Novel appearance of placental nuclear monoamine oxidase: Biochemical and histochemical evidence for hyperserotonomic state in preeclampsia-eclampsia

Vibha R. Gujrati, PhD,[a] Kirpa Shanker, PhD,[a] Satya Vrat, MD,[a] Chandravati, MS,[b] and Surendra S. Parmar, PhD[a]

Lucknow, India

OBJECTIVE: The aim of this study was to explore the relevance of placental monoamine oxidase at the subcellular level in the etiology of the hyperserotonomic state in preeclampsia-eclampsia.
STUDY DESIGN: The study was conducted on placentas from 20 normal pregnant women and 25 women with varied severity of preeclampsia-eclampsia. Placental serotonin and subcellular monoamine oxidase activity were determined. Histochemical localization of monoamine oxidase was done in placental sections and cell isolates.
RESULTS: Placental serotonin increases with severity ($r_{systolic}$ 0.84, $r_{diastolic}$ 0.83) and monoamine oxidase decreases ($r_{systolic}$ 0.86, $r_{diastolic}$ 0.79). Placental monoamine oxidase showed marked changes in preeclampsia-eclampsia. Histochemical localization of monoamine oxidase showed diffused low activity evenly throughout the cytoplasm and nucleus of the syncytiotrophoblastic cells in preeclampsia-eclampsia; in contrast, normal placenta showed high activity in the cytoplasm without any activity in the nucleus of syncytiotrophoblastic cells. Detection of monoamine oxidase activity in nuclei of the placenta in preeclampsia-eclampsia is a novel finding. Monoamine oxidase activity at the subcellular level further strengthens this observation. A severity-dependent decrease was present in the nuclei of placentas with preeclampsia-eclampsia. The use of specific substrates and inhibitors revealed the presence of monoamine oxidase in mitochondria and nucleus.
CONCLUSION: The study delineates an impaired catabolism of placental serotonin in preeclampsia-eclampsia. The novel appearance of monoamine oxidase in nuclei in proximity to its normal site and low activity resulting in a hyperserotonomic state may lead to preeclampsia-eclampsia. (Am J Obstet Gynecol 1996;175:1543-50.)

Key words: Monoamine oxidase, serotonin, placenta, preeclampsia-eclampsia

Serotonin (5-hydroxytryptamine) plays a pivotal role in pregnancy,[1] and a hyperserotonomic condition has been documented in preeclampsia-eclampsia by various workers.[2-4] Preeclampsia-eclampsia is classified by its classic triad of hypertension, edema, and proteinuria, and severe hypertension today is a major morbidity factor in high-risk pregnancies. The study of the role played by serotonin in preeclampsia was prompted by the fact that a serotonin-induced placental vasculature spasm was tenfold greater than that seen with norepinephrine.[5]

In our earlier studies we showed a generalized hyperserotonomic state in preeclampsia-eclampsia[4, 6] with a central focus on blood platelets (hemodynamics). This prompted us to carry out the current investigation with a view to establish a correlation between serotonin metabolism and severity of preeclampsia-eclampsia. A major factor in the regulation of the serotonin level in body is its catabolism by the enzyme monoamine oxidase (E.C.1.4.3.4), which is well documented in human tissues.[7] The localization of monoamine oxidase by histochemistry has been demonstrated in human tissues, including placenta.[8, 9] In tissues monoamine oxidase is documented as particulate enzyme[7, 10]; however, occasionally monoamine oxidase activity is also encountered biochemically in the microsomal fraction.[11] Therefore the intracellular site of the enzyme-bearing membrane-component is still debatable. Histochemical studies were carried out to support the biochemical findings at the subcellular level. Furthermore, studies with specific inhibitors of monoamine oxidase were performed to ascertain the nature of placental monoamine oxidase.

From the Departments of Pharmacology and Therapeutics[a] and Obstetrics and Gynaecology,[b] King George's Medical College.
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Reprint requests: K. Shanker, PhD, Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow 226 003, India.

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Material and methods

Selection of cases

Control group. Human placentas were obtained near or at term from normal healthy women with normal deliv-

eries or cesarean sections aged 20 to 30 years (primigravid 8, secundiparas 6, multiparas 6).

