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The effect of dietary supplementation with linoleic and gammalinolenic acids on the pressor response to angiotensin II—a possible role in pregnancy-induced hypertension?

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1 Dietary supplementation with 3 g/day linoleic acid, 32 mg/day gammalinolenic acid and co-factors for prostaglandin synthesis was given to 10 pregnant and 10 non-pregnant subjects for a week. Their pressor response to the infusion of three doses of angiotensin II (AII) (pregnant: 4, 8, 16 ng kg^{-1} min^{-1}: non-pregnant: 1, 2, 4 ng kg^{-1} min^{-1}) was then compared with that of 40 pregnant and 24 non-pregnant controls who had not been given such supplementation.

2 Dietary supplementation was not associated with changes in basal systolic or diastolic blood pressure or heart rate during the week of treatment in pregnant or non-pregnant subjects. Basal systolic blood pressure, diastolic blood pressure and heart rate values did not differ between the treated and untreated subjects in each group.

3 The diastolic pressor response to AII was significantly less after treatment at all doses; the effect was more marked in the pregnant subjects.

4 The systolic response to AII, normally less than the diastolic, was somewhat blunted in the treated pregnant patients at the two higher infusion doses. No significant effect was found in the non-pregnant group.

5 Evidence from other studies suggests that increasing plasma linoleic acid concentrations leads to increased plasma concentrations of epoprostenol (prostacyclin, PGI_2) while increased availability of gammalinolenic acid is associated with a rise in prostaglandin E_1 and E_2 production.

6 Pregnancy-induced hypertension is associated with a diminished tissue production of both epoprostenol and E series prostaglandins, and with an enhanced pressor response to AII. Dietary supplementation with linoleic acid, gammalinolenic acid or other polyunsaturated fatty acids may be of use in preventing or slowing the development of the disease.

Keywords renin angiotensin II prostaglandins pregnancy toxaemia fatty acids

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Introduction

An increased dietary content of polyunsaturated fatty acids has been advocated, on the basis of epidemiological studies, for the prevention of cardiovascular disease (Grundy *et al.*, 1982) although the underlying mechanism has yet to be fully elucidated. Various small-scale studies have been reported concerning the effects of dietary supplementation with both plant and animal polyunsaturated fatty acids on platelet kinetics and prostaglandin and thromboxane formation (Goodnight *et al.*, 1981; Brox *et al.*, 1981; Epstein *et al.*, 1982; Lorenz *et al.*, 1983). One such supplement is evening primrose oil, which is rich in linoleic acid and, to a lesser extent, gammalinolenic acid (Table 1) precursors of prostaglandin E_2 and prostaglandin E_1 respectively.

Vascular reactivity to angiotensin II (AII) is reduced in pregnancy (Abdul-Karim & Assali, 1961; Chesley *et al.*, 1965). This may be due to the higher circulating levels of vasodilator prostaglandins found in pregnancy. In pregnancy-induced hypertension, vascular sensitivity to AII becomes progressively greater and may reach non-pregnant values (Talledo *et al.*, 1968; Gant *et al.*, 1973). This results in a loss of protection against the normally high circulating levels of AII found in pregnancy. It seems reasonable to suggest that this effect may be due to defective production of prostaglandins, whether it be through enzyme deficiency, co-factor deficiency or dietary deficiency of essential prostaglandin precursors. Such defective production has been repeatedly demonstrated in pregnancy-induced hypertension (Robinson *et al.*, 1979; Remuzzi *et al.*, 1980; Bussolino *et al.*, 1980).

It was therefore felt to be of interest to determine the effects on the pressor response to AII in normotensive pregnancy and non-pregnant subjects of supplementing polyunsaturated fatty acids intake with evening primrose oil and some co-factors required for prostaglandin synthesis. This dual approach was undertaken since there is as yet no evidence as to whether a substrate deficiency, a deficiency in such known co-factors as zinc and vitamin B_6, or inadequate enzyme function underlies the prostaglandin deficiency in pregnancy-induced hypertension. Thus by considering two potential factors together we could determine whether further, more specific, investigation was warranted.

