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Monoamine oxidase in developing rat renal cortex: effect of dexamethasone treatment

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Abstract

The expression of the biogenic amine degrading enzyme monoamine oxidases-A and -B depends on several factors including regional distribution, development and hormonal environment. In the present study, we investigated the expression of monoamine oxidases in developing kidney and their regulation by dexamethasone treatment. Immunoblots and enzyme assays, performed using [^{14}C]5-hydroxytriptamine and [^{14}C]β-phenylethylamine as substrates for monoamine oxidases-A and -B, respectively, showed that monoamine oxidase-A is the isoenzyme largely predominant in 9-day-old rats renal cortex. Experiments performed in 5-week-old rats showed an increase in monoamine oxidase-B activity and a decrease in monoamine oxidase-A activity and substrate affinity. The changes of monoamine oxidase-A activity and affinity were mimicked by dexamethasone treatment (0.60 mg/kg body weight injected subcutaneously three times at intervals of 24 h) of 9-day-old rats. In contrast, dexamethasone administration induced a modification of monoamine oxidase-B activity opposite to that found between 9-day- and 5-week-old rats. Dexamethasone treatment did not modify immunoreactivity and mRNA corresponding to monoamine oxidases-A and -B indicating that changes of enzyme activities were unrelated to regulation of protein synthesis and mRNA turnover. These results show that monoamine oxidases-A and -B are differently expressed in developing renal cortex and are regulated by dexamethasone treatment. © 2001 Published by Elsevier Science B.V.

Keywords: Monoamine oxidase; Dexamethasone; Renal cortex; Development; (Rat)

1. Introduction

Monoamine oxidases (MAOs, EC 1.4.3.4), enzymes located in the outer mitochondrial membrane, catalyze the oxidative deamination of several neurotransmitters (i.e. dopamine, norepinephrine, serotonin) and exogenous amines (i.e. tyramine) (Weyler et al., 1990). Based on their substrate preference and inhibitor specificity, two types of monoamine oxidase (A and B) have been identified (Weyler et al., 1990; Youdim and Finberg, 1991; Johnston, 1968; Cesura and Pletscher, 1992). Monoamine oxidase-A preferentially deaminates 5-hydroxytryptamine (5-HT) and is inhibited by low concentration of clorgyline; monoamine oxidase-B has a greater affinity for β-phenylethylamine and is irreversibly inhibited by low concentration of deprenyl. These two isoenzymes are encoded by distinct genes (Bach et al., 1988; Lan et al., 1989; Shih, 1990) that probably derive from the same ancestral gene (Grimsby et al., 1991). Several studies suggested that altered levels of monoamine oxidases are implicated in the etiology of some psychiatric (Brummer et al., 1993) and neurodegenerative disorders (Jarman et al., 1993; Sparks et al., 1991; Strolin-Benedetti and Dostert, 1992).

Monoamines oxidases-A and -B are widely distributed in various peripheral organs and the expression of each isoenzyme depends on several factors including regional distribution (Saura et al., 1992; Holschneider et al., 1998), development (Kalaria and Harik, 1987; Leung et al., 1993), aging (Saura et al., 1994) and hormonal environment (Youdim et al., 1989; Ma et al., 1993; Cvijic et al., 1994, 1995; Chakravorty and Halbreich, 1997).

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The kidney contains one of the highest monoamine oxidase activity of the body (Saura et al., 1992; Fernandes and Soares-da-Silva, 1992). In all species in which renal monoamine oxidases were investigated, both monoamine oxidase isoforms have been detected in the cortex and medulla. The functional properties of monoamine oxidases have been particularly investigated in renal proximal tubule cells. In these cells, monoamine oxidases represent the major metabolic pathways for degradation of serotonin and dopamine, two biogenic amines playing a critical role in regulation of tubular sodium reabsorption (Hubbard and Henderson, 1995; Soares-da-Silva et al., 1996; Vieira-Coelho et al., 1997; Aperia, 2000). We have recently shown that glomerular mesangial cells also express monoamine oxidase-A that is responsible for the regulation of extracellular serotonin concentration (Pizzinat et al., 1999). In addition to their role in the control of substrate availability, monoamine oxidases may participate to the regulation of renal cell functions through the generation of hydrogen peroxide. Indeed, we have recently shown that, in intact rat renal proximal tubule cells, hydrogen peroxide produced by monoamine oxidases during dopamine and tyramine degradation induces sequential extracellular signal-regulated kinase (ERK) activation and cell proliferation (Vindis et al., 2000). These data suggest that monoamine oxidases may play a critical role in the regulation of the normal or pathological function of the kidney.