Study group. Human placentas were obtained from patients with blood pressures in the range of 140/90 to 210/140 mm Hg, proteinuria (0.5 to 4 gm albumin/day), and edema (legs +, legs and hands ++, generalized +++) without or with convulsions (preeclampsia-eclampsia) and aged 20 to 35 years (primigravid 10, secundiparas 8, multiparas 7).

Chemicals. 5-Hydroxytryptamine creatinine sulfate and kynuramine dihydrobromide were obtained from Sigma (St. Louis) and nitroblue tetrazolium from Calbiochem (Los Angeles). Clorgyline was obtained from May & Baker, Dagenham, United Kingdom, and deprenyl (selegiline hydrochloride) was a generous gift from Prof. J. Knoll, Budapest.

Methods

The current study was conducted in pregnant women admitted to Queen Mary's Hospital, King George's Medical College, Lucknow. Placental specimens were obtained immediately after vaginal delivery or cesarean section near or at term. The basal membrane and blood vessels were teased away and the adhering blood was removed by several washings with mannitol–ethylenediaminetetraacetic acid–sucrose buffer and normal saline solution. Pieces from various cotyledons of placenta were cut and stored at −5° C until analyzed for monoamine oxidase and serotonin. For histochemical studies small triangular blocks of 3 mm thick pieces were cut, and frozen sections of 8 to 10 μm were prepared immediately.

Placental serotonin content. Placental tissues were homogenized in ice-cold hydrochloric acid (20% wt/vol). Serotonin was extracted from the tissues by shaking with borate buffer (pH 10.0, 0.5 mol/L) and *n*-butanol, washing with borate buffer (pH 10.0, 0.1 mol/L), and finally extracted into the hydrochloric acid phase. The method has been described previously.[4] Recovery with the current method was 75% to 80%.

Placental monoamine oxidase

BIOCHEMICAL STUDIES

SUBCELLULAR FRACTIONATION. After thorough washings with mannitol–ethylenediaminetetraacetic acid–sucrose buffer placental tissues were homogenized in isotonic sucrose (ice-cold) in a glass homogenizer with a Teflon pestle at a speed of 2500 revolutions/min, and a 10% (wt/vol) homogenate was prepared. The nuclear and mitochondrial fractions were separated by differential centrifugation in REMI K-24 (cold centrifuge). The pellets obtained at 600*g* and 20,000*g*, respectively, were washed with sucrose, resuspended in isotonic sucrose, and used within 1 hour.

CHARACTERIZATION OF SUBCELLULAR COMPONENTS. The nuclear fraction (600*g* pellet) was characterized by the ratio of deoxyribonucleic acid/ribonucleic acid. The deoxyribonucleic acid content was measured with diphenylamine[12] and ribonucleic acid with orcinol[13] as color-developing agents with modifications. The mitochondrial fraction (20,000*g* pellet) was characterized by the cytochrome C–oxidase activity.[14]

MONOAMINE OXIDASE ACTIVITY. Monoamine oxidase activity was determined spectrophotofluorometrically.[4] The 2.0 ml reaction mixture comprised phosphate buffer (pH 8.0, 0.1 mol/L) and 0.1 to 2.0 mg of enzyme protein and kynuramine at 4.0×10^{-6} mol/L. The reaction was incubated at 37° C for 30 minutes and terminated by trichloroacetic acid (10% wt/vol). The fluorescence was measured in sodium hydroxide with excitation at 315 nm and emission at 380 nm. Enzyme activity is expressed in units per milligram of protein per unit of time.

SPECIFIC INHIBITORS OF MONOAMINE OXIDASE. Effects of specific inhibitors of monoamine oxidase—clorgyline and deprenyl—were determined on monoamine oxidase activity in preparations obtained from mitochondrial and nuclear fractions of placental tissues at a final concentration of 10^{-4} to 10^{-6} mol/L. The enzyme activity was measured after 10 minutes of pretreatment with inhibitors.

HISTOCHEMICAL STUDIES

MONOAMINE OXIDASE ACTIVITY. For histochemical studies frozen sections 8 to 10 μm thick were subjected to histochemical localization of monoamine oxidase activity within 1 to 2 hours.[8] Sections were incubated in a medium comprising serotonin (10 mg), nitroblue tetrazolium (5 mg), phosphate buffer (pH 8.0, 0.1 mol/L), and water for 1 hour in an incubation chamber maintained at 37° C. Simultaneously, sections also incubated without the substrate (5-hydroxytryptamine) acted as control. After incubation the sections were thoroughly rinsed with distilled water and mounted in glycerol. They were examined under the microscope for the presence of formazan granules at different magnifications (Tiyoda FM-220, Tokyo).

