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The effect of ovariectomy on phenylalanine and tyrosine metabolism

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Summary. Although the regulatory activity of steroid hormones on amino acid metabolism has been described, no information is published on the effect of ovariectomy. We studied the influence of ovariectomy in Wistar rats determining the amino acids phenylalanine and tyrosine in liver, kidney, plasma and urine. 32 animals were used in the study, 12 animals were sham operated, 9 animals were ovariectomized and 11 rats were ovariectomized and supplemented with estradiol. No quantitative changes were detected comparing liver and kidney phenylalanine and tyrosine between the groups (sham operated rats liver phenylalanine 2,53nM/mg ± 1,07; liver tyrosine 1.95nM/mg ± 0.92; kidney phenylalanine 2.16nM/mg ± 0.53; kidney tyrosine 1.80nM/mg ± 0.39. Ovariectomized rats showed liver phenylalanine 3.07nM/mg ± 1.14; liver tyrosine 2.63nM/mg ± 1.01; kidney phenylalanine 2.30 nM/mg ± 0.74; kidney tyrosine 1.93nM/mg ± 0.63. Ovariectomized and estradiol supplemented rats presented with liver phenylalanine 2.84nM/mg ± 1.40; liver tyrosine 2.35nM/mg ± 1.28; kidney phenylalanine 1.91nM/mg ± 0.26, kidney tyrosine 1.67nM/mg ± 0.23.). When, however, the phenylalanine/tyrosine ratio in the liver was evaluated, ovariectomized rats showed a significant decrease of the quotient ($p = 0.001$). The phenylalanine/tyrosine ratio was restored by estradiol replacement. Our findings show that phenylalanine and tyrosine metabolism is under estradiol control. The effect on the metabolic changes could be mediated by enzyme systems as phenylalanine hydroxylase, tyrosine hydroxylase and tyrosine aminotransferase. Our results would be compatible with previous reports on the stimulatory effect of estradiol on these enzymes. The kidney phenylalanine/tyrosine ratio was unaffected by ovariectomy and/or estradiol replacement which can be easily explained by different pools, enzyme activities, filtration/reabsorption effects, etc.

The urinary P/T ratio was decreased by ovariectomy and restored by estradiol replacement indicating endocrine control of renal reabsorption and secretion mechanisms.

Keywords: Amino acids – Ovariectomy – Phenylalanine – Tyrosine – Interorgan metabolism

Introduction

Interactions between the endocrine system and amino acid metabolism are well known and documented. The effect of ovariectomy on amino acid metabolism, however, was not described in literature. The effect of glucocorticoids on amino acid metabolism on contrary, was studied extensively and on a molecular basis. The effect of corticosteroids, insulin, glucagon on amino acid metabolism was studied at the molecular biological level of transcription and translation (Rasmussen et al., 1988). Hormone influences at the enzymatic level have been reported as well: Tyrosine aminotransferase (Svec, 1988), tyrosine hydroxylase (Pasqualini et al., 1991), phenylalanine hydroxylase (Haper et al., 1986) are under strict endocrine control. Neither the effect of ovariectomy nor the deprivation of estradiol or related estrogens was reported. The aim of our study was to examine hepatic, renal, serum, urinary phenylalanine and tyrosine levels to test the hypothesis that phenylalanine and tyrosine metabolism are under control of ovarian hormones. Phenylalanine and tyrosine were selected as sufficient background information on renal and hepatic metabolism and handling is available. As amino acid transport for amino acids is not a limiting factor due to high transport kinetics (Partridge, 1983), the simple determination of amino acids in different compartments would allow conclusions on the effect of ovarial hormones.

Materials and methods

Animals

32 Wistar rats, white female, (Shaw's farm, UK), were used in the experiments. 12 animals were sham operated, 9 animals were ovariectomized by the dorsal surgical approach and 11 rats were ovariectomized and supplemented with estradiol (17beta-estradiol acetate, Sigma, E 7879) subcutaneously, 20μg/kg body weight, 3 times per week.