Methods

Subjects

Some basal data concerning the subjects studied is summarised in Table 2. Pregnant patients were recruited from women previously accepted for the therapeutic termination of pregnancy following counselling by a consultant gynaecologist unconnected with the project. A minimum period of a week was required between counselling and admission for those patients given dietary supplementation. Since admission was frequently arranged sooner than this time, random allocation to treatment or control groups was not possible. However, since the timing of admission was determined by the consultant gynaecologist, and not by one of the authors, a degree of randomisation had been applied. Non-pregnant subjects came from the academic, medical and nursing staff of University Hospital, Nottingham. No subject had a personal history of metabolic, hypertensive or

Table 1 Constituents of Efamol and Efavit

(a) Efamol (per capsule)	Oil of evening primrose (linoleic acid 73% gammalinolenic acid 8%)	500 mg
	Edible gelatine capsule	225 mg
	Natural vitamin E	10 mg
(b) Efavit (per tablet)	Vitamin C	125 mg
	Vitamin B_6	25 mg
	Niacin	7.5 mg
	Zinc sulphate	2.5 mg
	Lactose	39 mg
	Starch	39 mg
	Talc	7 mg
	Stearic acid	7 mg
	Acacia	2 mg

Table 2 Some basal data concerning the groups of subjects studied, mean values ± s.e. mean

Group		*Age (years)*	*Weight (kg)*	*Gestation age (weeks)*	*Blood pressure*		*Heart-rate (beats/min)*
					Systolic (mm Hg)	*Diastolic*	
Pregnant	Supplement (n = 10)	22.9 ± 2.2	58.1 ± 2.1	14.9 ± 0.2	108.0 ± 2.3	66.1 ± 1.8	79.7 ± 2.6
	Control (n = 40)	21.9 ± 1.0	57.4 ± 1.4	15.6 ± 0.2	106.6 ± 1.4	65.3 ± 1.1	75.3 ± 1.8
Non-pregnant	Supplement (n = 10)	28.4 ± 1.4	63.7 ± 2.6	—	109.7 ± 2.5	70.9 ± 1.2	67.0 ± 2.1
	Control (n = 24)	28.5 ± 1.1	66.5 ± 2.1	—	110.6 ± 1.4	73.8 ± 1.0	66.8 ± 1.5

renovascular disease, and none was known to be taking any medication. The study was approved by the local Ethics Committee, and all patients gave written informed consent.

Protocol

Ten pregnant and ten non-pregnant (five men, five women) subjects each ingested eight capsules of evening primrose oil ('Efamol', Efamol Ltd, London) and eight tablets of mineral and vitamin supplements ('Efavit', Efamol Ltd, London) daily for 7 days in addition to their normal, unrestricted diet. The composition of 'Efamol' and 'Efavit' is given in Table 1, from which it will be seen that 2.92 g linoleic acid and 32 mg gammalinolenic acid per day were given in the supplements. Forty pregnant and 24 non-pregnant (seven men, 17 women) received no supplementation and served as controls.

Systemic blood pressure and heart rate was recorded after 20 min recumbency before starting dietary supplementation in the two study groups. The increase in blood pressure in response to the intravenous infusion of angiotensin II was determined in all patients using the same basic experimental regime. Indwelling cannulae (Argyle Medicut 16 or 18G, Sherwood Industries) were placed in each antecubital fossa. Normal saline was infused continuously at 1 ml min^{-1} via the right arm using an IVAC drop counter (IVAC Corporation, San Diego, California). The cannula in the left arm was used for blood sampling for hormone and electrolyte determinations. These results will be reported elsewhere.