ISOLATED PLACENTAL FRACTIONS. Monoamine oxidase activity was also demonstrated microscopically in nuclei (600*g* fraction) and mitochondria (20,000*g* fraction). A thin film of suspension was prepared on microscopic slides from nuclear and mitochondrial isolates. The film was thoroughly air dried and processed similarly for the histochemical localization of monoamine oxidase activity.

SPECIFIC INHIBITOR STUDIES. Placental frozen sections obtained from both groups were pretreated with clorgyline and deprenyl in a concentration of 10^{-4} to 10^{-6} mol/L in phosphate buffer for 15 minutes and then incubated in the incubation medium for 1 hour and processed as described above.

Statistical analysis. The significance of difference between preeclampsia-eclamptic and control normotensive pregnant women were determined by one-way analysis of variance, and statistical significance was inferred at $p <$

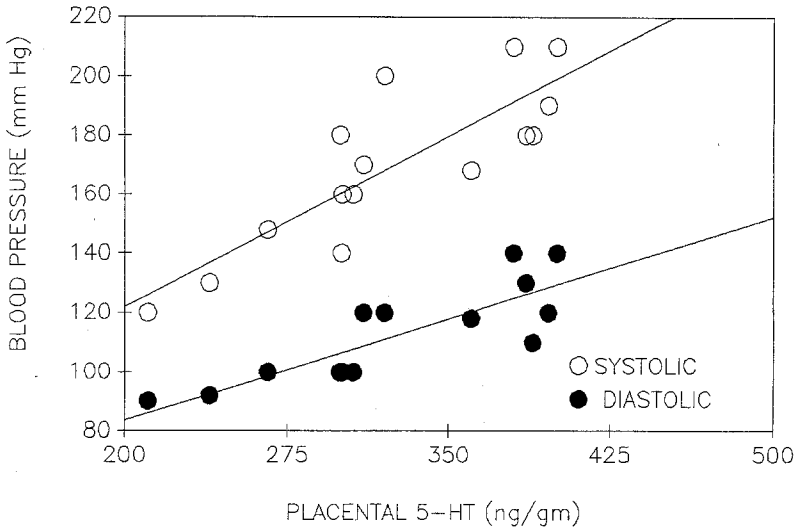

Fig. 1. Scattergram showing relationship of placental serotonin content with systolic blood pressure (*open circles*) and diastolic blood pressure (*solid circles*) in group with preeclampsia-eclampsia ($n = 15$). Correlation coefficient for systolic blood pressure $r = 0.838$, $p < 0.001$, and for diastolic blood pressure $r = 0.835$, $p < 0.001$. *5-HT*, 5-Hydroxytryptamine.

Table I. Placental serotonin content in normal pregnant and preeclamptic-eclamptic subjects

Group	*No.*	*Age (yr)*	*Arterial blood pressure*		*Proteinuria (gm)*	*Edema (+)*	*Convulsions (%)*	*Serotonin content (ng/gm tissue)*
			Systolic (mm Hg)	*Diastolic (mm Hg)*				
Normal	14	24.85 ± 0.94	114.0 ± 1.85	77.42 ± 0.92	0	0	0	174.01 ± 9.74
PET	15	27.13 ± 1.13	170.93 ± 7.20	112.00 ± 4.21	1.83 ± 0.24	1.33 ± 0.14	40	324.16 ± 15.34*

Values are mean ± SEM. Convulsions were present in eclamptic patients (6/15). *PET*, Preeclampsia-eclampsia.
*$F = 61.78$, $p = 0.245 \times 10^{-7}$.

0.05. Correlation was studied by linear multiple regression analysis of the data of each individual subject with the least-squares method.

Results

Biochemical studies

Placental serotonin. In normal pregnant subjects the blood pressure ranged from 100/70 to 120/85 mm Hg and the placental serotonin content was 174.01 ± 9.74 ng/gm. In preeclampsia-eclampsia the blood pressure ranged from 140/90 to 210/140 mm Hg and the placental serotonin content was 324.16 ± 15.34 ng/gm, statistically higher than the control group (Table I). The placental serotonin level had a direct correlation with the systolic blood pressure ($r = 0838$) and diastolic blood pressure ($r = 0.835$) in preeclampsia-eclampsia, as depicted in Fig. 1.