After a period of 8 weeks animals were sacrificed by diethylether treatment.

Experiments

Blood was drawn by cardiac puncture and spun down after clotting.

Amino acid determinations were performed in serum, urine, liver and kidney specimen. In order to rule out clearance influences, urinary amino acids were related to creatinine.

Amino acid analyses were performed by a standard chromatographical technique. A Beckmann autoanalyzer 7300/6300 was used. Buffers used were lithium citrate Beckmann 338063, 338064, 338065. For ninhydrin detection Nin rx (Beckmann 339069) was applied. The flow rate was 30 ml/h. Gradient and chromatographical technique applied are shown in Fig. 1.

Liver and kidney amino acids: For this purpose organ samples were weighed and taken into 4 ml of 0.05M phosphate buffer pH 7.0 containing 10 percent sodium dodecyl sulphate (SDS) and homogenised by a Potter. Sample preparation: 160 μl of sample were added to 160 μl of 0.5% SDS and incubated for 15 min at room temperature. 200 μl 10% sulfosalicylic acid and 280 μl of 0.5M lithium hydroxide (Fisher Scientific L 128) were added and spun down at 3000 $\times$ g for 10 minutes. 250 μl of the supernatant were added to 250 μl of dilution buffer Li-S, Beckman 338084).

This solution was used to fill the loop and 100 μl were injected.

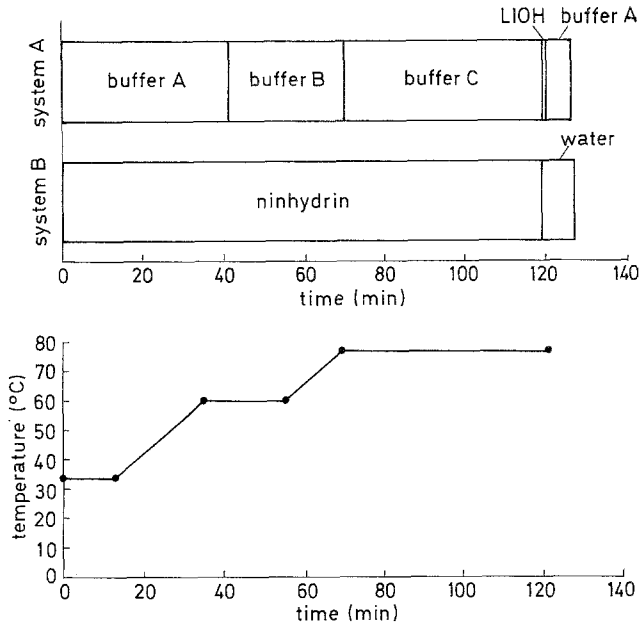

Fig. 1. Gradient and chromatographical technique applied

Statistical calculation

Wilcoxon test for comparison of the groups and the linear regression coefficient r for correlations were used for evaluation of results (SAS, User's Guide, 1987).

Results

The results are listed in Tables 1–3.

Discussion

A schematic overview is given in Fig. 2.

As shown in the Results no significant differences of liver phenylalanine and tyrosine could be detected comparing the groups.

Liver phenylalanine and tyrosine correlated significantly in all the groups. When the ratio of liver phenylalanine to tyrosine, however, was calculated, the effect of the ovariectomy could be noticed:

The phenylalanine/tyrosine quotient was significantly higher in the sham operated group than in the ovariectomized panel. This effect could be interpreted by increased phenylalanine hydroxylase activity. Phenylalanine hydroxylase is the initial and limiting enzyme in the degradative pathway for phenylalanine (Kaufmann, 1987). An effect of estradiol or ovariectomy has not been published up to now. Estradiol replacement after ovariectomy restored the phenylalanine/tyrosine Quotient (P/T) indicating that estradiol and not other ovarial hormones were responsible for the effect observed.

The stimulating effect of estradiol on liver tyrosine aminotransferase has been reported (Nemeth et al., 1984) and could have been responsible for the phenome-

Table 1.

