ELSEVIER

European Journal of Pharmacology 338 (1997) 89–95

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Pharmacological characterisation and autoradiographic localisation of a putative dopamine D_3 receptor in the rat kidney

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Received 22 May 1997; revised 19 August 1997; accepted 26 August 1997

Abstract

The pharmacological profile and the microanatomical localisation of a putative dopamine D_3 receptor in the rat renal cortex were investigated using radioligand binding assay and light microscope autoradiography techniques. [^{3}H]7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetraline ([^{3}H]7-OH-DPAT) was used as a ligand. [^{3}H]7-OH-DPAT was bound specifically to sections of renal cortex. The binding was time-, temperature- and concentration-dependent, of high affinity and guanine nucleotide-insensitive. The dissociation constant (K_d) value was 0.57 ± 0.02 nM and the maximum density of binding sites (B_{max}) was 62.4 ± 3.5 fmol/mg tissue. The pharmacological profile of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex suggests the labelling of a dopamine D_3 receptor. Light microscope autoradiography revealed the accumulation of the radioligand primarily within cortical tubules and to a lesser extent in the glomerular tuft. In glomeruli, binding sites were found mainly in mesangium and mesangial cells. The demonstration of a putative dopamine D_3 receptor in slide-mounted sections of rat renal cortex suggests that appropriate radioligand binding assay techniques combined with autoradiography, may contribute to characterise peripheral dopamine receptor subtypes. © 1997 Elsevier Science B.V.

Keywords: Dopamine D_3 receptor; Kidney; Radioligand binding assay; Autoradiography; Cortical tubule; Glomerulus

1. Introduction

Dopamine exerts important renal effects including regulation of sodium excretion, enhancement of diuresis, vasodilatation and decrease in renal resistance (Bello-Reuss et al., 1982; Bell, 1993). These effects are mediated through the interaction with specific dopamine receptors. Brain and peripheral dopamine receptors were divided into dopamine D_1-like and D_2-like receptors on the basis of their interaction with cellular effector systems (Sibley and Monsma, 1992; Gingrich and Caron, 1993; Strange, 1993). Dopamine D_1-like receptors are coupled positively with adenylate cyclase and stimulate phospholipase C (Kebabian and Calne, 1979; Felder et al., 1989; Sibley and Monsma, 1992; Gingrich and Caron, 1993). Dopamine D_2-like receptors are coupled negatively or uncoupled with adenylate cyclase (Kebabian and Calne, 1979; Sibley and Monsma, 1992; Gingrich and Caron, 1993). Moreover, these receptors interact with calcium and potassium channels and interfere with phosphatidylinositol metabolism and release of arachidonic acid (Sibley and Monsma, 1992; Gingrich and Caron, 1993; Yamaguchi et al., 1995). The application of molecular biology to dopamine receptor research has shown that the picture of dopamine receptors is more complicated than that it was considered until a few years ago and dopamine receptors consist of at least 5 subtypes (Sibley and Monsma, 1992; Gingrich and Caron, 1993). The dopamine D_1-like receptors super family includes two receptor subtypes, the D_1 and D_5 sites (named D_{1A} and D_{1B} in the rat) (Sibley and Monsma, 1992; Gingrich and Caron, 1993; Felder et al., 1993; Yamaguchi et al., 1995). Dopamine D_2-like receptors include two

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isoforms of the D_2 receptor (D_{2S} and D_{2L}), as well as a dopamine D_3 and D_4 receptor (Sibley and Monsma, 1992; Gingrich and Caron, 1993).

