Br. J. clin. Pharmac. (1985), **20**, 500–502

Determinants of plasma α_1-acid glycoprotein (AAG) concentrations in health

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The concentration of α_1-acid glycoprotein (AAG) was measured in plasma from 200 healthy subjects belonging to 78 family units. The AAG concentration varied markedly between individuals (mean 0.77, range 0.36–1.46 g l^{-1}). When the genetic contribution to the variability was assessed, the only significant correlation observed was that between husband and wife and this was weak. We conclude that in addition to the known effects of age and gender, environmental (rather than genetic) factors largely determine the variance of AAG concentrations.

Keywords α_1-acid glycoprotein genetic factors environmental factors

Introduction

α_1-acid glycoprotein (AAG) and albumin are the two major drug binding proteins in plasma. Both acidic and basic drugs bind to human albumin, whereas AAG has so far only been shown to bind basic drugs. Plasma concentrations of AAG may be altered in disease, and thus change the extent of plasma drug binding (Piafsky, 1980). However, there is little information about the factors responsible for individual variability of the plasma concentration of AAG in health. We have therefore undertaken a family study to determine the relative contribution of genetic and environmental influences on plasma concentration of AAG in health.

Methods

Two hundred healthy ambulant individuals belonging to 78 family units and aged 18 years or over volunteered for the study which had met with the approval of the local ethics committee. Two subjects were Italian and two subjects were of Asian origin. Their antipyrine clearances formed the basis of another study (Blain *et al.*, 1982). Blood was obtained by direct venepuncture into lithium heparin tubes and the plasma separated, and stored at −20° C. AAG concentrations were determined in plasma by single radial immunodiffusion (Mancini *et al.*, 1965). In all instances, the stated family relationships were compatible with the blood group antigens on twelve red cell loci. All subjects had a normal full blood count, plasma urea, creatinine, electrolytes, bilirubin, aspartate transaminase, alkaline phosphatase and serum albumin and globulin. Smoking habits, oral contraceptive usage, height, weight, gender and age were recorded in all subjects. No patient (other than those taking oral contraceptives) was taking any prescribed drug. The distribution of red cell blood group loci was not significantly different from that previously reported for the Tyneside area indicating that the sample was polymorphically typical of the population (Papita, 1973). The estimates of heritability for height and weight

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were also similar to those previously reported for the general population (Blain *et al.*, 1982), indicating that the sample was also polygenically typical of the general population from which it was drawn.

Correlations were performed where appropriate by least squares correlation analysis. Differences between means were examined using the unpaired sample *t*-test and in all cases $P < 0.05$ was taken as the minimal degree of statistical significance.

Results

The two hundred volunteers were aged between 18 and 72 years and 196 of these were of white British descent.

The plasma AAG concentration varied widely in the group (range 0.36–1.46 g l^{-1}, see Figure 1). The mean value for the group was 0.77 g l^{-1} ± 0.15 s.d. ($n = 200$). The mean concentration in males, however, was significantly greater than in females (0.814 g l^{-1} ± 0.183 s.d. $n = 100$ *vs* 0.739 g l^{-1} ± 0.168 $n = 100$, $P < 0.01$). The concentration of AAG increased significantly with age in females ($r = 0.358$, $P < 0.05$) but not in males ($r = 0.075$ NS). There was no significant difference between the plasma AAG concentration of non-smokers and smokers either in the males or in the females. The mean ages of non-smokers and smokers (of either sex) were not significantly different. Twenty-four female subjects were taking an oral oestrogen/progesterone contraceptive preparation. The mean AAG concentration in this group (0.67 ± 0.15 g l^{-1}) did not differ significantly from the mean AAG concentration in 24 age matched (to within 3 years) females not receiving any contraceptive pill (0.72 ± 0.13 g l^{-1}).

The genetic contribution to the variability in AAG concentration was assessed after correction for gender and for age in females. The correlation coefficients between family members' AAG concentrations are shown in Table 1. The mid-parent values were the mean of the corrected AAG concentrations of the two parents. The only significant correlation observed was that between husband and wife ($r = 0.268$, $P < 0.05$, $n = 65$).

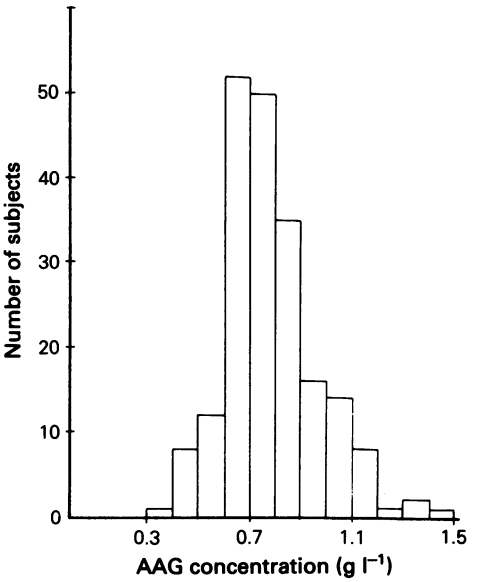

Figure 1 Histogram showing the distribution of AAG concentrations in the 200 subjects studied.

Discussion

The values for plasma AAG concentrations in our population are similar to those previously reported for healthy individuals (Storiko, 1968). We have also shown a small (9%) but significant

Table 1 Correlation coefficients (mean ± s.e. mean) for AAG between the various groups studied

Correlation (*x*)	(*y*)	*d.f.*	*Correlation coefficient*	P
Mid-parent	Offspring	29	–0.098 ± 0.18	NS
Father	Offspring	37	0.082 ± 0.16	NS
Father	Son	16	0.095 ± 0.24	NS
Father	Daughter	19	0.136 ± 0.21	NS
Mother	Offspring	43	0.039 ± 0.02	NS
Mother	Son	20	–0.151 ± 0.04	NS
Mother	Daughter	21	0.277 ± 0.04	NS
Sibling	Sibling	17	0.225 ± 0.22	NS
Husband	Wife	63	0.268 ± 0.12	$P < 0.05$

difference between males and females. This trend has been observed in previous studies but did not reach statistical significance (Routledge *et al.*, 1981). We were unable to demonstrate a significant effect of the oral contraceptive in females as shown in other studies (Song *et al.*, 1970; Routledge *et al.*, 1981): we have no explanation for this. One study has shown a small age-related increase in AAG occurring in both sexes (Davis *et al.*, 1985) and our failure to observe an increase in males may have been due to the relatively smaller age range in the present study. The poor correlation between mid-parent and offspring shown in Table 1 provides no evidence for an additive genetic contribution to the population variance of AAG concentrations, but clearly, a minor genetic contribution remains possible. The suggestion that the variance in AAG concentration is mainly determined by environmental factors is supported by the significant correlation between spouses, all of whom cohabited. It is also supported by the poor correlation between plasma AAG concentration ($r = 0.40$) reported by Storiko (1968) in 11 pairs of identical twins. The lack of correlation for AAG concentration between siblings in our study (16 of whom lived apart) suggests that the environmental influences are not long-term.

In conclusion, we believe that in addition to the known effects of age and gender, environmental (rather than genetic) factors largely determine the variance of AAG concentrations. Although these factors are not clearly understood, they result in marked variability in plasma protein binding for those drugs where AAG is the major binding protein.

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(Received 23 May 1985, accepted 27 July 1985)