zepam liberation but also by its specific antagonizing effect to oxazepam.

The parallel time profile of the antimetrazol effect and the brain levels of oxazepam lead to the same conclusion as the constant oxazepam levels following administration of antimetrazol ED_{50} values: the esters of oxazepam do not appear to contribute to the anticonvulsant effect. Compound 12 seems to antagonize the antimetrazol effect of oxazepam.

Comparison of the muscle-relaxant ED_{50} values at 5 min (Table II) shows that compound 7 is still equipotent to oxazepam, while the bulky compound 12 is much less potent. However, since the muscle-relaxant ED_{50} values are not accompanied with constant oxazepam brain levels (Table IV, part b), total brain levels do not properly represent the site of the muscle-relaxant effect of the benzodiazepines and conclusions cannot be drawn for this intrinsic activity. Instead, the results for the dissociation of muscle-relaxant and anticonvulsant effects support the notion that the sites of action are different.[21]

Experimental Section

Materials. Oxazepam-2-^{14}C was synthetized as previously described.[22] Its labeled and nonlabeled esters were prepared by known methods.[15] Specific radioactivity of the compounds ranged between 1.9 and 3.2 mCi/mmol. Metrazol (pentylenetetrazol) was purchased from Fluka.

Drug Administration. Oxazepam and its esters were administered intravenously to male mice of the CFLP strain (outbred albino, 19–21 g of body weight) 5–240 min prior to investigation. Respective doses were diluted with distilled water from a solution, the composition of which was as follows: 5 mg of test compund, 2 mL of propylene glycol, 1 mL of Chremofor EL (propylene glycol sicin oleate), and 7 mL of distilled water.

Antimetrazol Activity.[23] Test compounds were injected iv 5–240 min prior to sc administration of 125 mg/kg of metrazol in distilled water. Animals were classified as protected if tonic-extensor convulsions did not occur within 60 min of observation.

Muscle Relaxant Effect.[24] Animals were selected and trained to maintain on a rotating rod (diameter, 20 mm; revolution frequency, 12 min^{-1}) for 120 s. The number of animals falling down was expressed as a percentage of the dose group totals. Respective ED_{50} values and their confidence limits were determined according to Litchfield and Wilcoxon.[25]

Brain levels of oxazepam and its esters were determined as previously described.[15]

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Characterization of α-Adrenoceptor Populations. Quantitative Relationships between Cardiovascular Effects Initiated at Central and Peripheral α-Adrenoceptors

Pieter B. M. W. M. Timmermans,* Adriaan de Jonge, Jacques C. A. van Meel, Frieda P. Slothorst-Grisdijk, Egbert Lam, and Pieter A. van Zwieten

Department of Pharmacy, Division of Pharmacotherapy, University of Amsterdam, Plantage Muidergracht 24, 1018 TV Amsterdam, The Netherlands. *Received September 3, 1980*

The agonist selectivities of central (medullary) and peripheral (vascular) α-adrenoceptors were compared in order to investigate a possible similarity among these two α-adrenoceptor populations. Linear regression equations were derived between the α-adrenergic potencies, mediated by these two types of α-adrenoceptors for 21 structurally dissimilar α-adrenoceptor agonists. Hypotensive potency after intravenous administration to anesthetized, normotensive rats was determined as a measure of central α-adrenergic activity and expressed as pC_{25}, obtained from log dose–response curves. Peripheral α-adrenergic potency was quantified by means of the hypertensive effect elicited in pithed, normotensive rats after intravenous injections, yielding pC_{60} as the biological variable. A most significant linear relationship was generated between central hypotensive activity (pC_{25}) and peripheral hypertensive potency (pC_{60}), provided that log P' (octanol/buffer; pH 7.4, 37 °C) was included into the regression in a parabolic form. This result indicates that the central (medullary) α-adrenoceptors and the peripheral (vascular) α-adrenoceptor sites, which are excited by the drugs in question, make identical demands upon their agonists. The difference in accessibility to these peripheral and central α-adrenoceptor populations is adequately accounted for by a parabolic description in log P'. The apparent contradiction of this finding with the suggestion that central, hypotensive α-adrenoceptors are of the α_2 type and peripheral, vascular α-adrenoceptors belong to the α_1 subpopulation is discussed. The recent identification of an additional subclass of postsynaptic, vascular α_2-adrenoceptors and the lack of pronounced differential stimulating activity of the agonists at peripheral α-adrenoceptors may explain the present findings and clarify the paradox.

