Erythrocytic cation transport receptor numbers and activity in pregnancies complicated by essential hypertension and pre-eclampsia

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Abstract

Various functions of erythrocytic cation transport were studied in normotensive and hypertensive pregnancy (women with pre-eclampsia and essential hypertension). The results showed that in pregnancy there is an increase in the number of erythrocytic glycoside binding sites accompanied by a proportional increase in the active inward transport of rubidium (used as a substitute for potassium). There was no evidence of an effect of pregnancy on intraerythrocytic sodium concentrations. These changes were apparently entirely attributable to pregnancy and not affected by pre-eclampsia or essential hypertension.

It is suggested that these alterations indicate an adaptive increase in sodium pump numbers and activity secondary to a tendency for the intraerythrocytic sodium concentration to rise during pregnancy and compensating for that tendency.

Introduction

Several abnormalities of cation transport have been described in the erythrocytes and leucocytes of patients with essential hypertension.¹ In pregnancy hypertension may occur either as an already existing condition or as a manifestation of pre-eclampsia. We have therefore studied several different functions of cation transport in the erythrocytes of women with and without hypertension in pregnancy to see whether there are abnormalities and, if so, to what extent these might be attributable to pregnancy and to what extent attributable to hypertension. We have reported briefly on our findings elsewhere.²

Patients and methods

We studied 18 women with pre-eclampsia and 15 with essential hypertension. For each woman with pre-eclampsia or essential hypertension a normotensive woman with an uncomplicated pregnancy was chosen to match for parity and for gestation to within one week. Each woman was studied while pregnant at some time after the 28th week of gestation and again at six weeks post partum.

Criteria for pre-eclampsia were: a systolic blood pressure ≥ 140 mm Hg and diastolic pressure ≥ 90 mm Hg during the third trimester; a rise in diastolic blood pressure of at least 25 mm Hg

compared with the first blood pressure recorded during pregnancy (before 20 weeks of gestation in all cases); and persistent proteinuria of at least ++ on Albustix testing.

The women with essential hypertension had diastolic blood pressures ≥ 90 mm Hg or systolic blood pressures ≥ 140 mm Hg, without treatment, at the time of booking before 20 weeks of gestation. This group included nine women who had received treatment for essential hypertension before pregnancy but whose treatment had been withdrawn when pregnancy was diagnosed. In two instances antihypertensive drugs (methyldopa and atenolol) were later re-introduced.

Cation transport measurements on the women's erythrocytes were carried out as follows using methods detailed elsewhere^{3,4}: (a) the maximal ability of the erythrocyte membranes to bind ³H-digoxin specifically in vitro was taken as a measure of the number of Na⁺,K⁺-adenosine triphosphatase cation transport sites on the membranes; (b) the ability of the erythrocytes to transport rubidium-86 (⁸⁶Rb uptake) was taken as a measure of the activity of Na⁺,K⁺-adenosine triphosphatase (rubidium functioning as a substitute for potassium); (c) the intraerythrocytic sodium concentration was measured.

Statistical analyses were made using Student's paired or unpaired *t* test, as appropriate.

Results

PATIENT CHARACTERISTICS

Age and gestation at the time of sampling did not differ among the groups (table I). Ten of the 18 women with pre-eclampsia and five of the 15 with essential hypertension were primiparous.

Table II gives the systolic, diastolic, and mean arterial pressures of the women with essential hypertension and pre-eclampsia. "Booking" pressures were those taken at the first clinic attendance before 20 weeks; "study" pressures were the maximum pressures taken no more than five days before blood sampling; "postpartum" pressures were those recorded six weeks after delivery. In both groups of women the pressures at the time of study were significantly higher than those at booking and six weeks after delivery ($p < 0.005$ or better in all cases). The women with essential hypertension had significantly higher pressures than the women who developed pre-eclampsia both at booking and after delivery ($p < 0.001$ in all cases), but there were no differences in the pressures taken at the time of study.

CATION TRANSPORT MEASUREMENTS

Figure 1 shows the maximal erythrocytic ³H-digoxin binding and ⁸⁶Rb uptake and the intraerythrocytic sodium concentrations in the two groups of hypertensive women compared with their respective matched normotensive controls. Figure 2 gives these measurements for the pregnant women compared with their own postpartum values.

