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International Union of Pharmacology X. Recommendation for Nomenclature of α_1-Adrenoceptors: Consensus Update

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The IUPHAR Subcommittee on Nomenclature for Adrenoceptors has recently summarized evidence pertaining to the classification and nomenclature of α_1-adrenoceptor subtypes (Bylund et al., 1994). However, recent disclosures in the literature indicate that a consensus statement regarding adrenoceptor nomenclature is timely.

At least three native α_1-adrenoceptors have been identified pharmacologically. Furthermore, three distinct α_1-adrenoceptors have been cloned. Unfortunately, the relationship between the native and recombinant α_1-adrenoceptor subtypes, and the nomenclature used to identify them, has not been internally consistent and has led to substantial confusion in the field. We now present the scheme shown in Table 1 as a unifying concept.

Since the initial identification of the α_{1A}- and α_{1B}-adrenoceptor subtypes nearly one decade ago (Morrow and Creese, 1986; Han et al., 1987; Minneman, 1988), the pharmacological characteristics of the α_1-adrenoceptor subtypes in functional and radioligand binding assays have been well established. Subsequently, three recombinant α_1-adrenoceptor proteins were identified. [Note: in the discussion that follows, lower case subscripts are used to denote the recombinant α_1-adrenoceptor subtypes, and upper case subscripts refer to the native α_1-adrenoceptors found in tissues or cells. This convention is used only to establish the origin of the receptor and does not imply any pharmacological differences between the native and recombinant receptors].

A hamster α_{1b}-adrenoceptor protein was shown to have a pharmacological profile that corresponded to that of the native α_{1B}-adrenoceptor (Cotecchia et al., 1988). The next α_1-adrenoceptor to be cloned, which was obtained from the bovine brain, had affinities for agonists and antagonists that were consistent with those expected for the native α_{1A}-adrenoceptor; however, this recombinant receptor was partially inactivated by the alkylating agent, chloroethylclonidine, and lacked expression at an mRNA level in the rat tissues known to have α_{1A}-adrenoceptor pharmacology. This led to the clone being considered as a novel α_1-adrenoceptor subtype and was therefore designated as the α_{1c}-adrenoceptor (Schwinn et al., 1990, 1991). A third α_1-adrenoceptor was subsequently cloned from rat cortex and was designated as the α_{1a}-adrenoceptor, based on localization of mRNA for this clone in the expected rat tissues, as well as having a lower sensitivity to irreversible alkylation by chloroethylclonidine and a higher sensitivity to WB-4101 than the recombinant α_{1b}-adrenoceptor (Lomasney et al., 1991). However, an identical recombinant rat α_1-adrenoceptor subtype was independently identified by Perez et al. (1991) and was shown to have affinities for several selective antagonists that differed markedly from the native α_{1A}-adrenoceptor. Because the receptor cloned by Schwinn et al. (1990) had previously been designated as the α_{1c}-adrenoceptor and because the cloned α_{1b}-adrenoceptor corresponded to the native α_{1B}-adrenoceptor, Perez et al. (1991) denoted the newly cloned rat α_1-adrenoceptor as the α_{1d}-adrenoceptor. This latter recombinant receptor is currently designated as either the α_{1a}-, α_{1d}-, or $\alpha_{1a/d}$-adrenoceptor by various authors. As a direct result of these early attempts to subclassify the α_1-adrenoceptor subtypes, with the available antagonists, significant confusion existed in the field regarding the nomenclature of the α_1-adrenoceptors.