Sham operated rats

Tabular presentation showing means, standard deviation and range of parameters

	Mean	Std Dev	Range
Serum:in µM/l			
Phenylalanine	92	17	73-125
Tyrosine	57	12	41-84
Quotient Phe/Tyr	1.7	0.4	1.0-2.1
Urine:per creatinine			
Phenylalanine	0.0023	0.003	0.00047-0.011
Tyrosine	0.0027	0.0041	0.0005-0.014
Quotient Phe/Tyr	1.3	0.8	0.2-3.0
Liver:in nM/mg			
Phenylalanine	2.5	1.1	1.1-4.6
Tyrosine	1.95	0.9	0.9-3.8
Quotient Phe/Tyr	1.3	0.1	1.2-1.6
Kidney:in nM/mg			
Phenylalanine	2.2	0.5	1.6-3.2
Tyrosine	1.8	0.4	1.4-2.7
Quotient Phe/Tyr	1.2	0.1	1.1-1.5

Ovariectomized rats

Tabular presentation showing means, standard deviation and range of parameters

	Mean	Std Dev	Range
Serum:in µM/l			
Phenylalanine	88	15	76-111
Tyrosine	56	17	38-89
Quotient Phe/Tyr	1.7	0.5	0.93-2.41
Urine:per creatinine			
Phenylalanine	0.0032	0.0042	0.0006-0.011
Tyrosine	0.0098	0.012	0.0007-0.03
Quotient Phe/Tyr	0.5	0.3	0.1-0.9
Liver:in nM/mg			
Phenylalanine	3.1	1.1	1.8-4.8
Tyrosine	2.6	1.00	1.5-4.0
Quotient Phe/Tyr	1.2	0.06	1.1-1.3
Kidney:in nM/mg			
Phenylalanine	2.3	0.7	1.8-3.8
Tyrosine	1.9	0.6	1.5-3.3
Quotient Phe/Tyr	1.2	0.1	1.1-1.5

Ovariectomized rats with estradiol replacement

Tabular presentation showing means, standard deviation and range of parameters

	Mean	Std Dev	Range
Serum:in µM/l			
Phenylalanine	65	16	46-105
Tyrosine	38	7	25-49
Quotient Phe/Tyr	1.8	0.5	1.2-2.8
Urine:per creatinine			
Phenylalanine	0.0066	0.01	0.0005-0.033
Tyrosine	0.0030	0.0030	0.00062-0.011
Quotient Phe/Tyr	1.7	0.9	0.8-3.3
Liver:in nM/mg			
Phenylalanine	2.8	1.4	1.5-5.5
Tyrosine	2.3	1.3	1.0-4.8
Quotient Phe/Tyr	1.3	0.1	1.1-1.5
Kidney:in nM/mg			
Phenylalanine	1.9	0.3	1.5-2.3
Tyrosine	1.7	0.2	1.3-2.1
Quotient Phe/Tyr	1.1	0.03	1.12-1.19

Table 2. Tabular presentation of the results of Wilcoxon analysis comparing the groups

	sham operated vs. ovariectomized rats		sham operated vs. ovariectomized rats & E2		ovariectomized vs. ovariectomized rats & E2	
	p=	t=	p=	t=	p=	t=
Serum:						
Phenylalanine	0.7	0.4	0.0006*	3.4	0.004*	2.9
Tyrosine	0.6	0.5	0.0002*	3.7	0.006*	2.8
Quotient Phe/Tyr	0.99	0	0.8	0.3	0.8	1.9
Urine:						
Phenylalanine	0.7	0.4	0.2	1.3	0.4	0.8
Tyrosine	0.098	1.7	0.2	1.2	0.2	1.3
Quotient Phe/Tyr	0.02*	2.3	0.3	1.1	0.007*	2.7
Liver:						
Phenylalanine	0.5	0.7	0.9	0.1	0.6	0.6
Tyrosine	0.1	1.5	0.7	0.3	0.4	0.9
Quotient Phe/Tyr	0.001*	3.1	0.15	1.5	0.08	1.7
Kidney:						
Phenylalanine	0.7	0.4	0.4	0.9	0.3	1.1
Tyrosine	0.8	0.3	0.5	0.7	0.5	0.06
Quotient Phe/Tyr	0.95	0.05	0.2	1.4	0.2	1.2
Probabilities lower than 0.05 are labelled with an asteriks						

