PLASMA AMINO ACIDS IN SUBJECTS TAKING ORAL CONTRACEPTIVES

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Oral contraceptives are known to influence the metabolism of lipids, carbohydrates and proteins. Robinson (1962), and Marmorston (1963) have shown that the administration of the oral contraceptive, Enovid, decreases serum cholestrol and increases serum phospholipids. Alterations in glucose metabolism are known to occur in pregnancy and after administration of estrogen, and oral contraceptives. A decrease in glucose tolerance is observed in 50% of patients receiving oral contraceptives (Drill, 1966). Gershberg *et al* (1964) reported an increase in the level of fasting blood glucose in subjects receiving Envoid. Relatively little is known as far as protein metabolism is concerned. Craft and Wise (1969) studied the plasma alpha amino nitrogen level during the proliferative and secretory phases of the menstrual cycle, both in normal women and in those taking oral contraceptives. They found a lowering of plasma alpha amino nitrogen values during the secretory phase in both the groups, but the fall was greater in cases taking oral contraceptives as compared to normal women. These findings of Craft and Wise (1969) in normal women are consistant with the findings of Soupart (1960), and of Singh, Saini and Bajaj (1971) who reported a general lowering of the plasma concentration of all amino acids during the secretory phase of the menstrual cycle. In view of these findings and in view of findings of Craft and Wise (in subjects taking oral contraceptives) it was anticipated that plasma amino acids would show a definite fall during the secretory phase in the menstrual cycle of women taking oral contraceptives; it was also anticipated that these changes would be more pronounced than in normal subjects. However, the present study reveals certain unexpected findings that are reported in this paper.

Material and Methods

The subjects for this study were twenty normal healthy women who had been taking oral contraceptives for periods ranging from one to three years. The preparation used was Ovulen-Fe-28 (Searle) containing 1 mg ethynodiol diacetate and 0.1 mg of mestranol. Two fasting blood samples were taken, one when the subject had been on pills for 20-25 days, and the second when the menstrual bleeding had set in. The samples were investigated for amino acids by unidimensional paper chromatography as described by Singh, Saini and Bajaj

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(1971). Using this method the amino acids separated out into a number of groups. Each group has been quantitated in terms of one amino acid as indicated in Table 1.

TABLE I

Amino Acid Groups Separated From Human Plasma by Unidimensional Chromatography

Group	Amino acids	Amino acids in in terms of which spot was quantitated
I	Leucine	Leucine
	Isoleucine	
II	Valine	Valine
	Methionine	
III	Alanine	Alanine
IV	Threonin	Threonin
	Glutamic acid	
V	Glycine	Glycine
	Serine	
	Glutamine	
	Taurine	

Observations

The levels of plasma amino acids in the twenty subjects studied during, the menstrual and the secretory phases, are given in Table II.

From these Tables it is seen that the mean values are lower in the secretory phase as compared to the menstrual phase not only for total amino acids but also for each individual amino acid. However, paired 't' tests show that the observed differences are significant only for amino acids of group V (Glycine, serine, glutamine and taurine). These findings are compared with those in subjects not receiving oral contraceptives, and their significance discussed below.

Discussion

A comparison of the findings of the present investigation on subjects taking the oral contraceptive Ovulen, with those in subjects not taking the drug (Singh *et al,* 1971) reveal the following interesting facts (Compare Table 2 with Table 3 of Singh *et al,* 1971).

(a) There is a fall in the plasma amino acid levels during the secretory phase in both groups. In the control group the fall is statistically significant in the case of amino acids of group I, group II, group III and for total amino acids. However, in the group taking the contraceptive, results are not significant in any of these groups. They are also not significant for total amino acids, but are significant for amino acids of groups V.

(b) The mean plasma levels of all groups of amino acids except those of group IV, are higher in the control subjects than in those taking Ovulen, both in the menstrual and in the secretory phases of the menstrual cycle (Table IV). These differences are statistically significant in most cases.

(c) The mean plasma levels of amino acids of group IV are higher in the subjects taking ovulen than those in control subjects. The difference is significant at the 1% level during the menstrual phase. During the secretory phase the difference is not significant but this is probably due to small size of the sample as the value of 't' (1.99) almost reaches the 5% significance level (2.03).

The lowering of plasma amino acids has been attributed to the catabolic action of progestrone. This is shown by the work of Landau and Lugibihl (1961) who found increased urinary nitrogen excretion in both men and women after administration of progestrone. The increase in urinary nitrogen was mainly due to urea and there was no significant variation in the excretion of urinary amino acids. They therefore concluded that reduced plasma levels of amino acids were not caused by increased urinary excre-

TABLE II

Plasma Amino Acid Levels (μg/lm) in 20 Subjects Taking Oral Contraceptives During Menstrual (M) and Secretory Phase (S) of the Menstrual Cycle