Arterial blood pressure was monitored at 2 min intervals using the Arteriosonde Doppler Automatic Blood Pressure Recorder (Roche Medical Electronics, Cranbury, New Jersey). Heart rate was derived from the electrocardiogram. The blood pressure was allowed to stabilize for at least 20 min until random fluctuations in diastolic blood pressure were within 6 mm Hg. An initial blood sample was taken and after 10 min further stabilization angiotensin II (Hypertension, Ciba-Geigy, Basle) was infused via the indwelling cannula of the right arm so that it was flushed through by the saline infusion. The AII was infused using a variable delivery pump (B. Braun, Melsungen) at rates of 0.3, 0.6 and 1.2 ml min^{-1}. This delivered AII doses of 4, 8 and 16 ng kg^{-1} min^{-1} to pregnant patients and 1, 2 and 4 ng kg^{-1} min^{-1} to non-pregnant patients. Each infusion step lasted 10 min. A blood sample was taken at the end of the third step and the AII infusion was discontinued. A 30 min recovery period was allowed for final stabilization of the blood pressure.

Calculations

The basal systolic and diastolic blood pressure was calculated as the mean of the stable blood pressure on either side of the infusion. The evoked blood pressure response to AII was calculated as the difference between the mean diastolic or systolic pressure over the last 6 min of each step of the infusion compared with the basal pressure.

The threshold for response to AII was calculated as that dose of AII required to evoke a 5 mm Hg rise in diastolic pressure. For this purpose the linear relationship between log 10 AII and evoked rise in diastolic blood pressure:

$$y = a + bx$$

was used, where y = evoked response (mm Hg), a = intercept on the y axis, b = slope relating dose and response and x = infused dose of AII (log 10). This identity has previously been used by other workers investigating the pressor effect of AII (Chinn & Düsterdieck, 1972).

Mean values are quoted ± s.e. mean throughout. Student's *t*-test has been used where appropriate to test for significance of differences in paired samples. Student's unpaired *t*-test has been used, following an *F* test to determine suitability for unpaired data. Linear regression analysis has been carried out by the method of least squares.

Results

A number of male subjects were studied in both the treatment and control non-pregnant groups. Since neither their basal blood pressures, nor the systolic or diastolic pressor responses to AII differed between men and women in either treatment group, the data have been pooled.

It can be seen from Table 2 that age, weight, gestation age, systolic and diastolic pressure and heart rate were very closely matched in the pregnant subjects and their controls, and in the non-pregnant subjects and controls. The relative hypotension and tachycardia in both groups of patients is, of course, characteristic of second trimester pregnancy.

No overall change in systolic or diastolic blood pressure or heart rate was found in either pregnant or non-pregnant patients during dietary supplementation (Table 3). Basal systolic pressure, diastolic blood pressure and heart rate were effectively identical at the start of the infusion in the treated and untreated patients of both groups (Table 2). Figures 1 and 2 summarise the evoked change in systolic and diastolic blood pressure during the administration of AII to pregnant and non-pregnant patients respectively. It will be seen that in both study groups the administration of Efamol and Efavit was associated with a blunting of the diastolic pressor response to AII which was more pronounced in the pregnant group ($P < 0.001$ at all doses of AII, compared with $P < 0.02$, $P < 0.02$, $P < 0.01$ in the non-pregant group). The systolic pressor response to AII is normally less pronounced than the diastolic (see Figures 1 and 2). Dietary supplementation was associated with some blunting of this response in the pregnant patients at the two higher doses of AII used ($P < 0.01$ for both) but was without statistically significant effect in the non-pregnant group. Although the calculated diastolic threshold dose of AII was higher in both groups receiving dietary supplementation (2.95 ± 0.24 compared with 2.40 ± 0.17 ng kg^{-1} min^{-1} in the pregnant and 1.87 ± 0.51 compared with 0.91 ± 0.09 ng kg^{-1} min^{-1} in the non-pregnant groups), these differences failed to reach statistical significance.

AII at the highest doses given was usually associated with a small reflex bradycardia; the magnitude of this effect did not differ within the groups.

