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Cyclosporin Treatment Alters Prostanoid and Thromboxane Production by Rat Isolated Kidney Mitochondria

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Abstract—This study was designed to investigate the effects of chronic treatment with cyclosporin A (CSA) on the endogenous synthesis of prostanoids (PGs) and thromboxane (Tx) by renal isolated medullary and cortical mitochondria. The administration of CSA, dissolved in 10% ethanol in olive oil, to male Wistar rats (20 mg kg^{-1} day^{-1} i.p.) for 14 days resulted in alterations in mitochondrial biosynthesis of immunoreactive PGs. The endogenous synthesis of thromboxane by medullary and cortical mitochondria isolated from CSA-treated rats was significantly enhanced by 120 and 55%, respectively, whereas the synthesis of prostaglandin E_2 by medullary mitochondria was reduced by 35%. The synthesis of prostaglandin $F_{2\alpha}$ and prostacyclin was not affected by CSA treatment. The conversion of exogenous arachidonic acid to PGs and Tx by cortical mitochondria isolated from CSA-treated rats was significantly increased. In addition, CSA treatment resulted in i) a reduced acylation of arachidonic acid into medullary phospholipids by 25% and into medullary and cortical triglycerides by 33 and 27%, respectively, and ii) an increase in cortical and medullary triglycerides. We suggest that the alterations in the endogenous mitochondrial production of PGs and Tx caused by CSA, may play a role in the impairment of membrane mediated functions.

Cyclosporin A (CSA) is a potent immunosuppressive drug that has a widespread application in organ transplantation, but it is nephrotoxic. Treatment with it may result in a decrease in glomerular filtration, renal blood flow, urine flow and body weight (Sullivan et al 1985). The biochemical mechanisms underlying these nephrotoxic effects are still unclear.

Recently, it was suggested that CSA-nephrotoxicity may be caused by an alteration of mitochondrial respiration and energy production (Jung & Pergande 1985; Jung et al 1987). Structural alterations of renal mitochondria have been observed in patients receiving CSA (Mihatsch et al 1981) and an inhibited respiratory and phosphorylating capacity of mitochondria treated with CSA or isolated from rats treated with CSA was reported (Jung et al 1987).

The acute and chronic effects on kidney function caused by CSA were attributed, partially, to alterations in the production of prostanoids. For example, chronic treatment with CSA caused a reduction in prostaglandin E_2 (PGE_2) formation in isolated glomeruli and papillae of rat kidneys (Stahl & Kudelka 1986) and increased the excretion of thromboxane (Tx) A_2 metabolites in the urine, especially TxB_2 and 2,3-dinor TxB_2 (Kawazuchi et al 1985; Foegh et al 1987). The administration of a PGE_2 analogue has been demonstrated to prevent CSA-induced nephrotoxicity in rats (Makowka et al 1985).

Mitochondrial fractions isolated from the medulla of rabbit and rat kidneys contain prostaglandin synthase activity (Bohman & Larsson 1975; Erman & Raz 1981), which converts arachidonic acid mainly into PGE_2. The potent capacity of the mitochondria to synthesize PGE_2 is even more clearly seen when measuring prostaglandin generation from endogenous, lipid-esterified arachidonate (Erman & Raz 1981). The present study was designed to investigate the effect of chronic treatment with CSA on the endogenous production of prostanoids by rat isolated medulla and cortex mitochondria.

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Materials and Methods

Experiments were performed on male Wistar-rats (bred at the Beilinson Medical Center, Israel) of 250–270 g. The rats were kept in group cages and had free access to tap water and a standard chow (Purina). The studies were performed after four days acclimatization then the rats were injected with CSA 20 mg kg^{-1} day^{-1} (i.p) or its vehicle (10% ethanol in olive oil), for 14 days. At day 14 the rats were housed in individual metabolic cages and 24 h urine collections were taken. On day 15, the rats were anaesthetized with ether, blood was withdrawn for the determination of creatinine, blood urea nitrogen (BUN), and potassium before death, after which the kidneys were removed for the preparation of renal slices and isolation of mitochondria.