Biochemical, functional, radioligand binding assay and autoradiographic studies have shown that the kidney expresses dopamine D_1-like and D_2-like receptors (Felder et al., 1989; Amenta, 1990; Lokhandwala and Amenta, 1991). However, so far, the characterisation of renal dopamine receptor subtypes was accomplished primarily with molecular biology techniques. These studies have found that rat kidney expresses dopamine D_{1A} and D_{1B} receptors as well as dopamine D_{2L}, D_3 and D_4 receptor subtypes (Gao et al., 1994; Matsumoto et al., 1995; O'Connell et al., 1995). The functional role of dopamine D_1-like receptors in the kidney has been widely investigated (Lokhandwala and Amenta, 1991), whereas less information is available on renal dopamine D_2-like receptors. The present study was designed to analyse the pharmacological profile and the microanatomical localisation of the dopamine D_3 receptor subtype in the rat renal cortex. A preliminary account of this investigation was presented to the 6th International Conference on Peripheral Dopamine (Amenta, 1996).

2. Materials and methods

2.1. Animal and tissue preparation

Male Wistar rats (300–350 g body weight, $n = 10$) were obtained from Charles River (Calco, Italy). The animals were killed by decapitation under ether anaesthesia. The kidneys were removed and washed in an ice-cold 0.9% NaCl solution to remove blood. The cortex was separated from the medulla and processed as indicated below. Renal cortices were frozen in isopentane cooled with liquid nitrogen, mounted in a -20°C microtome cryostat chamber and cut serially. Sections (8 μm thick) were mounted on pre-weighed gelatine-coated microscope slides and used for radioligand binding assay and light microscope autoradiography.

2.2. Radioligand binding experiments

Sections of rat renal cortex were incubated for 60 min at 23°C in a HEPES [4-(2-hydroxyethil)-1-piperazine ethanesulfonic acid]-based buffer constituted by 20 mM HEPES, 1 mM ethylenedinitrilo-tetraacetic acid (EDTA), 1 mM ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA), and 120 mM NaCl (pH 7.4) with increasing concentrations (0.1–5 nM) of [^{3}H]7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetraline ([^{3}H]7-OH-DPAT). Non-specific binding was defined by incubating parallel sections with the radioligand in the presence of 1 μM (+)-butaclamol or 10 μM dopamine. The incubation buffer is reported to be the most suitable for labelling dopamine D_3 receptor (Vile et al., 1995). The incubation times and temperature chosen gave the highest specific:non-specific binding ratio in a series of preliminary experiments. At the end of the incubation sections were washed in ice-cold incubation buffer (2×5 min) to remove unbound radioligand and were rinsed quickly in distilled water. Sections were then wiped onto Whatman GF-B glass fibre filters and put into scintillation vials which were counted by liquid scintillation spectrometry.

The pharmacological specificity of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex was assessed by incubating some sections with a 0.5 nM radioligand concentration in the presence of increasing concentrations of compounds active at dopamine (apomorphine, (+)-butaclamol, clozapine, domperidone, dopamine, haloperidol, 7-OH-DPAT, quinpirole, SCH 23390 and (−)sulpiride), serotonin (ketanserin, methysergide and serotonin), adrenergic (phentolamine and (−)-propranolol) and sigma ((+)-pentazocine) receptors. Competing drugs were used in 5–7 concentrations ranging from 1 nM to 0.1 mM. [^{3}H]7-OH-DPAT displacement curves by dopamine were performed in the presence or in the absence of 300 μM guanosine triphosphate (GTP). At the end of incubation, the sections were processed as described above.

2.3. Light microscope autoradiography

The autoradiographic localisation of [^{3}H]7-OH-DPAT binding sites to sections of rat renal cortex was accomplished using a high resolution nuclear emulsion-coated coverslips technique (Young and Kuhar, 1979), to identify cellular elements expressing a putative dopamine D_3 receptor. Sections were incubated in the above buffer for 60 min at 23°C with a 0.5 nM [^{3}H]7-OH-DPAT concentration in the presence or in the absence of 10 μM dopamine or 1 μM (+)-butaclamol to define non-specific binding. At the end of incubation, the sections were washed with ice-cold buffer (2×5 min), rinsed quickly in distilled water and air-dried. Ilford L4 nuclear emulsion (diluted 1:1 with distilled water)-coated coverslips were attached to the slides containing renal cortex sections. After exposure for 4–6 weeks in light-tight boxes, autoradiographs were developed in Kodak D-19, fixed in Agefix Agfa, stained with toluidine blue and viewed under a Zeiss Axiophot light microscope equipped with bright- and dark-field optics.