Placental monoamine oxidase. Table II depicts monoamine oxidase activity in placental tissues from both groups. A significant decrease in monoamine oxidase activity was observed in preeclampsia-eclamptic placentas on comparison with normal placentas when expressed either in weight of tissue or specific activity of the enzyme. This decrease in monoamine oxidase activity further showed a correlation with systolic blood pressure ($r = 0.858$) and diastolic blood pressure ($r = 0.788$) of the subjects, as shown in Fig. 2.

At the subcellular level, a different pattern of monoamine oxidase activity was noted in placentas with preeclampsia-eclampsia, as reported in Table II. In normal placenta monoamine oxidase activity was localized in the mitochondrial fraction (33.93 ± 2.97 units), which was significantly decreased in preeclampsia-eclampsia placenta (19.43 ± 2.03 units). It is interesting to note that in preeclampsia-eclampsia placenta the nuclear fraction showed significant monoamine oxidase activity (10.94 ± 1.07 units), whereas the normal placental nuclear fraction was completely devoid of any monoamine oxidase activity.

Studies with specific inhibitors—clorgyline and deprenyl—showed that the enzyme preparations obtained from mitochondrial and nuclear fractions from both groups were inhibited by clorgyline and deprenyl at all

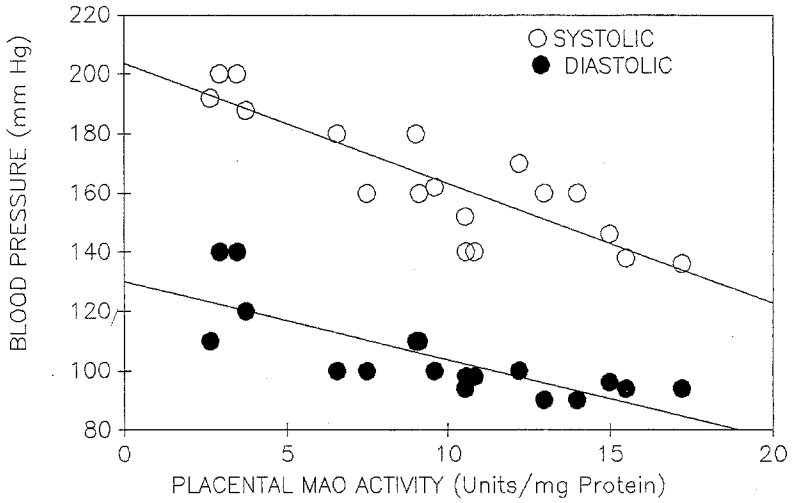

Fig. 2. Scattergram showing relationship of placental monoamine oxidase *(MAO)* activity with systolic blood pressure (*open circles*) and diastolic blood pressure (*solid circles*) in group with preeclampsia-eclampsia ($n = 18$). Correlation coefficient for systolic blood pressure $r = 0.858$, $p < 0.001$, and for diastolic blood pressure $r = 0.788$, $p < 0.001$.

Table II. Monoamine oxidase activity in total placental homogenate and in mitochondrial and nuclear fractions in normal and preeclamptic-eclamptic subjects

			Arterial blood pressure		*MAO activity*			
					Total placental homogenate		*Mitochondrial fraction (units/mg protein)*	*Nuclear fraction (units/mg protein)*
Group	*No.*	*Age (yr)*	*SBP (mm Hg)*	*DBP (mm Hg)*	*units/gm tissue*	*units/mg protein*		
Normal	15	25.00 ± 0.89	111.33 ± 2.26	77.06 ± 1.15	565.70 ± 31.65	15.27 ± 1.56	33.93 ± 2.97	0.00*
PET	18	27.10 ± 1.21	164.66 ± 4.99	104.66 ± 3.54	245.00 ± 19.90	9.62 ± 0.58	19.43 ± 2.03	10.94 ± 1.07
Statistical analysis (ANOVA)					$F = 38.14$, $p = 0.219 \times 10^{-4}$	$F = 5.90$, $p = 0.0218$	$F = 18.24$, $p = 0.00018$	$F = 104.89$, $p = 0.261 \times 10^{-10}$

Values are mean ± SEM. *SBP*, Systolic blood pressure; *DBP*, diastolic blood pressure; *MAO*, monoamine oxidase; *PET*, preeclampsia-eclampsia; *ANOVA*, analysis of variance.