Renal inner medulla pairs from each of two rats and the cortices from each rat served for mitochondrial preparations. Briefly, the cortex and/or medulla were homogenized (5mL g^{-1} tissue) in Krebs buffer containing 10 mM Tris-HCl (pH 7·4), and the homogenate was fractionated by differential centrifugation at 1500 *g* for 10 min (Jouan refrigerated centrifuge C.411), and the resulting supernatant was centrifuged at 10 000 *g* for 15 min at 4°C (Servall RC-2). The pellets obtained consisted almost exclusively of mito-

chondria, as was verified by electron microscopy. These were suspended in Krebs buffer containing 10 mM Tris-HCl (pH 7·4) and incubated in final volume of 1·0 mL. Incubations were carried out at 37°C for 30 min with shaking and were terminated by the addition of indomethacin, 100 μg, then immediate freezing. Samples were kept frozen for one or two weeks until the determination of prostanoids and thromboxane, by RIA on the unextracted samples, as described by Shohat et al (1987). Results are expressed as ng of immunoreactive prostanoid (mg protein^{-1}) in 30 min. Protein was determined by the method of Lowry et al 1951.

Incorporation study

Slices of renal inner medulla and cortex from vehicle and CSA-treated rats were incubated in the final volume of 1·5 mL for 30 min at 37°C in Krebs buffer containing 10 mM Tris-HCl (pH 7·4) in the presence of [^{3}H]arachidonic acid (AA, 4 μCi, 4 μg). At completion of the incubation the slices were rinsed twice in Krebs-buffer containing bovine serum albumin 1 mg mL^{-1}, then the medium was removed and the tissue immediately homogenized in 20 mL of chloroform–methanol (2:1 v/v, Polytron homogenizer), acidified and extracted. The lipid residue was applied to Silica Gel G plates (Merck, Darmstadt, FRG) and chromatographed concurrently with authentic polar and neutral lipid standards using as a solvent system light petroleum (b.p. 30°–60°C)–diethylether—acetic acid (84:15:1 v/v/v). The regions on the plate corresponding to the position of cholesterol esters, free fatty acids, triglycerides, diglycerides and phospholipids were scraped. The radioactivity in these regions and the mass of phospholipids, and triglycerides were determined by liquid scintillation spectrometry (LKB Wallac, 1217 Rackbeta) and colorimetric assays, respectively. Triglycerides were determined by measuring glycerol after alcoholic alkaline hydrolysis and phospholipids were measured by determining inorganic phosphorus after degradation as described previously (Erman et al 1985).

CSA as a pure powder was a generous gift of Sandoz Company (Basel, Switzerland). Prostanoids and lipid standards were purchased from Sigma (Petah-Tikva, Israel). Rabbit anti PGE_2, anti $PGF_{2\alpha}$, anti 6-keto $PGF_{1\alpha}$, and anti TxB_2 were obtained from Bio-Yeda (Rehovot, Israel). Tritiated radioactive prostanoids; PGE_2 (160 Ci mmol^{-1}), $PGF_{2\alpha}$ (177 Ci mmol^{-1}), 6-keto $PGF_{1\alpha}$ (150 Ci mmol^{-1}) and TxB_2 (210 Ci mmol^{-1}) and tritiated arachidonic acid (84 Ci mmol^{-1}) were purchased from Amersham (Buckinghamshire, UK).

Statistical analysis

Results were expressed as mean ± s.e.m. The data were analysed by unpaired Student's *t*-test. A P value less than 0·05 was considered significant.

Results

CSA administration to Wistar rats (20 mg kg^{-1} day^{-1} i.p.) for 14 days caused a significant increase in plasma creatinine, blood urea nitrogen, and hyperkalaemia and a reduction in creatinine clearance, urine volume and body weight. These parameters were not different in vehicle-treated rats compared with untreated rats (Table 1).

The endogenous synthesis of prostanoids by mitochondria isolated from renal medulla and cortex of CSA-treated rats was altered. The synthesis of TxA_2, measured as its stable metabolite TxB_2, in both medullary and cortical mitochondria preparations was significantly greater (4·4 ± 1·1 vs 2·0 ± 0·3, and 0·84 ± 0·1 vs 0·54 ± 0·06 ng (mg prot.)$^{-1}$ per 30 min, respectively) in rats treated with CSA, whereas the synthesis of PGE_2 by isolated medullary mitochondria was significantly reduced (39·2 ± 5·9 vs 60·9 ± 6·4 ng (mg prot.)$^{-1}$ per 30 min) in those rats (Fig. 1). CSA treatment did not affect the endogenous synthesis of $PGF_{2\alpha}$ or prostacyclin, measured as 6-keto $PGF_{1\alpha}$.