The developmental and hormonal regulation of monoamine oxidases in kidney has not been clearly defined. In previous studies, we showed that postnatal period is characterized by mitochondrial proliferation in the immature kidney and that glucocorticoids modulate the normal maturation profile of mitochondrial enzymes, such as medium-chain acyl-CoA dehydrogenase and malate dehydrogenase (Djouadi et al., 1994, 1996). On the other hand, several reports support the hypothesis that steroid hormones can affect monoamine oxidase activity in different tissues (Holzbauer and Youdim, 1983; Youdim et al., 1989; Cvijic et al., 1994) as well as in cultured cells of peripheral origin (Edelstein and Breakefield, 1981, 1986; Carlo et al., 1996).

The aim of this study was to investigate whether the activity and expression of renal cortex monoamine oxidases-A and -B are regulated during development and their potential regulation by glucocorticoids.

2. Materials and methods

2.1. Dexamethasone treatment

Experiments have been performed in rats according to the Declaration of Helsinki and international accepted principals in animal care and experiments. Young rats were obtained from pregnant Wistar rats bred and mated in our laboratory. Nine-day-old rats were injected subcutaneously with vehicle (sterile isotonic saline solution containing ethanol 1:12, vol/vol; $n = 8$) or vehicle plus dexamethasone (0.60 mg/kg body weight; $n = 8$), three times at intervals of 24 h. Kidneys were quickly removed 24 h after the last injection, under ketamine anesthesia (100 mg/kg body weight, Imalgene, Rhône-Merieux, Lyon, France), immediately frozen in liquid nitrogen and stored at −80°C. Cortex was dissected by hand at −20°C.

2.2. Crude membrane preparations from renal cortex

Cortex was homogenized with a Dounce homogenizer in 50 mM potassium phosphate buffer, pH 7.4 containing protease inhibitors (10 μg/ml bacitracine, 0.1 mM phenylmethylsulfonyl fluoride and 2 μg/ml soybean trypsin inhibitor), filtered through a gauze and centrifuged twice at 18,000 rpm for 20 min at 4°C. The pellet was resuspended in the same buffer, homogenized through a syringe (0.5×16 mm needle) and used immediately or stored at −80°C until assayed. Protein concentration in the supernatant was measured according to Lowry's method (Lowry et al., 1951) (Bio-Rad DC protein assay) with gamma globulin as a standard.

2.3. Monoamine oxidase activity

Renal cortical homogenates (200 μl/200 μg protein) were incubated for 20 min at 37°C with various concentrations of [^{14}C]5-hydroxytryptamine (10–500 μM) or [^{14}C]β-phenylethylamine (1–100 μM). Clorgyline (10^{-6} M) or deprenyl (5×10^{-7} M) were used to define specific monoamine oxidases-A or -B activity, respectively. The concentration of these inhibitors has been chosen by performing inhibition curves in crude membrane preparations from rat renal cortex. The reaction was ended by addition of 1 ml HCl 2 N at 4°C. Radioactive metabolites were extracted by addition of 2 ml of ethylacetate/toluene (vol/vol) and the radioactivity contained in the organic phase was counted in a liquid scintillation spectrometer at 97% efficiency.