Table 3 Dietary supplementation for 1 week was not associated with changes in systolic or diastolic blood pressure or heart rate in either pregnant or non-pregnant subjects, mean values ± s.e. mean

	Pregnant		*Non-pregnant*	
	Before	*After*	*Before*	*After*
Systolic blood pressure (mm Hg)	109.9 ± 1.8	108.0 ± 2.3	114.0 ± 1.7	109.7 ± 2.5
Diastolic blood pressure (mm Hg)	64.1 ± 1.8	66.1 ± 1.8	71.7 ± 1.7	70.9 ± 1.2
Heart rate (beats/min)	76.8 ± 2.9	79.7 ± 2.6	67.6 ± 2.4	67.0 ± 2.4

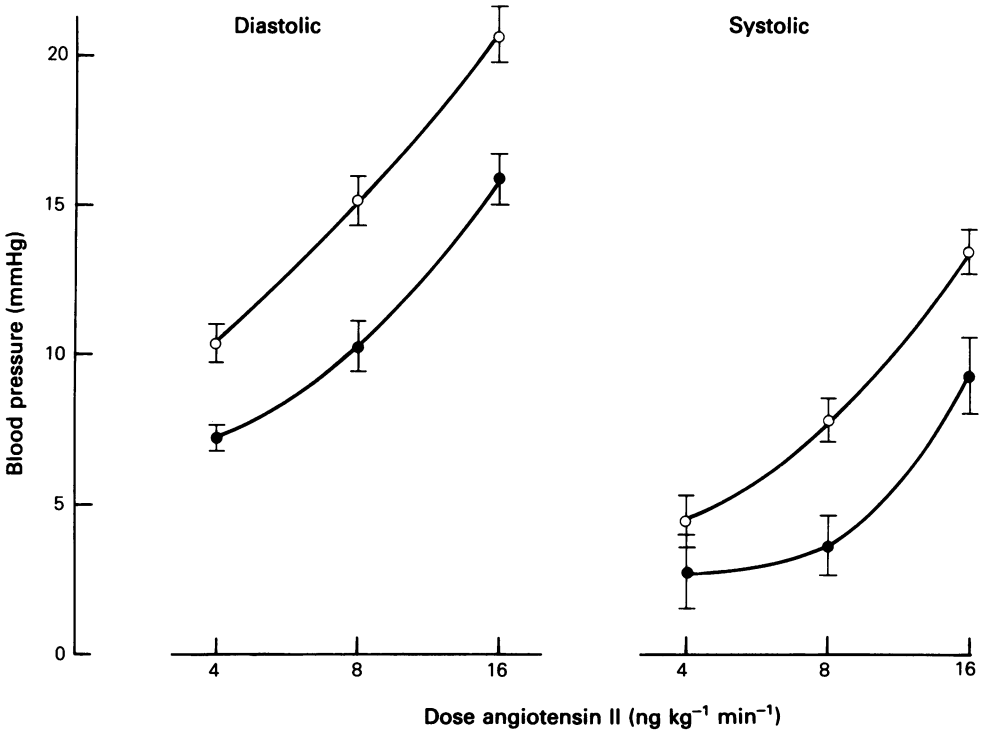

Figure 1 Dietary supplementation with ~3 g linoleic acid, ~ 32 mg gammalinolenic acid and various cofactors for prostaglandin production given to 10 pregnant patients each day for a week was associated with a significant diminution in diastolic pressor response to angiotensin II at all doses studied ($P >$ 0.001 for all). There was a slight but statistically-significant effect on systolic response at the two higher doses ($P < 0.01$). ○ control group, ● supplemented group.