To evaluate the effects of CSA treatment on cortical mitochondrial cyclo-oxygenase activity, mitochondria preparations were incubated in the presence of exogenous arachidonic acid. The results show that the synthesis of PGE_2, TxB_2 and $PGF_{2\alpha}$ by cortical mitochondria isolated from CSA-treated rats was significantly increased (Fig. 2).

The reports that CSA inhibited the mitochondrial electron transport system (Jung et al 1987), Ca^{2+}-dependent pore in heart mitochondria (Crompton et al 1988), and the observation that CSA treatment resulted in alterations in the endogenous production of eicosanoids, all membranal systems, lead us to suggest that CSA may interfere with the integrity of membranes. We tested this hypothesis with regard to the incorporation of radioactive arachidonic acid (AA) into renal medulla and cortex lipids. The incorporation of [^{3}H]AA into tissue lipids (d min^{-1}/100 mg tissue) was not significantly different in the vehicle vs CSA group either in

Table 1. Effects of CSA administration on plasma creatinine, creatinine clearance, blood urea nitrogen (BUN), plasma potassium, urine volume and body weight.

Group	Plasma creatinine (mg dL^{-1})	Creatinine clearance (mL min^{-1})	BUN (mg dL^{-1})	K^+ (mequiv L^{-1})	Urine volume (mL)	Body wt (g)
Control (n = 10)	0·45 ± 0·02	1·34 ± 0·12	21·1 ± 0·9	4·40 ± 0·15	33·3 ± 3·0	278·0 ± 4·8
Vehicle (n = 18)	0·48 ± 0·07	1·34 ± 0·06	19·8 ± 1·1	4·54 ± 0·12	32·2 ± 2·1	280·6 ± 5·8
CSA (n = 18)	0·65 ± 0·03	0·73 ± 0·07	31·7 ± 2·3	4·93 ± 0·08	17·1 ± 2·9	259·8 ± 7·4
P Value CSA vs Vehicle	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	< 0·05

Rats received injections of CSA or vehicle or were untreated for 14 days. Values are mean ± s.e. P values for vehicle vs control were not significant.

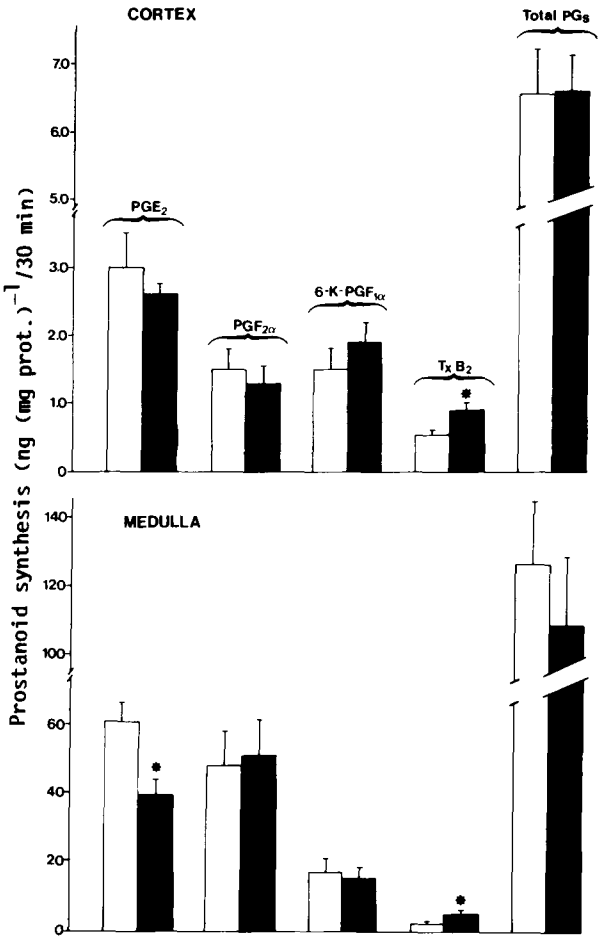

FIG. 1. The effect of CSA treatment on the endogenous prostanoids synthesis by isolated renal cortical and medullary mitochondria. Mitochondria isolated from CSA (n = 20, ■) or vehicle treated rats (n = 20, □) were incubated for 30 min at 37°C in Krebs buffer containing 10 mM Tris-HCl (pH 7·4). Incubations were terminated by the addition of indomethacin, 100 μg and PGs and TxB_2 were determined by RIA. Values are mean ± s.e.; * indicates $P < 0{\cdot}02$ relative to the corresponding value in vehicle preparations.