In our studies on quantitative structure–activity relationships in α-adrenergic drugs, we have attempted to characterize α-adrenoceptor populations in more detail. A possible similarity between peripheral (vascular) and central (medullary) α-adrenoceptors has been investigated. These two particular types of α-adrenergic receptors play a major role in the acute circulatory effects of α-adrenergic drugs. Their participation in blood-pressure control is illustrated by the action of the antihypertensive drug clonidine (catapres) injected intravenously. Being an α-adrenoceptor stimulant, clonidine initially triggers peripheral, vascular α-adrenoceptors, which results in a transient hypertensive effect. Subsequently, a long-lasting hypotensive phase is observed, which is caused by cloni-

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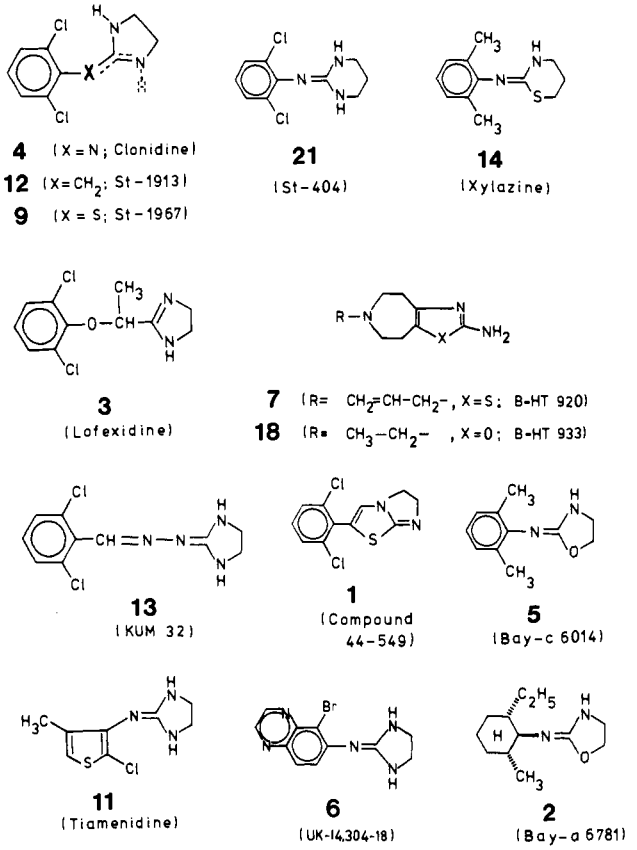
Chart I. Structural Formulas of 14 Dissimilar α-Adrenoceptor Agonists Used in This Study[a]



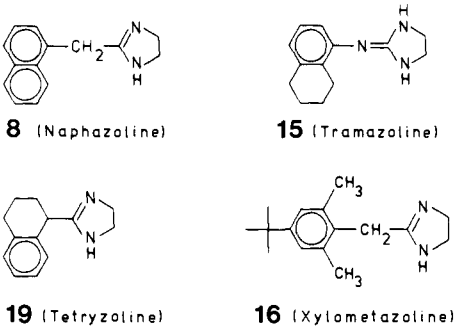
[a] The numbering refers to Table I.

dine's stimulation of central α-adrenoceptors located at medullary sites (for reviews see ref 1–3).

We could establish that within a series of clonidine and 12 of its structurally closely related imidazolidines (2-, 2,4-, and 2,4,6-substituted derivatives) the centrally induced depressor activity correlated linearly with the peripherally provoked pressor activity, provided that the ability of the compounds to penetrate into the brain is included into the correlation by means of the octanol/buffer (pH 7.4) partition coefficient.[4] In contrast to previous conclusions,[5-8] this result is in favor of a comparable drug specificity of peripheral (vascular) and central (medullary) α-adrenoceptors. The difference in accessibility of the agonists to these two types of α-adrenoceptors is accounted for by the apparent partition coefficient. In a preliminary report we have extended the validity of this conclusion to a set of 12 structurally dissimilar α-adrenoceptor agonists.[9]