2.4. Immunoblot

Renal cortex membranes were solubilized in sample buffer (60 mM Tris–HCl, pH 6.8, 10% glycerol, 2% sodium dodecyl sulfate (SDS), 1% β-mercaptoethanol and 0.05% bromophenol blue) at 100°C for 5 min. Thirty-five micrograms of membrane protein were loaded per well on to denatured (SDS) polyacrylamide gel (stacking 4%, 400 V, 50 mA, 1 h; running 8%, 400 V, 75 mA, 4 h; migration buffer: Tris–HCl 24 mM, glycerol 132 mM, SDS 10%, pH 8.3). Resolved protein were electrotransferred to polyvinylidene difluoride by semi-dry electroblotting (Trans-blot SD, Bio-Rad, Richmond, CA), and blots were saturated

overnight with 5% non-fat dried milk in wash buffer (phosphate buffer saline (PBS) pH 7.5, 0.1% Tween 20), washed twice and incubated for 1 h at room temperature with rabbit polyclonal antisera to monoamine oxidases-A and -B. The polyclonal antisera were obtained from rabbits immunized with the peptide TNGGQERKFVGGSGQ corresponding to amino acids 211–227 for monoamine oxidase-A and 202–216 for monoamine oxidase-B. The specificity of the antiserum was defined as previously described (Lanier et al., 1995). After two washing, blots were incubated with peroxidase labeled anti-rabbit immunoglobulin G for 40 min. Bound antibodies were detected using enhanced chemiluminescence (Amersham Life Sciences, USA) and exposure to Amersham Hyperfilm™-MP film. Rat liver protein preparations were used as control in order to identify monoamine oxidase-A (~ 60 kDa) and monoamine oxidase-B (~ 55 kDa) protein.

2.5. Reverse transcriptase polymerase chain reaction (RT-PCR)

Total RNA was extracted from frozen powdered renal cortex by the method described by Chomczynski and Sacchi (1987). Briefly, 100–200 mg powdered cortex was homogenized in a mixture containing sodium citrate, guanidium isothiocyanate, sarcosyl and β-mercaptoethanol. Total ARN was extracted by addition of 0.1 volume sodium acetate and 1 volume of a mixture phenol/chloroform/isoamyl alcohol. The extracted RNA was precipitated with isopropanol and washed with 70% ethanol. The RNA pellet was resuspended in 200 μl of sterile water. The purity and yield of total RNA were determined spectrophotometrically by measuring the absorbance of an aliquot at 260 and 280 nm. RNA was checked by agarose gel electrophoresis for the integrity of the 18S and 28S rRNA bands.

First-strand cDNA was synthesized by using 0.5 μg of total RNA (previously DNase traited) in a total volume of 20 μl containing 0.25 μg oligo(dT) 12-18, 0.50 mM dNTPs, 5 mM dithiothreitol, 32 U RNase inhibitor, 200 U SuperScript™ II and 5X RT buffer (4 μl). After RNA denaturation (10 min at 70°C immediately followed by a cooling on ice), the first-strand cDNAs were obtained after 10 min at 23°C and 75 min at 37°C. The RT mixture was then heated at 95°C for 6 min and chilled on ice.

For monoamine oxidases-A and -B, 7 μl of each cDNA preparation was amplified. PCR amplification was performed in a final volume of 50 μl PCR 1X buffer containing 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 60 pm of each specific primers and 2 U Taq polymerase. The samples were denatured at 93°C for 2 min and 30 s and PCR performed on a DNA thermal cycler (Perkin Elmer), with denaturation at 95°C for 1 min, annealing at 56°C for 1 min and 30 s and extension at 72°C for 1 min, for 33 cycles. The final cycle was followed by a 10-min extension step at 72°C to ensure that the amplified DNA was double stranded. In order to evaluate the PCR products comparatively, we amplified at the same time and for 20 cycles, 6 μl of the same sample cDNA encoding the glyceraldehyde-3-phosphate dehydrogenase (GAPDH), used as standard. The absence of contaminants was routinely checked by RT-PCR assays of negative control samples in which the RNA was replaced by sterile water or SuperScript™ II was omitted. Primers for monoamine

