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METABOLISM OF AN ORAL TRYPTOPHAN LOAD BY WOMEN AND EVIDENCE AGAINST THE INDUCTION OF TRYPTOPHAN PYRROLASE BY ORAL CONTRACEPTIVES

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1 A single oral L-tryptophan load (0.245 mol/kg: 50 mg/kg) was given to young women taking no drugs or taking an oral contraceptive.

2 Following tryptophan administration, plasma tryptophan concentrations rose approximately 5 fold reaching a peak 1–2 h after the load. Plasma kynurenine concentrations also rose reaching a peak 3 h after the load. Plasma tryptophan changes were the same in both groups but kynurenine concentrations were lower in the oral contraceptive group 1, 2 and 3 h after the load.

3 There was very little increase in urinary tryptophan or 5-hydroxyindoleacetic acid excretion in the 24 h following the load and just over a doubling of indoleacetic acid excretion. The excretion of these compounds was similar in both groups.

4 The group taking an oral contraceptive excreted less kynurenine in the urine than the control group both during the 24 h before the load and the 24 h following the load, although the percentage increase following the load was much greater in the oral contraceptive group.

5 In agreement with previous studies it was found that women on oral contraceptives excreted significantly greater quantities of 3-hydroxykynurenine and xanthurenic acid following the tryptophan load and 3-hydroxyanthranilic acid values also tended to be raised.

6 The volume of distribution, plasma clearance and plasma half-life of tryptophan was similar in both groups of subjects.

7 It is concluded that, in agreement with other studies, the excretion of certain tryptophan metabolites is raised in women on oral contraceptives. However, the data on plasma clearance indicates that, contrary to previous hypotheses this change is not attributable to an increase in the activity of liver tryptophan pyrrolase. Other possible reasons such as a relative deficiency of vitamin B_6 are discussed.

Introduction

Depression is one of the recognized side effects in women taking oral contraceptives (OC) occurring in 5–7% of such women (Herzberg & Coppen, 1970; Herzberg, Johnson & Brown, 1970; Adams, Rose, Folkard, Wynn, Seed & Strong, 1973). There have been attempts to link the pathogenesis of this mood change with changes in peripheral tryptophan metabolism.

Tryptophan is metabolized along two main pathways (Figure 1). The quantitatively major route is the kynurenine-niacin pathway, while the other main pathway results in the formation of 5-hydroxytryptamine (5-HT), a putative neurotransmitter in the brain which has been suggested to be involved in the control of mood (for review see Green & Grahame-Smith, 1975). The first enzyme of the niacin pathway is liver tryptophan pyrrolase (L-tryptophan-2,3,-dioxygenase, EC 1.13.1.12) which is induced by hydrocortisone and corticosterone (Knox & Auerbach, 1955). Induction of this enzyme by hydrocortisone in rat liver is associated with a decrease in brain 5-HT (Green & Curzon, 1968) presumably as the result of decreased availability of tryptophan (Green, Sourkes & Young,

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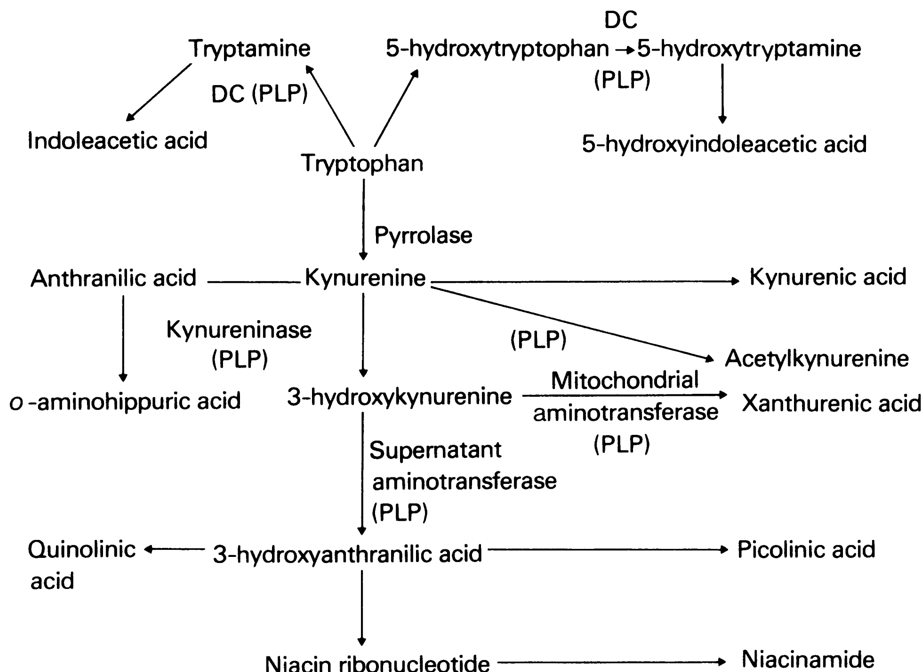

