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Title (type in CAPITAL LETTERS): CHARACTERIZATION OF THE α_1-ADRENOCEPTOR SUBTYPE MEDIATING THE CONTRACTILE RESPONSE IN HUMAN AND RABBIT CORPUS CAVERNOSUM

α-Adrenoceptor (AR) antagonists have been used for the treatment of male erectile dysfunction. Recent pharmacological and functional studies have suggested the presence of more than one α_1-adrenoceptor subtype in human corpus cavernosum (1-3). Although some discrepancies have been found between human and rabbit cavernosal tissue (4), the rabbit is usually the animal species used to evaluate the effect of drugs.

Aims of Study:

This study attempted to identify the α_1-adrenoceptor subtype mediating contractile response in isolated cavernosal tissue from normal adult rabbits and in human cavernosal strips, and compared the pharmacology of novel adrenoceptor ligands in these tissues.

Methods:

In order to characterize the α_1-adrenoceptor subtype(s) present in corpus cavernosum tissue, organ bath experiments were performed on biopsies of human corporal tissue obtained from patients undergoing penile prosthesis implantation for impotence and on rabbit tissue isolated after CO_2 asphyxiation. Cumulative concentration-response curves to norepinephrine, a non-selective adrenoceptor agonist, were constructed, in presence of an α_2-AR antagonist (idazoxan). Strips of tissue were incubated for 90 minutes in the absence or presence of antagonist before a second agonist curve was constructed. The antagonists which were examined include prazosin (non selective), cyclazosin (α_{1B}-AR selective), BMY 7378 (α_{1D}-AR selective), RS-100329 and Ro70-0004 (α_{1A}-AR selective; (5); (6)).

Contractions were recorded as changes in tension from baseline and expressed as a percentage of the maximum response of the first agonist concentration-effect curve. Antagonist affinity estimates were determined by the method of Arunlakshana and Schild (7).

Radioligand binding studies were undertaken using intact CHO-K1 cells stably expressing human cloned α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors. Affinity estimates (pK_i) were determined according to Cheng and Prusoff (8). Methodology and part of the data have previously been reported (5).

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Results:

Antagonist	Human cloned adrenoceptor subtypes (pK_i)			Human CC (pK_B)	Rabbit CC (pA_2/pK_B)
	α_{1A}	α_{1B}	α_{1D}		
Prazosin	9.0	9.9	9.5	8.4	8.1
Cyclazosin	7.9	9.3	8.2	7.3	7.8
BMY 7378	6.2*	6.7*	8.2*	ND	6.3
RS-100329	9.6	7.5	7.9	9.2	8.9
Ro70-0004	8.9	7.1	7.2	8.8	8.5

Values are from (5).

*: values from (9).

ND: not determined.

Conclusions:

The antagonist affinity estimates suggest that α_{1A}-adrenoceptors mediate norepinephrine-induced contraction of rabbit and human corpus cavernosum.

References:

(1) J. Urol. (1995), 153, 222-227.

(2) Receptor (1996), 5, 145-157.

(3) J. Urol. (1998), 160, 597-600.

(4) Gen. Pharmac. (1995), 1107-1111.

(5) Br. J. Pharmacol. (1999), in press.

(6) Neurourol. Urodynam. (1996), 15, 345.

(7) Br. J. Pharmacol. (1959), 14, 48-58.

(8) Biochem. Pharmacol. (1973), 22, 3099-3108.

(9) Br. J. Pharmacol. (1995), 115, 981-986.