*Nuclear fraction of normal placental tissue was devoid of monoamine oxidase activity.

concentrations (10^{-4} to 10^{-6} mol/L); a relatively lesser inhibition was observed with deprenyl (Table III).

SEROTONIN CONTENT AND MONOAMINE OXIDASE ACTIVITY IN PREECLAMPTIC AND ECLAMPTIC PLACENTA. The eclamptic placenta showed a significantly higher serotonin content (378.61 ± 12.08 ng/gm) than was found in preeclamptic placenta (287.86 ± 14.64 ng/gm) (Table IV). A decrease in monoamine oxidase activity showed a direct correlation with severity (i.e., greater decrease in monoamine oxidase activity was observed in eclamptic placenta than in preeclamptic placenta). Furthermore, at the subcellular level monoamine oxidase activity detected in the preeclamptic mitochondrial fraction showed 25.46 ± 2.01 units and the eclamptic mitochondrial fraction exhibited statistically decreased activity, 12.02 ± 1.17 units (Table IV). Monoamine oxidase activity of the nuclear fraction from preeclamptic placenta showed 13.21 ± 0.32 units, statistically higher than eclamptic nuclear activity of 8.09 ± 0.90 units.

HISTOCHEMICAL LOCALIZATION OF PLACENTAL MONOAMINE OXIDASE. On microscopic examination monoamine oxidase activity was observed as diffuse dark blue to violet formazan granule formation in the cytoplasm of syncytiotropholbastic cells in the presence of 5-hydroxytryptamine and nitroblue tetrazolium in normal placenta. Formazan granules in the control study by omission of 5-hydroxytryptamine in the incubation mixture were not seen.

Sections from normal placenta revealed high-density formazan granules throughout the cytoplasm of syncytiotrophoblastic cells, with central negative staining giving rise to a honeycomb appearance under microscopic examination; connective and stromal tissues did not show any formazan granules (Fig. 3, *A*). In contrast, the

sections from placentas with preeclampsia-eclampsia revealed diffused low-density formazan granules distributed evenly throughout the syncytiotrophoblastic cells without negative nuclear space (Fig. 3, *B*), which is clearly evident in an isolated syncytiotrophoblastic cell from preeclampsia-eclampsia placenta (Fig. 4). Nevertheless, the sections from both normal and preeclampsia-eclamptic placenta showed a normal histologic pattern of hematoxylin-eosin staining.

Histochemical studies with isolated mitochondria and nuclei from both groups gave a clear in situ picture. Histochemically mitochondrial fraction from both control and preeclampsia-eclampsia placenta showed monoamine oxidase activity, low-density formazan granules in preeclampsia-eclampsia placental sections in contrast to dark granules in normal placental sections. The nuclear isolates from normal placenta did not show any enzyme activity on histochemical studies. In preeclampsia-eclampsia placenta nuclear isolates demonstrated the site of monoamine oxidase activity on the nuclear membrane and nucleoplasm. Moreover, the monoamine oxidase activity demonstrated that in nuclei of preeclampsia-eclampsia placenta varied with severity of the syndrome. The nuclei isolated from preeclamptic placenta showed low-density formazan granules distributed evenly on nuclear membrane and nucleoplasm (Fig. 5, *A*), whereas the nuclei from eclamptic placenta revealed dense granules clustering on the nuclear membrane only (Fig. 5, *B*). This observation further confirms our biochemical finding.

Specificity of the histochemical localisation of monoamine oxidase was confirmed by the absence of formazan granule formation either by eliminating 5-hydroxytryptamine (substrate control) or pretreatment with the specific monoamine oxidase inhibitors clorgyline and deprenyl. On treatment with clorgyline no staining was observed at all concentrations, whereas with deprenyl at 10^{-6} mol/L little staining was observed and no staining was observed at other concentrations.