Figure 1 Tryptophan metabolism. A simplified diagramatic metabolic pathway.
PLP: pyridoxal phosphate
DC: aromatic amino acid decarboxylase.

1975; Green, Woods, Knott & Curzon, 1975). Since oestrogen administration increases plasma corticosterone concentrations (Keller, Richardson & Yates, 1969) various authors have suggested that oestrogens might increase pyrrolase activity which in turn would decrease brain 5-HT synthesis, thereby producing the mood change (for example see Rose, 1966; Rose & Braidman, 1971; Rose, 1972; Winston, 1973; Adams *et al.*, 1973; Grant, 1975; Wynn, 1975; Malik-Ahmadi & Behrmann, 1976).

The evidence for increased pyrrolase activity is that urinary excretion of several niacin pathway metabolites, namely 3-hydroxykynurenine, xanthurenic acid and sometimes 3-hydroxyanthranilic acid (Figure 1) is higher in women taking oral contraceptives following administration of an oral tryptophan load. The hypothesis therefore clearly relies on the combination of indirect observations on both humans and rats brought together in a unified theory.

There is still no convenient method of assessing *in vivo* pyrrolase activity in man. Recently, however, a specific method has been developed for measuring kynurenine in plasma (Joseph & Risby, 1975) and it has been shown that hydrocortisone pretreatment in rats leads to an increased concentration of kynurenine in the medium circulating through a perfused rat liver (Green, Woods & Joseph, 1976). Furthermore pyrrolase activity measured *in vitro* correlated well with the appearance of kynurenine (Green *et al.*, 1976). . It has also been shown that increased pyrrolase activity in rats is associated with increased plasma concentrations of kynurenine following a tryptophan load (Joseph, Young & Curzon, 1976). We felt therefore that an index of pyrrolase activity in humans could be measured by assessing both the rates of tryptophan and kynurenine appearance and disappearance in plasma following an oral tryptophan load. This communication reports the results of such a study together with observation on the production of urinary tryptophan metabolites following the tryptophan load.

Methods

Subjects

Healthy young female volunteers (mean age 24 years; range 19–39 years) were recruited from the medical students and from members of various hospital departments for this study. None of the subjects was

taking any drugs other than oral contraceptives (in the case of the experimental group) and all subjects avoided alcohol ingestion both the day before and the day of the load since it has been reported that alcohol induces tryptophan pyrrolase activity (Badaway & Evans, 1972). The oral contaceptives taken are listed in Table 1; all experimental subjects had been on oral contraceptives for at least 6 months and no control subject had taken oral contraceptives for at least 3 months. In most cases the tryptophan load was administered between 15 and 20 days after the start of the menstrual cycle.

Protocol

The protocol is outlined in Table 2. A 24 h urine collection (over 10 ml glacial acetic acid) was taken from 10.00 h–10.00 h, the bladder having been voided immediately prior to the start of the collection. At the end of this collection period (10.00 h) a 10 ml blood sample was taken from the antecubital vein into a lithium heparin tube, a 5 h urine collection initiated and the subject was given a 0.245 mol/kg (50 mg/kg) oral tryptophan load. L-tryptophan was given by crushing Optimax tablets (without vitamin supplement) (Batch 72101; Cambrian Pharmaceuticals) and suspending the powder in an orange drink. This was done because of the size and number of tablets to be taken and to try and minimize individual variation in drug absorption. Further venous blood samples (10 ml) were taken at 11.0 h, 12.00 h, 13.00 h and 15.00 h. At 15.00 h a third urine collection was started and continued until 10.00 h the next day. Subjects were not fasted before administration of the load and were allowed to take coffee, tea and lunch during the experiment.

