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Distribution and Function of Peripheral α-Adrenoceptors in the Cardiovascular System

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RUFFOLO, R. R., JR. *Distribution and function of peripheral α-adrenoceptors in the cardiovascular system.* PHARMACOL BIOCHEM BEHAV 22(5) 827–833, 1985.—α-Adrenoceptors may be subdivided based on their anatomical distribution within the synapse. Presynaptic α-adrenoceptors are generally of the α_2-subtype and modulate neurotransmitter liberation *via* a negative feedback mechanism. Postsynaptic α-adrenoceptors are usually of the α_1-subtype and mediate the response of the effector organ. Although this "anatomical" subclassification is generally applicable, many exceptions exist. A more useful classification of α-adrenoceptor subtypes is based on a pharmacological characterization in which selective agonists and antagonists are used. Peripheral α-adrenoceptors are critical in the regulation of the cardiovascular system. Postsynaptic α-adrenoceptors in arteries and veins represent a mixed population of α_1/α_2-adrenoceptors, with both subtypes mediating vasoconstriction. In the peripheral arterial circulation, postsynaptic vascular α_1-adrenoceptors are found in the adrenergic neuroeffector junction, whereas postsynaptic vascular α_2-adrenoceptors are located extrajunctionally. In the venous circulation, it appears that α_2-adrenoceptors may be predominantly junctional, whereas α_1-adrenoceptors may be predominantly extrajunctional. It has been proposed that junctional α-adrenoceptors will respond predominantly to norepinephrine liberated from sympathetic neurons, whereas extrajunctional α-adrenoceptors likely respond to circulating catecholamines. The functional role of extrajunctional α-adrenoceptors may be more important in disease states such as hypertension and congestive heart failure where circulating levels of catecholamines may be high and contribute to the maintenance of elevated vascular resistance. α_2-Adrenoceptors are also associated with the intima and may play a role in the release of an endogenous relaxing factor from the endothelium. In the heart, postsynaptic α_1-adrenoceptors mediate an increase in the contractile state of the myocardium with little or no change in heart rate. It appears that the inotropic effects of dobutamine may be mediated, at least in part, through stimulation of postsynaptic myocardial α_1-adrenoceptors. Both α_1- and α_2-adrenoceptors have been identified in the kidney, and their functions are just beginning to be understood. Renal α_1-adrenoceptors may regulate renal blood flow and gluconeogenesis. Renal α_2-adrenoceptors may also regulate renal blood flow as well as inhibit renin secretion.

α_1-Adrenoceptors α_2-Adrenoceptors Vasculature Arteries Veins Heart Kidney

THE existence of postsynaptic α-adrenoceptors located on effector organs and mediating their response has been known for many years. However, the existence of presynaptic α-adrenoceptors which, when activated, reduce neurotransmitter release *via* a negative feedback mechanism, is a fairly recent observation (for reviews see [36, 69, 81]). Langer [35] proposed that the postsynaptic α-adrenoceptor which mediates the response in an effector organ be termed α_1 and that the presynaptic 'autoreceptor' be termed α_2. A similar classification has been presented by Berthelsen and Pettinger [6] after a comprehensive review of the literature. More often than not, this "anatomical" subclassification holds true. However, sufficient evidence exists to indicate that not all α_1-adrenoceptors are located postsynaptically [34] and not all α_2-adrenoceptors are located presynaptically [73]. Particularly in the vasculature, postsynaptic α_2-adrenoceptors mediating vasoconstriction have been demonstrated to coexist along with 'classical' postsynaptic α_1-adrenoceptors [15, 16, 21, 72].

