig. 1. The effect of age and sex on human SAP levels. Each value is the mean $\pm$ S.D. $^{*}P < 0.01$, $^{**}P < 0.001$ compared with the male at the corresponding age.

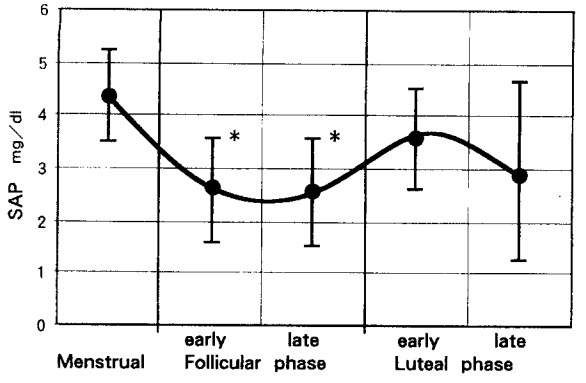

Fig. 2. Serial determination of SAP in normal women with ovulatory cycles. Shown is the mean ± S.D. of six women aged 20–21 years. *$P < 0.01$ compared with the level in the menstrual phase.

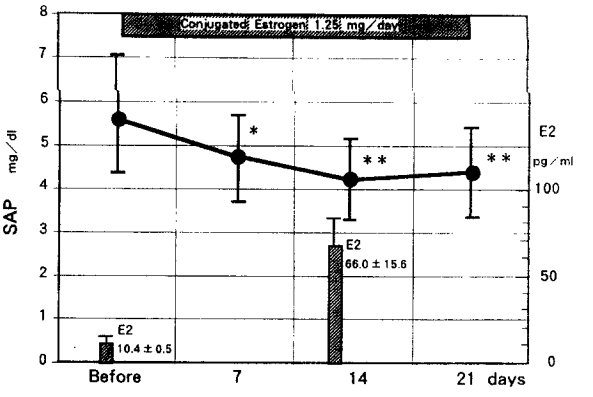

Fig. 3. Effect of estrogen on the SAP level in post-menopausal women. Shown is the mean ± S.D. of 34 women who were 45–64 years. *$P < 0.01$, **$P < 0.001$ compared with the level before the administration of estrogen.

mg/dl). The average level of SAP in the 12 sera samples obtained from 50–59 year females was 5.45 ± 0.81 mg/dl, and those in the 10 sera obtained from the 50–59 year males was 5.54 ± 1.25 mg/dl. The SAP levels in the serum of subjects over 60 years were 5.82 ± 1.13 mg/dl for 117 women and 6.34 ± 1.37 mg/dl for 75 men. In the sera of subjects older than 50 years, the mean concentration of SAP was lower in females than in males, but this was not significant ($P > 0.05$).

3.2. SAP concentration in women with normal menstrual cycle

The average SAP level in the follicular phase was significantly ($P < 0.01$) lower than that in the menstrual phase (menstrual: 4.36 ± 0.90 mg/dl, early follicular: 2.61 ± 0.99 mg/dl, late follicular: 2.54 ± 1.06 mg/dl, early luteal: 3.61 ± 0.92 mg/dl, and late luteal phase: 2.86 ± 1.79 mg/dl) (Fig. 2).

3.3. Effect of E on the SAP levels in postmenopausal women

After the administration of 1.25 mg of conjugated E, the SAP level decreased ($P < 0.01$) from the prelevel of 5.64 ± 1.40 mg/dl to 4.71 ± 0.99 mg/dl on the 7th day, and further decreased ($P < 0.001$) to 4.26 ± 0.98 mg/dl on the 14th day (Fig. 3). On the 21st day the SAP level was 4.40 ± 1.06 mg/dl, which was significantly ($P < 0.001$) lower than the prelevel. The serum concentrations of E2 in these women were 10.4 ± 0.5 pg/ml before administration, and increased to 66.0 ± 15.6 pg/ml on the 14th day of Premarin administration. There was a significant negative correlation between E2 and SAP levels ($n = 68$, $r = -0.588$, $Y = 5.871 - 0.024X$, $P < 0.0001$; Fig. 4). Premarin administration was effective in relieving climacteric symptoms such as hot flushes and headaches in 26 (76%) out of the 34 women.