Analytical procedures

Blood was centrifuged at 2500 *g* for 5 min, plasma removed and kept at −20°C until analysis for tryptophan and kynurenine. Total urine volumes were measured and an aliquot frozen (−20°C) for subsequent analysis of tryptophan, kynurenine, 3-

Table 1 Oral contraceptives being taken, with their formulation and number of subjects on each preparation

Drug	*Oestrogen*	*Dose (μg)*	*Progestogen*	*Dose (mg)*	*Number of subjects*
Eugynon 30	Ethinyloestradiol	30	dl-norgestrel	0.5	4
Microgynon 30	Ethinyloestradiol	30	d-norgestrel	0.15	3
Ovranette	Ethinyloestradiol	30	d-norgestrel	0.15	2
Eugynon 50	Ethinyloestradiol	50	dl-norgestrel	0.5	1
Ovulen 50	Ethinyloestradiol	50	Ethynodioldiacetate	1.	1
Minilyn	Ethinyloestradiol	50	Lynestrenol	2.5	1
Gynovlar 21	Ethinyloestradiol	50	Norethisterone	3	1
Lyndiol	Ethinyloestradiol 3-methylether (mestranol)	75	Lynestrenol	2.5	1*

* Subject on this drug for 2.5 years and then 1 month before study on Ovranette.

Table 2 Outline of experimental protocol. For details see text. The tryptophan load was taken immediately after the blood was collected at 10.00 h Day 2. Total experimental period: 48 h.

Day	*Period*	*Time*	*Load*	*Blood*	*Urine*
1	Control	10.00			1st collection (start)
2	Experimental	10.00	Tryptophan 50 mg/kg	10 ml	1st collection (end); 2nd collection (start)
		11.00		10 ml	2nd collection
		12.00		10 ml	2nd collection
		13.00		10 ml	2nd collection
		15.00		10 ml	2nd collection (end); 3rd collection (start)
3		10.00			3rd collection (end)

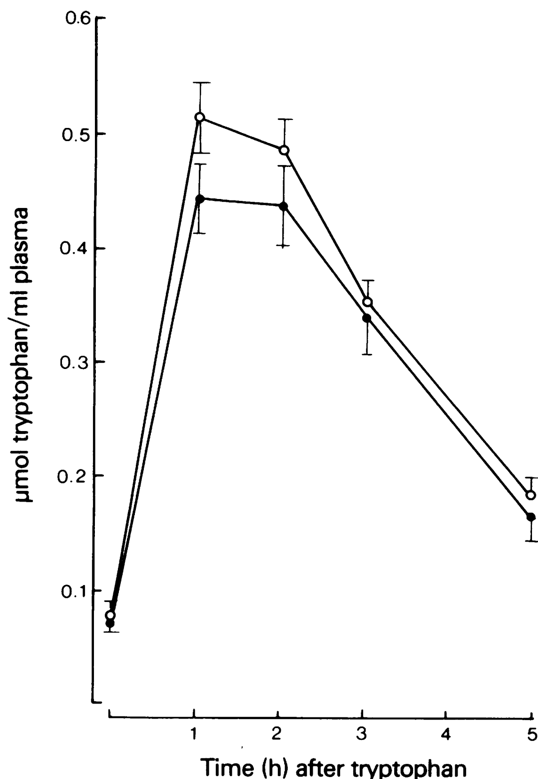

Figure 2 Plasma tryptophan concentrations during the 5 h following administration of an oral tryptophan load (50 mg/kg). Each point shows mean and bars indicate ± s.e. mean of the ten control subjects (O) and fourteen subjects on oral contraceptives (●).

hydroxykynurenine, 3-hydroxyanthranilic acid, xanthurenic acid, 5-hydroxyindoleacetic acid and indoleacetic acid.

Plasma and urine tryptophan concentrations were measured using the method of Denckla & Dewey (1967). Plasma and urine kynurenine concentrations were measured by a modification of the method of Joseph & Risby (1975) in which the method was scaled down by 50%; in addition, the perchloric acid/Tiron step was not eliminated from the urinary method as had been suggested. 3-hydroxykynurenine and 3-hydroxyanthranilic acid were measured by the column chromatographic methods of Price, Brown & Yess (1965) as modified by Heeley (1965). Xanthurenic acid was separated by thin layer chromatography as described by Walsh (1965) except that silica gel plates were used. Quantitation was achieved by scraping the fluorescent spot from the plate, eluting with 0.01 N NaOH and reading the native fluorescence at activation: 350 nm, fluorescence: 440 nm (both uncorrected) using an Aminco–Bowman spectrophotofluorometer. 5-hydroxyindoleacetic acid was determined by the method of Udenfriend, Weissbach & Brodie (1958). Indoleacetic acid was measured spectrophotofluorimetrically using the method described by Coppen, Shaw, Malleson, Eccleston and Grundy (1965) except that all volumes were reduced by 50%.

