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Review

The elusive α_{1D}-adrenoceptor: molecular and cellular characteristics and integrative roles

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Abstract

α_1-Adrenoceptors seem to play key roles in cardiovascular, genitourinary, and central nervous system functions. This review will be focused on α_{1D}-adrenoceptors. These receptors have intrinsic activity, and many of the more commonly used antagonists are in reality inverse agonists. α_{1D}-Adrenoceptors are phosphorylated in the basal state, and the natural agonists, adrenaline and noradrenaline, increase their phosphorylation; similar effects are induced by direct activation of protein kinase C and through activation of nonadrenergic receptors. Interestingly, a large proportion of α_{1D}-adrenoceptors are located in intracellular vesicles. Such intracellular location can be changed to surface expression through the use of inverse agonists and coexpression of α_{1B}-adrenoceptors, which seem to act as pharmacological chaperons for proper plasma membrane insertion. The α_{1D}-adrenoceptor amino terminus seems to contain a signal that keeps the receptor intracellularly, but interaction with other proteins may also contribute. The precise relationship between the intrinsic activity, phosphorylation, and intracellular location is currently unknown. α_{1D}-Adrenoceptor activation induces contraction in a variety of vessels, and a role in the control of blood pressure has been suggested. Studies using young prehypertensive and adult spontaneously hypertensive rats as well as knockout mice suggest that vascular α_{1D}-adrenoceptors are involved in the genesis/maintenance of hypertension.

Keywords: α_{1D}-Adrenoceptor; Receptor phosphorylation; Vascular tone; Hypertension

Contents

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1. Introduction

The natural adrenergic amines, adrenaline and noradrenaline, are among the more important regulators of physiological functions and biochemical processes in our organism, through their release by the adrenal medulla and related chromaffin structures and the sympathetic nervous system. Their actions are mediated through three subfamilies of receptors (the α_1-, α_2- and β-adrenoceptors), each of them comprising three members (i.e., the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, the α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors, and the β_1-, β_2- and β_3-adrenoceptors; Hieble et al., 1995). All these receptors are members of the G protein-coupled receptors whose general structure includes an extracellular N-terminal domain, a C-terminal intracellular tail, and seven transmembrane helixes connected by three extracellular and three intracellular loops (Hieble et al., 1995).

α_1-Adrenoceptors seem to play key roles in cardiovascular, genitourinary, and central nervous system functions. In the cardiovascular system, these receptors regulate processes, such as cardiac muscle and arteriolar smooth muscle contraction, and have been implicated in pathological processes, such as cardiac hypertrophy or ischemia-induced cardiac arrhythmias. In the genitourinary tract, these receptors participate in the contraction of diverse structures containing smooth muscle, and they are implicated in the pathogenesis of benign prostatic hypertrophy. α_1-Adrenoceptors are particularly abundant in the central nervous system, but their roles are just beginning to be unraveled. Several reviews covering different aspects of this subfamily of receptors have already appeared (García-Sáinz et al., 1999, 2001; Graham et al., 1996; Hague et al., 2003; Tanoue et al., 2002, 2003; Zhong and Minneman, 1999). This review will be focused only on one member of this family, the α_{1D}-adrenoceptor. This receptor has been particularly difficult to study, but recently very interesting data have been published, which have shed light on its physiological roles, its regulation at molecular and cellular levels, and might suggest new avenues for therapeutic intervention.

2. Molecular aspects

During the late eighties and early nineties of the previous century, the three distinct α_1-adrenoceptors were cloned (Hieble et al., 1995). Due to the lack of really selective agonists and antagonists for the different subtypes, the correlation between the cloned receptors and those pharmacologically defined in different tissues became very complex, generating great confusion in the field, which lead to the odd nomenclature we currently use (Hieble et al., 1995). Initially, it was thought that the cloned rat α_{1D}-adrenoceptor was the α_{1A} subtype (Lomasney et al., 1991), but cloning and expression of the same receptor by another group lead to the proposal that such receptor corresponded indeed to a novel subtype, i.e., the α_{1D} adrenoceptor (Perez et al., 1991). The human α_{1D}-adrenoceptor was cloned subsequently (Forray et al., 1994; Schwinn et al., 1995; Weinberg et al., 1994) and the gene located at chromosome 20.