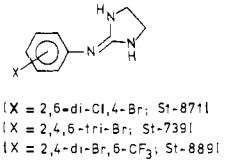
In order to verify a general applicability of such a correlation, the present paper reports on a quantitative comparison between central and peripheral cardiovascular activities of 21 α-adrenoceptor stimulants which differ in chemical structure and vary greatly in overall lipophilic properties. The structural formulas of 14 compounds are given in Chart I. Compounds with different bridges between both cyclic parts, dissimilar hetero rings and aromatic as well as nonaromatic moieties, were used. Included were also the classical α-adrenoceptor stimulants naphazoline, tramazoline, tetryzoline, and xylometazoline (Chart II). Three clonidine-like imidazolidines (Chart III) were added to the series because of their pronounced lipophilicity.

Chart II. Structural Formulas of Four More Classical α-Sympathomimetic Agents Employed in the Present Study[a]



[a] The numbering refers to Table I.

Chart III. Structural Formulas of Three Clonidine-like Phenyl-Substituted Imidazolidines with Pronounced Lipophilic Properties[a]



[a] The numbering refers to Table I.

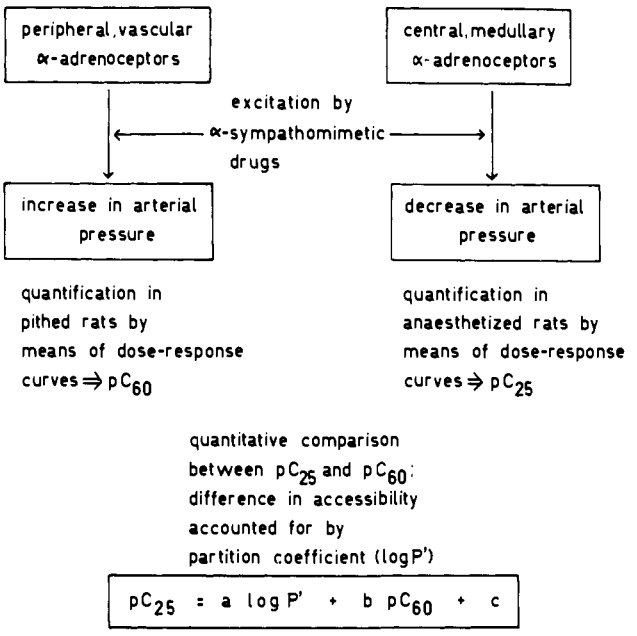


Figure 1. Schematic representation of the two α-adrenoceptor populations investigated, the biological effects mediated by them upon stimulation, and the procedure followed to derive a relationship between central and peripheral α-adrenergic activities of α-adrenoceptor agonists.

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Table I. Hypotensive (pC_{25}) and Hypertensive (pC_{60}) Activities and Apparent Partition Coefficients (log P'; pH 7.4, 37 °C) of 21 Structurally Dissimilar α-Adrenoceptor Agonists[a]

no.	compd	pC_{25} obsd	pC_{25} calcd	$\lvert\Delta pC_{25}\rvert$	pC_{60}	log P'
1	44-549	2.77	2.26	0.51	2.40	2.02
2	Bay-a 6781	2.32	2.27	0.05	2.11	1.39
3	lofexidine	2.09	2.11	0.02	1.99	0.73
4	clonidine	2.04	1.96	0.08	1.78	0.85
5	Bay-c 6014	1.96	1.75	0.21	1.51	1.28
6	UK-14 304-18	1.55	1.53	0.02	1.56	0.31
7	B-HT 920	1.43	1.03	0.40	0.69	1.09
8	naphazoline	0.95	0.96	0.01	1.83	−0.52
9	St-1967	0.88	1.50	0.62	1.24	1.36
10	St-871	0.84	0.99	0.15	1.22	2.31
11	tiamenidine	0.69	0.80	0.11	1.20	−0.17
12	St-1913	0.68	0.36	0.32	1.17	−0.53
13	KUM 32	0.63	0.26	0.37	0.23	2.12
14	xylazine	0.62	0.39	0.23	−0.02	1.34
15	tramazoline	0.55	0.79	0.24	1.80	−0.62
16	xylometazoline	0.26	1.19	0.93	1.12	0.40
17	St-739	−0.02	0.29	0.31	0.65	2.51
18	B-HT 933	−0.14	−0.42	0.28	−0.41	0.05
19	tetryzoline	−0.16	−0.42	0.26	0.90	−0.90
20	St-889	−1.02	−0.86	0.16	−0.26	2.80
21	St-404	−1.31	−1.15	0.16	−0.79	−0.34

[a] For experimental details, see Experimental Section. The data have been used to generate eq 1–7. Calculated pC_{25} values were obtained from eq 7.