Mathematical methods

The half-times of the terminal exponentials of tryptophan elimination from the plasma were calculated by least-squares linear regression using a Hewlett–Packard model 9810A desk-top computer. The areas under the curves (AUC) of the tryptophan plasma concentration versus time curve were calculated using the trapezoidal rule for the first part of the curve above basal concentrations and integration of the terminal exponential phase between the onset of the terminal phase and the time to return to basal concentrations. The use of these calculations assumes that basal concentrations would remain constant during the period of study.

Plasma clearance was calculated using the equation

$$\text{Clearance} = \text{Dose}/\text{AUC}$$

and apparent volume of distribution (V_d) using the equation

$$V_d = \text{Dose}/\text{AUC} \times \beta$$

where $\beta = \ln 2/T\frac{1}{2}$.

Comparison between the two groups was made using Student's two-tailed unpaired *t* test.

Results

Plasma tryptophan changes following an oral tryptophan load

No difference was observed in plasma tryptophan concentrations between the control and oral contraceptive (OC) group before administration of the load (Figure 2). Following oral tryptophan administration there was a rapid rise in plasma tryptophan with peak values occurring between 1 and 2 h after the administration (Figure 2) in agreeement with the observation of Joseph & Risby (1975). No statistical difference was observed between the two groups with regard to either time to peak or maximum plasma values achieved. The decline in plasma concentration (2–5 h) was exponential with a plasma half-life of just over 2 h (Table 3) that was almost identical in both groups. Plasma clearance was very similar in both groups as was the apparent volume of distribution.

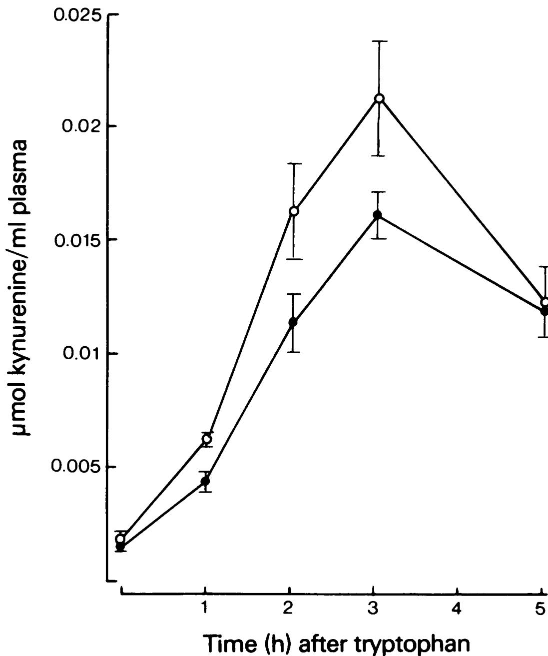

Figure 3 Plasma kynurenine concentrations during the 5 h following administration of an oral tryptophan load (50 mg/kg). Each point shows mean and bars indicate ± s.e. mean of the ten control subjects (O) and fourteen subjects on oral contraceptives (●). Oral contraceptive group show lowered plasma kynurenine concentrations which are significantly different from the control group 1 h ($P<0.01$), 2 h ($P<0.05$) and 3 h ($P<0.05$) following the tryptophan load.

Plasma kynurenine changes following an oral tyrptophan load

No difference was observed in initial plasma kynurenine concentrations between the control and OC group before administration of the load (Figure 3). Following oral tryptophan administration there was a rise in the plasma kynurenine concentration reaching peak about 3 h after the tryptophan ingestion. While there was no difference in the time to peak values the OC group showed significantly lower values at 1, 2 and 3 h after the load.

Urinary tryptophan excretion

Urinary tryptophan excretion during the control period was identical in both groups (Table 4). Following tryptophan administration there was very little increase in tryptophan excretion, only 10 µmol (2 mg) more being excreted during the 24 h period following the load. OC administration did not affect this excretion (Table 4). This suggests that renal clearance of tryptophan is almost negligible and is not altered by OC administration.

