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A comparison of the selectivity of α and β-antagonists for the human α1A, α1B, α1D, β1 and β2-adrenoceptors.

R. G. Proudman, J. G. Baker. Cell signalling, University of Nottingham, Nottingham, United Kingdom.

Introduction: Both α1-adrenoceptor antagonists (e.g. doxazosin) and β1-adrenoceptor antagonists (e.g. bisoprolol) are used to manage hypertension (1,2). α1-antagonists are also widely used for benign prostatic hypertrophy (BPH). Clinically used β-blockers are not very selective for the β1 over the β2-adrenoceptor and thus are contraindicated in those who also have asthma (2). This study therefore compared the affinity and selectivity of ligands across the α1 and β-adrenoceptor subtypes (α1A, α1B, α1D, β1 and β2).

Methods: Stable CHO-K1 cell lines were generated expressing each of the human α1-adrenoceptors (3). ^{3}H-prazosin (α1A, α1B and α1D) and ^{3}H-CGP12177 (β1 and β2) whole cell binding assays were conducted (2hr incubation at 37°C (2)) with 134 ligands reported to interact with the human α1 and β-adrenoceptors.

Results: The affinity (KD values) for ^{3}H-prazosin were: α1A 0.71nM, α1B 0.87nM, α1D 1.05nM (4) and ^{3}H-CGP 12177 β1 0.42nM, β2 0.17nM (2). Carvedilol, known as a dual α1 and β-blocker, had high affinity for all 5 receptors, whereas labetolol, also considered a dual antagonist, had poor affinity for the α1B and α1D-adrenoceptors (see Table 1). Subtype selective ligands (i.e. those with selectivity of >100-fold) were identified (Table 1) in agreement with previous studies (e.g. 1, 2). Of the 134 ligands examined, no ligand was found that was α1B-selective. Whilst several drugs used for their neurological or psychiatric properties had high α1A-adrenoceptor affinity (also see (4)), none had high β1-affinity. Lisuride, generally considered to be a dopamine and 5-HT ligand, was the only other ligand with high β2-adrenoceptor affinity (see Table 1).

Conclusion: Whilst subtype selective ligands exist for the α1A, α1D, β1 and β2-adrenoceptors, no subtype selective ligand was found for the α1B-adrenoceptor. Carvedilol had high affinity for all 5 adrenoceptors. Whilst most ligands regarded as α-blockers or β-blockers were indeed highly selective for their respective subtype, silodosin and naftapidil (α1-antagonists) also had high affinity for the human β2-adrenoceptor, making these less attractive drugs for those with both benign prostatic hypertrophy and asthma. With the exception of lisuride, the other neurological or psychiatric ligands with high α1-affinity had very poor affinity for the β-adrenoceptors. The selectivity of these ligands for the human α2-adrenoceptors remains to be determined.

References:

(1)Docherty JR (2010) *Cell. Mol. Life Sci.* **67:** 405-417.
(2)Baker JG (2005) *Br J Pharmacol*. **144:** 317-322.
(3)Nojimoto FD et al., (2010) *Neuropharmacology* **59:** 49-57
(4)Baker et al., abstract at this meeting

Table 1. Log KD values (mean ± sem of n separate experiments) for ligands binding to the human α1A, α1B, α1D, β1 and β2-adrenoceptors. Where a two-component inhibition of specific binding was seen, this is given as log KD site 1, log KD value site 2 and % response at site 1.