The α_{1D}-adrenoceptors of rats and humans are very similar but not identical with an overall sequence identity of 83%. The rat homologue has a length of 561 amino acids with a protein molecular weight of 59,364 Da, whereas the human receptor has 572 amino acids with a protein molecular weight of 60,462 Da. Photoaffinity labeling of human and rat α_{1D}-adrenoceptors gave estimated M_r of ~70–80 KDa (García-Sáinz et al., 2001, 2004; Schwinn and Kwatra, 1998). Potential *N*-glycosylation sites have been detected at amino acids N^{60} and N^{76} at the rat α_{1D}-adrenoceptor. It is possible that glycosylation may explain the difference observed between the protein molecular weight and the estimated M_r but, certainly, other factors may participate. The potential transmembrane domains and the connecting intracellular and extracellular loops of these two α_{1D}-adrenoceptors are very similar with nearly identical lengths and sequences varying in 0–1 amino acids per segment. The main difference exists in the amino and carboxyl tails. The amino terminus of the human receptor has 95 amino acids, whereas the rat receptor has only 90; similarly, the carboxyl cytoplasmic tail of the human receptor has 167 amino acids, and the rat receptor only 161 amino acids.

The availability of the crystal structure of rhodopsin at different resolutions has been a great breakthrough in our understanding of the three-dimensional structure of G protein-coupled receptors. Through the use of molecular modeling, different groups (Carrieri et al., 2001; Cotecchia et al., 1998; Porter et al., 1996) have been able to construct three-dimensional models of α_1-adrenoceptors. A particularly interesting finding was that a key lysine residue in transmembrane α-helix 7 is involved in the activation of α_{1B}-adrenoceptors (Porter et al., 1996). This lysine residue forms a salt bridge with a conserved aspartic acid in transmembrane α-helix 3 in the basal nonactive state, and agonists seem to promote disruption of such salt bridge (Porter et al., 1996). Molecular dynamics and docking studies of α_{1D}-adrenoceptors are consistent with such salt bridge disruption in the process of receptor activation (Carrieri et al., 2001). Interestingly, such lysine is conserved only in the α_1-adrenoceptor subfamily, whereas it is substituted by neutral or polar residues in the α_2 subtypes and by hydrophobic residues in the β-adrenoceptor subfamily (Carrieri et al., 2001; Porter et al., 1996).

Expression of the messenger RNA of α_{1D}-adrenoceptors has been studied in rat and human tissues (Graham et al., 1996; Lomasney et al., 1991; Price et al., 1994; Rokosh et al., 1994). It has been observed that in human it is abundant in the aorta, cerebral cortex, and prostate, and it is also

present in the heart, lung, kidney, and spleen; in rats it is particularly abundant in vas deferens, aorta, cerebral cortex, and hippocampus. Detection of the receptor protein has been difficult due to low density in most tissues to the extent that their presence in rat tissues was once questioned (Yang et al., 1997).

We still lack selective pharmacological tools for the study of these receptors. BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7,9-dione dihydrochloride) is the most useful agent at present. This compound shows great selectivity for α_{1D}-adrenoceptors (p*K* ~8) as compared to the α_{1A} and α_{1D} subtypes (p*K* ~6) but it is also a 5-HT_{1A} receptor partial agonist (Goetz et al., 1995). Certainly, to characterize a receptor, the use of different antagonists (such as tamsulosin, niguldipine, prazosin, phentolamine, etc.) is required to obtain the characteristic order of potency. At this point, there is no really selective agonist for this receptor subtype. Oxymetazoline and cirazoline have low affinity for α_{1D}-adrenoceptors, which helps to differentiate them from the α_{1A} subtype (Horie et al., 1995). The relative order of potency of agonists is also of help to obtain the pharmacological profile. Development of selective agonists and antagonists for this receptor subtype is an area in which work is required and likely would be of therapeutic value (see below).