Urinary excretion of various tryptophan metabolites

The urinary excretion of kynurenine was examined both during the control day and following the administration of the tryptophan load. The excretion of xanthurenic acid, 3-hydroxykynurenine and 3-hydroxyanthranilic was only studied during the load day however as Rose & Braidman (1971) using similar methods showed that the measurement of these tryptophan metabolites is only possible after a tryptophan load.

The excretion of kynurenine during the control period was found to be decreased in those subjects taking OC. During the load day the percentage increase in kynurenine excretion from the control value was greater in the OC group (1400%) than the control group (375%). Nevertheless the absolute excretion of kynurenine by the OC group was only about 60% of the control values (Table 5).

The OC group excreted more xanthurenic acid than the controls and this value reached statistical significance during the second collection period and for the total collection period (Table 5). The large variation in xanthurenic acid excretion observed by others (e.g. Rose, 1966) was also seen in this study (control range 29–73, OC range 34–312 both in µmol/24 h).

Excretion of 3-hydroxykynurenine was also

Table 3 The plasma half-life ($T_{\frac{1}{2}}$), plasma clearance and apparent volume of distribution (V_d) of tryptophan following an oral tryptophan load (50 mg/kg)

Group	$T_{\frac{1}{2}}$ (h)	Correlation	AUC ($\mu g\ ml^{-1}\ h$)	Plasma clearance ($ml\ kg^{-1}\ min^{-1}$)	Apparent V_d (l/kg)
Control	2.12 ± 0.15	0.983 ± 0.010	291 ± 30	0.716 ± 0.082	0.572 ± 0.074
OC	2.20 ± 0.13	0.980 ± 0.011	330 ± 18	0.792 ± 0.057	0.488 ± 0.027

Details of mathematical methods given in **Methods** section. AUC = area under plasma tryptophan versus time curve. Results show mean ± s.e. mean of determinations on the ten control subjects and fourteen subjects on oral contraceptives (OC).

increased in the OC group but only during the first collection period and there was no significant difference in the total 24 h excretion (albeit the mean excretion was higher (Table 5). 3-hydroxyanthranilic acid excretion showed a tendency to be raised in the OC group but this was not statistically significant.

One control subject showed grossly elevated excretion of xanthurenic acid, 3-hydroxykynurenine and kynurenine (raised approximately eight times the standard deviation of the other nine subjects) and was therefore excluded from the statistical anlysis.

Urinary 5-hydroxyindoleacetic acid excretion

It is almost certain that urinary 5-HIAA excretion is indicative of peripheral 5-HT metabolism and that the contribution from central 5-HT metabolism is negligible. Nevertheless a lack of availability of tryptophan for adequate brain 5-HT synthesis might also be seen in the peripheral metabolism of this amine. We therefore investigated the urinary excretion of 5-HIAA in our control and OC subjects.

There was no statistically significant difference in 5-HIAA excretion between the controls and OC groups (Table 6). Furthermore administration of an oral tryptophan load did not influence the excretion of 5-HIAA by either group (Table 6).

Urinary indoleacetic acid excretion

We also investigated the excretion of the tryptamine metabolite indoleacetic acid (IAA) both before and after administration of the oral tryptophan load to both groups.

There was no significant difference in the IAA excretion between the two groups during the control 24 h urine collection (Table 6). Nor was there any difference between the two groups in the excretion of IAA following the tryptophan load although the mean value was raised in the OC group (Table 6). However unlike 5-HIAA, excretion of IAA was increased by tryptophan administration.

Discussion

The renal clearance of tryptophan following an oral tryptophan load is negligible (Table 4) and the

Table 4 Total urinary excretion of tryptophan by control subjects and those on oral contraceptives (OC). Results expressed as mean ± s.e. mean of the excretion by the ten control subjects and fourteen subjects. Results in total μmol excreted during collection periods stated in table

	Collection times			
	Control period 10.00 h–10.00 h (24 h)	*10.00 h–15.00 h (5 h)*	*Experimental period 15.00 h–10.00 h (19 h)*	*Total (24 h)*
Control	34.11 ± 2.35	16.76 ± 2.64	28.52 ± 2.89	45.24 ± 1.86
OC	34.41 ± 3.62	16.76 ± 3.53	26.96 ± 2.10	43.72 ± 3.08

Table 5 Total urinary excretion of various tryptophan metabolites by control subjects and those on oral contraceptives (OC). Results expressed as mean ± s.e. mean of the excretion by the nine control subjects and fourteen OC subjects. Results show total μmol metabolite excreted during collection period stated in table.