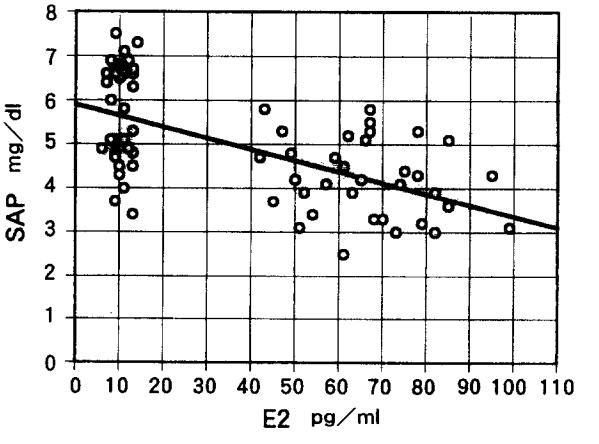

Fig. 4. Correlation between estradiol and the level of SAP ($n = 68$, $r = -0.588$, $Y = 5.871 - 0.024X$, $P < 0.0001$).

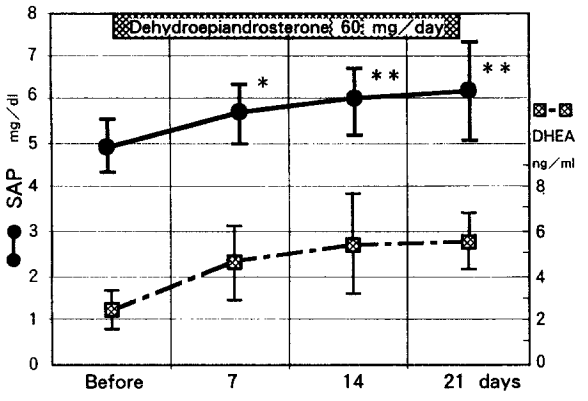

Fig. 5. Effect of DHEA on the SAP level in postmenopausal women. Shown is the mean ± S.D. of 16 women who were 45–55 years. $^{*}P < 0.01$, $^{**}P < 0.001$ compared with the level before the administration of DHEA.

3.4. Effect of DHEA on the SAP levels in postmenopausal women

After the oral administration of 60 mg of DHEA, the SAP level increased ($P < 0.01$) from the prelevel of 4.97 ± 0.76 mg/dl to 5.67 ± 0.77 mg/dl on the 7th day, and further increased ($P < 0.001$) to 5.96 ± 0.93 mg/dl on the 14th day (Fig. 5). On the 21st day, the SAP level was 6.17 ± 1.20 mg/dl, which was significantly ($P < 0.001$) higher than that prior to administration. The serum concentration of DHEA in these women was 2.5 ± 1.0 ng/ml before administration, and increased to 4.5 ± 1.7 ng/ml, 5.3 ± 2.4 ng/ml, and 5.4 ± 1.3 ng/ml, on the 7th, 14th, and 21st days, respectively. There was a significant correlation between DHEA and SAP levels ($n = 50$, $r = 0.572$, $Y = 3.625 + 0.321X$, $P < 0.0001$). DHEA administration was effective in ameliorating climacteric symptoms such as hot flushes and headaches in 12 (75%) of the 16 women.

3.5. Effect of T on the SAP levels in perimenopausal women

The serum concentration of SAP in perimenopausal women was constant before and after administration of T in this short-term study (preadministration: 4.47 ± 1.21 mg/dl and on the 14th day after T injection: 4.53 ± 1.06 mg/dl).

