Alpha-Adrenergic Receptor-Blocking Properties of Six Phenethylamine Derivatives *In Vitro*

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Abstract □ The α-adrenergic receptor-blocking activity of six phenethylamine congeners was studied on the isolated rabbit ileum and uterus. The results obtained indicated that α-receptor blockade varied with the size and number of substituent groups on the terminal nitrogen and the α-carbon atom of the side chain. Activity is lost by disubstitution on the α-carbon atom or shifting the methoxy group from the *ortho*- to the *para*-position in the phenyl ring. One compound, U-0277, had a direct musculotropic action on the uterus. None of the compounds was as potent as phentolamine.

Keyphrases □ Phenethylamine derivatives—α-adrenergic blocking □ Structure-activity relationship—phenethylamine derivatives □ Ileum, rabbit—phenethylamine derivatives, effect □ Uterus, rabbit—phenethylamine derivatives, effect

Ahlquist's (1) concept of adrenergic receptors implies that a structural complementarity would exist between the phenylethylamine moiety of the catecholamines and their receptors. Studies with the phenylethylamine derivatives have yielded information on the nature of substituent groups which determine the agonistic or antagonistic action of a drug on adrenergic receptors (2, 3). The present report describes the results of studies on the activity of six phenylethylamine derivatives on adrenergic receptors in isolated tissues.

MATERIALS AND METHODS

Ileal strips and uteri of estrogen-progesterone-treated rabbits were suspended in 40-ml. baths containing Locke-Ringer solution (NaCl, 9 g.; KCl, 0.42 g.; $MgCl_2$, 0.2 g.; $CaCl_2$, 0.24 g.; $NaHCO_3$, 0.5 g.; and dextrose, 0.5 g./l.), thermostatically regulated at 37.5° and aerated with 95% oxygen and 5% carbon dioxide. All doses of drugs were administered in a volume of 0.5 ml. to 1 ml. using micromolar concentrations. A dose of the antagonist was added to the bath 1 min. prior to administering a dose of the agonist, which was allowed to act for 30 sec. Five strips of each tissue were used for each drug and the results were statistically analyzed by the Litchfield-Wilcoxon method (4). The doses of the drugs used were: *l*-epinephrine-*d*-bitartrate, 4.5×10^{-3} μ*M*; *l*-norepinephrine-*d*-bitartrate, 4.7×10^{-3} μ*M*; *l*-phenylephrine hydrochloride, 2.4×10^{-2} μ*M*; *l*-isoproterenol-*d*-bitartrate, 4.1×10^{-3} μ*M*; phentolamine methanesulfonate, 3×10^{-3} to 1.5×10^{-2} μ*M*; *o*-methoxy-*N*,α,α-trimethylphenethylamine hydrochloride (U-0588), 1 to 5 μ*M*; *N*-benzyl-*o*-methoxy-*N*, α-dimethylphenethylamine hydrochloride (U-0277), 3.5×10^{-2} to 7.9×10^{-1} μ*M*; *N*-benzyl-*o*-methoxy-*N*, α-dimethylphenethylamine-*N*-oxide hydrochloride (U-06217), 1.5×10^{-1} to 6.2 μ*M*; *N*-isopropyl-*o*-methoxy-α-methylphenethylamine hydrochloride (U-0287), 2.1×10^{-1} to 8.6 μ*M*; *p*-methoxy-*N*, α-dimethylphenethylamine hydrochloride (U-0891), 1 to 5 μ*M*; *dl*-*o*-methoxy-*N*, α-dimethylphenethylamine hydrochloride (U-0433), 2.3 to 21.6 μ*M*.

RESULTS

The relative order of potency of the adrenergic blocking drugs compared to phentolamine on the rabbit ileum is shown in Table I. The most active compound, U-0277, was about 17 times less potent than phentolamine. Table II gives the comparison of the various adrenergic blockers on the uterus. The most active drug, U-06217, was 125 times less potent than phentolamine. U-0277 produced uterine contractions in all doses studied. These contractions were not blocked by phentolamine and thus could not be due to the stimulatory action of U-0277 on α-adrenergic receptors in the uterus. No other compound exhibited such musculotropic action.

U-06217, U-0287, U-0433, and U-0277 produced a reversible α-receptor blockade because washing the tissues removed the blocking drug and control responses were again obtained with epinephrine, norepinephrine, and phenylephrine. U-0588 and U-0891 were completely inactive on both tissues. None of the six phenethylamine congeners produced α- or β-receptor stimulation or β-receptor blockade.