Recently, reports from several laboratories have shown clearly that the affinities of an extensive series of competitive antagonists for inhibition of radioligand binding of [^{3}H]prazosin to the expressed α_{1c}-adrenoceptor correlates highly with their affinities for binding sites in native tissues that are known to possess α_{1A}-adrenoceptors (Testa et al., 1995; Ford et al., 1994; Saussy et al., 1994; Faure et al., 1994; Langer et al., 1994). These results strongly suggest that the recombinant α_{1c}-adrenoceptor in fact represents the native α_{1A}-adrenoceptor (Ford et al., 1994). However, one significant discrepancy that needed to be explained between the α_{1c}-adrenoceptor clone identified by Schwinn et al. (1990) and the native α_{1A}-adrenoceptor was the differ-

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Abbreviations: IUPHAR, International Union of Pharmacology; mRNA, messenger ribonucleic acid; SNAP 5089, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid N-[3-(4,4-diphenylpiperidin-1-yl)propyl]amide methyl ester; BMY 7378, 8-[2-(4-(2-methoxyphenyl) piperazin-1-yl)ethyl]-8-azaspiro[4,5]decane-7,9-dione; SK&F 105854, 7-chloro-2-bromo-3,4,5,6-tetrahydro-4-methylfuro[4,3,2-ef]-[3]benzazepine.

TABLE 1
Nomenclature for the α_1-adrenoceptor subtypes

α_1-Adrenoceptor subtype			Human chromosome location	Functional response†	Binding assay‡	Chloroethylclonidine sensitivity	Selective antagonist
Native	Cloned (new nomenclature)	Cloned* (historical nomenclature)					
α_{1A}	α_{1a}	α_{1c}	C8	Rat kidney	Rabbit liver Rat submaxillary gland	±§	SNAP-5089 (+) Niguldipine 5-Methylurapidil Indoramin
α_{1B}	α_{1b}	α_{1b}	C5	Rat spleen‖	Rat liver Rat spleen	++++	
α_{1D}	α_{1d}	α_{1a}, α_{1d} $\alpha_{1a/d}$	C20	Rat aorta¶		+++	BMY 7378 SK&F 105854

* To be discontinued.
† α_1-Adrenoceptor agonist-induced contraction.
‡ As identified using radioligand bindings assays in native tissues.
§ Sensitivity to chloroethylclonidine may be species-dependent.
‖ Prazosin-sensitive component.
¶ May not be a homogeneous population (van der Graaf *et al.* 1993, 1994).

ence observed in the sensitivity of the recombinant receptor to alkylation by chloroethylclonidine. It now seems that this difference in sensitivity to chloroethylclonidine results from differences in experimental conditions, the character of the membrane in which the receptor is expressed, and/or to species differences in chloroethylclonidine sensitivity of the recombinant α_{1c}-adrenoceptor. Studies comparing chloroethylclonidine sensitivity of the three recombinant rat (Laz et al., 1994) or human (Forray et al., 1994a; Schwinn et al., 1995) α_1-adrenoceptor subtypes expressed in identical cell lines show a significantly lower degree of inactivation (20 to 25%) of the α_{1c}-adrenoceptor compared with either the α_{1b}- or $\alpha_{1a/d}$-adrenoceptors (75 to 90%). The greater sensitivity of the bovine homolog to chloroethylclonidine, as initially reported (Schwinn et al., 1990), might have resulted from differences in experimental conditions or possibly to species differences between the rat and bovine α_{1c}-adrenoceptor (Forray et al., 1994b). As observed with these recombinant α_{1c}-adrenoceptors, species variation seems to account for the differences in chloroethylclonidine sensitivity observed between α_1-adrenoceptors in rabbit liver (originally designated as α_{1C}) and guinea pig liver (designated as α_{1A}) (Garcia-Sainz et al., 1992). Comparison of the binding affinities of a series of competitive α_1-adrenoceptor antagonists in rabbit liver with those in chloroethylclonidine-pretreated rat hippocampus, an α_{1A}-adrenoceptor preparation, showed an excellent correlation (Testa et al., 1993, 1995). Some other reported differences between the recombinant α_{1c}-adrenoceptor and the native α_{1A}-adrenoceptor, such as the affinity of (+)-niguldipine, also seem to be attributable to slightly different characteristics of the α_{1c}-adrenoceptor that depend primarily upon the species from which the receptor is cloned (Forray et al., 1994b). Recent data show both rat and human α_{1c}-adrenoceptors to have a high affinity for (+)-niguldipine (0.1 to 3 nM; Weinberg et al., 1994; Forray et al., 1994a; Laz et al., 1994).