Procedure. The localization of the α-adrenoceptors involved, the physiological effects mediated by them upon stimulation, as well as the procedure followed in obtaining the biological variables are schematically outlined in Figure 1 (for details see Experimental Section). In brief, hypotensive activity was determined following intravenous administration to anesthetized, normotensive rats. For reasons to be discussed under Discussion, it is very probable that after intravenous application to anesthetized, normotensive rats the decrease in arterial pressure originates from an action within the central nervous system. This inhibitory action was quantified by means of log $1/C_{25}$ (pC_{25}), calculated from log dose–response curves (C_{25} = dose, μmol/kg, required to invoke a 25% decrease in mean arterial pressure). According to the same method, the peripheral hypertensive activity was measured in pithed, normotensive rats and expressed as pC_{60} (C_{60} = dose, μmol/kg, associated with an increase in mean arterial pressure by 60 mmHg). Linear correlation studies were performed between pC_{25} and pC_{60}. The difference in accessibility to both α-adrenoceptor populations was adequately accounted for by consideration of the apparent octanol/aqueous buffer (pH 7.4; 37 °C) partition coefficient (log P').

Central Hypotensive and Peripheral Hypertensive Activities. Intravenous administration of the drugs to anesthetized, normotensive rats provoked a biphasic effect on arterial pressure. After an initial transient pressor response, a more persistent fall in blood pressure was noticed. The log dose–response curves shown in Figure 2 were obtained by plotting the maximal decreases in mean arterial pressure (percent of initial preinjection value) against the α-adrenoceptor agonist dose on a logarithm scale. This figure shows the wide range of hypotensive potencies covered by the drugs. The hypotensive activities were calculated as pC_{25} (see above) from these dose–response curves. The values are reported in Table I.

Intravenous injections of the substances into pithed, normotensive rats induced dose-dependent increases in mean arterial pressure. This peripherally mediated vasoconstriction was measured (mmHg) and plotted against the log dose. The resulting log dose–response curves of some compounds have been compiled in Figure 3. Hypertensive potency was expressed as pC_{60} (see above) calculated from these curves. The numerical values have been enumerated in Table I.

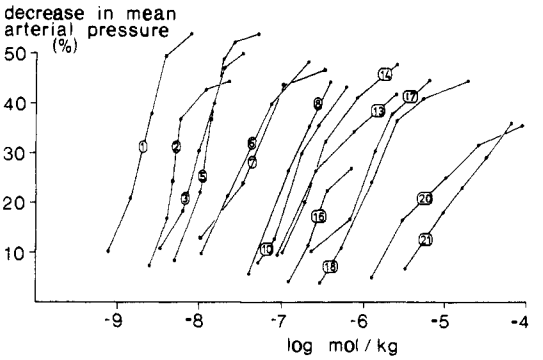

Figure 2. Log dose–response characteristics with respect to the maximal depressor effect of some structurally different α-adrenoceptor agonists following intravenous administration to anesthetized, normotensive rats. Data points are presented as mean values taken from five to six individual experiments. The numbering refers to Table I.

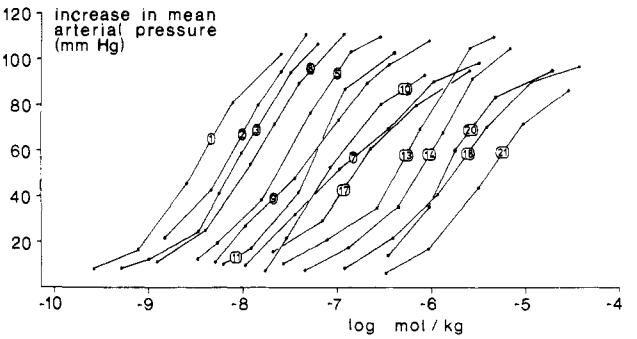

Figure 3. Log dose–response characteristics with respect to the hypertensive effect of some structurally dissimilar α-adrenoceptor agonists following intravenous injections into pithed, normotensive rats. Data points are mean values out of five to six separate experiments. The numbering refers to Table I.