		Collection times			
Metabolite measured	*Group*	*Control period 10.00 h–10.00 h (24 h)*	*10.00 h–15.00 h (5 h)*	*Experimental period 15.00 h–10.00 h (19 h)*	*Total (24 h)*
Kynurenine	Control	22.75 ± 1.56	68.52 ± 18.14	39.62 ± 17.91	108.11 ± 22.42
	OC	4.08 ± 0.52*	39.36 ± 7.58	22.45 ± 8.63	61.82 ± 11.11†
3-OH Kynurenine	Control	ND	212.09 ± 29.37	356.38 ± 41.52	568.48 ± 52.45
	OC	ND	539.15 ± 97.32§	448.66 ± 92.27	987.8 ± 168.12
Xanthurenic acid	Control	ND	9.27 ± 2.87	39.70 ± 6.63	48.97 ± 6.09
	OC	ND	31.31 ± 11.46	96.82 ± 25.41†	128.14 ± 25.07‡
3-OH Anthranilic acid	Control	ND	109.80 ± 10.58	199.47 ± 45.03	305.03 ± 39.93
	OC	ND	165.81 ± 25.42	195.16 ± 37.91	365.30 ± 58.49

Different from respective control *$P < 0.001$, †$P < 0.05$, ‡$P < 0.025$, §$P < 0.01$. ND Not determined.

metabolism by the other major metabolic pathways to 5-HIAA and IAA is not greatly altered, and is similar in the control and OC group (Table 6). Removal of tryptophan from the circulation must probably therefore be largely by uptake and by metabolism by hepatic tryptophan pyrrolase. The apparent volume of distribution of tryptophan is the same in both groups and corresponds closely (34–40 l) with the normal total body volume making it unlikely that oral contraceptives alter uptake of tryptophan by tissues. Thus the fact that the plasm half-life, area under the plasma tryptophan curve and plasma clearance are identical in the control and OC groups indicates strongly that the rate of tryptophan metabolism by liver tryptophan pyrrolase is the same in both groups. We are thus unable to confirm the suggestion of others that oral contraceptives induce tryptophan pyrrolase.

On the other hand we are able to confirm the findings of other workers over several years (e.g. Rose, 1966; Adams *et al.*, 1973; Leklem, Brown, Rose, Linkswiler & Arend, 1975; Luhby, Brin, Gordon, Davis, Murphy & Spiegel, 1971) that women taking OC show increased urinary excretion of xanthurenic acid and 3-hydroxykynurenine in the first few hours following an oral tryptophan load and our results were quantitatively similar to those of these workers. We also observed, in agreement with Rose (1966) a tendency to raised 3-hydroxyanthranilic acid in the OC group. This indicates that our failure to demonstrate increased pyrrolase activity while on OC is not due to the current oral contaceptives having a lower content of oestrogen than a few years ago. This is also indicated by our observation that there was no difference in the metabolic responses of the subjects on the low oestrogen dose contraceptives (30 μg) to those on the higher dose oral contraceptives (50 μg or 75 μg).

Unlike previous reports (e.g. Adams *et al.*, 1973; Leklem *et al.*, 1975; Rose & Adams, 1972; Price, Thornton & Mueller, 1967) an increased excretion of kynurenine by OC subjects was not observed either before or during the tryptophan load although the OC group showed a much greater percentage increase in kynurenine excretion following the load. Indeed absolute excretion of kynurenine by the OC group was lower. Furthermore the peak of plasma kynurenine was lower in the OC group. Since the production of kynurenine from tryptophan appears to be the same in both groups these observations suggest that perhaps the catabolism of kynurenine is different in the OC group in that it is broken down more rapidly to other metabolites such as acetylkynurenine, excretion of which is raised in OC users (Leklem *et al.*, 1975).

We are unable to explain the difference between our observations and those of other workers in regard to kynurenine excretion except to point out that the method of kynurenine analysis used in this study appears to be extremely specific (Joseph & Risby, 1975). It might be that other methods were also detecting raised levels of some of the other metabolites such as 3-hydroxykynurenine.