In addition to sensitivity to chloroethylclonidine and affinity for subtype-selective antagonists, the tissue distribution of the α_1-adrenoceptor clones was important in the initial nomenclature assigned to the cloned α_1-adrenoceptors. In the original description of the bovine recombinant α_{1c}-adrenoceptor, the lack of expression of this mRNA by Northern analysis in any rat tissue studied and its presence in rabbit liver were among the key factors involved in not equating this clone with the native α_{1A}-adrenoceptor (Schwinn et al., 1991; see Minneman, 1988 for review of rat tissue expression of α_1-adrenoceptor subtypes). Recently, both Northern blot analysis using rat α_1-adrenoceptor probes (Faure et al., 1994), and RNase protection assays using rat probes (Price et al., 1994) have demonstrated the presence of the α_{1c}-adrenoceptor in every rat tissue originally described as containing the α_{1A}-adrenoceptor.

Because the majority of experimental evidence now strongly suggests the identity of the α_{1c}- and α_{1A}-adrenoceptors, we propose that the designation, α_{1c}-adrenoceptor, be discontinued, and that the native and recombinant receptors be referred to as α_{1A}- and α_{1a}-adrenoceptors, respectively, with the upper and lower case subscripts being retained to differentiate between the native and the recombinant receptor. We also propose that, as suggested by Ford et al., (1994), the designation of α_{1D}-adrenoceptor be adopted for those native receptors, and α_{1d}-adrenoceptor for the cloned receptors, that have the pharmacological profile of the recombinant adrenoceptor previously designated as $\alpha_{1a/d}$-adrenoceptor. Hence, the designation of α_{1c} (or α_{1C}) is no longer recommended to describe the characteristics of any recombinant of native α_1-adrenoceptor, and in addition, the term $\alpha_{1a/d}$-adrenoceptor should no longer be used. This revised nomenclature now allows internally

consistent terms to be used in referring to native α_1-adrenoceptors (or α_1-adrenoceptor-mediated responses) and the three recombinant α_1-adrenoceptor subtypes thus far identified (table 1); this new nomenclature will be used in the remainder of this manuscript.

Functional responses have been attributed to each of the α_1-adrenoceptor subtypes (i.e., α_{1A}, α_{1B}, and α_{1D}). This assignment has been facilitated by the identification of subtype-selective α_1-adrenoceptor antagonists. As noted above, the calcium channel antagonist, (+)-niguldipine, shows selectivity for the recombinant α_1-adrenoceptor (Forray et al., 1994a; Weinberg et al., 1994). Structural modification of (+)-niguldipine has led to an analog, SNAP 5089, having no activity as a calcium channel antagonist, but enhanced (100-fold) selectivity for the α_{1a}-adrenoceptor versus the other two α_1-adrenoceptor subtypes (Gluchowski et al., 1994). 5-Methylurapidil has 30- to 100-fold higher affinity for α_{1a}- than for α_{1b}- and α_{1d}-adrenoceptors when the commonly available animal receptors (α_{1a}, bovine; α_{1b}, hamster or rat; α_{1d}, rat) are used (Ford et al., 1994; Testa et al., 1995; Michel and Insel, 1994). However, several studies that compared the affinity of this antagonist for the rat (Laz et al., 1994) with human (Forray et al., 1994a; Testa et al., 1995; Schwinn et al., 1995) α_1-adrenoceptor subtypes have shown the α_{1d}-adrenoceptor to have affinity for 5-methylurapidil that is intermediate between the α_{1a}- and α_{1b}-adrenoceptors. Indoramin and its analog, SNAP-1069, demonstrate approximately 10-fold selectivity for the α_{1a}-adrenoceptor compared with the other two recombinant α_1-adrenoceptor subtypes (Forray et al., 1994a). Recently, antagonists having 50- to 100-fold selectivity for the α_{1d}-adrenoceptor have been reported. These include BMY 7378 (Saussy et al., 1994) and SK&F 105854 (Hieble et al., 1995). No competitive α_{1B}-adrenoceptor antagonist of comparable selectivity has been reported to date, although sensitivity to irreversible inactivation by chloroethylclonidine can still be used to differentiate α_{1B}- and α_{1D}-adrenoceptors from the α_{1A}-adrenoceptor in many species, as long as the experimental conditions are specified. Oxymetazoline, a partial agonist at α_1-adrenoceptors, has selective affinity for the α_{1a}-adrenoceptor (Foglar et al., 1995; Schwinn et al., 1995; Minneman et al., 1994) and several imidazolines, including oxymetazoline, have substantially higher intrinsic activities at the α_{1a}-adrenoceptor compared with the other two subtypes (Minneman et al., 1995).