Since many exceptions exist to the anatomical subclassification of postsynaptic α_1- and presynaptic α_2-adrenoceptors, criteria for a "pharmacological" subclassification have been developed which employ highly selective α-adrenoceptor agonists and antagonists as pharmacological tools (Table 1). Among agonists, phenylephrine, methoxamine and cirazoline are highly selective for α_1-adrenoceptors, whereas clonidine, α-methylnorepinephrine, UK-14,304, B-HT 920 and B-HT 933 are selective for α_2-adrenoceptors. The natural neurotransmitter, norepinephrine, is relatively nonselective while the hormone, epinephrine, displays a slight selectivity for α_2-adrenoceptors [6].

Antagonists have also proven to be valuable tools with which to probe and subclassify α-adrenoceptors. Prazosin, which has been introduced clinnically to treat hypertension, is a potent and highly selective α_1-adrenoceptor antagonist with a dissociation constant of approximately 1 to 10 nM for α_1-adrenoceptors, and a selectivity for α_1-adrenoceptors (over α_2) on the order of 100 to 1,000 fold. Other potent and selective competitive α_1-adrenoceptor antagonists include WB-4101 and corynanthine. Yohimbine, rauwolscine and idazoxan are selective antagonists of α_2-adrenoceptors. Several of the more common α-adrenoceptor antagonists, such as phentolamine and tolazoline, are relatively nonselective. The selectivities of several α-adrenoceptor agonists and antagonists useful in investigating and subclassifying α-adrenoceptors are listed in Table 1.

TABLE 1

SELECTIVITIES OF α-ADRENOCEPTOR AGONISTS AND ANTAGONISTS

α_1-Adrenoceptor Selective	Nonselective	α_2-Adrenoceptor Selective
	Agonists	
Phenylephrine	Norepinephrine	Clonidine*
Methoxamine	Epinephrine	α-Methylnoradrenaline*
Cirazoline		B-HT 920
Amidephrine		B-HT 933
St 587		UK-14,304
Sgd 101/75		M-7
2,5-Dimethoxytolazoline		TL-99
3,5-Dimethoxytolazoline		guanfacine*
(−)-Dobutamine		2,3-Dimethoxytolazoline
SK&F 89748		
	Antagonists	
Prazosin	Phentolamine	Yohimbine
WB-4101	Tolazoline	Rauwolscine
Corynanthine		Idazoxan (RX 781094)
Azapetine		RS21361
BE-2254		SK&F 86466
(+)-3-O-Methyldobutamine		
Phenoxybenzamine		

*Selectivity may not be sufficiently high to be useful in receptor subclassification.

PERIPHERAL α-ADRENOCEPTORS IN THE CARDIOVASCULAR SYSTEM

Arteries

The predominant innervation to the vasculature is adrenergic, where postganglionic sympathetic nerve terminals liberate norepinephrine in response to electrical stimulation. The liberated norepinephrine will activate postjunctional α-adrenoceptors which, in turn, mediate vasoconstriction and a concomitant increase in total peripheral vascular resistance and blood pressure. In addition, the liberated neurotransmitter will activate prejunctional α_2-adrenoceptors which inhibit further norepinephrine release *via* the negative feedback system. The presynaptic autoinhibitory α_2-adrenoceptor at the vascular neuroeffector junction has been studied extensively [67] and is similar to the α_2-adrenoceptor found presynaptically in other tissues.

The nature of the postjuctional α-adrenoceptor which mediates vasoconstriction has been the target of many recent investigations. In most nonvascular tissues, the postjunctional α-adrenoceptor is of the α_1-subtype. While postsynaptic α-adrenoceptors in the vasculature were identified early on, recent studies *in vivo* indicate that postsynaptic α_1-adrenoceptors in blood vessels do not represent one homogeneous population. Drew and Whiting [21] identified two types of α-adrenoceptors mediating pressor responses in the cat and rat. One type was prazosin-sensitive and classified as α_1, while the second prazosin-resistant type was not classified at that time. Subsequent investigations occurring simultaneously and independently by several groups [17, 20, 72] indicated that α_1- and α_2-adrenoceptors coexist in the vasculature of the rat, and both subtypes are located postjunctionally and mediate vasoconstriction. Similar results have been obtained in the dog [12], rabbit [44] and man [23].