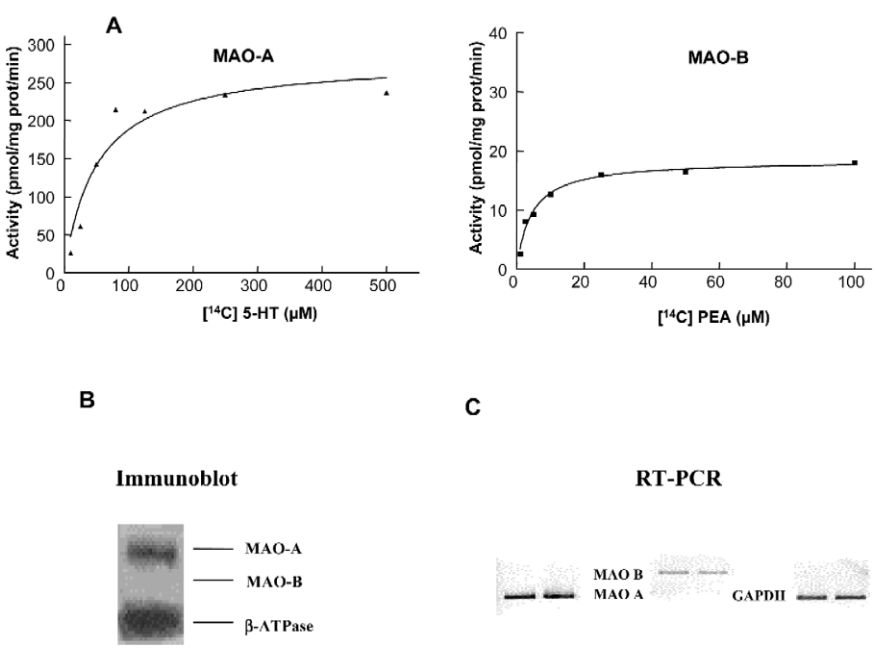

Fig. 1. Monoamine oxidases-A and -B in 9-day-old rats. Enzyme essays (A), immunoblots (B) and RT-PCR (C) were performed in membrane preparations or RNAs from renal cortex of 9-day-old rats as described in Materials and methods. The data are representative of eight separate experiments.

oxidase-A (Kuwahara et al., 1990) were defined by bases 1537–1556 5′-GTGGCTCTTCTCTGCTTTGT-3′ (sense), 2037–2015 5′-AGTGCCAAGGGTAGTGTGTATCA-3′ (antisense) and by bases 1478–1497 5′-TCCCAGCAA-GACCCATTACC-3′ (sense), 2315–2291 5′-TGACAAA-GACAAGACTCCCATTCTC-3′ (antisense) for mono-amine oxidase-B (Ito et al., 1988). The PCR products were predicted to be 500 and 837 base pairs in length for