Table III. Inhibition of placental monoamine oxidase from normal subjects and subjects with preeclampsia-eclampsia by clorgyline and deprenyl at subcellular level

Inhibitor (mol/L)	*Normal placenta (mitochondrial MAO)*	*PET placenta*	
		Mitochondrial MAO	*Nuclear MAO*
Clorgyline			
10^{-4}	100	100	100
10^{-5}	95	100	80
10^{-6}	80	90	55
Deprenyl			
10^{-4}	70	70	40
10^{-5}	70	65	20
10^{-6}	49.15	60	20

Values are percent inhibition determined against control experiments devoid of inhibitors in reaction medium. *MAO*, Monoamine oxidase; *PET*, preeclamptic-eclamptic.

Comment

The current study reveals the impaired catabolism of placental serotonin in preeclampsia-eclampsia. The novel finding in this study is the presence of monoamine oxidase in the nuclei of syncytiotrophoblastic cells of placental tissue in preeclampsia-eclampsia as demonstrated both biochemically and histochemically. These observations were also correlated with the clinical syndrome of preeclampsia-eclampsia. Hypertension was chosen as the primary parameter for the severity of preeclampsia-eclampsia.

In preeclampsia-eclampsia, placental serotonin tends to increase with clinical severity of the disease, which supports the finding of other workers.[3, 15] Sagone and Arrotta[16] have hypothesized that raised serotonin and its accumulation in placenta leads to its diffusion to adjacent uterine endometrial area, finally causing powerful vasoconstriction resulting in insufficiency of oxygen and other nutrients that ultimately affects the placental functions with various toxic effects. In the current study we observed raised serotonin levels, showing a correlation with the blood pressure of the patient with preeclampsia-eclampsia, emphasizing a direct involvement of serotonin. Weiner et al.[17] showed beneficial effects of ketanserin, a serotonin receptor antagonist, on hypertension in preeclampsia-eclampsia. Serotonin has a powerful vasoconstrictive action on placental and uterine vasculature and uterine musculature.[18, 19] In our earlier studies[4, 6] we reported that an increase in serotonin occurs in preeclampsia-eclampsia in placenta, blood, and platelets, which might be due to an increased synthesis or a decreased catabolism of serotonin in situ. Serotonin-synthesizing enzymes (e.g., tryptophan hydroxylase and decarboxylase) have not yet been reported in placenta. Therefore impaired catabolism of serotonin might be the logical alternative explanation. Results from the current study show that placental monoamine oxidase is significantly reduced in preeclampsia-eclampsia, which is in agreement with others,[16, 20] and this decrease showed a correlation with severity of preeclampsia-eclampsia in this study.

An important finding of the current study is a difference in the subcellular localization pattern of monoamine oxidase in placentas in preeclampsia-eclampsia. Monoamine oxidase activity measured in different fractions of normal and preeclampsia-eclampsia placental tissues revealed that mitochondrial fraction was predominantly rich in the enzyme that was significantly reduced in preeclampsia-eclampsia. In cells monoamine oxidase has been shown to be localized in mitochondria.[7, 10] Isoenzymes of monoamine oxidase are well documented, and localization has been demonstrated in outer and

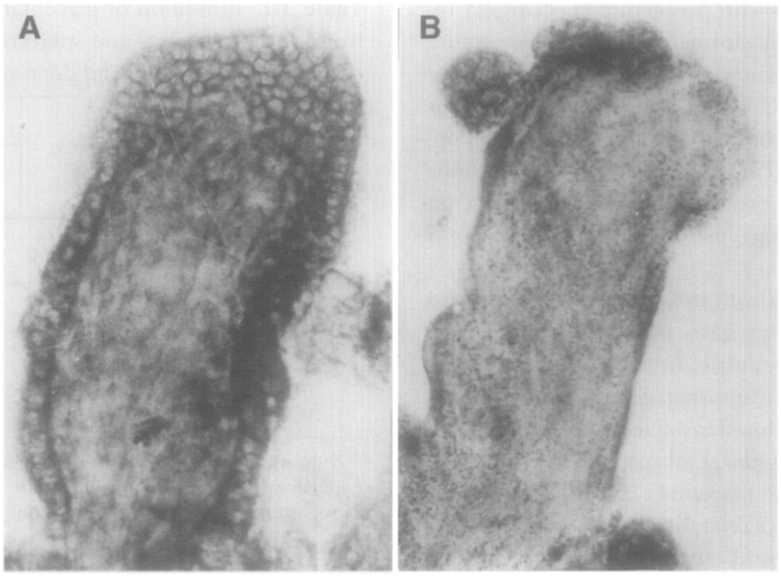

Fig. 3. Chorionic villi from normal placenta showing formazan granules arranged perinuclearly in syncytiotrophoblastic cells to give honeycomb appearance (**A**) and from preeclampsia-eclampsia placenta showing absence of honeycomb appearance of formazan granules in syncytiotrophoblastic cells (**B**). (**A** and **B**, Original magnification ×400.)

