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X. Recommendation for Nomenclature of
\( \alpha_1 \)-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 \( \alpha_1 \)-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 \( \alpha_1 \)-adrenoceptors have been identified pharmacologically. Furthermore, three distinct \( \alpha_1 \)-adrenoceptors have been cloned. Unfortunately, the relationship between the native and recombinant \( \alpha_1 \)-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 \( \alpha_{1A} \)- and \( \alpha_{1B} \)-adrenoceptor subtypes nearly one decade ago (Morrow and Creese, 1986; Han et al., 1987; Minneman, 1988), the pharmacological characteristics of the \( \alpha_1 \)-adrenoceptor subtypes in functional and radioligand binding assays have been well established. Subsequently, three recombinant \( \alpha_1 \)-adrenoceptor proteins were identified. [Note: in the discussion that follows, lower case subscripts are used to denote the recombinant \( \alpha_1 \)-adrenoceptor subtypes, and upper case subscripts refer to the native \( \alpha_1 \)-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 \( \alpha_{1B} \)-adrenoceptor protein was shown to have a pharmacological profile that corresponded to that of the native \( \alpha_{1B} \)-adrenoceptor (Cotecchia et al., 1988). The next \( \alpha_1 \)-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 \( \alpha_{1A} \)-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 \( \alpha_{1A} \)-adrenoceptor pharmacology. This led to the clone being considered as a novel \( \alpha_1 \)-adrenoceptor subtype and was therefore designated as the \( \alpha_{1A} \)-adrenoceptor (Schwinn et al., 1990, 1991). A third \( \alpha_1 \)-adrenoceptor was subsequently cloned from rat cortex and was designated as the \( \alpha_{1A} \)-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 \( \alpha_{1B} \)-adrenoceptor (Lomasney et al., 1991). However, an identical recombinant rat \( \alpha_1 \)-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 \( \alpha_{1A} \)-adrenoceptor. Because the receptor cloned by Schwinn et al. (1990) had previously been designated as the \( \alpha_{1C} \)-adrenoceptor and because the cloned \( \alpha_{1B} \)-adrenoceptor corresponded to the native \( \alpha_{1B} \)-adrenoceptor, Perez et al. (1991) denoted the newly cloned rat \( \alpha_1 \)-adrenoceptor as the \( \alpha_{1C} \)-adrenoceptor. This latter recombinant receptor is currently designated as either the \( \alpha_{1C} \), \( \alpha_{1A} \), or \( \alpha_{1D} \)-adrenoceptor by various authors. As a direct result of these early attempts to subclassify the \( \alpha_1 \)-adrenoceptor subtypes, with the available antagonists, significant confusion existed in the field regarding the nomenclature of the \( \alpha_1 \)-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 \( \alpha_{1C} \)-adrenoceptor correlate highly with their affinities for binding sites in native tissues that are known to possess \( \alpha_{1A} \)-adrenoceptors (Testa et al., 1995; Ford et al., 1994; Saussey et al., 1994; Faure et al., 1994; Langer et al., 1994). These results strongly suggest that the recombinant \( \alpha_{1C} \)-adrenoceptor in fact represents the native \( \alpha_{1A} \)-adrenoceptor (Ford et al., 1994). However, one significant discrepancy that needed to be explained between the \( \alpha_{1A} \)-adrenoceptor clone identified by Schwinn et al. (1990) and the native \( \alpha_{1A} \)-adrenoceptor was the differ-
ence observed in the sensitivity of the recombinant receptor to alklylation 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 α1c-adrenoceptor. Studies comparing chloroethylclonidine sensitivity of the three recombinant rat (Laz et al., 1994) or human (Forray et al., 1994a; Schwinn et al., 1995) α1-adrenoceptor subtypes expressed in identical cell lines show a significantly lower degree of inactivation (20 to 25%) of the α1c-adrenoceptor compared with either the α1b- or α1d-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 in chloroethylclonidine sensitivity of the recombinant receptor. In the original description of the bovine recombinant α1c-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 α1C-adrenoceptor (Schwinn et al., 1991; see Minneman, 1988 for review of rat tissue expression of α1-adrenoceptor subtypes). Recently, both Northern blot analysis using rat α1-adrenoceptor probes (Faure et al., 1994), and RNase protection assays using rat probes (Price et al., 1994) have demonstrated the presence of the α1c-adrenoceptor in every rat tissue originally described as containing the α1A-adrenoceptor.