There was no difference in respect of any of the measurements

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TABLE I—Age and gestation at time of study during pregnancy. Figures are medians (ranges in parentheses)

Group	Age (years)	Gestation (weeks, days)
Pre-eclampsia (n = 18)	25 (17-36)	33.5 (28.1-38.4)
Matched controls	24 (17-30)	33.3 (28.3-38.0)
Essential hypertension (n = 15)	28 (20-32)	34.4 (28.2-37.2)
Matched controls	25 (17-34)	34.5 (28.5-37.0)

between the normotensive controls and either the pre-eclamptic women or those with essential hypertension. After delivery, however, ³H-digoxin binding and ⁸⁶Rb uptake fell significantly in all cases. By contrast, there was no change at all in the intraerythrocytic sodium concentrations after delivery.

In all three groups of women there was a significant correlation between ³H-digoxin binding and ⁸⁶Rb uptake both before and after delivery (*r* = 0.49; *p* < 0.01 for the combined groups). There was no relation, however, between either of these measurements and the intraerythrocytic sodium concentration in any group.

Discussion

Our data suggest that during pregnancy there is increased activity of Na⁺,K⁺-adenosine triphosphatase (as assessed by the inward transport of rubidium) due to an increase in the quantity

of Na⁺,K⁺-adenosine triphosphatase present in the cell membrane (as assessed by specific ³H-digoxin binding). The increase in the amount of Na⁺,K⁺-adenosine triphosphatase was proportional to the increase in its activity. In other words, the activity of each site was not changed during pregnancy. We did not measure the affinity of binding and so cannot say whether there was also altered affinity of Na⁺,K⁺-adenosine triphosphatase for digoxin. The data also suggest that these changes in Na⁺,K⁺-adenosine triphosphatase function are not affected by or related to blood pressure, since the results in the two hypertensive groups of women were indistinguishable from those in the non-hypertensive women.

Despite the increase in numbers of digoxin binding sites and the increase in pump activity the intraerythrocytic sodium concentration remained unchanged during pregnancy. Since an increase in pump activity would be expected to lead to a

TABLE II—Systolic, diastolic, and mean arterial blood pressures (mm Hg) at different times during study. Values are means [SD in square brackets]

Group	"Booking" pressure	"Study" pressure	Postpartum pressure
	Systolic pressure		
Pre-eclampsia	116.9 [14.6] (n = 17)	164.1 [16.5] (n = 18)*	123.3 [11.2] (n = 16)
Essential hypertension	151.5 [16.9] (n = 14)†	161.4 [11.2] (n = 15)*‡	142.9 [15.7] (n = 13)†
	Diastolic pressure		
Pre-eclampsia	70.6 [8.3] (n = 17)	112.1 [11.5] (n = 18)*	79.1 [10.4] (n = 16)
Essential hypertension	87.5 [9.6] (n = 14)†	103.2 [7.2] (n = 15)*	92.5 [5.7] (n = 13)†
	Mean arterial pressure (diastolic + (systolic-diastolic)/3)		
Pre-eclampsia	85.9 [8.6] (n = 17)	130.2 [12.0] (n = 18)*	94.7 [10.0] (n = 16)
Essential hypertension	108.7 [8.0] (n = 14)†	122.2 [5.3] (n = 15)*	109.3 [8.2] (n = 13)†

* Different from booking and postpartum pressures (*p* < 0.005 or better).
† Different from corresponding pre-eclamptic pressures (*p* < 0.001).
‡ Different from booking pressure by paired test of 14 sets of data.

FIG 1—³H-Digoxin binding, ⁸⁶Rb uptake, and intraerythrocytic sodium concentrations (Na_i) in women with pre-eclampsia and essential hypertension compared with matched normotensive controls. Bars represent SD.
Conversion: SI to traditional units—⁸⁶Rb: 1 μmol/l ≈ 8.6 μg/100 ml. Na_i: 1 mmol/l = 1 mEq/l.