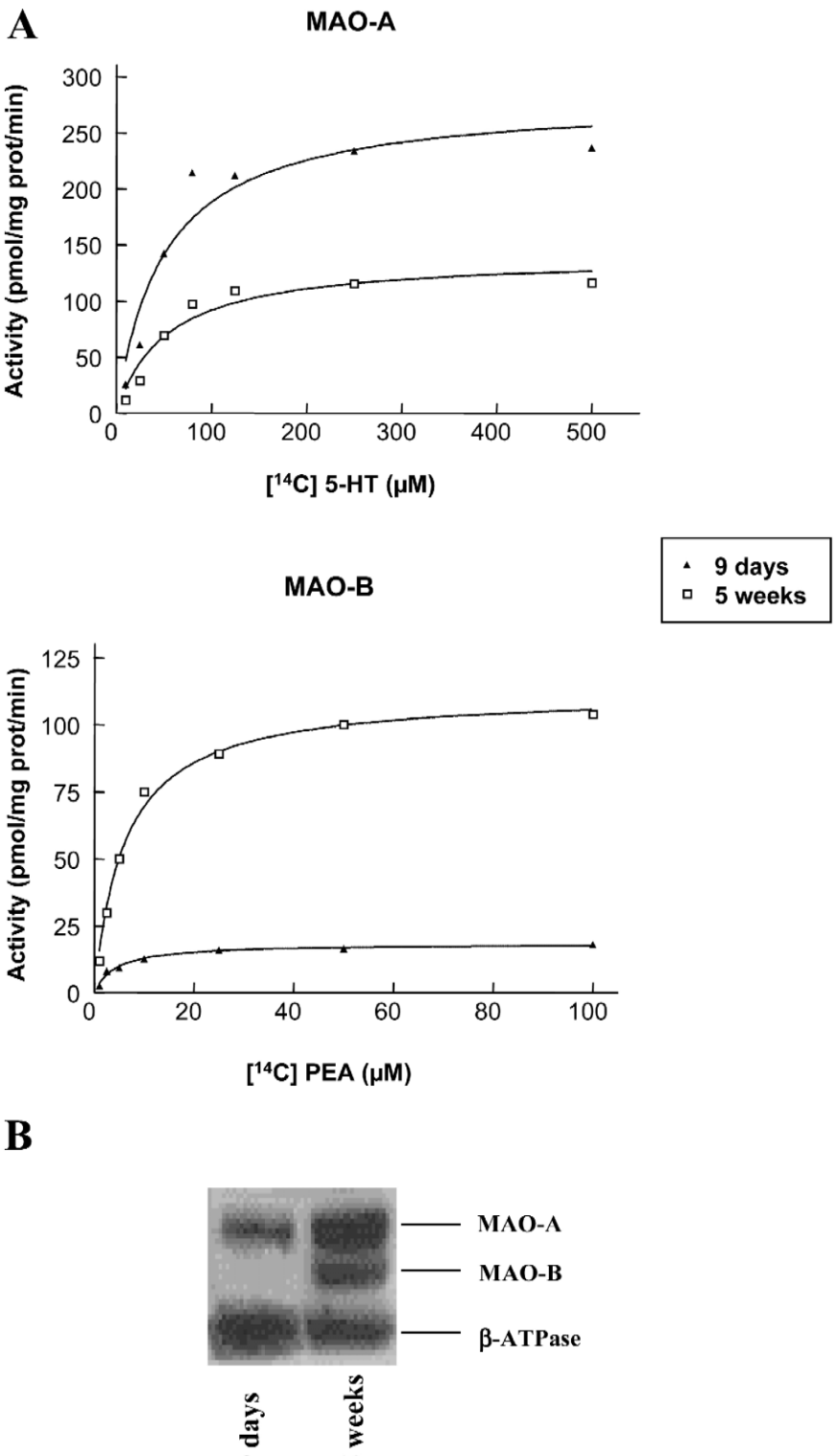

Fig. 2. Monoamine oxidases-A and -B in 9-day- and 5-week-old rats. Enzyme essays (A) and immunoblots (B) were performed in membrane preparations from renal cortex of 9-day- and 5-week-old rats as described in Materials and methods. The data are representative of eight separate experiments.

monoamine oxidases-A and -B, respectively. The sequence of primers for GAPDH (Goppelt-Struebe et al., 1996) was defined by bases 510–529 5′-AATGCATCCTGCACCAC-CAA-3′ (sense) and 980–960 5′-GTCATTGAGAGC-AATGCCAGC-3′ (antisense). The expected size of the amplification product for GAPDH was 470 base pairs.

After amplification, 10 μl of each PCR product was electrophoresed through a 1.6% agarose gel and stained with ethidium bromide. The gel was photographed with Polaroid Type 665 film (positive/negative; Polylabo, Strasbourg, France) over ultraviolet light at the same exposure and developing time. The bands on the negative film were scanned and quantified using an image-analysis system (Elecphor™, CRIS, Toulouse, France).

2.6. Statistical analysis

Results are expressed as means ± S.E.M. The statistical comparison of the results was obtained using the Student's unpaired *t*-test (Prism™ GraphPad, San Diego, USA) and differences were considered significant at $P < 0.05$.