Correlations. The relationships shown in eq 1–7 were derived between central hypotensive activity (pC_{25}) and

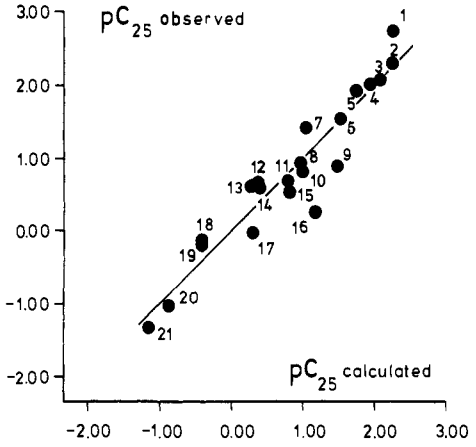

Figure 4. Relationship between the central hypotensive activities of 21 structurally different α-adrenoceptor agonists observed after intravenous application to anesthetized, normotensive rats and the values calculated by using eq 7. The numbering refers to Table I.

peripheral hypertensive potency (pC_{60}) and/or lipophilicity (log P').

$$pC_{25} = 0.996\ (\pm 0.32)\ pC_{60} - 0.201 \quad (1)$$

$$n = 21;\ r = 0.828;\ s = 0.609;\ F = 41.42$$

$$pC_{25} = 0.148\ (\pm 0.45)\ \log P' + 0.716 \quad (2)$$

$$n = 21;\ r = 0.157;\ s = 1.072;\ F = 0.48$$

$$pC_{25} = -0.565\ (\pm 0.36)\ (\log P')^2 + 1.163\ (\pm 0.75)\ \log P' + 0.943 \quad (3)$$

$$n = 21;\ r = 0.622;\ s = 0.873;\ F = 5.68$$

$$pC_{60} = -0.058\ (\pm 0.37)\ \log P' + 1.092 \quad (4)$$

$$n = 21;\ r = 0.074;\ s = 0.900;\ F = 0.11$$

$$pC_{60} = -0.200\ (\pm 0.37)\ (\log P')^2 + 0.302\ (\pm 0.77)\ \log P' + 1.173 \quad (5)$$

$$n = 21;\ r = 0.267;\ s = 0.893;\ F = 0.69$$

$$pC_{25} = 0.207\ (\pm 0.24)\ \log P' + 1.015\ (\pm 0.31)\ pC_{60} - 0.393 \quad (6)$$

$$n = 21;\ r = 0.857;\ s = 0.576;\ F = 24.78$$

$$pC_{25} = -0.387\ (\pm 0.16)\ (\log P')^2 + 0.895\ (\pm 0.33)\ \log P' + 0.887\ (\pm 0.21)\ pC_{60} - 0.098 \quad (7)$$

$$n = 21;\ r = 0.945;\ s = 0.376;\ F = 47.03$$

The linear correlation between pC_{25} and pC_{60} is given by eq 1. This relationship indicates that within the present series of dissimilar α-adrenoceptor stimulants both biological variables are correlated to an appreciable degree. Equation 2 formulates the linear relationship between central hypotensive activity (pC_{25}) and log P'. This correlation is statistically irrelevant but is improved to a meaningful level upon inclusion of a squared term in log P' ($F_{1,18} = 10.64$; $F_{1,18;p=0.005} = 10.22$), resulting in eq 3. This equation explains 39% ($= r^2$) of the variance in hypotensive activity of the α-adrenoceptor stimulating agents.

In contrast, the correlation between hypertensive activity (pC_{60}) and log P' (eq 4) does not satisfy at all. Relationship 5, which is derived for an additional $(\log P')^2$, is also inappropriate. So far, the results suggest that lipophilicity, expressed as log P', will certainly contribute to the hypotensive activity which is centrally mediated. In this case, a parabolic dependence on log P' appeared most suitable. On the other hand, this parameter will be of minor importance in determining the hypertensive potency induced peripherally.