The number of silver grains developed in the glomerular tuft and in cortical tubules in [^{3}H]7-OH-DPAT autoradiographs was assessed by quantitative image analysis. Three areas of 500 μm^2 including at least one glomerular tuft were randomly selected in sections of rat renal cortex. Five consecutive sections 20 μm apart per animal ($n = 5$) incubated with 0.5 nM [^{3}H]7-OH-DPAT alone or plus 1 μM (+)-butaclamol to define non-specific binding were examined. Analysis was done using dark-field optics with a $\times 40/1.0$ objective lens to obtain a final magnification

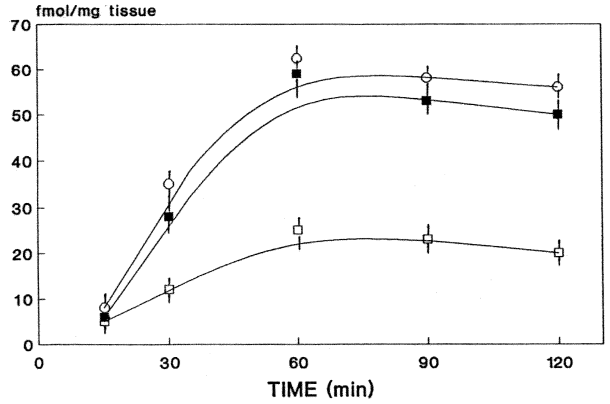

Fig. 1. Influence of different incubation times and temperatures (23°C, ○; 37°C, ■; and 4°C, □) on specific [^{3}H]7-OH-DPAT binding to sections of rat renal cortex ($n = 10$). Data are presented as mean ± S.E.M.

of ×400. The images were transferred from the microscope to a Quantimet 500 image analyser (Leica, Cambridge), connected to the microscope. Silver grains developed in [^{3}H]7-OH-DPAT autoradiographs were counted independently for the glomerular tuft and the cortical tubules using an automatic programme of the image analyser.