Table IV. Serotonin content and monoamine oxidase activity in whole homogenate, mitochondrial and nuclear fractions of preeclamptic and eclamptic placental tissues

Group	*Arterial blood pressure (mm Hg)*		*Serotonin content* (ng/gm)*	*MAO activity (U/mg protein)†*		
	Systolic (range)	*Diastolic (range)*		*Whole homogenate*	*Mitochondrial fraction*	*Nuclear fraction*
Preeclamptic	140-190	90-120	287.86 ± 14.64	12.62 ± 0.92	25.46 ± 2.01	13.21 ± 0.32
Eclamptic	180-210	110-140	378.61 ± 12.08	5.86 ± 1.07	12.02 ± 1.17	8.09 ± 0.90
Statistical analysis (ANOVA)			$F = 23.91$, $p = 0.00024$	$F = 25.48$, $p = 0.00018$	$F = 13.46$, $p = 0.00207$	$F = 7.44$, $p = 0.01492$

Values are mean ± SEM. *MAO*, Monoamine oxidase; *ANOVA*, analysis of variance.
*Preeclamptic, $n = 9$; eclamptic, $n = 6$.
†Preeclamptic, $n = 10$; eclamptic, $n = 8$.

inner membranes and intramembranously, depending on the nature of the isoenzymatic form. Investigators have assigned monoamine oxidase as a marker enzyme for mitochondrial outer membrane.[7] However, some workers have also encountered the enzyme activity in microsomes.[11]

The most extraordinary finding of this study is the presence of enzymatic activity of monoamine oxidase in nuclei of syncytiotrophoblastic cells, as observed both biochemically and histochemically in preeclampsia-eclamptic placenta in contrast to normal placenta, completely devoid of any monoamine oxidase activity in nuclei. Alessandrescu and Ciobataru[21] observed histochemically diffused monoamine oxidase activity in sections of preeclampsia-eclamptic placenta; however, they did not offer an explanation. This finding was further confirmed by subcellular fractionation. Our findings suggest an additional site for monoamine oxidase from its original site (i.e., nucleus and mitochondria in preeclampsia-eclampsia). Moreover, this shift appeared to be severity dependent, as evident from both biochemical and histochemical studies in isolated cell fractions.

Monoamine oxidase is documented to exist as A and B isoenzymatic forms, classified on specific substrate and inhibitor studies.[22, 23] The monoamine oxidase present in mitochondria and nuclei from both groups on treatment with specific substrates (5-hydroxytryptamine, kynuramine, etc.) and inhibitors (clorgyline and deprenyl) exhibited similar behavior, suggesting that no isoenzymatic transformation has taken place and that the predominant form is A. This further confirms that in preeclampsia-eclampsia a shift of monoamine oxidase from its normal site has occurred.

In the genesis of preeclampsia-eclampsia genetic fac-

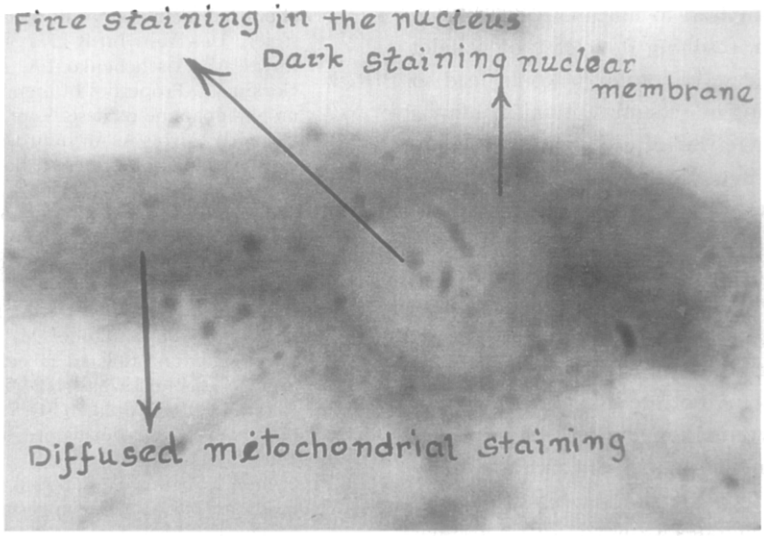

Fig. 4. Isolated syncytiotrophoblastic cell from placenta with preeclampsia-eclampsia showing diffused formazan granules in cytoplasm and in nuclear areas. (Original magnification ×1000.)