Because the majority of experimental evidence now strongly suggests the identity of the α1c- and α1A-adrenoceptors, we propose that the designation, α1c-adrenoceptor, be discontinued, and that the native and recombinant receptors be referred to as α1A- and α1a-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 α1D-adrenoceptor be adopted for those native receptors, and α1d-adrenoceptor for the cloned receptors, that have the pharmacological profile of the recombinant adrenoceptor previously designated as α1d-adrenoceptor. Hence, the designation of α1D (or α1C) is no longer recommended to describe the characteristics of any recombinant of native α1-adrenoceptor, and in addition, the term α1b-adrenoceptor should no longer be used. This revised nomenclature now allows internally

<table>
<thead>
<tr>
<th>α1-Adrenoceptor subtype</th>
<th>Human chromosome location</th>
<th>Binding assay</th>
<th>Chloroethylclonidine sensitivity</th>
<th>Selective antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native</td>
<td>Cloned (new nomenclature)</td>
<td>Cloned* (historical nomenclature)</td>
<td>Functional response†</td>
<td>Rat kidney</td>
</tr>
<tr>
<td>α1A</td>
<td>α1a</td>
<td>α1c</td>
<td>C8</td>
<td>Rabbit liver</td>
</tr>
<tr>
<td>α1B</td>
<td>α1b</td>
<td>α1b</td>
<td>C5</td>
<td>Rat spleen</td>
</tr>
<tr>
<td>α1D</td>
<td>α1d</td>
<td>α1a, α1d</td>
<td>C20</td>
<td>Rat aorta</td>
</tr>
</tbody>
</table>

* To be discontinued.
† α, Adrenoceptor agonist-induced contraction.
‡ As identified using radioligand binding 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).
consistent terms to be used in referring to native \( \alpha_1 \)-adrenoceptors (or \( \alpha_1 \)-adrenoceptor-mediated responses) and the three recombinant \( \alpha_1 \)-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 \( \alpha_1 \)-adrenoceptor subtypes (i.e., \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \)). This assignment has been facilitated by the identification of subtype-selective \( \alpha_1 \)-adrenoceptor antagonists. As noted above, the calcium channel antagonist, \((+)-\)niguldipine, shows selectivity for the recombinant \( \alpha_{1A} \)-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 \( \alpha_{1A} \)-adrenoceptor versus the other two \( \alpha_1 \)-adrenoceptor subtypes (Gluchowski et al., 1994). 5-Methylurapidil has 30- to 100-fold higher affinity for \( \alpha_{1A} \)- than for \( \alpha_{1B} \)- and \( \alpha_{1D} \)-adrenoceptors when the commonly available animal receptors (\( \alpha_{1A} \)- bovine; \( \alpha_{1B} \)- hamster or rat; \( \alpha_{1A} \)- 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 \( \alpha_{1A} \)-adrenoceptor versus the other two \( \alpha_1 \)-adrenoceptor subtypes have shown the \( \alpha_{1D} \)-adrenoceptor to have affinity for 5-methylurapidil that is intermediate between the \( \alpha_{1A} \)- and \( \alpha_{1B} \)-adrenoceptors. Indoramin and its analog, SNAP-1069, demonstrate approximately 10-fold selectivity for the \( \alpha_{1A} \)-adrenoceptor compared with the other two recombinant \( \alpha_1 \)-adrenoceptor subtypes (Forray et al., 1994a). Recently, antagonists having 50- to 100-fold selectivity for the \( \alpha_{1A} \)-adrenoceptor have been reported. These include BMY 7378 (Sassay et al., 1994) and SK&F 106854 (Hieble et al., 1995). No competitive \( \alpha_{1B} \)-adrenoceptor antagonist of comparable selectivity has been reported to date, although sensitivity to irreversible inactivation by chloroethylcinnamidine can still be used to differentiate \( \alpha_{1B} \)- and \( \alpha_{1D} \)-adrenoceptors from the \( \alpha_{1A} \)-adrenoceptor in many species, as long as the experimental conditions are specified. Oxymetazoline, a partial agonist at \( \alpha_1 \)-adrenoceptors, has selective affinity for the \( \alpha_{1A} \)-adrenoceptor (Poglars et al., 1995; Schwinn et al., 1995; Minneman et al., 1994) and several imidazolines, including oxymetazoline, have substantially higher intrinsic activities at the \( \alpha_{1A} \)-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 \( \alpha_{1A} \)-adrenoceptor (Ford et al., 1994; Clarke et al., 1994; testa et al., 1993, 1995); however, this system seems to be a useful functional model for the \( \alpha_{1A} \)-adrenoceptor. The binding affinities of \( \alpha_1 \)-adrenoceptor antagonists in rat submaxillary gland and human prostate correlate closely with their affinities for the native \( \alpha_{1A} \)-adrenoceptor, and this correlation also holds for the recombinant \( \alpha_{1A} \)-adrenoceptor (Ford et al., 1994; Clarke et al., 1994; Testa et al., 1993, 1995). Messenger RNA for the \( \alpha_{1A} \)-adrenoceptor has been found in human prostate at higher levels than for the other \( \alpha_1 \)-adrenoceptor subtypes (Price et al., 1993). However, a population of prazosin-resistant \( \alpha_1 \)-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 \( \alpha_1 \)-adrenoceptor activation.