non of decreased P/T ratio after ovariectomy. There are, however, no reports on the effect of ovariectomy on tyrosine aminotransferase.

The second enzyme with known regulation by estradiol, tyrosine hydroxylase, could have been responsible for the reduced P/T ratio as well: Babu described elevated (brain) tyrosine hydroxylase levels in ovariectomized rats with estradiol substitution (Babu and Vijayan, 1984). Pharmacological doses of estradiol in healthy rats are also known to increase (brain) tyrosine hydroxylase (Blum et al., 1987). There are no data available on the liver enzyme.

No significant differences of renal phenylalanine and tyrosine or P/T ratio was observed. This could easily be explained by the fact that the three enzyme systems discussed are not active in the kidney. According to Young and Parsons rat kidney phenylalanine hydroxylase is less than 10 percent of that in liver (Young and Parsons, 1973). Renal clearance and renal handling of phenylalanine and tyrosine might have compensated the shift of the P/T ratio. Interconversions, synthetic as well as effects of reabsorption and filtration are suggested to modify the ratio in the kidney as well. As the kidney is a major source of peptidases (Kenny and Maroux, 1982) the enormous flux from degradation derived amino acid pool would be able to modify the renal P/T ratio. Furthermore, there is a renal net uptake of phenylalanine and tyrosine determining the individual renal amino acid pattern (Silbernagl, 1988).

Our findings that no differences between urinary phenylalanine and tyrosine could be revealed are in agreement with renal amino acid patterns.

The urinary P/T ratio, however, showed a decreased P/T ratio. Simple filtration is therefore not to be incriminated as serum P/T ratio is unaffected by ovariectomy and no correlation between serum and urinary P/T ratio was found. The reduced urinary P/T ratio must have resulted from reabsorption and

Table 3.
Sham operated rats
Tabular presentation of correlations presenting the correlation coefficients (r) and probabilities (p)