It is now accepted that vasoconstriction may be mediated by a mixed population of postsynaptic vascular α_1- and α_2-adrenoceptors. The physiological function and/or distribution of these receptors is beginning to be understood. By using a variety of α_1-selective, α_2-selective and nonselective α-adrenoceptor antagonists, Yamaguchi and Kopin [83] observed that the pressor responses to exogenously administered catecholamines were selectively antagonized by α_2-adrenoceptor blockers. Conversely, the pressor response evoked by sympathetic nerve stimulation was selectively antagonized by α_1-adrenoceptor blockers. These authors postulated that postsynaptic α-adrenoceptors located at the neuroeffector junction (i.e., junctional receptors) were of the α_1-subtype, while those located away from the neuroeffector junction (i.e., extrajunctional receptors) were of the α_2-subtype.

Support for the concept of junctional α_1- and extrajunctional α_2-adrenoceptors in the arterial circulation has been obtained in perfused cat spleen where increases in perfusion pressure elicited by nerve stimulation, norepinephrine and phenylephrine were found to be differentially inhibited by selective α_1- and α_2-adrenoceptor antagonists [38]. The response to nerve stimulation and phenylephrine were abolished by the selective α_1-adrenoceptor antagonist, prazosin, with the response to norepinephrine being only partially inhibited. Based on the known α_1-adrenoceptor selectivity of phenylephrine and the nonselective activity of norepinephrine, the results were compatible with the notion that neuronally released norepinephrine interacted with junctional α_1-adrenoceptors, which could also be activated by exogenously administered phenylephrine and norepinephrine. Postsynaptic vascular α_2-adrenoceptors in this model were proposed to reside extrajunctionally since they were not activated by norepinephrine released from sympathetic nerves, but could be stimulated by exogenously administered norepinephrine. In further studies using neuronal uptake inhibitors, Langer and coworkers [38,39] have shown that postjunctional vascular α_1-adrenoceptors are located in the vicinity of the neuronal uptake pump ($uptake_1$) and that postjunctional α_2-adrenoceptors are positioned away from this site. These results, and those obtained by Wilffert *et al.* [82], strongly suggest the existence of junctional α_1- and extrajunctional α_2-adrenoceptors located postsynaptically in the arterial circulation.

The physiological role of the postsynaptic junctional α_1-adrenoceptors appears to be in maintaining resting vascular tone. Presumably, these receptors which are located in the vicinity of the neuro-vascular junction would interact with endogenous norepinephrine liberated from sympathetic nerves. The physiological role of the extrajunctional α_2-adrenoceptors is not fully understood. It has been suggested that the extrajunctional α_2-adrenoceptors would not normally interact with liberated norepinephrine since they are located at a distance from the adrenergic nerve terminal, and the highly efficient neuronal uptake pump keeps synaptic levels of norepinephrine sufficiently low and thereby prevents diffusion of the neurotransmitter to the extrajunctional sites [38]. It has been proposed that the extrajunctional α_2-adrenoceptors may respond to circulating epinephrine acting as a blood-borne hormone [39]. Although circulating catecholamines may be below the levels required to exert a phys-

iological effect, it has been suggested that in times of stress, these levels may be elevated to threshold levels where postsynaptic vascular α_2-adrenoceptors are activated [14]. It has also been suggested that the contribution made by arterial extrajunctional α_2-adrenoceptors to total peripheral vascular resistance may be greater in certain hypertensive states than in normotensive patients (F. Buhler, personal communication), implying that postsynaptic vascular α_2-adrenoceptors may play an important role in pathophysiological states such as hypertension and possibly congestive heart failure, where circulating catecholamine levels are high [41]. It is unclear at the present time whether epinephrine is, in fact, responsible for stimulating the extrajunctional α_2-adrenoceptors in these states, since circulating levels of norepinephrine are particularly high and could account, at least in part, for their activation.