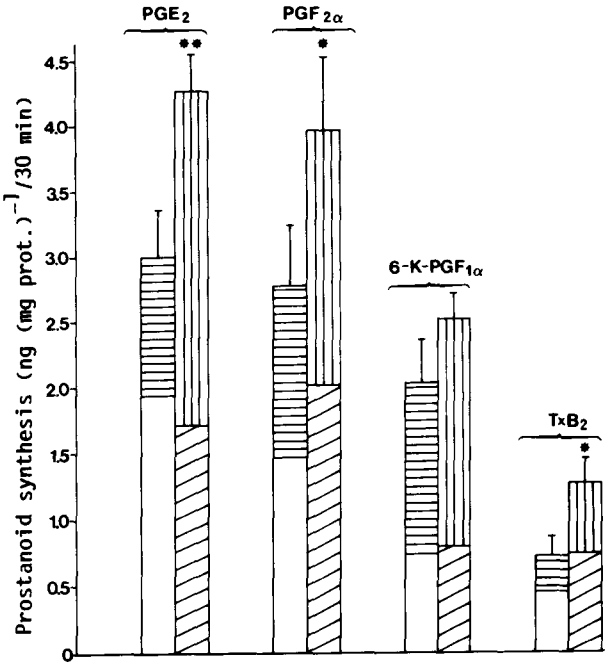

FIG. 2. Prostanoids and thromboxane generation by isolated cortical mitochondria. Cortical mitochondria isolated from vehicle (n = 5) or CSA-treated rats (n = 5) were incubated for 30 min at 37°C in the absence (open column) or presence (diagonally hatched column) of exogenous arachidonic acid (AA, 5 μg) and the media were analysed for PGs and TxB_2. The conversion of exogenous AA to the various PGs in vehicle (horizontally hatched column) or CSA group (vertically hatched column) was calculated by subtracting the endogenous synthesis from the total synthesis in presence of AA. Values are mean ± s.e.; * indicates $P < 0{\cdot}05$, ** indicates $P < 0{\cdot}01$ relative to the corresponding value in vehicle preparations.

the medulla or in the cortex. However, differences in the incorporation of radioactive AA to the main tissue lipids were observed. The relative incorporation (%) of [^{3}H]AA into medullary and cortical phospholipids was significantly reduced by 22 and 15%, respectively, in the CSA group (Table 2), although no significant differences in the total mass of phospholipids were observed. The relative incorporation of [^{3}H]AA into triglycerides in the vehicle vs CSA group was not significantly different in the medulla, but was enhanced in the cortex of rats treated with CSA. Yet, triglyceride content in the medulla and cortex of CSA-treated rats was significantly greater than in vehicle-treated rats (Table 3). Therefore, AA incorporation into medullary phospholipids and triglycerides expressed as the radioactivity incorporated per μmol phospholipids or triglycerides, was decreased by 25 and 33%, respectively, and into cortical triglycerides by 27% (Table 4).

Discussion

CSA treatment, in a dose which induces nephrotoxicity, affects endogenous eicosanoid production by renal isolated mitochondria. The results show that medullary and cortical mitochondria isolated from rats treated with CSA generated significantly more thromboxane than the vehicle-treated rats, while the synthesis of PGE_2 was reduced significantly only in the medullary mitochondria and that of prostacyclin remained unchanged. The endogenous biosynthesis of prostanoids is a measure of the combined activities of lipase(s) and the prostaglandin synthase enzymes. The release of AA from its esterified pools is most likely catalysed by mitochondrial phospholipase A_2, which is present in mitochondrial membranes and is activated by Ca^{2+} ions (Erman & Raz 1981; Erman et al 1982). The observation that the total endogenous synthesis of PGs and Tx by the medullary and cortical mitochondria from CSA-treated rats was not significantly different from the vehicle group, even though alterations in individual PGs were observed, indicates that CSA did not alter the release of AA from its esterified pools. This suggests that CSA treatment did not alter the lipase(s) activity in the mitochondria. Recently, Broekemeier et al (1989) reported that CSA does not interact with rat liver mitochondrial phospholipase A_2. It was suggested that CSA inhibits phospholipase activity in vascular smooth muscle cells (Kurtz et al 1987) and renal mesangial cells (Stahl et al 1989) probably due to its binding to calmodulin, a soluble cytosolic enzyme, and antagonizing its activity (Colombani et al 1985).