2.7. Materials

Wistar rats were from IFFA-CREDO (Lyon, France), [^{14}C]5-hydroxytryptamine (5-HT), [^{14}C]3-phenylethylamine and polyvinylidene difluoride membranes were purchased from Dupont de Nemours (Boston, MA, USA). Acrylamide, bisacrylamide and Tween 20 were obtained from Bio-Rad (Hercules, CA, USA). Deprenyl and clorgyline were provided by Research Biochemical International (Natick, MA, USA). Taq DNA polymerase, SuperScript™ II, dNTPs and oligo(dT) 12-18 were from Life Technologies (Cergy Pontoise, France). RNAguard RNase inhibitor was provided by Pharmacia Biotech (Saclay, France). All remaining drugs and chemicals of analytical grade were purchased from Sigma (St. Louis, MO, USA).

3. Results

In a first series of experiments, the expression of monoamine oxidases was investigated in renal cortex membranes of 9-day-old rats. Monoamine oxidases-A and -B were identified by enzyme assays (Youdim and Finberg, 1991; Johnston, 1968; Cesura and Pletscher, 1992; Knoll and Magyar, 1972) and immunoblot; mRNA encoding for each isoenzyme were quantified by RT-PCR. As shown in Fig. 1A, enzyme assays showed that [^{14}C]5-HT and [^{14}C]β-phenylethylamine, used as substrates for monoamine oxidases-A and -B, respectively, were oxidized in a dose-dependent manner after incubation with rat renal cortex membrane preparations. Both immunoblot and RT-PCR supported the predominant expression of the monoamine oxidase-A isoform. Indeed, as shown in Fig. 1B, immunoblot using the polyclonal anti-monoamine oxidases-A and -B antibody, revealed a ~60-kDa band corresponding to monoamine oxidase-A whereas monoamine oxidase-B (~55 kDa) was undetectable. According to these results, semi-quantitative RT-PCR showed a strong signal corresponding to the amplification product of monoamine oxidase-A cDNA and a very weak signal for the cDNA band relative to monoamine oxidase-B (Fig. 1C).

Enzyme assays performed in renal cortex of 5-week-old rats showed opposite changes in monoamine oxidases-A and -B activities during postnatal development. Indeed, as compared to 9-day-old rats, monoamine oxidase-A activity decreased (1.6-fold) whereas monoamine oxidase-B activity increased (5.8-fold) in 5-week-old rats (Fig. 2A, Table 1). The changes in enzyme activities were associated to a decrease in the K_m values (Table 1). The increase in the amount of monoamine oxidase-B was confirmed by immunoblots showing the appearance of the corresponding immunoreactive band. In contrast, immunoblots did not reveal a decrease in monoamine oxidase-A immunoreactivity as expected based on the results obtained by enzyme assays (Fig. 2B).

As previous reports showed that steroid hormones are critical for the regulation of mitochondrial renal proteins during development, we investigated the effect of dexamethasone treatment on monoamine oxidases-A and -B expression in renal cortex from 9-day-old rats. Rat treatment with three injections of dexamethasone showed a decrease in both V_{max} and K_m of monoamine oxidase-A for [^{14}C]5-hydroxytriptamine oxidation similar to that observed between 9-day- and 5-week-old rats (Table 1). In contrast, the modification of monoamine oxidase-B activity induced by dexamethasone treatment was significantly different from those observed during postnatal development. Indeed, after dexamethasone treatment, monoamine oxidase-B activity decreased and its apparent affinity for

Table 1
Monoamine oxidase activity in rat renal cortex: effect development and dexamethasone treatment

	9-day-old ($n = 8$)	9-day-old + dexamethasone ($n = 8$)	5-week-old ($n = 8$)
MAO A			
V_{max} (pmol/min/mg protein)	250.5 ± 18	133 ± 4*	155 ± 14*
K_m (μM)	95.5 ± 9	75 ± 4**	73 ± 5**
MAO B			
V_{max} (pmol/min/mg protein)	20.1 ± 1	10.2 ± 0.4*	116 ± 10*
K_m (μM)	11.1 ± 1.2	12 ± 0.7	6.5 ± 0.7***

* $P < 0.001$ versus 9-day-old rats.
** $P < 0.05$ versus 9-day-old rats.
*** $P < 0.01$ versus 9-day-old rats untreated or treated with dexamethasone.