Receptor-effector coupling in arteries. Although α_1- and α_2-adrenoceptors exist postjunctionally in arteries, and both subtypes mediate vasoconstriction, recent evidence suggests that α_1- and α_2-adrenoceptors may be coupled differently to their respective vasoconstrictor processes [10, 57, 79]. The nature of this difference between α_1- and α_2-adrenoceptor coupling to arterial vasoconstriction may be reflected in quantitatively different "occupancy-vasoconstriction response" relationships as well as qualitatively different mechanisms for the translation of stimuli into vasoconstrictor responses.

The relationship between α_1-adrenoceptor occupancy by agonists and vasoconstrictor response has been studied *in vitro* for many years [7, 49, 59]. In general, nonlinear occupancy-response relationships have been obtained in most arterial vessels, with approximately 6% α_1-adrenoceptor occupancy by full agonists being required for half-maximal vasoconstriction. "Spare" α_1-adrenoceptors are commonly found. A direct comparison of the occupancy response relationships for α_1- and α_2-adrenoceptor-mediated arterial vasoconstriction has not been performed *in vitro* due to the difficulty in demonstrating α_2-adrenoceptor-mediated vasoconstrictor effects in arterial preparations in isolated organ baths. However, from studies *in vivo* where α_2-adrenoceptor-mediated arterial vasoconstriction is easily quantified, evidence for differences in α_1- and α_2-adrenoceptor occupancy-response relationships has been accumulated. Irreversible alkylation of postsynaptic vascular α_1-adrenoceptors by phenoxybenzamine *in vivo* produces marked rightward shifts in the dose response curves of α_1-adrenoceptor agonists with no depression of the maximum response, whereas α_2-adrenoceptor alkylation by phenoxybenzamine is associated with depressed maximum vasoconstrictor responses with only small rightward shifts in the dose-response curves to α_2-adrenoceptor agonists [27, 52, 57]. It appears, therefore, that a more favorable relationship exists between α_1-adrenoceptor occupancy and vasoconstrictor response than between α_2-adrenoceptor occupancy and vasoconstrictor response, and that the degree of "receptor reserve" is greater for postsynaptic vascular α_1-adrenoceptors than for postsynaptic vascular α_2-adrenoceptors, at least for the particular agonists used in these studies [27, 52, 57].

Calcium utilization. Recently, its has been shown that the pressor response mediated by postjunctional vascular α_1-adrenoceptors is resistant to antagonism by calcium slow channel blocking agents, suggesting that α_1-adrenoceptors do not rely heavily upon extracellular calcium to produce vasoconstriction. In contrast, vasoconstriction elicited by postjunctional α_2-adrenoceptors appears to be critically dependent upon extracellular calcium as evidenced by the extreme sensitivity of this response to inhibition by the calcium channel blocking agents [10,79].

The proposal that α_1- and α_2-adrenoceptor-mediated vasoconstriction *in vivo* results from utilization of different calcium pools has met with some criticism [27, 55, 75], and is inconsistent with *in vitro* studies in which α_1-adrenoceptor-mediated vasoconstriction is found to be highly sensitive to antagonism by calcium channel blockers [3, 4, 75, 76, 78]. As a possible explanation for the resistance of the α_1-adrenoceptor mediated vasoconstrictor process *in vivo* to antagonism by calcium channel blockers, it has been argued [27, 52, 55] that the large receptor reserve known to exist for postsynaptic vascular α_1-adrenoceptors would "buffer" this process from antagonism by any noncompetitive antagonists, including calcium channel blockers, in accord with receptor theory [2]. When the large α_1-adrenoceptor reserve is removed by phenoxybenzamine pretreatment [55], or where α_1-adrenoceptor *partial agonists* are investigated for which no α_1-adrenoceptor reserve exists [55], α_1-adrenoceptor mediated vasoconstriction appears to be equally sensitive as α_2-adrenoceptor mediated vasoconstriction to inhibition by calcium channel antagonists. It appears, therefore that *both* α_1- and α_2-adrenoceptor-mediated vasoconstriction are highly dependent upon the mobilization of extracellular calcium.