The vasoconstrictor response to \( \alpha_1 \)-adrenoceptor stimulation in some blood vessels is mediated by \( \alpha_{1B} \)-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 \( \alpha_{1B} \)-adrenoceptors (Minneman, 1988). Correlation of the ability of a series of antagonists (including the selective \( \alpha_{1D} \)-adrenoceptor antagonist, BMY 7378) to block norepinephrine-induced contraction of rat aorta with their affinities for the recombinant \( \alpha_{1A} \)-adrenoceptor subtypes has been used to assign the functional response in the rat aorta to the \( \alpha_{1D} \)-adrenoceptor (Saussy et al., 1994). These recent findings may explain the inability of previous studies to assign clearly the functional \( \alpha_1 \)-adrenoceptor responses of this blood vessel to either the \( \alpha_{1A} \)- or \( \alpha_{1B} \)-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 \( \alpha_1 \)-adrenoceptors that have relatively low affinity for prazosin. It has been postulated therefore that \( \alpha_1 \)-adrenoceptors also may be functionally differentiated into three groups (i.e., \( \alpha_{1A} \), \( \alpha_{1D} \), \( \alpha_{1N} \)) 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 \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \)-adrenoceptors, all of which have high affinity for both prazosin and HV-723, are members of the \( \alpha_{1H} \)-adrenoceptor family of subtypes (Oshita et al., 1992). We propose, therefore, that when sufficient and consistent characterization of the prazosin-insensitive \( \alpha_1 \)-adrenoceptors, or other novel \( \alpha_1 \)-adrenoceptors, is made using functional, radioligand binding and molecular biology techniques, they may be added to the current \( \alpha_1 \)-adrenoceptor subclassification scheme as \( \alpha_{1B} \)-adrenoceptors, \( \alpha_{1F} \)-adrenoceptors, etc. However, at present, and based on the limited existing data regarding other \( \alpha_1 \)-adrenoceptor subtypes, we do not propose additional nomenclature beyond the \( \alpha_{1A} \) (\( \alpha_{1A} \)-adrenoceptor, \( \alpha_{1B} \)-adrenoceptor) and \( \alpha_{1D} \)-adrenoceptor for the \( \alpha_1 \)-adrenoceptor subtypes, as indicated in this nomenclature update.

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