3. Cellular aspects

Essentially, in all systems studied, α_1-adrenoceptors are coupled to pertussis toxin-insensitive G proteins, which activate phosphoinositide turnover (see, for example, Perez et al., 1993; Vázquez-Prado and García-Sáinz, 1996). In the overall α_1-adrenergic response, different signaling pathways participate including adenylyl cyclase/cyclic AMP (Perez et al., 1993; Shinoura et al., 2002), arachidonic acid release via phospholipase A_2 activation (Kawanabe et al., 2001; Perez et al., 1993), modulation of ionic channels (Kawanabe et al., 2001), activation of mitogen-activated protein kinases (MAP kinases) such as extracellular regulated kinase (ERK 1/2) (Israilova et al., 2004; Keffel et al., 2000; McCune et al., 2000; Waldrop et al., 2002), stimulation of protooncogene messenger RNA expression (Alcántara-Hernández et al., 2000; Chen et al., 1999; García-Sáinz et al., 1998), and transcriptional responses (Minneman et al., 2000; Zhong et al., 2001). Great effort has been devoted to clarify how these pathways are linked, but in spite of the large amount of information, no clear picture has emerged. One of the main difficulties is that most pathways are very interconnected, and that the information they convey is in many aspects redundant. Another important problem is that depending on the receptor density and the "cellular context" (i.e., the availability and concentration of molecular elements that the cell express), there is variation in the response. In spite of these difficulties, it is becoming clear that the three α_1-adrenoceptor subtypes share a large proportion, but not all, of their effects (Hague et al., 2003; Hu et al., 1999; Keffel et al., 2000; McCune et al., 2000).

An observation in most of these studies is that the coupling efficiency of α_1-adrenoceptor subtypes varies, being the α_{1D} subtype the less effective (Chen et al., 1999; Theroux et al., 1996; Vázquez-Prado and García-Sáinz, 1996; Zhong et al., 2001). Nevertheless, there are cases in which this is not the case (Kawanabe et al., 2001; Keffel et al., 2000). Related to this is the fact that rat α_{1D}-adrenoceptors exhibit constitutive activity. We observed that when an "antagonist", such as BMY 7378, chloroethylclonidine, or prazosin, was added to cells loaded with the fluorescent indicator, Fura-2, to quantify intracellular Ca^{2+} concentration, a clear dose-dependent decrease in fluorescence was observed (García-Sáinz and Torres-Padilla, 1999). Interestingly, WB4101 was much less effective in inducing such effect and antagonized the action of the other agents (García-Sáinz and Torres-Padilla, 1999). These data clearly indicated that rat α_{1D}-adrenoceptors have intrinsic activity, and that some of the antagonists were actually inverse agonists (García-Sáinz and Torres-Padilla, 1999). Subsequent studies by another group showed that α_{1D}-adrenoceptors have a high degree of basal inositol phosphate production and extracellular signal regulated kinase (ERK) activity, which were reduced by prazosin (McCune et al., 2000). Later studies showed that the other subtypes also display intrinsic activity (Rossier et al., 1999); we have confirmed such findings, but in our experience, the intrinsic activity of the α_{1D} subtype is much more evident (unpublished data). Previously, D'Ocon and coworkers had suggested the existence of a population of constitutively active α_1-adrenoceptors in rat aorta and that some traditional antagonists acted as inverse agonists (Noguera et al., 1996). These receptors belong to the α_{1D}-adrenoceptor subfamily (Gisbert et al., 2000) and seem to play a modulatory role, preventing abrupt changes in pressure (Ziani et al., 2002); as expected, the action of these constitutively active receptors is linked to cytosol-free Ca^{2+} concentration and phosphoinositide turnover (Gisbert et al., 2003).

It is a frequent observation that G protein-coupled receptors are mainly localized at the plasma membrane with a minor fraction located in intracellular vesicles, representing newly formed receptors on their way to the plasma membrane, and receptors that have been internalized and that are either being processed towards degradation or recycling to the plasma membrane. It is also well known that receptor activation and other stimuli are associated to increased receptor endocytosis (Claing et al., 2002). In the case of α_1-adrenoceptors, there is a large amount of evidence that this is the case for the α_{1B} subtype, i.e., the vast majority of the receptors are located in the plasma membrane and are internalized in response to adrenaline or noradrenaline (Hague et al., 2004b; McCune et al., 2000). However, it has been consistently reported that the in the case of the α_{1A} subtype, a significant proportion of the

receptor protein is located intracellularly under basal conditions and that such proportion further increases after agonist stimulation (Chalothorn et al., 2002; Mackenzie et al., 2000). Interestingly, α_{1D}-adrenoceptors seem to be predominantly located in intracellular vesicles and only a small fraction at the plasma membrane (Chalothorn et al., 2002; Hague et al., 2004b; McCune et al., 2000). The possible reason(s) for such location is(are) intriguing; several nonexcluding possibilities exist.