Norepinephrine-induced vasoconstriction in the isolated perfused rat kidney seems to be mediated entirely by the α_{1A}-adrenoceptor (Ford et al., 1994; Clarke et al., 1995); hence this system seems to be a useful functional model for the α_{1A}-adrenoceptor. The binding affinities of α_1-adrenoceptor antagonists in rat submaxillary gland and human prostate correlate closely with their affinities for the native α_{1A}-adrenoceptor, and this correlation also holds for the recombinant α_{1a}-adrenoceptor (Ford et al., 1994; Clarke et al., 1994; Testa et al., 1993, 1995). Messenger RNA for the α_{1A} adrenoceptor has been found in human prostate at higher levels than for the other α_1-adrenoceptor subtypes (Price et al., 1993). However, a population of prazosin-resistant α_1-adrenoceptors (see last paragraph) may also be present in human prostate (Takeda et al., 1993; Muramatsu et al., 1994, 1995), and may contribute to the functional response of the prostate to α_1-adrenoceptor activation.

The vasoconstrictor response to α_1-adrenoceptor stimulation in some blood vessels is mediated by α_{1B}-adrenoceptors (Han et al., 1990; Muramatsu et al., 1995), as is the prazosin-sensitive component of norepinephrine-induced contraction in rat spleen (Sulpizio and Hieble, 1993). Radioligand binding studies in rat spleen and rat liver have detected a relatively pure population of α_{1B}-adrenoceptors (Minneman, 1988). Correlation of the ability of a series of antagonists (including the selective α_{1D}-adrenoceptor antagonist, BMY 7378) to block norepinephrine-induced contraction of rat aorta with their affinities for the recombinant α_1-adrenoceptor subtypes has been used to assign the functional response in the rat aorta to the α_{1D}-adrenoceptor (Saussy et al., 1994). These recent findings may explain the inability of previous studies to assign clearly the functional α_1-adrenoceptor responses of this blood vessel to either the α_{1A}- or α_{1B}-adrenoceptors (Oriowo and Ruffolo, 1992), although other functional data still suggest a mixed receptor population in this tissue (Van der Graaf et al., 1994).

Some tissues, including certain blood vessels (Muramatsu et al., 1990, 1995) and rat spleen (Sulpizio and Hieble, 1993), seem to possess α_1-adrenoceptors that have relatively low affinity for prazosin. It has been postulated therefore that α_1-adrenoceptors also may be functionally differentiated into three groups (i.e., α_{1H}, α_{1L}, α_{1N}) based on the sensitivity to prazosin as well as to another antagonist, HV-723 (Muramatsu et al., 1990). It also has been proposed that those receptors that are now designated as α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, all of which have high affinity for both prazosin and HV-723, are members of the α_{1H}-adrenoceptor family of subtypes (Oshita et al., 1992). We propose, therefore, that when sufficient and consistent characterization of the prazosin-insensitive α_1-adrenoceptors, or other novel α_1-adrenoceptors, is made using functional, radioligand binding and molecular biology techniques, they may be added to the current α_1-adrenoceptor subclassification scheme as α_{1E}-adrenoceptors, α_{1F}-adrenoceptors, etc. However, at present, and based on the limited existing data regarding other α_1-adrenoceptor subtypes, we do not propose additional nomenclature beyond the α_{1A} (α_{1a})-adrenoceptor, α_{1B} (α_{1b})-adrenoceptor and α_{1D} (α_{1d})-adrenoceptor for the α_1-adrenoceptor subtypes, as indicated in this nomenclature update.

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