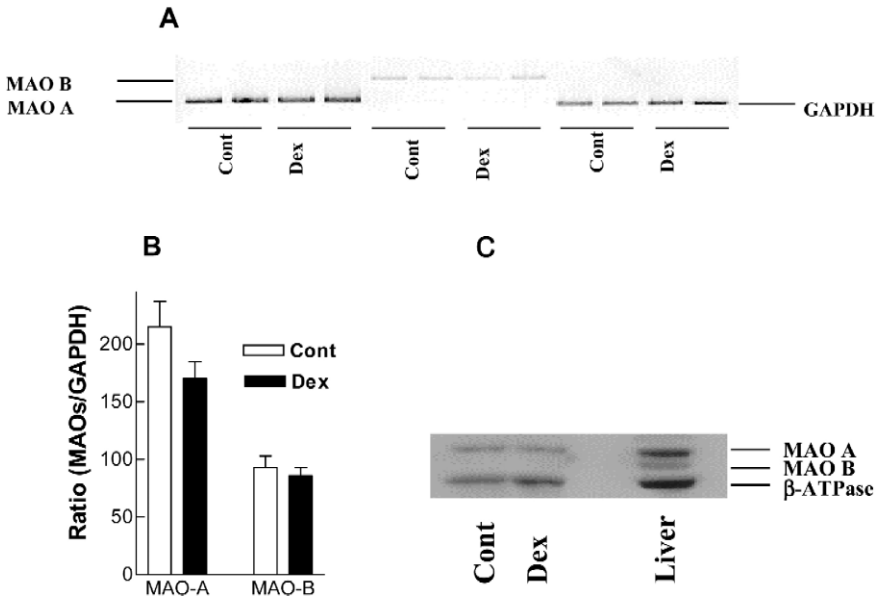

Fig. 3. Effect of dexamethasone treatment on monoamine oxidases in 9-day-old rats. (A) Semi-quantitative RT-PCR was performed as described in Materials and methods. The relative expression of each enzyme isoform was determined as the ratio of the optical densities relative to monoamine oxidases-A or -B bands to the optical density of the GAPDH band. (B) The histogram represents the average of eight distinct experiments. (C) Immunoblots were performed in membrane preparations from control (cont) and dexamethasone (Dex)-treated rats. The data are representative of eight differents experiments.

[^{14}C]β-phenylethylamine was unchanged (Table 1). In order to determine whether modifications in monoamine oxidases activities by dexamethasone were related to changes of mRNA turnover and protein synthesis, mRNA and protein corresponding to monoamine oxidases were measured by semi-quantitative RT-PCR and immunoblot, respectively. As shown in Fig. 3, monoamine oxidases-A and -B mRNA expression and immunoreactivity were not significantly modified after dexamethasone administration.

4. Discussion

Although kidney contains large amounts of monoamine oxidases, the impact of these enzymes on renal function, their distribution along the nephron and the mechanism of their regulation are still not fully elucidated. In the present study, we investigated the monoamine oxidases-A and -B expression during kidney development and the potential regulation by glucocorticoids. Based on previous studies showing that enzyme assays may not reflect the real amount of each monoamine oxidase isoenzyme expressed in a given tissue (Singer and Ramsay, 1993), we decided to quantify monoamine oxidases-A and -B by both immunoblot and enzyme assays and to determine the expression of their relative mRNA by semi-quantitative RT-PCR. By combining these different approaches, we showed that the amount and the subtype of monoamine oxidases expressed in renal cortex depend, in part, on age, kidney maturation and glucocorticoid activity.