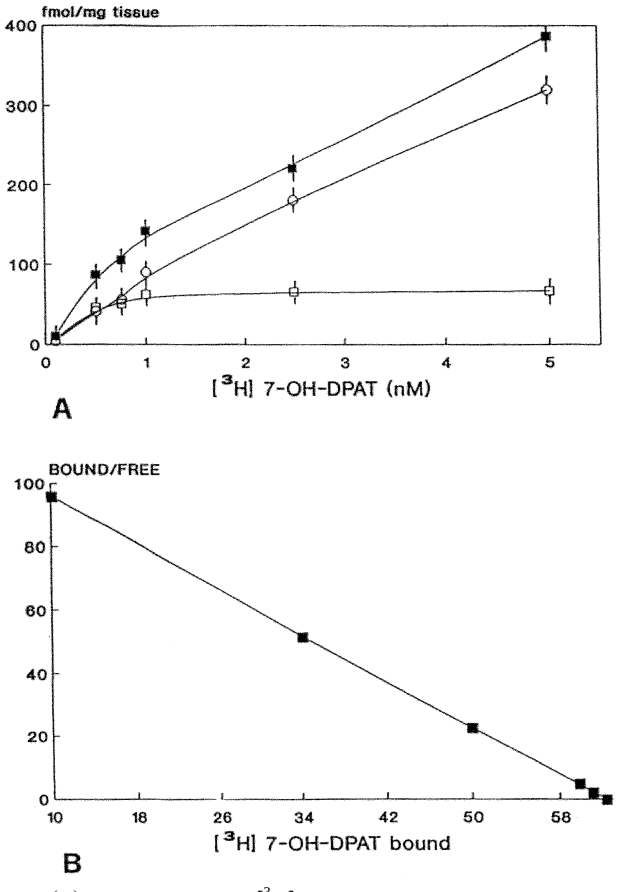

Fig. 2. (A) Saturation curve of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex. Sections were incubated with the radioligand alone (total binding: ■) or plus 1 μM (+)-butaclamol to define non-specific binding (○). Specific binding values (□) were obtained by subtracting non-specific from total binding. Data are presented as mean ± S.E.M. ($n = 10$). (B) Scatchard analysis of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex ($n = 10$). The B_{max} value averaged 62.4 ± 3.5 fmol/mg tissue.

2.4. Data analysis

Data from binding experiments were calculated with the RADLIG programme (McPherson, 1994). In competition experiments, the inhibition constant (K_i) was calculated from values obtained in independent experiments performed in triplicate using 6–8 displacer concentrations. The Student's *t*-test was used for evaluating the significance of differences in the density of silver grains developed in the glomerular tuft and in cortical tubules. Data are expressed as the mean ± S.E.M. of experiments carried out in triplicate per '*n*' animals.

2.5. Chemicals

[^{3}H]7-OH-DPAT (specific activity 160 Ci/mmol) was purchased from Amersham Radiochemical Centre (Amersham, UK). Clozapine and methysergide were obtained from Sandoz Pharma (Basel, Switzerland), ketanserin was obtained from Janssen (Beerse, Belgium). Other chemicals were purchased from Research Biochemi-

Table 1
Pharmacological profile of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex

Compounds	K_i (nM)
Agonists	
Apomorphine	14.4 ± 0.32
Dopamine with 300 μM GTP	8.90 ± 0.10
Dopamine without GTP	9.87 ± 0.07
7-OH-DPAT	1.06 ± 0.02
Quinpirole	4.7 ± 0.21
Serotonin	> 5000
Antagonists	
Clozapine	200 ± 15.4
Domperidone	65.6 ± 3.5
Haloperidol	3.9 ± 0.20
Ketanserin	2430 ± 102
Methysergide	> 5000
(+)-Pentazocine	> 5000
Phentolamine	> 5000
(−)-Propranolol	> 5000
SCH 23390	992 ± 24.3
(−) Sulpiride	15.3 ± 0.12

[^{3}H]7-OH-DPAT binding was assayed as described in Section 2. Values represent the competitor dissociation constant (K_i). Each figure is the mean ± S.E.M. of five to seven experiments performed in triplicate. For references on the pharmacological specificity of the compounds tested, see Lévesque et al. (1992) and Gingrich and Caron (1993).