Second messengers. The biochemical correlates of α_1- and α_2-adrenoceptor-mediated arterial vasoconstriction are poorly understood. While both α-adrenoceptor subtypes may utilize extracellular calcium to evoke vasoconstrictor responses, it is unlikely that the steps leading up to calcium translocation are the same for postsynaptic vascular α_1- and α_2-adrenoceptors. In most α_1-adrenoceptor mediated systems [46], including the vasculature [80], calcium translocation is secondary to enhanced phosphatidylinositol turnover [46], the later induced as a direct consequence of agonist interaction with α_1-adrenoceptors.

Densensitization of rabbit aorta to the α_1-adrenoceptor-mediated vasoconstrictor effects of epinephrine is not associated with a loss of postsynaptic vascular α_1-adrenoceptors, but rather is associated with a loss of the epinephrine-induced increase in phosphatidylinositol turnover (B. B. Hoffman, personal communication). It appears. therefore, that desensitization in rabbit aorta is the direct result of "uncoupling" between α_1-adrenoceptor occupancy and vasoconstrictor response, with the critical coupling step of phosphatidylinositol turnover being dampened as a result of exposure to high concentrations of agonists.

Vasoconstriction mediated by postsynaptic vascular α_2-adrenoceptors, although equally dependent (or more so) upon mobilization of extracellular calcium, most likely is not secondary to increases in phosphatidylinositol turnover. While most, if not all, α_1-adrenoceptor mediated responses are linked to phosphatidylinositol turnover, α_2-adrenoceptor-mediated responses are not [50]. In many systems, α_2-adrenoceptor mediated responses are closely associated with inhibition of adenylate cyclase. However, it is not known at present whether pressor responses elicited by postsynaptic vascular α_2-adrenoceptors result from α_2-adrenoceptor mediated inhibition of vascular adenylate cyclase.

Endothelium. An interesting role for endothelial α_2-adrenoceptors has recently been proposed [1,22]. It has been observed that vasoconstriction produced by α_2-adrenoceptor

agonists is enhanced *in vitro* by removal of endothelium. The current working hypothesis is that endothelial α_2-adrenoceptors can stimulate the release of an endogenous endothelial relaxant factor [22], which in turn produces a functional antagonism of the vasoconstrictor response. In this regard, endothelial α_2-adrenoceptors may function in much the same manner as bradykinin and muscarinic cholinergic receptors which are known to mediate the release of an endogenous relaxant factor from the endothelium [11,25].

Veins

There are many parallels that may be drawn between α-adrenoceptors and α-adrenergic mechanisms on the arterial and venous sides of the circulatory system; however, some striking differences exist. While the arterial circulation has been studied in great detail, our knowledge of the venous circulation is less complete due to the inherent difficulties in monitoring venous pressures, tones and resistances *in vivo*. However, a great deal of information concerning α-adrenergic pharmacology in veins has accumulated from *in vitro* studies using canine saphenous vein which is considered by some to be a prototypic venous blood vessel.

As is the case in the arterial circulation, postsynaptic vascular α_1- and α_2-adrenoceptors coexist in the venous circulation, and both α-adrenoceptor subtypes mediate vasoconstriction. This has been most clearly demonstrated in canine saphenous vein where vasoconstriction can be shown to be mediated either by α_1- or α_2-adrenoceptors [13, 15, 64, 70]. As is the case in the arterial circulation [57], α_1-adrenoceptors mediate a quantitatively greater vasoconstrictor response than α_2-adrenoceptors [24]; however, the relative contribution made by α_2-adrenoceptors may be far more important in the venous circulation than in the arterial circulation [77].