FIG 2—Antepartum and postpartum ³H-digoxin binding, ⁸⁶Rb uptake, and intraerythrocytic sodium concentrations (Na_i) in women with pre-eclampsia, essential hypertension, and normal blood pressure. Bars represent SD.
Conversion: SI to traditional units—⁸⁶Rb: 1 μmol/l ≈ 8.6 μg/100 ml. Na_i: 1 mmol/l = 1 mEq/l.

reduction in the intraerythrocytic sodium concentration, these observations suggest that there is an initial increase in intraerythrocytic sodium concentration in pregnancy which in turn leads to adaptive changes in the erythrocyte membrane and a consequent increase in pump numbers and activity. That such adaptive changes occur has been demonstrated both in the erythrocytes of patients taking digoxin and in HeLa cells in experiments in vitro. During short term digoxin treatment, in vitro erythrocytic ^3H -digoxin binding is reduced owing to occupation of binding sites by the therapeutically administered digoxin, and as a consequence ^{86}Rb uptake by the erythrocytes falls and the intraerythrocytic sodium concentration rises.⁵⁻⁶ During long term treatment, however, the intraerythrocytic sodium concentration returns to pretreatment values, and this is accompanied by a return to pretreatment values of the number of sites available for binding ^3H -digoxin (even in the presence of the therapeutically administered digoxin) and of the activity of those sites.⁶⁻⁷ There may even be an increase in Na^+/K^+ -adenosine triphosphatase activity during long term digoxin.⁶ Evidence that these adaptive changes during long term treatment may be due to the initial rise in intraerythrocytic sodium concentration comes from the in vitro experiments of Lamb and his colleagues in HeLa cells. Incubation of HeLa cells for 24 hours with low concentrations of ouabain, or with ethacrynic acid, or in a medium containing a low concentration of potassium, causes an increase in the number of ouabain binding sites.⁸⁻¹⁰

All of these procedures raise the intracellular sodium concentration, and the production of binding sites is well related to the intracellular sodium concentration. Lithium, which substitutes for sodium within the cell, also causes an increase in ouabain binding sites.¹⁰

The lack of change in intraerythrocytic sodium concentration in pregnancy (expressed in mmol/l of cells) cannot be explained by a change in intraerythrocytic sodium content accompanied by a concomitant change in red cell volume, since in a separate series of experiments we found no differences in mean red cell volume when comparing pregnant with non-pregnant women (Moore and Redman, unpublished data).

We therefore postulate that the increase in pump numbers and activity occurs as an adaptive response to a need to maintain normal intraerythrocytic sodium concentrations.

There are now beginning to appear reasonably consistent reports on changes in erythrocytic cation transport in pregnancy, although there are a few apparent discrepancies. In 1962 Lowenstein showed that ^{86}Rb uptake by red cells increased by about 45% during pregnancy, reaching a maximum towards term.¹¹ Even by six weeks after delivery ^{86}Rb uptake had not returned to non-pregnant values. This suggests that the differences that we observed between values of both ^3H -digoxin binding and ^{86}Rb uptake near term and those found six weeks after delivery represent underestimates of the true differences in values between pregnant and non-pregnant values. More recently, Worley *et al* have reported increased erythrocytic sodium-lithium countertransport during pregnancy,¹² and since our original report² others have reported increases in erythrocytic glycoside binding.¹³⁻¹⁴ Finally, several groups of workers have found no effect of pregnancy on erythrocytic and leucocytic sodium content or concentrations,¹⁵⁻¹⁷ although in one study there was a significant decrease in intraerythrocytic content.¹⁴

So far as the effects of hypertension in pregnancy on transmembrane cation transport are concerned, both we and others¹²⁻¹⁴⁻¹⁶⁻¹⁷ have found similar results in erythrocytic and leucocytic transmembrane cation transport functions when comparing normotensive with hypertensive pregnancies. By contrast, however, Forrester and Alleyne found an increase in intracellular sodium concentration and a decrease in the rate constant for sodium efflux in the leucocytes of women with

pre-eclampsia compared with normotensive pregnant women,¹⁸ while Weissberg *et al* found that there was an increase in total sodium flux in hypertensive compared with normotensive pregnancy¹⁵—a result which contrasts both with the erythrocyte data that we and Worley *et al* have reported and with the leucocyte data of Forrester and Alleyne. We can find no clear reason for these discrepancies, although they may have been due to technical differences in measurements in vitro or to differences in the matching of control subjects for comparison with hypertensive patients, since cation transport may be altered by a wide variety of other circumstances, including age and race.

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