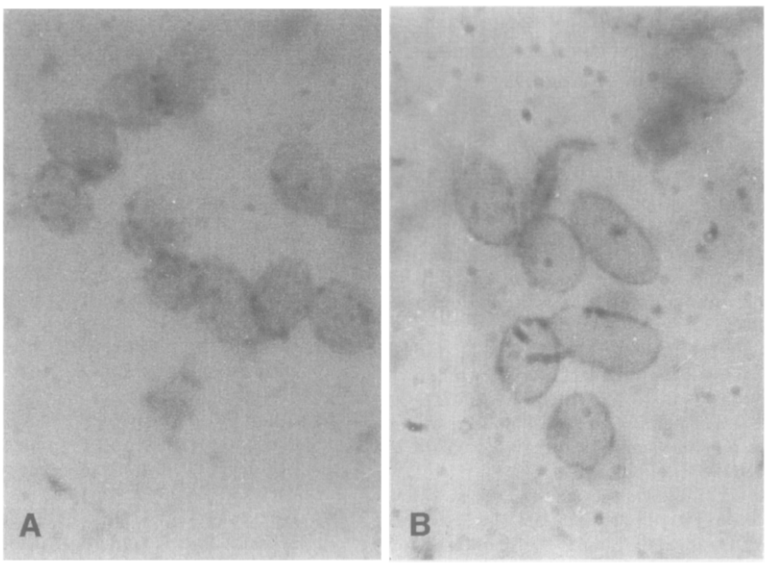

Fig. 5. Photomicrograph of nuclei from preeclamptic placenta showing low-density formazan granules throughout nucleoplasm and lightly stained nuclear membrane **(A)** and dense formazan granules along the nuclear membrane of eclamptic placenta **(B)**. (**A** and **B**, Original magnification ×1000.)

tors have been implicated. Adam and Findlaysons[24] suggested environmental and hereditary factors. Chesley[24a] has shown preeclampsia in offspring or siblings of patients. Histochemically, in the current study an interesting preliminary finding we observed in some subjects whose placentas (n = 3, with infarctions) had the classic histochemical picture of monoamine oxidase as observed in this study in preeclampsia-eclampsia, although no clinical symptom of preeclampsia was present in these subjects. Later it was found that their previous pregnancies were complicated by preeclampsia-eclampsia, thus implicating that a defect in the enzyme system (monoamine oxidase) might be inherited.

Thus it may be concluded from the current findings that raised serotonin levels might be due to impaired catabolism in the placenta because of decreased monoamine oxidase activity along with an additional shift in localization of monoamine oxidase to the nuclei of syncytiotrophoblastic cells in preeclampsia-eclampsia placental tissue. Our earlier findings[4, 6] suggest that in utero the fetus produces serotonin, which is released into fetoplacental circulation and is partially metabolized by placental monoamine oxidase and the rest goes to the maternal circulation. In preeclampsia-eclampsia placental monoamine oxidase is highly reduced with a subsequent rise of serotonin in placenta and finally in blood

and platelets, which may lead to intravascular aggregation of platelets in situ, resulting in release of platelet contents. This local release of serotonin would lead to vasoconstriction, resulting in ischemia and microinfarcts in chorionic villi, characteristic of preeclampsia-eclamptic placenta. Release of necrotic materials from necrotizing syncytiotrophoblastic cells and trophoblastic microemboli may be acting as the triggering factor for the initiation of the cascade of disseminated intravascular coagulation,[25] platelet functions causing arteriolar deposition of fibrin in placenta, liver, and kidney.[26-28]

The current observations, in view of the existing pathophysiologic orientation of preeclampsia-eclampsia, gives strength to our contention that biochemical and anatomic alterations in placental monoamine oxidase appears to be the key factor leading to high serotonin levels, which in turn generates a cascade of events that may be implicated in the genesis of preeclampsia-eclampsia.

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