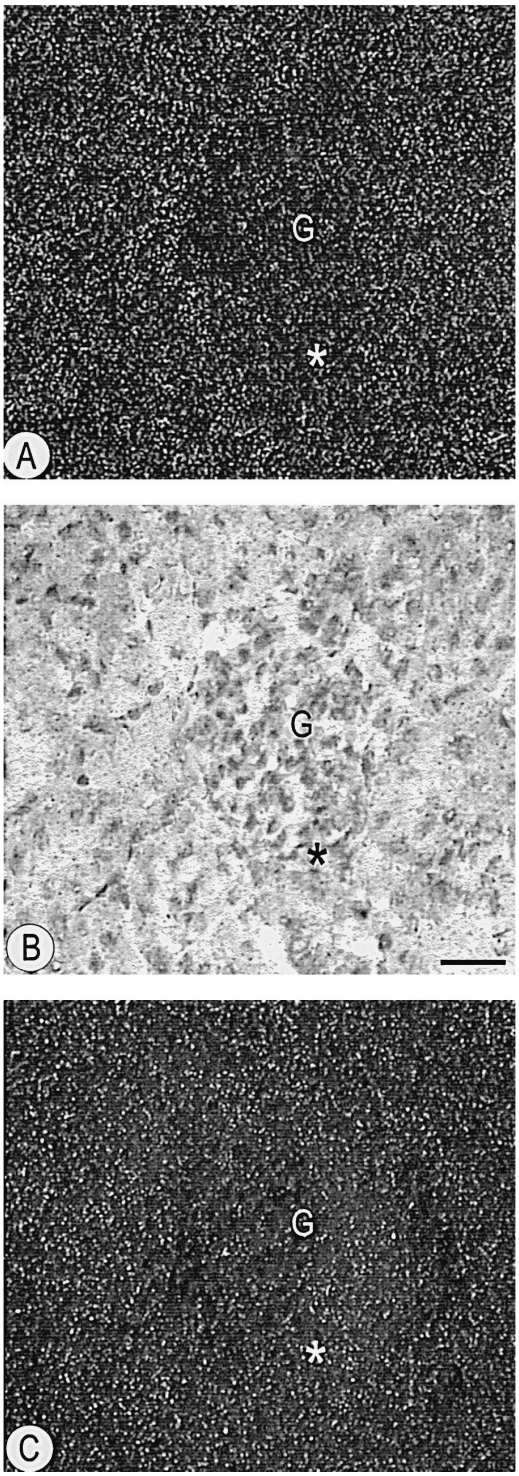

Fig. 3. Light microscope autoradiographs of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex. Micrographs (A) and (C) are dark-field pictures of sections exposed to 0.5 nM [^{3}H]7-OH-DPAT alone (A) or plus 1 μM (+)-butaclamol (C) to define non-specific binding. Micrograph (B) is a bright-field picture of (A) stained with toluidine blue to verify microanatomical details. Specific silver grains (sensitive to (+)-butaclamol displacement) were found primarily in cortical tubules and to a lesser extent in the glomerular tuft (G). The asterisk indicates a glomerular capsule. Calibration bar: 40 μm.

Table 2
Number of silver grains developed in a 500 μm^2 area of the different portions of rat renal cortex in [^{3}H]-7-OH-DPAT autoradiographs

	Total binding	Non-specific binding	Specific binding
Glomerular tuft	225 ± 15.3	65 ± 3.7	160 ± 11
Glomerular capsule	30 ± 2.5	29 ± 1.7	not detectable
Proximal convoluted tubule	505 ± 30.8	130 ± 6.9	357 ± 29[a]
Distal convoluted tubule	385 ± 20.2	130 ± 6.9	275 ± 17[b]

Sections were incubated with 0.5 nM [^{3}H]7-OH-DPAT alone (total binding) or plus 1 μM (+)-butaclamol to define non-specific binding. Specific binding values were obtained by subtracting non-specific from total binding. Data are the mean ± S.E.M. of 15 independent measurements per animal ($n = 5$) performed by image analysis as indicated in the text. Proximal tubules were differentiated from distal tubules by the presence of brush border membrane.
[a] $P < 0.01$ vs. glomerular tuft.
[b] $P < 0.01$ vs. glomerular tuft or proximal convoluted tubule.

cals International (Natick, MA, USA) or Sigma (St. Louis, MO, USA).

3. Results

[^{3}H]7-OH-DPAT was bound specifically to sections of rat renal cortex. The binding was time-, temperature- (Fig.

