THE EFFECT OF MATERNAL TOXAEMIA AND DIABETES ON TRANSPLACENTAL GRADIENTS OF FREE AMINO ACIDS

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Earlier studies (Christensen and Streicher, 1948) have demonstrated that amino nitrogen levels are greater in foetal than in maternal plasma and that this difference is lessened in toxæmia of pregnancy (Clemetson and Churchman, 1954). For normally-delivered full-term infants of healthy mothers, the mean ratio of these concentrations is 1.7 (1.4-2.0):1. Crumpler, Dent and Lindan (1950), with paper chromatography, and Glendening, Margolis and Page (1961) using continuous flow column chromatography have confirmed that this difference also holds for all common amino acids with the possible exception of proline. This study demonstrates the effect on these gradients of maternal toxæmia and diabetes.

Subjects and Methods

Umbilical vein and maternal vein samples were taken immediately after delivery from seven normal healthy fasting mothers with uncomplicated pregnancies, from three with pre-eclampsia and from two with diabetes (Table 1). Plasma aliquots were at once deproteinized (Stein and Moore, 1954) and assayed for amino acids (Moore, Spackman and Stein, 1958) using a Beckman/Spinco amino acid analyser. No values are given for tryptophan which is not quantitatively recovered by this technique or for glutamine which is eluted with asparagine, as well as being variably destroyed during deproteinization. The reproducibility of a single plasma sample for all stages of this assay, as expressed by the coefficient of variation, ranged from $\pm 2.6\%$ to $\pm 7.6\%$ with a mean from all amino acids of $\pm 5.7\%$ excepting half cystine and histidine, which gave values of $\pm 10\%$.

Results and Discussion

Brief clinical details of the foetal-maternal pairs are given in Table 1; the data for the amino acid levels and for the foetal-maternal ratios (FMR) are shown in Table 2. In every instance levels are higher in the foetal plasma than in the maternal by factors that range from 1.6 to 3.1 to 1. These

results are in accordance with the previous observations of Glendening *et al.* (1961) who found similar ratios for 12 amino acids, proline excepted, in two paired and in several unpaired foetal-maternal samples.

Values for these ratios in the abnormal pregnancies are, with few exceptions, uniformly low. Individually significant differences are observed in a group of structurally unrelated amino compounds primarily for taurine, alanine and histidine as well as, to a lesser extent, for glycine and phenylalanine. Nothing is known of the effects of one amino acid on another in transport across the placenta in man; although Christensen and Streicher (1948) have shown that in the guinea-pig maternal loading with histidine, methionine or proline would inhibit transplacental glycine transport, whereas 1-glutamic acid loading would not. However, since homeostasis was not disturbed on the maternal side in these abnormal cases, it might be supposed that transport inter-relations would be unchanged and that the whole pattern of differences in the foetal-maternal ratios could be judged using a binomial distribution test. If this is done as in Table 2 additional evidence is obtained of an impairment of transplacental amino acid transport in diabetes and toxæmia. From this and previous data it is not yet possible to suggest a mechanism whereby this might interfere with foetal protein metabolism.

Summary

Using the technique of continuous flow column chromatography, transplacental amino acid gradients have been shown to be significantly impaired in three subjects with pre-eclampsia and two with diabetes when compared to normal controls.

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TABLE 1
CLINICAL INFORMATION ABOUT FOETAL-MATERNAL PAIRS

Case No.	Mother			Infant	
	Age (years)	Parity	Gestational Complications	Birth Weight (g.)	Neonatal Complications
1	39	2	None	2,510	None
2	22	0	None	3,070	None
3	18	0	None	3,110	None
4	21	0	None	3,750	None
5	19	0	None	3,000	None
6	23	1	None	2,600	None
7	18	0	None	2,860	None
8	20	1	Pre-eclampsia	3,500	Died: pneumonia
9	17	0	Pre-eclampsia	3,520	None
10	18	0	Pre-eclampsia	3,390	None
11	28	2	Pre-diabetes	2,840	None
12	20	0	Diabetes (Class B)	4,030	Hypoglycaemia; macrosomia