The function of G protein-coupled receptors such as α_{1D}-adrenoceptors is tightly regulated, and phosphorylation seems to be one of the major molecular mechanisms through which this regulation is accomplished (Claing et al., 2002; García-Sáinz et al., 2000). The phosphorylation state of these receptors seems to modulate receptor sensitivity and therefore cellular responsiveness. Phosphorylation is considered the initial step in the process of desensitization. Current evidence indicates that in homologous desensitization, agonists-activated receptors interact with G proteins, which leads to guanine nucleotide exchange and to the release of Gβγ complexes. Such complexes recruit soluble G protein-coupled receptor kinases, which catalyze receptor phosphorylation. β-Arrestins bind phosphorylated receptors, stabilizing an uncoupled state of the receptors and act as bridges that bind clathrin molecules that initiate receptor internalization (Claing et al., 2002). Second messenger-activated protein kinases, such as protein kinases A and C, also promote receptor phosphorylation, eliciting heterologous desensitization (Claing et al., 2002; García-Sáinz et al., 2000). Recently, we have been able to provide evidence that human and rat α_{1D}-adrenoceptors are subjected to regulation by phosphorylation (García-Sáinz et al., 2001, 2004). These receptors are phosphorylated in the basal state and in the presence of agonists or phorbol esters, such phosphorylation is markedly increased (García-Sáinz et al., 2001, 2004). In addition, we observed that the rat receptor is also phosphorylated in response to cell stimulation by nonadrenoceptor agonists, such as endothelin, lysophosphatidic acid, and bradykinin (García-Sáinz et al., 2001), suggesting heterologous modulation through receptor phosphorylation as observed for the α_{1B} subtype (García-Sáinz et al., 2000).

Considering these aspects, it is possible that the intracellular location of α_{1D}-adrenoceptors could be the result of their intrinsic activity, which could trigger phosphorylation and internalization. This possibility has already been tested by McCune et al. (2000), whom observed that prazosin, which exhibits inverse agonists properties, promotes the redistribution of the receptors from the intracellular vesicles to the plasma membrane. These data are very convincing. Nevertheless, the possibility that other processes might participate is worth considering.

It is known that misfolded proteins are detected by the quality control machinery of the cells and are targeted for degradation. In some cases, putatively misfolded receptors accumulate in intracellular vesicles. Interestingly, through the use of compounds that permeate the plasma membrane, it is possible to rescue these receptors and allow them to reach the plasma membrane and even function (Morello et al., 2000; Petaja-Repo et al., 2002; Smith et al., 1998). These "pharmacological chaperones" represent a new class of pharmacological agents with enormous potential for therapeutics (Morello et al., 2000; Petaja-Repo et al., 2002; Smith et al., 1998). It was recently reported that antagonists were able to up-regulate the expression of α_{1B}-adrenoceptor mutants defective in G protein coupling (Prinster et al., 2003). Such effect was insensitive to cycloheximide or actinomycin D excluding the possibilities that de novo protein synthesis or transcriptional mechanisms might participate (Prinster et al., 2003). The authors suggested that ligand-induced protection to instability and proteolysis might participate. These data make us wonder if a similar process might also play a role in the inverse agonist-promoted redistribution of α_{1D}-adrenoceptors from intracellular vesicles to the plasma membrane discussed above (McCune et al., 2000).

Hague et al. (2004b) made very recently an interesting contribution to this matter. Formerly considered exclusively as monomeric entities, it is now clear that G protein-coupled receptors form homo- and heterodimers and that such association may have consequences in their pharmacological properties and their function/regulation (Salahpour et al., 2000). α_{1D}-Adrenoceptors form heterodimers with α_{1B}-adrenoceptors, and when they are coexpressed, the α_{1D}-adrenoceptors translocate to the cell surface (Hague et al., 2004b). Using mutants of the α_{1B}-adrenoceptor, these authors showed that receptors truncated in the amino and carboxyl termini were also able to induce this effect (Hague et al., 2004b). The data suggest that the hydrophobic core of α_{1B}-adrenoceptors acts as a chaperone for the proper insertion of α_{1D}-adrenoceptors into the plasma membrane. It should be mentioned that the same group has shown that the amino terminus of the human α_{1D}-adrenoceptor prevents cell surface expression; that is, the whole receptor is found primarily in intracellular compartments, whereas the amino terminus-truncated mutant is translocated to the plasma membrane (Hague et al., 2004a). Furthermore, chimeras of the other subtypes containing the α_{1D}-adrenoceptor amino terminus have markedly decreased membrane densities (Hague et al., 2004a). These data suggest that the amino terminus region of α_{1D}-adrenoceptors contains a transplantable signal for regulating the subcellular location of the receptor. It is very interesting that coexpression of α_{1B}-adrenoceptors can overcome the function of such signal (Hague et al., 2004a,b).