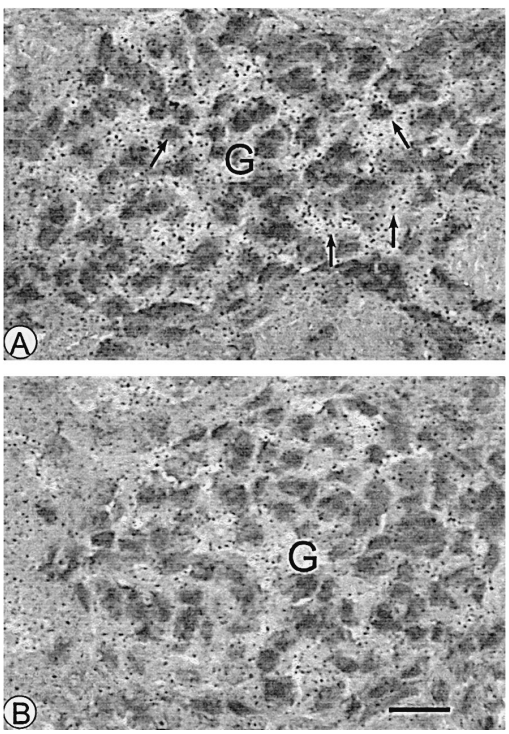

Fig. 4. Bright-field light microscope autoradiographs of [^{3}H]7-OH-DPAT binding to glomerular tuft stained with toluidine blue. Sections were exposed to 0.5 nM [^{3}H]7-OH-DPAT alone (A) or plus 1 μM (+)-butaclamol (B) to define non-specific binding. Glomerular silver grains were accumulated primarily in mesangial cells and mesangium (arrows). Calibration bar: 20 μm.

1), concentration-dependent (Fig. 2A) and reversible (data not shown). Scatchard analysis of [^{3}H]7-OH-DPAT isotherms revealed a single class of high affinity sites (Fig. 2B). The dissociation constant (K_d) value was 0.57 ± 0.02 (Fig. 2A). The maximum density of binding sites (B_{max}) value was 62.4 ± 3.5 fmol/mg tissue (Fig. 2B).

Data on the pharmacological profile of [^{3}H]7-OH-DPAT binding to sections of rat renal cortex are summarised in Table 1. As shown, the rank order of potency of competitors of [^{3}H]-7-OH-DPAT binding was 7-OH-DPAT > haloperidol > quinpirole > dopamine > apomorphine > (−)-sulpiride > domperidone > clozapine > SCH 23390 > ketanserin. Methysergide, (+)-pentazocine, phentolamine, (−)-propranolol and serotonin did not compete with [^{3}H]7-OH-DPAT binding to sections of rat renal cortex (Table 1). Analysis of displacement curves of [^{3}H]7-OH-DPAT binding by dopamine, revealed that the addition of GTP to the incubation medium did not affect significantly the competition of [^{3}H]7-OH-DPAT binding by dopamine (Table 1).

Light microscope autoradiography revealed the highest accumulation of silver grains within cortical tubules and to a lesser extent within the glomerular tuft (Fig. 3 and Table 2). Quantitative autoradiography revealed that density of silver grains was higher in proximal convoluted tubules (Table 2). Analysis of high resolution light microscope autoradiographs revealed that in the glomerular tuft [^{3}H]7-OH-DPAT was bound primarily to mesangium and mesangial cells (Fig. 4).

4. Discussion

The dopamine D_3 receptor is a recently characterised guanine-insensitive dopamine receptor subtype belonging to the dopamine D_2-like receptors super family. This site was suggested to mediate the anti-psychotic effects of neuroleptics (Sokoloff et al., 1992). In the brain, dopamine D_3 receptor characteristic and anatomical localisation were analysed by molecular biology, pharmacological and autoradiographic studies (Bouthenet et al., 1991; Lévesque et al., 1992; Boundy et al., 1993, Levant and De Souza, 1993; Ricci et al., 1995, 1996).