	Group I		Group II		Group III		Group IV		Group V		Total	
	M	S	M	S	M	S	M	S	M	S	M	S
1	25.2	14.0	25.2	14.0	22.4	16.8	42.0	19.6	25.2	19.6	140.0	84.0
2	30.8	33.6	28.0	33.6	33.6	44.8	44.8	95.2	30.8	22.4	168.0	229.6
3	36.4	30.8	39.2	39.2	36.4	61.6	78.4	44.8	44.8	36.4	235.2	212.8
4	25.2	25.2	33.6	28.0	44.8	30.8	50.4	25.2	22.4	14.0	176.4	123.2
5	36.4	28.0	39.2	28.0	30.8	19.6	64.4	56.0	61.6	36.4	232.4	168.0
6	25.2	28.0	19.6	25.2	19.6	22.4	50.4	33.6	30.8	19.6	145.6	128.8
7	30.8	33.6	30.8	30.8	53.2	36.4	70.0	33.6	42.0	25.2	226.8	159.6
8	39.2	14.0	42.0	8.4	50.4	8.4	42.0	8.4	30.8	5.6	204.4	44.8
9	33.6	25.2	30.8	22.4	56.0	61.6	78.4	30.8	42.0	22.4	240.8	162.4
10	16.8	33.6	16.8	36.4	33.6	42.0	30.8	53.2	33.6	42.0	131.6	207.2
11	53.2	30.8	64.4	30.8	61.6	33.6	100.8	44.8	50.4	25.2	330.4	165.2
12	36.4	36.4	36.4	36.4	39.2	47.6	112.0	112.0	56.0	44.8	280.0	277.2
13	25.2	42.0	25.2	36.4	30.8	33.6	30.8	56.0	36.4	36.4	148.4	204.4
14	30.8	28.0	33.6	28.0	42.0	28.0	33.6	33.6	33.6	28.0	173.6	145.6
15	30.8	33.6	28.0	30.8	42.0	25.2	30.8	44.8	42.0	33.6	173.6	168.0
16	19.6	30.8	19.6	33.6	39.2	56.0	36.4	56.0	28.0	36.4	142.8	212.8
17	39.2	30.8	42.0	30.8	47.6	33.6	61.6	33.6	33.6	28.0	224.0	156.8
18	22.4	19.6	22.4	16.8	42.0	16.8	39.2	19.6	33.6	25.2	159.6	98.0
19	25.2	28.0	30.8	36.4	42.0	44.8	50.4	42.0	36.4	36.4	184.8	187.6
20	39.2	30.8	42.0	36.4	33.6	33.6	56.0	30.8	22.4	33.6	193.2	165.2

TABLE III

Mean Plasma Amino-acid Levels in Cases Taking Oral Contraceptives

Amino-acids	Menstrual		Secretory		't' test	Signi-ficance
	Mean	S.E.	Mean	S.E.		
Group I	31.08	1.87	28.84	1.54	P <0.5	—
Group II	32.48	2.66	29.12	1.83	P <0.5	—
Group III	40.04	2.37	34.86	3.33	P <0.50	—
Group IV	55.16	5.12	43.68	5.45	P <0.50	—
Group V	36.82	2.32	28.56	2.17	P <0.02	+
Total	195.5	11.52	170.0	15.05	P <0.1	—

TABLE IV

Comparison of Mean Plasma Amino Acid Levels in Subjects Taking Oral Contraceptives (ovulen) With Those of Normal Controls

	Normal subjects	Subjects on oral contraceptives	P (unpaired 't' test)	Significance
A. 1-5 day of cycle				
Group I	37.28	31.08	<0.05	+
Group II	43.12	32.48	<0.01	+
Group III	47.75	40.04	<0.01	+
Group IV	39.62	55.16	<0.01	+
Group V	43.68	36.82	<0.1	—
Total	211.26	195.50	<0.5	—
B. 20-25 day of cycle				
Group I	33.04	28.84	<0.05	+
Group II	35.42	29.12	<0.05	+
Group III	37.61	34.86	<0.5	—
Group IV	29.26	43.68	<0.1	—
Group V	38.78	28.56	<0.01	+
Total	174.15	170.0	<0.05	+

tion but by increased amino acid utilization by the liver.

The observation that plasma amino acid levels are lower in subjects taking oral contraceptives than in normal controls can therefore be explained by presuming that, in the former, levels of progestrone are higher than normal throughout the cycle. As amino acid levels in them are lower than normal even in the menstrual phase it is not surprising that the fall during the secretory phase is less marked than in normal controls, and is therefore not statistically significant for the sample studied.

Significant findings of the present series of investigations, not brought out by earlier workers, are

(a) that the metabolic effects of progestrone do not affect all amino acids equally (See para 'a' of discussion above) and

(b) that the effects of oral contraceptives on amino acid metabolism are different from those in normally menstruating women, both in quantity and in quality.

In this connection the findings regarding amino acids of group IV are of special interest (See para 'c' of discussion above). The observed alterations in protein metabolism caused by oral contraceptives may well be of considerable practical significance and need to be kept in mind in evaluating the long term effects of these drugs.

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