One possible reason for the changed excretion of tryptophan metabolites by women on OC suggested by the work of Mason & Gullekson (1960) demonstrated that sulphate esters of oestrogens interfere *in vitro* with the activity of some pyridoxal phosphate-dependent enzymes by competing for sites on the apoenzyme. Rose, Strong, Adams & Harding (1972) suggested that esters formed from the oestrogenic component of oral contraceptives may reach sufficient concentrations in the liver to inhibit supernatant kynureninase but that kynurenine aminotransferase, protected in the mitochondria, retains its activity and metabolises the accumulating 3-hydroxykynurenine to xanthurenic acid. The observations of Leklem *et al.* (1975) is consistent with this theory since they showed that when B_6 deficiency is sufficiently severe the build up of 3-hydroxykynurenine exceeds that of xanthurenic acid suggesting that B_6 deficiency impaired mitochondrial aminotransferase activity. Also consistent with these hypotheses are the observations that the abnormal excretion of tryptophan metabolites seen in subjects taking OC returns to normal after vitamin B_6 administration (Adams *et al.*, 1973; Rose, 1966; Luhby *et al.*, 1971).

Such changes would be expected to occur whether or not pyrrolase activity was induced. Our results in

Table 6 Total urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) and indoleacetic acid (IAA) in control subjects ($n=9$) and those on oral contraceptives ($n=14$) (OC). Results expressed as mean ± s.e. mean of the total μmol excreted during collection periods stated in table.

Metabolite measured	Group	Collection times: Control period 10.00 h–10.00 h (24 h)	Experimental period 10.00 h–15.00 h (5 h)	Experimental period 15.00 h–10.00 h (19 h)	Total (24 h)
5-HIAA	Control	31.98 ± 7.85	8.11 ± 1.72	24.45 ± 5.76	32.56 ± 6.65
	OC	23.24 ± 2.56	7.06 ± 0.84	16.64 ± 1.98	23.71 ± 2.51
IAA	Control	42.17 ± 4.51	50.17 ± 8.80	51.02 ± 8.05	100.62 ± 14.62
	OC	56.28 ± 8.34	58.05 ± 7.25	79.88 ± 14.28	137.88 ± 16.45

no way contradict the hypothesis of Rose and his colleagues (1972) since they suggest an alteration in the production of various tryptophan metabolites formed by the action of B_6 dependent enzymes.

The observation that urinary 5-HIAA excretion is unchanged following a tryptophan load is intriguing. Administration of tryptophan to a rat causes a large increase in brain 5-HIAA concentration (see for example Figure 6 in Marsden & Curzon, 1976) with brain 5-HT synthesis being markedly increased by tryptophan administration (Grahame-Smith, 1971). It is possible that in our study the blood platelets accumulated the increased 5-HT being formed in the periphery. On the other hand Curzon, Ettlinger, Cole & Walsh (1963) found an increase in urinary 5-HIAA of only 50% when giving monkeys approximately 1 g/kg L-tryptophan per day over a period of 2 months. This dose is 20 times that given in the current study and perhaps indicates that 5-HT synthesis cannot be accelerated (at least in the periphery) by tryptophan administration.

Tryptophan administration did however cause more than a doubling in the rate of urinary indoleacetic acid production in both the control and OC group, indicating increased formation of tryptamine and suggesting that aromatic amino acid decarboxylase activity is unchanged in the subjects taking oral contraceptives. Another possibility is that there is increased transamination in both groups following tryptophan.

Finally we come to the question of the cause of the mood change in some subjects on oral contraceptives. The suggestion that this could be related to an inhibition of 5-HT synthesis because of a deficiency of pyridoxal phosphate leading to decreased 5-hydroxytryptophan decarboxylase activity is not contradicted by our current findings and is supported by the observations of Adams *et al.* (1973) that the mood of some depressed subjects improved with the administration of vitamin B_6. While no impairment of peripheral 5-HT or tryptamine synthesis was observed in our study it should be remembered that none of the women reported that taking oral contraceptives had resulted in a subjective mood change. Clearly however the mood change is not simply related to pyridoxal phosphate deficiency as not all those subjects studied by Adams *et al.* (1973) showed an improved mood response following vitamin B_6 administration.

In conclusion therefore we show that while there are changes in tryptophan metabolism during oral contraceptive administration these may be caused by a relative vitamin B_6 deficiency but not by an increase in liver tryptophan pyrrolase activity.

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