		serum phenyl-alanine	serum tyrosine	serum P/T ratio	urine phenyl-alanine	urine tyrosine	urine P/T ratio	liver phenyl-alanine	liver tyrosine	liver P/T ratio	kidney phenyl-alanine	kidney tyrosine	kidney P/T ratio
serum	r=	1	0.13	0.64	0.51	0.13	0.56	0.09	0.16	0.37	0.44	0.58	0.15
phenylalanine	p=	0	0.70	0.03*	0.13	0.72	0.09	0.79	0.63	0.26	0.23	0.10	0.70
serum	r=	0.13	1	0.66	0.03	0.26	0.002	0.07	0.04	0.61	0.35	0.01	0.77
tyrosine	p=	0.70	0	0.02*	0.94	0.47	0.99	0.85	0.90	0.05*	0.36	0.97	0.02*
serum	r=	0.64	0.66	1	0.43	0.12	0.48	0.05	0.03	0.14	0.09	0.45	0.68
P/T ratio	p=	0.03*	0.02*	0	0.21	0.74	0.16	0.89	0.94	0.67	0.82	0.23	0.04*
urine	r=	0.51	0.03	0.43	1	0.23	0.75	0.12	0.12	0.02	0.61	0.84	0.10
phenylalanine	p=	0.13	0.94	0.21	0	0.53	0.01*	0.76	0.76	0.97	0.15	0.02*	0.83
urine	r=	0.13	0.26	0.12	0.23	1	0.35	0.23	0.24	0.11	0.62	0.76	0.20
tyrosine	p=	0.72	0.47	0.74	0.53	0	0.32	0.55	0.53	0.78	0.14	0.05*	0.67
urine	r=	0.57	0.002	0.48	0.75	0.35	1	0.40	0.42	0.11	0.69	0.89	0.19
P/T ratio	p=	0.09	0.99	0.16	0.01*	0.32	0	0.29	0.26	0.78	0.09	0.006*	0.69
liver	r=	0.09	0.07	0.05	0.12	0.23	0.40	1	0.98	0.93	0.65	0.83	0.14
phenylalanine	p=	0.79	0.85	0.89	0.76	0.55	0.29	0	0.0001	0.79	0.08	0.01*	0.74
liver	r=	0.16	0.04	0.03	0.12	0.24	0.42	0.98	1	0.28	0.74	0.90	0.08
tyrosine	p=	0.63	0.90	0.94	0.76	0.53	0.26	0.0001*	0	0.41	0.04*	0.003*	0.84
liver	r=	0.40	0.61	0.14	0.07	0.11	0.11	0.09	0.28	1	0.41	0.28	0.34
P/T ratio	p=	0.26	0.05*	0.67	0.97	0.78	0.78	0.79	0.41	0	0.31	0.49	0.41
kidney	r=	0.44	0.35	0.09	0.61	0.62	0.69	0.65	0.74	0.41	1	0.90	0.53
phenylalanine	p=	0.23	0.36	0.82	0.15	0.14	0.09	0.08	0.04*	0.31	0	0.0008*	0.15
kidney	r=	0.58	0.01	0.45	0.84	0.76	0.89	0.83	0.90	0.28	0.90	1	0.11
tyrosine	p=	0.10	0.97	0.23	0.02*	0.05*	0.007*	0.01*	0.003*	0.49	0.0008*	0	0.78
kidney	r=	0.15	0.77	0.68	0.10	0.20	0.19	0.14	0.08	0.34	0.53	0.11	1
P/T ratio	p=	0.70	0.02*	0.04*	0.83	0.67	0.69	0.74	0.84	0.41	0.15	0.78	0

Probabilities < 0.05 are labelled with an asteriks

Table 3 (continued)
Ovariectomized rats
Tabular presentation of correlations presenting the correlation coefficients (r) and probabilities (p)