4. Discussion

The normal levels of SAP in human sera reported by Pepys were 3.0 ± 1.0 mg/dl in adult females and 4.3 ± 1.4 mg/dl in adult males [17]. However, the relationship between age and SAP concentration has not been reported, and the effects of sex hormones on SAP concentration have also not been clarified. We measured the SAP levels in a large number of normal females and males of various ages. The ontogeny of SAP from neonates to subjects over 80 years is presented in Fig. 1. Although no differences in SAP level between the sexes were seen in samples from newborn to 14-year-old children, a difference was observed from puberty to climacterium for subjects aged 15–49 years ($P < 0.01$). The present results showed that the level of SAP in females during the reproductive years is lower than that in males, which may be related to the low incidence of arteriosclerosis in premenopausal women [11]. SAP has been shown to bind to fibril [21], C3bi, fibronectin, collagen, and phosphoryl-choline [20] and to be deposited in various tissues such as the glomerular basement membrane [22] and blood vessels [11]. SAP modulates the coagulation of blood through neutralization of the anticoagulant effects of glycosaminoglycans [23,24].

A highly elevated concentration of SAP has recently been suggested to be related to the progression of Alzheimer's disease [3,12]. The amyloid P component has been detected in the cerebral spinal fluid (CSF) of patients with Alzheimer's disease [25]. Because mRNA of amyloid P component has not been detected in the human brain, choroid plexus or meninges, SAP may need to be transported across the blood–brain barrier [26,27]. Transported SAP has been shown to be deposited in the amyloid fibrils of senile plaques and in neurofibrillary tangles, which prevents proteolysis of the amyloid fibrils in Alzheimer's disease [12] and then induces cell death in the cerebral cortex [28].

Paganini-Hill et al. have recently suggested that the increased incidence of Alzheimer's disease in postmenopausal women may be due to estrogen deficiency and that estrogen replacement therapy may be useful for preventing or delaying the onset

of this disease [15]. The prevalence rate of Alzheimer's disease among residents aged 65 or older was estimated at 1.7% [29], and the incidence of Alzheimer's disease is greater in women than in men [30]. In the present study, the effects of sex steroids on the level of SAP were examined in patients with climacteric syndrome who were treated with either conjugated E or DHEA. Conjugated E 1.25 mg/day, double the standard dose of Premarin®, was chosen to make clear the effect of E in this short-term (21 days) study. The serum concentration of SAP decreased after E administration and increased after DHEA administration. The SAP level in the follicular phase was significantly ($P < 0.01$) lower than that in the menstrual phase. As the SAP level decreased in response to E2, E therapy seems to be beneficial to decrease the serum level of SAP. Estrogen replacement therapy may delay the onset of Alzheimer's dementia by preventing the deposition of the amyloid P component. In contrast, DHEA administration may have an adverse effect by increasing the serum level of SAP. Nevertheless, DHEA administration was effective in relieving climacteric symptoms such as hot flushes and headaches in 12 (75%) of the 16 women. Morales et al. also reported that oral DHEA administration (50 mg) over a 6-month period was effective in relieving climacteric symptoms with a marked increase in perceived physical and psychological well-being for women (84%) [18]. Androgen therapy seems to be effective in relieving some climacteric symptoms.

In contrast to the SAP levels in humans, those in the Syrian hamster are high in females and almost nil in males [31]. The level of SAP decreased in the adult female hamster when given a daily injection of testosterone and increased in adult males after castration. Administration of diethylstilbestrol to adult male hamsters consistently resulted in the prolonged appearance of SAP in the serum [32]. These observations indicate that testosterone has a suppressive effect on the level of SAP in the hamster. It has recently been reported that the serum level of SAP was highly elevated in aged rodents, and this high level was decreased by DHEA administration [20,9]. The reasons for these differences in SAP level between species are unclear, SAP levels show opposite changes in response to E and DHEA between humans and rodents such as hamsters and rats, which reflects the problems of extrapolating the results of animal studies to man. The level of SAP in women was not changed on the 14th day after T injection. The lack of effect of T on SAP levels may be related to the short time frame. The level of SAP in human subjects decreased following administration of E, and increased on administration of DHEA. Thus, SAP seems to be a good marker for monitoring of the effects of hormone replacement therapy.

In conclusion, the present preliminary results support the hypothesis that estrogen replacement therapy may have a beneficial effect on Alzheimer's disease through the reduction of serum SAP level. Future trials are warranted to assess the effects of long-term administration of Premarin® at 0.625 mg/day or progesterone on the serum concentration of SAP.

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