An interesting discrepancy appears to exist between the anatomical distribution of postsynaptic vascular α_1- and α_2-adrenoceptors in arterial and venous blood vessels. As discussed earlier, in the arterial circulation, there appears to be preferential innervation of postsynaptic vascular α_1-adrenoceptors, with the α_2-adrenoceptors residing predominantly extrajunctionally [39,82]. In contrast, recent evidence indicates that in the venous circulation, the opposite may be true. That is, in canine saphenous vein, there appears to be a predominant and preferential innervation of postsynaptic vascular α_2-adrenoceptors, with the α_1-adrenoceptor being innervated to a lesser degree and residing predominantly extrajunctionally (P. M. Vanhoutte, personal communication). The functional significance of the preferential innervation of postsynaptic vascular α_2-adrenoceptors in canine saphenous vein is not known, but may be responsible, in part, for the exaggerated "α_2-nature" [77] of the venous circulation relative to the arterial circulation.

Calcium utilization in venous circulation. Vasoconstriction in venous blood vessels mediated by postsynaptic vascular α_1- and α_2-adrenoceptors appears to be critically dependent upon the translocation of extracellular calcium. In canine saphenous vein, vasoconstriction mediated by the α_1-adrenoceptor agonist, phenylephrine, and by the α_2-adrenoceptor agonist, M-7, are both inhibited by calcium slow channel antagonists, such as diltiazem and verapamil [37]. Although α_1- and α_2-adrenoceptor-mediated vasoconstriction of canine saphenous vein is predominantly dependent upon the translocation of extracellular calcium, evidence does exist to suggest that in this tissue, α_1-adrenoceptor agonists may also trigger, to a small and limited extent, the release of intracellular calcium [39,43].

Alpha-Adrenoceptors in Myocardium

The cardiac adrenergic neuroeffector junction is in many respects similar to neuroeffector junctions in other tissues as far as α-adrenoceptors are concerned. Presynaptic α_2-adrenoceptors on postganglionic sympathetic nerve terminals have been identified in isolated hearts from many species. As in other organs, the presynaptic α_2-adrenoceptors in myocardium, when activated, mediate an inhibitory effect on neurotransmitter release [18, 19, 29]. As such, α-adrenoceptor antagonists that are nonselective, or selective for α_2-adrenoceptors, may produce positive inotropic and chronotropic responses [5] by enhancing neurotransmitter liberation resulting from loss of the autoinhibition mediated by presynaptic α_2-adrenoceptors [68].

The predominant adrenoceptor located postsynaptically in the heart is the β_1-adrenoceptor which mediates a positive inotropic and chronotropic response [8]. However, postsynaptic α-adrenoceptors also exist in the hearts of many mammalian species, including man, and mediate a positive inotropic response with little or no change in heart rate [26, 47, 60, 61, 63]. Most physiological and radioligand binding data indicate that the postsynaptic α-adrenoceptor in myocardium is of the α_1-subtype [30, 51, 60]. The mechanism by which cardiac α_1-adrenoceptors increase force of myocardial contraction has not been established, but it appears not to be associated with the accumulation of cAMP or stimulation of adenylate cyclase [9], and in this respect, α_1-adrenoceptors differ from β_1-receptors in the myocardium. Other differences between α_1- and β_1-adrenergic effects in the heart include the rate of onset and duration of action which are particularly long for α_1-adrenoceptor mediated inotropic effects [62]. Furthermore, while β_1-adrenoceptor-mediated inotropic responses occur at all frequencies of stimulation, the effect mediated by α_1-adrenoceptors is apparent only at low frequencies [8].