Discussion

Plasma AII concentrations rise from early in gestation (Weir *et al.*, 1975) to levels which, in the non-pregnant adult, would be capable of exerting a pressor effect (Chinn & Düsterdieck 1972). The pregnant woman is protected from the potential vasoconstrictor effects of these high plasma AII concentrations by an apparently specific diminution in pressor responsiveness to the hormone (Abdul-Karim & Assali, 1961; Gant *et al.*, 1973; Broughton Pipkin *et al.*, 1982a,b) not shown with respect to noradrenaline (Chesley *et al.*, 1965; Lumbers, 1970). The markedly greater threshold for pressor activity of AII of the pregnant controls of this paper compared with that for the non-pregnant controls (2.40 ± 0.17 compared with 0.91 ± 0.09 ng AII kg^{-1} min^{-1}, $P \ll 0.001$) is in excellent agreement with these observations. This diminution is apparent by the tenth week of gestation, and is maximal at 18–22 weeks, only starting to fall in the third trimester (Gant *et al.*, 1973). It is not a direct consequence of the high endogenous levels of AII, since volume expansion, which suppresses endogenous activity of the renin-angiotensin system, is not associated with a change in pressor response (Everett *et al.*, 1978a).

Experiments in pregnant rabbits (O'Brien *et al.*, 1977) and humans (Everett *et al.*, 1978b; Jaspers *et al.*, 1981) have shown that the administration of prostaglandin synthetase inhibitors, such as indomethacin, is associated with an enhanced pressor response to AII. Conversely, the administration of prostaglandin E_2, prostaglandin E_1 or epoprostenol is associated with a blunting of response, which is more pronounced than in non-pregnant subjects (Broughton Pipkin *et al.*, 1982a,b, 1984). There is thus some evidence to suggest the involvement of vasodilator prostaglandins in the blunting of responsiveness to AII in pregnancy.

O'Brien & Broughton Pipkin (1979) found that pregnant rabbits fed on a diet deficient in

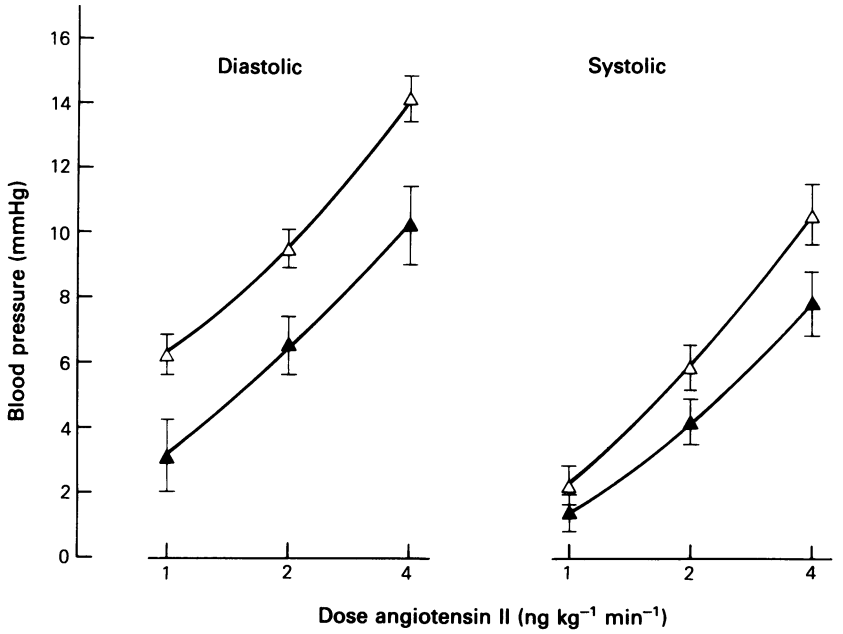

Figure 2 Dietary supplementation with ~3 g linoleic acid, ~32 mg gammalinolenic acid and various cofactors for prostaglandin production given to 10 non-pregnant subjects each day for a week was associated with a significant diminution in diastolic pressor response to angiotensin II at all doses studied ($P < 0.02$, $P < 0.02$, $P < 0.01$) but was without significant effect on the systolic response. △ control group, ▲ supplemented group.

essential fatty acids were significantly more sensitive to the pressor response effects of AII than control rabbits fed a standard diet. In human experiments, supplementation of a standard Western diet with cod liver oil which is rich in ω-3 polyunsaturated fatty acids such as eicosapentaenoic acid was, on the other hand, associated with a diminution in pressor response to noradrenaline and AII (Lorenz *et al.*, 1983).