DISCUSSION

The structural formulas of the test compounds, Table III reveal that these compounds differ from each other in having different arrangements of substituent groups on the terminal nitrogen atom, on the α-carbon atom next to the nitrogen atom,

Table I—Comparison of α-Receptor-Blocking Property on Isolated Rabbit Ileum

	Antagonist						Potency		
	Phenylephrine		Norepinephrine		Epinephrine				
	ED_{50} and Range, μ*M*[a]	Slope and Range	ED_{50} and Range, μ*M*	Slope and Range	ED_{50} and Range, μ*M*	Slope and Range	PE	NE	EP
Phentolamine	0.007 (0.004–0.013)	2.13 (1.8–3.6)	0.009 (0.006–0.014)	2.3 (1.16–3.5)	0.008 (0.007–0.019)	2.9 (1.3–3.9)	1.0	1.0	1.0
U-0277	0.13 (0.09–0.23)	2.35 (1.2–4.2)	0.138 (0.08–0.23)	2.65 (1.5–4.6)	0.21 (0.12–0.38)	2.93 (1.3–5.2)	0.06	0.07	0.06
U-06217	0.93 (0.67–1.6)	1.86 (0.8–3.9)	1.2 (0.7–2.1)	1.73 (1.1–3.6)	1.5 (0.9–2.9)	1.93 (0.9–3.7)	0.008	0.008	0.008
U-0287	1.6 (0.85–2.5)	1.92 (1.3–3.5)	1.96 (1.1–3.7)	2.2 (1.7–3.9)	2.3 (1.3–3.5)	2.7 (1.6–4.6)	0.004	0.005	0.005
U-0433	7.4 (5.2–9.6)	2.01 (1.7–3.9)	8.1 (6.5–10.9)	1.84 (1.2–3.7)	8.4 (5.1–11.6)	1.96 (0.9–4.2)	0.001	0.001	0.001

[a] $p = 0.05$.

Table II—Comparison of α-Adrenergic Receptor-Blocking Property on Isolated Rabbit Uterus

	Antagonist								
	Phenylephrine		Norepinephrine		Epinephrine		Potency		
	ED_{50} and Range, μM[a]	Slope and Range	ED_{50} and Range, μM	Slope and Range	ED_{50} and Range, μM	Slope and Range	PE	NE	EP
Phentolamine	0.006 (0.004–0.01)	2.01 (1.2–3.9)	0.01 (0.007–0.019)	2.2 (1.1–3.7)	0.008 (0.005–0.013)	2.54 (1.3–4.2)	1.0	1.0	1.0
U-06217	0.73 (0.56–1.2)	2.32 (1.2–4.2)	0.81 (0.52–1.3)	1.76 (0.9–3.8)	0.74 (0.63–1.2)	2.42 (1.9–4.9)	0.008	0.012	0.01
U-0287	1.91 (1.1–3.2)	1.96 (1.2–3.6)	2.4 (1.8–3.7)	1.78 (1.2–4.5)	2.5 (1.9–3.4)	2.1 (1.26–4.3)	0.003	0.004	0.003
U-0433	7.3 (5.1–11.2)	1.89 (0.96–3.7)	7.6 (4.3–10.1)	2.06 (1.3–4.3)	7.8 (5.9–10.3)	1.9 (0.9–3.9)	0.001	0.001	0.002
U-0277	Produces persistent contraction at all doses studied.								

[a] $p = 0.05$.

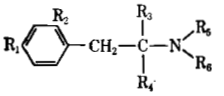

Table III—Structure-Activity Relationships of Phenethylamine Derivatives

Drug	Structure R_1	R_2	R_3	R_4	R_5	R_6	Activity
U-0433	H	OCH_3	H	CH_3	H	CH_3	α-Receptor block
U-0588	H	OCH_3	CH_3	CH_3	H	CH_3	Inactive
U-0891	OCH_3	H	H	CH_3	H	CH_3	Inactive
U-0287	H	OCH_3	H	CH_3	H	$CH(CH_3)_2$	α-Receptor block
U-0277	H	OCH_3	H	CH_3	CH_3	$CH_2C_6H_5$	α-Receptor block
U-06217[a]	H	OCH_3	H	CH_3	CH_3	$CH_2C_6H_5$	α-Receptor block

[a] *N*-Oxide of U-0277.

and in the ring. The β-carbon atom in the side chain has not been substituted in any of the compounds. The lack of intrinsic α-receptor activity endorses the view that substitution on the terminal nitrogen atom and on the α-carbon atom abolishes intrinsic activity on the α-receptors and a change from the stimulant to the blocking action occurs (5). Dimethyl substitution on the α-carbon atom in U-0588 results in the loss of α-receptor blocking activity indicating that more complex stereochemical characteristics are involved in this case. It appears that the size and the number of substituent groups on the terminal nitrogen atom determine the degree of the α-receptor blocking activity if the α-carbon atom next to the nitrogen is not fully substituted. U-0277 and U-06217 have bulky benzyl groups and show α-receptor blocking activity. Introduction of the *N*-oxide linkage in U-0277 to get U-06217 diminishes but does not eliminate the blocking activity. Moving the methoxyl group from the *ortho*- to the *para*-position in the phenyl ring as in U-0891 results in complete loss of α-receptor blocking activity. The lack of affinity of these drugs for β-adrenergic receptors was to be expected since the structural requirements for the β-receptor activity were not fulfilled (6).

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