The relationship between pC_{25} and pC_{60} (eq 1) was not improved significantly upon inclusion of log P' (eq 6) ($F_{1,18} = 3.25$; $F_{1,18;p=0.05} = 4.41$). However, the significance of eq 1 was greatly improved upon the introduction of a combination of log P' and $(\log P')^2$, yielding eq 7 ($F_{2,17} = 16.36$; $F_{2,17;p=0.001} = 10.97$). Equation 7 most significantly describes the central hypotensive activity of 21 structurally different α-adrenoceptor agonists as a function of their peripheral hypertensive potency and their overall lipophilic behavior. The latter variable is present in a parabolic form. Equation 7 accounts for 89% of the variance in the hypotensive data and provides calculated pC_{25} values which are close to the observed values obtained by pharmacological means (see Table I). The linear relationship between observed and calculated (eq 7) pC_{25} values is illustrated by Figure 4.

To summarize, the hypotensive activity (initiated at central α-adrenoceptors) of the compounds in this study can be correlated with their hypertensive potency (mediated via peripheral, vascular α-adrenoceptors) provided that lipophilicity (log P'), expressed as a parabolic function of log P', is incorporated into the equation.

Discussion

The compounds used in the present study comprise a structurally heterogeneous group. They are more or less related to the fundamental and classical imidazoli(di)ne structure. The substances were developed by several research teams with the aim of obtaining new nasal decongestants and/or centrally acting hypotensive drugs. Consequently, they all have one particular property in common, i.e., α-adrenoceptor stimulating activity. Some of these agents have been subjected to detailed pharmacological studies.[1,10-12] It is very likely that for the drugs in question the hypotensive effect, as quantified in the anesthetized, normotensive rat, is mediated by central α-adrenoceptors. The identical profiles of action observed after intravenous administration is in favor of this assumption. In fact, apart from clonidine itself, central hypotensive activity has been demonstrated for compounds **1**,[13] **2**,[14,15] **5**,[16] **6**,[17] **7**,[18] naphazoline (**8**),[19,20] **9**,[21] tiamenidine (**11**),[22,23] **12**,[21] xylazine (**14**),[24-27] tramazoline (**15**),[8] **18**,[18,28,29]

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tetryzoline (19),[8,30] and 21.[31] In many of these studies the involvement of central α-adrenoceptors has been verified explicitly. Other investigations showed a pronounced hypotensive effect after central administration via the cat's vertebral artery when compared to intravenous injections of the same amounts.[32] In conclusion, although the chemical structure of the compounds differ considerably, there is little doubt that they all exert a central hypotensive effect mediated via α-adrenoceptors and that stimulation of peripheral, vascular α-adrenoceptors by them leads to vasoconstriction.

For the present series of compounds, a statistically significant correlation was found between central hypotensive and peripheral hypertensive potencies so long as log P' was included in a parabolic manner. This result is consistent with the hypothesis that the structural requirements of central medullary α-adrenoceptors mediating hypotension are the same as those for peripheral vascular α-adrenoceptors which mediate vasoconstriction. The difference in accessibility of the compounds to the peripheral and central α-adrenoceptors at which these α-adrenergic effects are initiated is accounted for by the lipophilic properties of the drugs. The question then arises as to whether this relationship between central and peripheral α-adrenergic activity for the compounds studied is indeed parabolically related to lipophilicity (log P') which may, in turn, describe the penetration of the drugs into the brain from the blood. For clonidine and its structurally related imidazolidines, we have reported that the fraction of the amount of drug, administered intravenously, detected in the brain parabolically depended on overall lipophilic properties (log P').[33] For this reason it is very likely that log P' accounts for the difference in accessibility to peripheral, vascular α-adrenoceptors, which are freely accessible via the blood, and central, medullary α-adrenoceptors, which can only be reached after passage of the blood–brain barrier. This finding emphasizes the importance of log P' in the correlation derived in this study between central hypotensive and peripheral hypertensive activities. Moreover, for the case of very lipophilic agonists, the presence of log P' in a parabolic form is a prerequisite.