Although it is clear that myocardial α_1-adrenoceptors mediate a positive inotropic response with little or no change in heart rate, their functional significance is not known with certainty. Dobutamine is an inotropic agent that increases the force of myocardial contraction, and therefore cardiac output, at doses that do not significantly increase heart rate [40, 65, 74]. Although the inotropic effect of dobutamine is generally attributed to stimulation of myocardial β_1-adrenoceptors [74], there now exists sufficient evidence to suggest that the α_1-adrenoceptor-mediated effects of dobutamine contribute, at least in part, to the inotropic activity of the compound [32, 53, 56]. Thus, dobutamine is also a potent α_1-adrenoceptor agonist [32, 58] that produces an increase in cardiac output and stroke volume that is antagonized by phentolamine in cats [42] and by prazosin in rats [54].

It has been proposed that one site of action of dobutamine is the myocardial α_1-adrenoceptor [32,58]. Consistent with this hypothesis is the observation that the inotropic selectivity (over chronotropy) of dobutamine *in vitro* [32] and *in vivo* [53] is antagonized, in part, by α-adrenoceptor blockers. It is significant to note that the (−)-enantiomer of dobutamine which possesses predominantly α_1-adrenoceptor agonist activity, is a more selective inotropic agent *in vitro* and *in vivo* than the (+)-enantiomer which possesses predominantly β_1- and β_2-adrenoceptor agonist activity [53,56]. In addition, it

has been shown *in vivo* that the ability of dobutamine to increase cardiac output, stroke volume and left ventricular dp/dt results predominantly from the (−)-enantiomer, and these effects are significantly antagonized by the α_1-adrenoceptor blocker, prazosin [53,54]. Thus, while the functional significance of the myocardial α_1-adrenoceptor is still highly speculative, the accumulated data tend to suggest that the positive inotropic effect of dobutamine may be mediated, at least in part, through stimulation of myocardial α_1-adrenoceptors.

Renal Alpha-Adrenoceptors

The existence of α-adrenoceptors in the kidney has been suspected for many years since α-adrenergic drugs produce a variety of renal effects. The functions and locations of the renal α-adrenoceptors are now only beginning to be understood (for review, see [71]). Radioligand binding studies indicate that α_1- and α_2-adrenoceptors coexist in the kidneys of a variety of mammalian species; however, the number, proportion, and distribution of each α-adrenoceptor subtype may vary from species to species [31, 45, 71].

The anatomical location of the renal α-adrenoceptors, and the functions they subserve, are not completely understood. It is believed that α_1- and α_2-adrenoceptors coexist in the renal vasculature and mediate a vasoconstrictor response and thereby modulate, in part, renal blood flow [28]. Autoradiography studies in rat kidney indicate a high concentration of α_2-adrenoceptors associated with the intima in the renal vasculature (R. J. Summers, personal communication). Although the function of these intimal α_2-adrenoceptors is not known, their possible involvement in the release of an endogenous relaxing factor from the endothelium must be considered. In addition, autoradiographic studies also show a high concentration of α_2-adrenoceptors residing at the adventitial-medial junction in the renal vasculature, and these receptors may represent presynaptic α_2-adrenoceptors associated with the sympathetic innervation to the vasculature (R. J. Summers, personal communication). In the rat, α_2-adrenoceptors of the juxtaglomerular apparatus have been proposed to inhibit renin release [48,71]. Both α_1- and α_2-adrenoceptors have been proposed to alter electrolyte and fluid balance, but their exact roles are not fully understood. α-Adrenoceptors, possibly of the α_2-subtype, may enhance sodium and water reabsorption in the proximal convoluted tubule [71], whereas α_1-adrenoceptors in the proximal convoluted tubule promote gluconeogenesis [33].

The non-uniform and differential distribution of α_1- and α_2-adrenoceptors in the kidney, and the various functions these α-adrenoceptor subtypes subserve, such as regulation of renal blood flow, renin secretion, sodium and water reabsorption and gluconeogenesis, indicate the complex nature of α-adrenergic effects in this organ. No doubt our knowledge about renal α-adrenergic mechanisms will grow in the next several years with the intent that these sites may become important targets for drug action in disease states.

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