TABLE 2
TRANSPLACENTAL AMINO ACID GRADIENTS IN SEVEN NORMAL AND FIVE COMPLICATED PREGNANCIES

	Uncomplicated			Pre-eclampsia				Diabetes			
	Maternal Venous Plasma (μmol./litre) Mean ± S.D.	Nos. 1-7 Cord Vein Plasma (μmol./litre) Mean ± S.D.	Foetal : Maternal Ratio Mean ± S.D.	No. 8		No. 9		No. 10		No. 11	
				F	FMR	F	FMR	F	FMR	F	FMR
Taurine ..	62 ± 16	183 ± 34	3.1 ± 0.6	121	(1.3)	238	3.1	89	(1.7)	82	—
Aspartic ..	8.1 ± 4.6	16.6 ± 3.4	2.8 ± 2.3	Trace	—	16	1.1	Trace	—	Trace	—
Threonine ..	159 ± 51	267 ± 68	1.7 ± 0.3	263	1.7	194	1.4	252	1.6	304	1.3
Serine ..	77 ± 6	146 ± 12	1.9 ± 0.5	123	1.9	172	1.6	121	1.4	146	1.4
Proline ..	89 ± 26	146 ± 21	1.7 ± 0.4	128	1.5	103	1.2	101	1.1	151	1.0
Glutamic ..	91 ± 18	152 ± 36	1.7 ± 0.6	114	1.1	96	1.8	71	2.0	39	0.6
Glycine ..	114 ± 22	230 ± 20	2.1 ± 0.3	169	(1.6)	208	1.8	185	2.0	209	1.7
Alanine ..	282 ± 66	422 ± 128	1.7 ± 0.3	237	(1.0)	274	(0.8)	334	(1.1)	286	(1.1)
Valine ..	118 ± 13	204 ± 15	1.7 ± 0.8	176	0.8	210	1.3	149	1.4	213	1.7
β-Cystine ..	43 ± 12	71 ± 15	1.6 ± 0.5	80	1.4	65	0.9	50	1.0	63	1.0
Methionine ..	15 ± 5.5	20 ± 10	1.6 ± 0.6	14	1.2	Trace	—	9.6	1.2	18	1.4
Isoleucine ..	37 ± 7.3	71 ± 21	1.9 ± 0.4	47	1.5	67	1.3	42	1.2	54	(1.1)
Leucine ..	67 ± 10	114 ± 27	1.7 ± 0.3	84	1.3	131	1.3	80	1.4	98	1.4
Tyrosine ..	30 ± 7	63 ± 5	2.2 ± 0.5	64	1.6	53	1.6	42	1.8	47	2.0
Phenylalanine ..	39 ± 6	69 ± 10	1.8 ± 0.3	58	(1.1)	60	(0.8)	53	1.8	44	1.7
Ornithine ..	28 ± 7	79 ± 22	2.9 ± 0.9	91	3.6	72	2.3	—	—	64	2.7
Lysine ..	97 ± 16	298 ± 54	3.1 ± 0.4	277	3.3	275	2.6	218	2.8	235	2.7
Histidine ..	34 ± 10	75 ± 13	2.3 ± 0.4	74	(1.5)	73	(1.2)	84	2.0	80	(1.2)
Arginine ..	—	52 ± 13	—	45	2.0	—	—	Trace	—	94	4.7
p ..	—	—	—	<0.001		0.005		0.044		<0.005	
										<0.001	

S.D. = Standard deviation with Bessel correction for small sample bias = $\sqrt{\left(\frac{Ex^2}{n} - \bar{x}^2\right) \left(\frac{n}{n-1}\right)}$.

F = Concentration of free amino acid in cord venous plasma in μmol./litre.

FMR = Ratio of concentration of free amino acid in cord venous plasma to that in maternal venous plasma.

(0.7) = Bracketed figure for FMR indicating ≥ -2 S.D. from normal mean.

p = Probability of being normal calculated from the incidence of individual values for FMR of ≥ -2 S.D. from normal mean according to the binomial probability distribution $\binom{n}{x} p^x (1-p)^{n-x}$ omitting values for aspartic and arginine.

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