It may be concluded from these results that lipophilicity will account for the relative differences between peripherally mediated pressor activity and centrally induced depressor potency of α-adrenoceptor agonists. Consequently, the data indicate that the structural requirements of the α-adrenoceptors located centrally at medullary sites and those of the α-receptor sites situated in the periphery at the vascular wall are similar. Previously, we have reached a similar conclusion for clonidine-like imidazolidines[4] and for a limited number of structurally different α-receptor agonists.[9] However, this conclusion is at variance with the differential agonistic and antagonistic activities reported for some α-adrenoceptor stimulating and blocking agents.[5-8] However, different routes of administration had been employed and the importance of lipophilicity had not been analyzed quantitatively.

The present findings suggest that the central α-adrenoceptors causing hypotension upon stimulation and the peripheral α-adrenoceptors eliciting vasoconstriction upon excitation belong to the same class of α-adrenoceptors, since they make comparable demands upon their agonists. However, there exists firm evidence at present that the central hypotensive α-adrenoceptors possess the characteristics of the so-called α_2-adrenoceptors.[34-38] On the other hand, the vasoconstrictor α-adrenoceptor population in the vascular wall has frequently been referred to as α_1.[35,39,40] Apparently, we are faced with a paradox, since it is very unlikely that significant relationships can be derived between the pharmacological effects initiated at two distinct classes of α-adrenoceptors. The solution may be found in the recent identification of an additional class of vascular α-adrenoceptor sites with properties of α_2-adrenoceptors.[41-45] Apart from the more classical vascular α_1-adrenoceptors, these postsynaptic α_2-adrenoceptors also participate in drug-induced vasoconstriction. The majority of the drugs used in the present study are not markedly selective for vascular α_1- or α_2-adrenoceptors, as they are nearly equally effective at either receptor site (authors, unpublished data). Therefore, we submit that the significant relationship between peripheral and central α-adrenergic effects could be the result of a lack of pronounced selectivity for peripheral α_1- or α_2-adrenoceptors of the agonists used. It should be noted that such a relationship can only successfully be derived for relatively nonselective α-adrenoceptor agonists or for preferential stimulants of α_2-adrenoceptors. However, it cannot be accomplished for pure agonists of α_1-adrenoceptors. These particular drugs can induce vasoconstriction via excitation of vascular α_1-adrenoceptors but fail to decrease blood pressure, since they lack stimulating properties of (central) α_2-adrenoceptors.[46] Selective agonists of α_2-adrenoceptors will also fit in such a relationship, because α_2-adrenoceptors mediate both peripheral as well as central effects. Arguments in favor of this latter suggestion are presented by the new experimental compounds 7, 8, and 6. They are pure agonists of α_2-adrenoceptors with no affinity for α_1-adrenoceptor sites[44,45,47,48] and do not deviate from the

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present regression.

Experimental Section

Central Hypotensive Activity. Male, normotensive Wistar rats (weight 190–220 g) were anesthetized with an intraperitoneal injection of pentobarbitone sodium (75 mg/kg). The animals were artificially ventilated via a tracheal cannula connected to a Braun–Melsungen respiration pump with positive pressure. Rectal temperature was maintained at approximately 37 °C. Catheters were inserted into a jugular vein and into a common carotid artery for drug administration and the recording of arterial pressure, respectively. Arterial pressure was displayed continuously via a Statham P23 Db pressure transducer on a Hellige-HE 19 device. Animals were heparinized (about 1000 IU/kg) and left undisturbed for at least 20 min, thereby allowing circulatory parameters to stabilize. Rats possessing a mean arterial pressure lower than 100 or higher than 150 mmHg after equilibration were discarded. Drugs were injected intravenously in a volume of 0.1 mL/100 g of body weight. The sequence of substances and doses was randomized. One animal received one single dose only. Maximal decrease in mean arterial pressure attained by the drug injected was determined as percent of the preinjection value. A log dose–response curve was constructed for each compound from which the log of the reciprocal dose (μmol/kg) associated with a 25% decrease in mean arterial pressure (pC_{25}) was calculated.