Current ideas indicate that receptors form dynamic complexes with enzymes, anchoring and adaptor proteins; such dynamic complexes are organized and coordinated through specific protein–protein and protein–phospholipid interactions, and it is through these signaling networks that cellular responses are regulated (Pawson and Scott, 1997).

The heterodimerization of α_{1D}- and α_{1B}-adrenoceptors is a clear example of this, but it is not the only one. It has been reported that the multifunctional protein gC1qR interacts with the polyarginine motif of α_{1B}-adrenoceptors, and that this protein modulates the expression and subcellular location (Xu et al., 1999). The polyarginine motif is also present in the α_{1D}-adrenoceptor carboxyl tail, and it was recently reported that gC1qR and these receptors coimmunoprecipitate, which suggests that they form protein–protein complexes (Pupo and Minneman, 2003). It is likely that other proteins may also interact with these receptors, and that such interactions might have functional repercussions.

Under physiological conditions, cells are not activated by a single hormone or neurotransmitter, they are constantly receiving chemical signals present in the extracellular milieu. The oxymoron "constant variation" describes what cells face within the physiological/pathological limits compatible with life. As mentioned, the α_{1D}-adrenoceptor phosphorylation state is modulated by the activation of unrelated receptors (García-Sáinz et al., 2001). It is well known that most cells and tissues coexpress α_1-adrenoceptor subtypes. What happens to such cells when they are stimulated by adrenaline or noradrenaline? How are signals integrated? We currently do not have information for α_{1D}-adrenoceptors, but it has been recently reported that coexpression of the α_{1A} and α_{1B} subtypes results in enhanced responsiveness (Israilova et al., 2004).

4. Vascular α_{1D}-adrenoceptors: current status

α_{1D}-Adrenoceptors mediate contraction induced by adrenergic agents in several isolated rat arteries and regulate peripheral vascular tone in vivo, a phenomenon that seems to be triggered by aging (Ibarra et al., 1997). Rat arteries express all three α_1-adrenoceptor subtypes at the mRNA level (Piascik et al., 1994; Scofield et al., 1995). However, by using radioligand binding, α_1-adrenoceptor-directed antibodies and functional studies, one or a mixture of two α_1-adrenoceptors seem to predominate for the contraction of vascular smooth muscle (Piascik et al., 1995, 1997; Villalobos-Molina et al., 1997). α_{1D}-Adrenoceptors are functionally expressed in arteries, such as the aorta, iliac, carotid, mesenteric, and femoral arteries (Arévalo-León et al., 2003; Gisbert et al., 2000; Gómez-Zamudio et al., 2002; Piascik et al., 1995) The renal artery likewise expresses functional α_{1D}-adrenoceptors, which are important for contraction, although α_{1A}-adrenoceptors also participate in this function. Taken together, these data suggested that in vivo rat vasculature express these receptors and that they play an important role in the maintenance of blood pressure.

Functional expression of vascular α_{1D}-adrenoceptors seems to be age-dependent, since phenylephrine-induced pressor response (i.e., increase in blood pressure) in 1-month-old pithed Wistar rats was not blocked by BMY 7378, but 5-methylurapidil (α_{1A}-adrenoceptor antagonist) displaced the agonist effect 26-fold to the right. In contrast, in 5- to 6-month-old rats, the pressor response was significantly blocked by the three antagonists indicating that aging does influence α_{1D}-adrenoceptors functional expression (Ibarra et al., 1997). Consistent with those data, α_1-adrenoceptor radioligand binding competition experiments showed a homogeneous receptor population in aortic membranes of 1-month-old rats, and two or three receptor populations in adult and old rats (Gurdal et al., 1995). In addition, the maximal pressor response to phenylephrine in adult rats was higher than in the young, suggesting that α_{1D}-adrenoceptors could be better coupled to the contractile intracellular machinery or present in higher density (Ibarra et al., 1997).