Part of our results shows that, while both monoamine oxidase isoenzymes are highly expressed in renal cortex of adult rats, monoamine oxidase-A is largely predominant in renal cortex of 9-day-old rats. During development, monoamine oxidase-B activity and immunoreactivity, which are almost undetectable in renal cortex of 9-day-old rats, increased significantly within the first postnatal weeks and the relative amount of each monoamine oxidase isoform in renal cortex of 5-week-old rats reached levels similar to those previously reported (Pizzinat et al., 1999). In contrast to that observed for monoamine oxidase-B, monoamine oxidase-A activity and affinity for the substrate decreased significantly with age. It is noteworthy that the decrease in monoamine oxidase-A activity was not associated to a decrease in monoamine oxidase-A immunoreactivity. These results suggest that the change in monoamine oxidase-A activity is not related to a modification of the total amount of the isoenzyme, but more likely, to maturation processes shifting monoamine oxidase-A from an active to inactive conformation.

Our results show that, in rat renal cortex, the two monoamine oxidase isoenzymes are differently regulated during kidney maturation. A different regulation of monoamine oxidases-A and -B during development has been also reported for other organs. However, the relative changes of each isoenzyme seem to be tissue-specific. Indeed, in the rat heart, monoamine oxidase-B activity was the predominant form in 2- to 3-week-old animals while monoamine oxidase-A activity was very low and increased significantly with age, becoming predominant (Strolin-Be-

nedetti et al., 1992). On the other hand, in rat liver, both monoamine oxidase isoforms are highly expressed in prenatal liver and their activity increases significantly within the first 4 weeks after the partum and subsequently, remain essentially stable (Blatchfort et al., 1976; Della Corte and Tripton, 1980). Finally, in rat lung, both monoamine oxidase isoforms increase with age and the values of monoamine oxidases-A and -B activities reach the adult values at day 40 and 80, respectively (Ben-Harari and Youdim, 1981). Our results show that the maturation profile of renal cortex monoamine oxidases-A and -B differs from that described for other peripheral organs indicating that kidney may have specific factors regulating monoamine oxidases expression.

As previous studies showed that, in renal cortex, the expression of mitochondrial proteins is regulated by glucocorticoids (Djouadi et al., 1994, 1996), we investigated whether dexamethasone treatment could mimic the modifications of monoamine oxidases observed during kidney maturation. Monoamine oxidase-A activity and affinity were decreased by dexamethasone administration and reached values similar to those observed in 5-week-old rats. Interestingly, as observed for the modification of monoamine oxidase-A during development, monoamine oxidase-A immunoreactivity was not modified by dexamethasone treatment. The fact that we also did not observe changes in the levels of mRNA encoding monoamine oxidase-A strongly suggests that dexamethasone regulates monoamine oxidase-A by a mechanism independent of modification of protein synthesis and mRNA turnover. The similarities in monoamine oxidase-A modification observed in experiments performed in the developing kidney and during dexamethasone treatment strongly suggest that maturation of renal cortex monoamine oxidase-A depends in part, on glucocorticoid activity.

In contrast to the changes of monoamine oxidase-A observed in developing kidney, dexamethasone treatment decreased significantly monoamine oxidase-B activity suggesting that glucocorticoids probably are not responsible for modification of monoamine oxidase-B observed during maturation.

The different developmental modifications of monoamine oxidases-A and -B suggest that each isoenzyme may have peculiar age-dependent effects on renal function. The fact that monoamine oxidase-A is largely predominant in the renal cortex of 9-day-old rats clearly indicates that, in developing renal cortex, independently on the substrate specificity, catecholamine and serotonin are fully oxidated by monoamine oxidase-A. Based on our results showing that hydrogen peroxide produced by monoamine oxidases during substrate degradation regulate renal epithelial cell mitogenesis (Vindis et al., 2000), it is conceivable that monoamine oxidase-A may be involved in regulation of proximal tubule proliferation during development. The age-dependent increase in renal cortex monoamine oxidase-B suggests that, in adult renal cortex, the biogenic amines are potentially degraded by one or the other isoenzyme depending on the classical substrate specificity.

In conclusion, our results show that renal monoamine oxidases-A and -B are differently regulated during development and by glucocorticoids. We think that these results represent the first step to examine the consequences of age- and drug-dependent monoamine oxidase modifications on renal functions.

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