Table 2. The effect of CSA treatment on the incorporation of [^{3}H]arachidonic acid into renal tissue lipids. Slices of renal inner medulla and cortex from vehicle and CSA-treated rats were incubated for 30 min at 37°C in Krebs–Tris buffer (pH 7·4) containing [^{3}H]arachidonic acid (4 μCi, 4 μg). At completion of the incubation, the tissue lipids were extracted and the radioactivity of the major lipids classes: phospholipids (PLs) diglycerides (DG) triglycerides (TG) arachidonic acid (AA), were determined. Values are mean ± s.e.m.

			d min^{-1} × 10^{-6}	% Incorporation			
Tissue	Treatment		100 mg	PLs	DG	AA	TG
Medulla:	Vehicle	(n = 8)	1·18 ± 0·12	37·3 ± 0·8	10·4 ± 0·4	23·2 ± 1·0	26·8 ± 1·5
	CSA	(n = 8)	1·22 ± 0·07	29·1 ± 2·7***	11·5 ± 0·2*	28·8 ± 2·4*	22·5 ± 2·1
Cortex:	Vehicle	(n = 10)	1·20 ± 0·09	12·2 ± 0·5	7·4 ± 0·2	31·0 ± 1·0	46·7 ± 1·4
	CSA	(n = 10)	1·29 ± 0·05	10·4 ± 0·3**	7·4 ± 0·3	25·4 ± 1·0***	53·9 ± 2·2****

* : $P < 0·05$; ** : $P < 0·02$; *** : $P < 0·01$; **** : $P < 0·001$

Table 3. The effect of CSA treatment on renal tissue lipids. Slices of renal inner medulla (n = 8) and cortex (n = 10) from vehicle and CSA-treated rats were incubated as described in Legend to Table 2. At completion of the incubation, the tissue lipids were extracted and the mass of phospholipids and triglycerides were determined. Values are mean ± s.e.m.

	Phospholipids (μmol/100 mg)		Triglycerides (μmol/100 mg)	
Treatment	Medulla	Cortex	Medulla	Cortex
Vehicle	2·32 ± 0·29	4·10 ± 0·21	0·146 ± 0·014	0·146 ± 0·026
CSA	2·02 ± 0·14	3·92 ± 0·34	0·207 ± 0·022*	0·229 ± 0·023*
P Value	NS	NS	< 0·05	< 0·05

* $P < 0·05$

The reduced production of endogenous PGE_2, but not that of $PGF_2\alpha$ by medullary mitochondria, isolated from CSA-treated rats, may be caused by i) different effects of CSA on the various non-homogenous cell-type population in the renal medulla, ii) a selective inhibitory effect on the medullary PGH_2-PGE_2 isomerase. Yet, this effect did not reach significance in the renal cortex and/or iii) changes in mitochondrial membranes that may interfere with the transfer of PGH_2 to the enzyme PGH_2-PGE_2 isomerase.

The increased synthesis of PGs and Tx from exogenous AA by cortical mitochondria isolated from CSA-treated rats indicated that CSA treatment stimulated cortical mitochondrial cyclo-oxygenase activity. This finding fits with the reports demonstrating that CSA treatment slightly increased cyclo-oxygenase activity in vascular smooth muscle cells (Kurtz et al 1987) and stimulated its activity in macrophages (Fan & Lewis 1985). Yet, Stahl et al (1989) reported that CSA had no effect on cyclo-oxygenase activity in rat mesangial cell microsomes, although PGE_2 formation by rat mesangial cells in culture was inhibited by CSA treatment.