5. Functional vascular α_{1D}-adrenoceptors and hypertension

Hypertension is a pathological state characterized by an increase in peripheral vascular resistance (Marín, 1993); this increase in blood pressure is the most important risk factor for cardiovascular diseases, undoubtedly the first public health problem worldwide, mainly affecting the mature and elderly. Despite a vast amount of research, the events that lead to hypertension are poorly understood. Nevertheless, hypersensitivity of blood vessels to constrictor stimuli seems to be a major factor (Marín, 1993).

Hypersensitivity of vascular smooth muscle to noradrenaline has been suggested as an element involved in the increment and maintenance of blood pressure in spontaneously hypertensive rats and other models of hypertension (Takata and Kato, 1996). It has not been settled yet if during hypertension there are changes exclusively in a specific receptor subtype and/or alteration in the proportion of several receptors and/or postreceptor events.

It has been shown that that α_{1D}-adrenoceptors mediate contraction in the aorta, carotid, and mesenteric arteries of adult (6 months old) spontaneously hypertensive rats (Villalobos-Molina and Ibarra, 1996); a fact shared by arteries from normotensive Wistar Kyoto rats. α_1-Adrenoceptor stimulation evoked an important increase in the maximal pressor effect in adult rats, which could be explained by an increase in receptor number or a better coupling between α_{1D}-adrenoceptors and the intracellular contractile machinery of the vascular tissue (Villalobos-Molina and Ibarra, 1996).

Functional vascular α_{1D}-adrenoceptors seem to be present prior to the establishment of hypertension evidenced by α_{1D}-adrenoceptor actions in pithed 1-month-old spontaneously hypertensive rats (an age where there is no difference in blood pressure compared to age matched Wistar Kyoto rats). In young spontaneously hypertensive rats, phenylephrine-induced pressor effect was significantly

displaced to the right by BMY 7378, while it was not modified in the Wistar Kyoto rats (Villalobos-Molina et al., 1999). When adult Wistar Kyoto and spontaneously hypertensive rats were tested, BMY 7378 displaced the phenylephrine pressor effect in both rat strains; the displacement being greater in the adult spontaneously hypertensive rats (Villalobos-Molina et al., 1999). These results suggest that vascular α_{1D}-adrenoceptors are related to the pathogenesis/maintenance of hypertension.

As mentioned before, D'Ocon's group has demonstrated that a constitutively active α_{1D}-adrenoceptor population is responsible in maintaining contraction in rat aorta and other conductance vessels, but not in small, resistance arteries. The main role of these receptors seems to be retarding sudden changes in vessel diameter once the stimuli are removed (Gisbert et al., 2000; Ziani et al., 2002). Recently, this group suggested that constitutively active α_{1D}-adrenoceptors might play a pathogenic role, because the resting tone was similar in both Wistar Kyoto and spontaneously hypertensive rats arteries (aorta, iliac, and mesenteric) of young (6 weeks old) rats but was higher in adult hypertensive animals (Gisbert et al., 2002). The role of α_{1D}-adrenoceptors in the control of blood pressure was recently confirmed by disrupting (knockout) the gene for this receptor in mice; these animals have a significantly lower blood pressure (Tanoue et al., 2003).

6. Final remarks

Fourteen years have elapsed since the realization of the existence (cloning) of α_{1D}-adrenoceptors, great progress has been achieved but it is our conviction that further major advances in knowledge will take place in the coming years; knowledge that will help us to better understand their functional roles and might give us the power to perform therapeutic interventions. Knowledge on how α_{1D}-adrenoceptor expression, cellular location, and function are regulated is just beginning to emerge. The elucidation of their role(s) in vascular contraction and hypertension is similarly at an early stage. The development of selective agonists and antagonist is greatly needed for experimentation and eventual therapeutic use. Finally, it is worth mentioning that α_1-adrenoceptors are abundant in the central nervous system and that they are involved in important functions, such as learning or control of motor activities. What role(s) α_{1D}-adrenoceptors play is(are) currently unknown, but reasonable optimism allows us to think that it will no be so, for long.

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