Peripheral Hypertensive Activity. Normotensive rats (see above) were anesthetized with hexobarbitone sodium (150 mg/kg) administered intraperitoneally. The trachea was cannulated and, subsequently, the animals were pithed by means of a blunt needle introduced into the spinal canal via the orbit. Thereafter, ventilation was maintained artificially (see above). Rectal temperature was kept at about 37 °C. A catheter was placed into a jugular vein for the intravenous injection of drugs, and heparin (about 1000 IU/kg) was administered. Arterial pressure was taken from a common carotid artery and recorded continuously (see above). After a 20-min period of equilibration, increases in mean arterial pressure were determined (mmHg) after intravenous injections of single doses of the drugs. Substances as well as doses were applied in random order in a volume of 0.05 mL/100 g of body weight. No more than three or four separate measurements were made per animal. Recovery from the pressor effects was ensured between the subsequent doses. The peripheral hypertensive activity of the agonists was quantified by means of log dose–response curves, from which the log of the reciprocal dose (μmol/kg) required to cause an increase in mean arterial pressure of 60 mmHg (pC_{60}) was calculated.

Octanol/Buffer (pH 7.4; 37 °C) Partition Coefficient. Lipophilicity was measured as the log partition coefficient (log P') between octanol and 0.1 M phosphate buffer at physiological conditions (pH 7.4; 37 °C). Solutions of the drugs (approximately 10^{-4} M) were prepared in the octanol-saturated (37 °C) buffer. The wavelength at maximal absorbance was determined, and the absorbance was measured for a 1-mL sample in 2 mL of 0.2 N aqueous HCl/methanol (2:1), using a Unicam SP 1800 ultraviolet spectrophotometer. Adherence to Beer's law was confirmed. The buffer phase was shaken mechanically at 37 ± 1 °C with buffer-saturated octanol for 1 h. The residual emulsion was broken up by standing for 6 h. The concentration of the drug in the buffer phase after partitioning was assessed by ultraviolet spectroscopy (see above), and the apparent partition coefficient (P') was calculated.

Due to the absence of appropriate ultraviolet absorptions, the concentration of **2** in the aqueous phase before and after partitioning was determined by means of gas–liquid chromatography. For this purpose, a Perkin-Elmer series 3920 gas chromatograph was equipped with a flame-ionization detector (temperature, 250 °C; hydrogen flow, 2.9 mL/min; air flow, 100 mL/min) and a 1-mV Kipp recorder. A glass column (2 m × 2 mm i.d.) packed with 3% OV-17 on Chromosorb 750, 80–100 mesh, was used at an oven temperature of 180 °C and the injector at 230 °C. The carrier gas was helium at a flow rate of 2.6 mL/min. Aliquots of the buffer phase were injected in a volume of 5 μL. The gas chromatograms were evaluated by an integrating system (Spectra-Physics Autolab System IV).

The partition coefficients of **18** and **7** were obtained by potentiometric titration. After partitioning, the buffer phase was made alkaline to pH 12 and extracted three times with chloroform. After evaporation of the solvent the residue was taken up in 50% aqueous ethanol and titrated with 0.01 N HCl.

The log P' values of all compounds reported in Table I have been taken out of the mean P' values obtained from six partition experiments (SEM < 5%).

Correlations. Relationships were derived between central hypotensive activity (pC_{25}) and peripheral hypertensive potency (pC_{60}) and/or lipophilicity (log P') using the method of least-squares by means of a Wang 700B computer. The correlation coefficient (r), the standard deviation (s), and the significance of the regression (F) are given. The figures in parentheses are the 95% confidence limits. Inclusion of parameters was judged by application of the F test.

Drugs. Drugs used in this study and their sources were Bay-a 6781 (**2**), Bay-c 6014 (**5**), and xylazine hydrochloride (**14**) (Bayer); clonidine hydrochloride (**4**), KUM 32 hydriodide (**13**), St-404 nitrate (**21**), St-889 hydrobromide (**20**), St-1913 hydrochloride (**12**), St-1967 hydrochloride (**9**), and tramazoline hydrochloride (**15**) (Boehringer Ingelheim); B-HT 920 (**7**) and B-HT 933 dihydrochloride (**18**) (Thomae); compound 44-549 fumarate (**1**) (Sandoz Wander); lofexidine hydrochloride (**3**) (Merrell; manufacturer: Nattermann); naphazoline (**8**) and xylometazoline hydrochloride (**16**) (Ciba); St-739 (**17**) and St-871 hydrochloride (**10**) (ref 49); tetryzoline hydrochloride (**19**) and UK-14 304-18 tartrate (**6**) (Pfizer); and tiamenidine hydrochloride (**11**) (Hoechst). All compounds were dissolved in physiological saline.

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