Tx has been postulated to be a mediator contributing to the pathophysiology of a variety of disease processes like nephrotoxicity, hypertension, myocardial ischemia and stroke (Ogletree 1987). Various reports have suggested the involvement of thromboxane in the loss of cell integrity and its direct effect on membrane permeability. Recently, two Tx mimetics were demonstrated to induce lysis of feline and human erythrocytes (Brezinski et al 1987). In contrast, prostacyclin and its analogue, iloprost, and PGE_2 were demonstrated to be membrane stabilizers and cytoprotective (Finn et al 1987). Thus Tx and prostacyclin or PGE_2 may represent a labilizing/stabilizing pair of endogenous humoral substances. Our observations indicate that CSA treatment resulted in an increase in the ratio TxB_2/6-keto $PGF_{1\alpha}$ which is consistent with the idea of increase in the labilization of membranes. This observation and the findings that CSA caused morphological alterations in the proximal tubule (Sullivan et al 1985), swelling of mitochondria (Mihatsch et al 1981), an inhibited mitochondrial respiration (Jung et al 1987), and partitioning into phospholipids bilayers of lymphocytes membranes (LeGrue et al 1983) lead us to hypothesize that CSA interferes with the integrity of mitochondrial membranes and that this interference might be mediated or amplified by the enhanced synthesis of TxA_2.

Treatment with CSA, dissolved in olive oil, for 28 days resulted in increases in plasma cholestrol and triglyceride (TG) concentrations (Jevnikar 1988). Experiments to investigate whether CSA treatment affected the renal membranes,

Table 4. Incorporation of [^{3}H]arachidonic acid into major lipids in renal medulla and cortex. Slices of renal inner medulla and cortex were incubated as described in Legend to Table 2. At completion of the incubation the radioactivity in the phospholipids and triglycerides and their mass were determined. Values are mean ± s.e.

			Triglycerides (TG) (d min^{-1} μmol^{-1} TG) ($\times 10^{-5}$)	Phospholipids (PLs) (d min^{-1} μmol^{-1} PLs) ($\times 10^{-5}$)
Tissue	Treatment			
Medulla:	Vehicle	(n = 8)	21·70 ± 2·09	2·20 ± 0·12
	CSA	(n = 8)	14·58 ± 1·56*	1·65 ± 0·15**
Cortex:	Vehicle	(n = 10)	44·52 ± 2·68	0·33 ± 0·02
	CSA	(n = 10)	32·10 ± 3·40*	0·35 ± 0·03

* : $P < 0·05$; ** : $P < 0·02$

with regard to AA acylation into tissue lipids, indicated that CSA treatment caused an increase in the triglyceride mass of cortical and medullary slices and a reduced incorporation of AA into renal medullary phospholipids and triglycerides and into renal cortical triglycerides. Furthermore, there was also a small, but significant, decrease in the relative incorporation (%) of AA into renal cortical phospholipids. However, this decrease was not significant while expressing the incorporation as d min^{-1} (μmol phospholipid)$^{-1}$ most likely reflecting a wide standard deviation. Recently, Szamel et al (1986) demonstrated that CSA in a dose-dependent manner reduced AA incorporation into cell membrane phospholipids as a result of inhibition of lysophosphatide acyltransferase. Phospholipids are predominantly structural components of membranes. AA comprises about 20% of the esterified fatty acids in inner medulla phospholipids (Erman et al 1985), 24% in cortex phospholipids, and 1·5% in medulla and cortex triglycerides (Muller et al 1976). A decrease in the acylation of AA, particularly to phospholipids, may result in changes in structure and fluidity of membranes leading to functional alterations. Yet, the possibility that CSA itself may interact with the renal membranes, by virtue of its hydrophobic character, and that the enhanced synthesis of thromboxane would amplify the membranal alterations cannot be excluded. It has been suggested that CSA reacts with a mitochondrial component resulting in inhibiton of transition across the inner membrane in liver mitochondria (Broekemeier et al 1989).

This study has demonstrated that CSA treatment resulted in i) an increased thromboxane production by medullary and cortical mitochondria isolated from CSA-treated rats, and a decreased PGE_2 production by medullary mitochondria; ii) a reduced incorporation of AA into major renal lipids, and iii) changes in lipids content of medullary and cortical slices. We suggest that alterations in the production of prostanoids and thromboxane by kidney mitochondria caused by CSA treatment may play a role in the impairment of mitochondrial membrane-mediated functions.

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