		serum phenyl-alanine	serum tyrosine	serum P/T ratio	urine phenyl-alanine	urine tyrosine	urine P/T ratio	liver phenyl-alanine	liver tyrosine	liver P/T ratio	kidney phenyl-alanine	kidney tyrosine	kidney P/T ratio
serum phenylalanine	r=	1	0.26	0.37	0.50	0.10	0.94	0.24	0.30	0.59	0.07	0.31	0.79
	p=	0	0.50	0.33	0.66	0.03*	0.22	0.56	0.47	0.12	0.90	0.55	0.06
serum tyrosine	r=	0.26	1	0.78	0.90	0.85	0.97	0.09	0.14	0.36	0.63	0.42	0.72
	p=	0.50	0	0.01*	0.29	0.35	0.16	0.84	0.75	0.37	0.18	0.41	0.10
serum P/T ratio	r=	0.37	0.78	1	0.63	0.32	0.03	0.04	0.02	0.009	0.39	0.18	0.74
	p=	0.32	0.01*	0	0.57	0.79	0.98	0.93	0.96	0.98	0.44	0.74	0.09
urine phenylalanine	r=	0.50	0.90	0.63	1	0.94	0.33	0.35	0.41	0.77	0.77	0.84	0.63
	p=	0.66	0.29	0.57	0	0.02*	0.59	0.56	0.49	0.13	0.44	0.36	0.57
urine tyrosine	r=	0.10	0.85	0.32	0.94	1	0.59	0.25	0.30	0.66	0.98	0.95	0.20
	p=	0.03*	0.35	0.79	0.02*	0	0.30	0.69	0.62	0.23	0.13	0.20	0.87
urine P/T ratio	r=	0.94	0.97	0.03	0.33	0.59	1	0.49	0.43	0.11	0.94	0.89	0.34
	p=	0.22	0.16	0.98	0.59	0.30	0	0.40	0.47	0.86	0.22	0.30	0.78
liver phenylalanine	r=	0.24	0.09	0.04	0.35	0.25	0.49	1	0.99	0.16	0.24	0.41	0.46
	p=	0.56	0.84	0.93	0.56	0.69	0.40	0	0.0001*	0.65	0.65	0.41	0.35
liver tyrosine	r=	0.30	0.14	0.02	0.41	0.30	0.43	0.99	1	0.28	0.27	0.45	0.50
	p=	0.47	0.75	0.96	0.49	0.62	0.47	0.0001*	0	0.43	0.60	0.37	0.32
liver P/T ratio	r=	0.59	0.36	0.009	0.77	0.66	0.11	0.16	0.28	1	0.25	0.40	0.43
	p=	0.12	0.37	0.98	0.12	0.22	0.86	0.65	0.43	0	0.63	0.43	0.39
kidney phenylalanine	r=	0.07	0.63	0.39	0.77	0.98	0.94	0.24	0.27	0.25	1	0.94	0.23
	p=	0.90	0.18	0.44	0.44	0.13	0.22	0.65	0.60	0.63	0	0.002*	0.62
kidney tyrosine	r=	0.31	0.42	0.18	0.84	0.95	0.89	0.41	0.45	0.40	0.94	1	0.11
	p=	0.55	0.41	0.74	0.36	0.20	0.30	0.42	0.37	0.43	0.002*	0	0.82
kidney P/T ratio	r=	0.79	0.72	0.74	0.63	0.63	0.34	0.46	0.50	0.43	0.23	0.11	1
	p=	0.06	0.10	0.09	0.56	0.57	0.78	0.35	0.32	0.39	0.62	0.82	0

Probabilities < 0.05 are labelled with an asteriks

Table 3 (continued)
Ovariectomized rats with E2-replacement
Tabular presentation of correlations presenting the correlation coefficients (r) and probabilities (p)

		serum phenyl-alanine	serum tyrosine	serum P/T ratio	urine phenyl-alanine	urine tyrosine	urine P/T ratio	liver phenyl-alanine	liver tyrosine	liver P/T ratio	kidney phenyl-alanine	kidney tyrosine	kidney P/T ratio
serum	r=	1	0.45	0.59	0.01	0.06	0.02	0.27	0.27	0.20	0.35	0.44	0.53
phenylalanine	p=	0	0.17	0.054	0.97	0.88	0.96	0.42	0.41	0.55	0.40	0.28	0.17
serum	r=	0.45	1	0.43	0.06	0.11	0.25	0.31	0.38	0.43	0.01	0.16	0.85
tyrosine	p=	0.17	0	0.19	0.87	0.77	0.52	0.35	0.25	0.19	0.10	0.70	0.008*
serum	r=	0.0.59	0.43	1	0.11	0.09	0.24	0.05	0.10	0.19	0.32	0.28	0.17
P/T ratio	p=	0.054	0.19	0	0.78	0.81	0.53	0.89	0.78	0.58	0.45	0.50	0.69
urine	r=	0.01	0.06	0.11	1	0.98	0.69	0.07	0.05	0.10	0.04	0.01	0.23
phenylalanine	p=	0.97	0.87	0.78	0	0.0001*	0.04*	0.86	0.90	0.80	0.93	0.98	0.62
urine	r=	0.06	0.11	0.09	0.98	1	0.61	0.07	0.07	0.0007	0.11	0.05	0.40
tyrosine	p=	0.88	0.77	0.81	0.0001*	0	0.08	0.85	0.86	0.1	0.82	0.91	0.38
urine	r=	0.02	0.25	0.24	0.69	0.61	1	0.14	0.11	0.28	0.12	0.11	0.08
P/T ratio	p=	0.96	0.52	0.53	0.04*	0.08	0	0.71	0.78	0.47	0.80	0.82	0.86
liver	r=	0.27	0.31	0.05	0.07	0.07	0.14	1	0.99	0.58	0.55	0.63	0.30
phenylalanine	p=	0.42	0.35	0.89	0.86	0.85	0.71	0	0.0001*	0.06	0.16	0.10	0.47
liver	r=	0.27	0.38	0.10	0.05	0.07	0.11	0.99	1	0.65	0.54	0.62	0.33
tyrosine	p=	0.41	0.25	0.78	0.89	0.86	0.78	0.0001*	0	0.03*	0.17	0.10	0.43
liver	r=	0.20	0.43	0.19	0.10	0.0006	0.28	0.58	0.65	1	0.44	0.53	0.41
P/T ratio	p=	0.55	0.19	0.58	0.80	0.10	0.67	0.06	0.03*	0	0.27	0.18	0.32
kidney	r=	0.35	0.01	0.32	0.04	0.11	0.12	0.55	0.54	0.44	1	0.98	0.19
phenylalanine	p=	0.40	0.98	0.45	0.93	0.81	0.80	0.16	0.17	0.27	0	0.0001*	0.64
kidney	r=	0.44	0.16	0.28	0.01	0.05	0.11	0.63	0.62	0.53	0.98	1	0.01
tyrosine	p=	0.28	0.70	0.50	0.98	0.91	0.82	0.10	0.10	0.18	0.0001*	0	0.10
kidney	r=	0.53	0.85	0.17	0.23	0.40	0.08	0.30	0.33	0.41	0.19	0.02	1
P/T ratio	p=	0.17	0.008*	0.69	0.62	0.38	0.86	0.47	0.43	0.32	0.64	0.10	0