In the experiments here reported, dietary supplementation was with evening primrose oil, a rich source of linoleic acid (18:2, ω6), comparable in content with safflower oil (Epstein *et al.*, 1982), with gammalinolenic acid (18:3, ω6) and with various substances regarded as cofactors for prostaglandin production. The direct intravenous infusion of safflower oil in man is associated with a marked increase in excretion of the 6-keto prostaglandin $F_{1\alpha}$ metabolite of epoprostenol (Epstein *et al.*, 1982). A recent report has also shown that the daily ingestion of eight capsules of Efamol, the dose studied in this paper, is associated with a rise in plasma concentration of dihomogammalinolenic acid (Manku *et al.*, 1985). Dietary supplementation with pure gammalinolenic acid increases the capacity of platelets to synthesise prostaglandin E_1, and, to a lesser extent, prostaglandin E_2, and is associated with potentially antithrombotic changes in haemostatic function (Kernoff *et al.*, 1977). It was not possible to measure prostaglandin or epoprostenol metabolites in this study, but the blunting of pressor response obtained is consistent with that obtained when prostaglandin E_2, prostaglandin E_1 or epoprostenol are infused i.v. in women of comparable gestation age (Broughton Pipkin *et al.*, 1982a,b, 1984). Indeed, the threshold for diastolic pressor response to AII after supplementation was very close to that seen during the infusion of prostaglandin E_2 (2.95 ± 0.24 compared with 2.99 ± 0.22 ng kg^{-1} min^{-1}) and, not significantly lower than the thresholds with prostaglandin E_1, and epoprostenol of 3.51 ± 0.51 and 3.87 ± 0.81 ng kg^{-1} min^{-1} respectively. These thresholds are all higher than those in control patients not receiving treatment (1.62 ± 0.28 ng kg^{-1} min^{-1}). It thus seems probable that the dietary supplementation was associated with increased production of either prostaglandin E_1, E_2 or epoprostenol.

It is also possible that any increased production of E series prostaglandins was associated with the administration of 200 mg vitamin B_6, pyridoxine, each day, in the Efavit. This is

needed for the normal activity of delta-6-desaturase, which converts *cis*-linoleic acid to gamma linolenic acid (Witten & Holman, 1952). In this experiment, we did not attempt to differentiate between the effects of supplementation with substrate and of supplementation with precursors for prostaglandin synthesis. Having now demonstrated an apparent effect of such supplementation, futher experiments are being carried out in an attempt to identify the responsible factor(s).

Another factor which can influence vessel reactivity is tissue and plasma sodium content (Heistad *et al.*, 1971), raised plasma sodium concentrations being associated with enhanced response. However, in this study the plasma sodium concentrations were slightly but statistically-significantly higher in the pregnant treated group ($P < 0.05$), who had the lesser response, which is not in accordance with an effect of sodium ions on the pressor response.

Pregnancy-induced hypertension occurs in approximately one woman in ten in her first pregnancy. An enhanced pressor response to AII antedates the clinical hypertension and appears to be a specific feature of the disease (Talledo *et al.*, 1968; Gant *et al.*, 1973). A diminished vascular capacity to synthesize epoprostenol and E series prostaglandins is also well-documented in this condition (Remuzzi *et al.*, 1980; Bussolino *et al.*, 1980). We have now shown that simple dietary supplementation with linoleic acid, gammalinolenic acid and cofactors for prostaglandin production is, in second trimester pregnancy, associated with a diminution in pressor response to AII. Whether such supplementation could be of benefit in the prevention of pregnancy-induced hypertension remains to be determined.

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