Although the expression of dopamine D_2-like receptors in the kidney is documented by radioligand binding, autoradiographic and functional studies (Seri, 1990; Szabo et al., 1992; Rump and Schollmeyer, 1993; Cheung and Barrington, 1996), information on the renal dopamine D_3 receptor is sparse, with one report of a low abundance of D_3 receptor mRNA in whole kidney tissue, and another one of a good expression of the D_3 receptor gene in normotensive and spontaneously hypertensive rats (Gao et al., 1994). In this study we have observed that the putative dopamine D_3 receptor agonist [^{3}H]7-OH-DPAT (Lévesque et al., 1992) was bound to sections of rat renal cortex with a pharmacological profile consistent with the labelling of a dopamine D_3 receptor (Lévesque et al., 1992; Levant and De Souza, 1993; Ricci et al., 1995, 1996). In fact, compounds displaying a dopamine D_3 receptor specificity such as [^{3}H]7-OH-DPAT and quinpirole were more effective competitors of [^{3}H]7-OH-DPAT than compounds preferentially active on the dopamine D_2 receptor such as domperidone or on the dopamine D_4 receptor such as clozapine (Gingrich and Caron, 1993). Moreover, the binding was guanine-insensitive. This strongly supports the assumption that in our experimental conditions we have labelled a dopamine D_3 receptor. The sigma receptor antagonist (+)-pentazocine had no effect on [^{3}H]7-OH-DPAT binding to sections of rat kidney. This suggests that different from some recent evidence obtained in the central nervous system (Debonnel and De Montigny, 1996), [^{3}H]7-OH-DPAT does not bind sigma sites in rat renal cortex.

Pharmacological and functional evidence suggests that peripheral dopamine D_2-like receptors represent mainly a population of prejunctional sites (Clark, 1990b). Prejunctional dopamine D_2-like receptors modulating sympathetic neurotransmission were characterised in rabbit (Chevillard et al., 1980), dog (Bass and Robie, 1984), rat (Lokhandwala and Steenberg, 1984a,b; Rump et al., 1992) and human (Rump et al., 1993) renal nerves. Our experiments were performed on normally innervated kidneys. On the basis of our findings alone it is difficult to hypothesise whether the putative dopamine D_3 receptor we have characterised is or is not prejunctional. The observation of a specific [^{3}H]7-OH-DPAT binding in the glomerulus, which is known to be devoid of innervation (Vega et al., 1990) suggests that glomerular dopamine D_3 binding sites are not prejunctional. Since cortical tubules are supplied with a sympathetic innervation (Vega et al., 1990) further work is necessary to assess if the tubular dopamine D_3 receptor is or is not prejunctional. Our recent observations that the majority of tubular dopamine D_2-like receptors disappears after denervation (Barili et al., 1997) suggest that the tubular dopamine D_3 receptor characterised in this study may have a prejunctional localisation.

Light microscope autoradiography has shown that the renal dopamine D_3 receptor has a tubular and glomerular localisation. The tubular receptor is probably involved in electrolyte handling. The glomerular D_3 receptor is located in the mesangium. Biochemical pharmacology studies have documented a dopamine D_1-like effect on cyclic adenosine, 3′–5′ monophosphate (cAMP) accumulation in cultured rat mesangial cells (Schultz et al., 1987). Our study has shown that mesangial cells express also a putative dopamine D_3 receptor. The functional relevance of this site, if any, should be clarified in future studies.

It was suggested that an impaired dopaminergic function may represent a cause of hypertension (Jose et al., 1993). Agonists of peripheral dopamine D_1-like and D_2-like receptors were considered as possible candidates in the treatment of hypertension (Clark, 1990a,b). Molecular biology studies did not show differences in the expression of

dopamine D_3 receptor genes between normotensive Wistar Kyoto and spontaneously hypertensive rats (Gao et al., 1994). The development of a simple and reproducible radioligand binding assay protocol for the renal dopamine D_3 receptor such as in this study, will contribute to establish quantitative changes in the density or in the pharmacological profile of this dopamine receptor subtype in experimental and pathological conditions.

Acknowledgements

The present study was supported in part by a grant of the Italian National Research Council (C.N.R.). Dr. P.B. is a recipient of a C.N.R. fellowship (PFI). Computer assistance from Mr. Christian Fringuelli is also gratefully acknowledged.

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