Probabilities < 0.05 are labelled with an asteriks

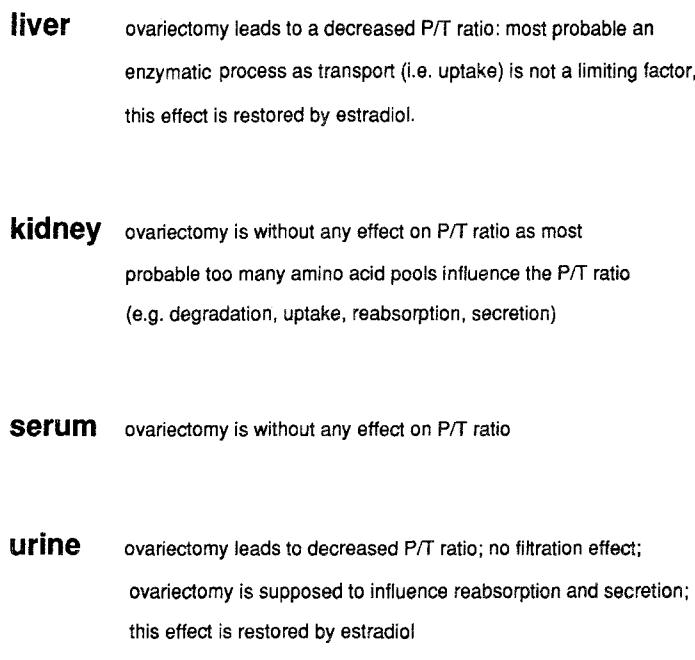

Fig. 2. Interpretation of major findings

secretion. Estradiol replacement after ovariectomy restores the urinary P/T ratio indicating specific endocrine control of reabsorption and secretion.

Summing up, we can conclude that liver P/T ratio is reduced by ovariectomy and readily restored by estradiol replacement. Endocrine influences seem to control the major enzyme systems involved in phenylalanine and tyrosine metabolism.

Effects observed on urinary P/T ratios were interpreted as endocrine influences on renal reabsorption and secretion mechanisms reversible after estradiol replacement. We therefore found a role for estradiol in hepatic phenylalanine and tyrosine metabolisms as well as on renal reabsorption and secretion mechanism.

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