	Log KD α1A	n	Log KD α1B	n	Log KD α1D	n	Log KD β1	n	Log KD β2	n
Dual α1 and β-adrenoceptor antagonists										
carvedilol	-8.35 ± 0.06	12	-7.84 ± 0.06	6	-8.40 ± 0.05	12	-8.75*		-9.40*	
labetolol	-7.32 ± 0.05	6	-5.93 ± 0.03	6	-6.02 ± 0.11	9	-7.63*		-8.03*	
Non-selective α-antagonists										
alfuzosin	-7.98 ± 0.04	6	-7.61 ± 0.07	5	-7.65 ± 0.12	9	>-3	5	-4.26 ± 0.06	4
cyclazosin	-8.89 ± 0.06	7	-8.68 ± 0.08	5	-9.59 ± 0.17 -6.85 ± 0.15 65.1 ± 3.9% site 1	10	No binding	5	-5.28 ± 0.05	4
doxazosin	-8.58 ± 0.09	6	-8.46 ± 0.05	8	-8.75 ± 0.10	10	-4.72 ± 0.06	5	-5.57 ± 0.01	6
ifenprodil	-7.66 ± 0.11	9	-6.49 ± 0.07	6	-7.57 ± 0.05 -5.25 ± 0.11 67.5 ± 3.4% site 1	14	-4.73 ± 0.06	4	-5.10 ± 0.07	4
naftapidil	-7.97 ± 0.03	6	-6.82 ± 0.06	6	-7.63 ± 0.10	7	-5.94 ± 0.08	4	-7.41 ± 0.08	4
phenoxybenzamine	-8.45 ± 0.12 -6.02 ± 0.08 77.7 ± 5.2% site 1	12	-7.69 ± 0.06 -5.57 ± 0.06 67.5 ± 2.5% site 1		-8.22 ± 0.11 -5.48 ± 0.12 54.0 ± 3.3% site 1	13	-3.94 ± 0.11	5	-4.34 ± 0.03	4
prazosin	-9.07 ± 0.04	8	-8.74 ± 0.06	8	-9.07 ± 0.05	10	>-4	4	-4.96 ± 0.10	3
Rec15-2615	-8.26 ± 0.10	6	-7.79 ± 0.09	6	-8.31 ± 0.09	6	-4.71 ± 0.04	4	-5.44 ± 0.04	4
RS17053	-8.35 ± 0.10	10	-6.59 ± 0.09	10	-7.03 ± 0.12	10	-5.46 ± 0.04	5	-6.41 ± 0.07	5
sertindole	-9.32 ± 0.08	8	-8.37 ± 0.07	7	-7.55 ± 0.10	10	-5.06 ± 0.02	4	-5.38 ± 0.05	4
tamsulosin	-9.67 ± 0.06	17	-8.12 ± 0.04	15	-9.57 ± 0.06 -5.85 ± 0.09 67.9 ± 1.9% site 1	24	-6.25 ± 0.08	4	-6.09 ± 0.07	4
terazosin	-7.93 ± 0.05	6	-7.95 ± 0.05	6	-8.06 ± 0.06	6	No binding	4	>-4	4
urapidil	-7.21 ± 0.02	5	-5.50 ± 0.07	7	-6.16 ± 0.06	7	-5.27 ± 0.05	4	-4.98 ± 0.01	4
WB4104	-9.03 ± 0.04	10	-7.39 ± 0.05	7	-8.66 ± 0.11 -5.77 ± 0.15 63.8 ± 2.7% site 1	19	-4.40 ± 0.05	4	-4.81 ± 0.09	4
Subtype-selective α-adrenoceptor antagonists										
5-methyl-urapidil	-8.23 ± 0.05	5	-6.06 ± 0.04	5	-5.18 ± 0.13	7	-6.12 ± 0.04	5	-5.00 ± 0.07	5
RS100329	-9.60 ± 0.05	10	-6.67 ± 0.07	7	-7.45 ± 0.08 -4.78 ± 0.12 66.1 ± 3.4% site 1	15	>-4	4	-4.74 ± 0.08	4
silodosin	-9.67 ± 0.04	8	-6.55 ± 0.08	8	-7.20 ± 0.12	8	-4.85 ± 0.04	4	-7.58 ± 0.13	4
BMY7378	-6.61 ± 0.05	5	-6.23 ± 0.05	6	-8.56 ± 0.07 -5.14 ± 0.15 66.1 ± 2.6% site 1	17	-4.08 ± 0.01	3	-4.34 ± 0.02	3

	Log KD α1A	n	Log KD α1B	n	Log KD α1D	n	Log KD β1	n	Log KD β2	n
Non-selective β-antagonists										
alprenolol	-6.28 ± 0.04	5	-4.80 ± 0.10	6	-5.09 ± 0.11	8	-7.83*		-9.04*	
bisoprolol	-3.92 ± 0.10	6	>-3	5	-3.91 ± 0.06	8	-7.83*		-6.70*	
bucindolol	-7.57 ± 0.07	5	-6.46 ± 0.04	5	-6.73 ± 0.12	8	-9.31**		-9.99**	
carazolol	-6.57 ± 0.03	5	-4.68 ± 0.05	6	-5.71 ± 0.09	8	-9.69**		-10.49**	
CGP 12177	-5.14 ± 0.05	6	>-4	5	-4.60 ± 0.06	7	-9.21*		-9.39*	
cyanopindolol	-5.59 ± 0.05	8	-4.91 ± 0.09	7	-5.64 ± 0.09	9	-10.39**		-11.09**	
pindolol	-5.40 ± 0.04	5	>-4	5	-4.88 ± 0.07	7	-8.57**		-9.23**	
propranolol	-4.91 ± 0.02	6	-3.98 ± 0.04	6	-4.57 ± 0.09	8	-8.16*		-9.08*	
SDZ 21009	-5.24 ± 0.07	6	>-4	6	-5.09 ± 0.05	9	-8.94**		-10.28**	
timolol	-4.67 ± 0.05	6	>-3	6	-4.22 ± 0.07	8	-8.27*		-9.26*	
Subtype selective β-antagonists										
CGP 20712A	-4.93 ± 0.10	5	>-4	5	-5.29 ± 0.11	7	-8.84 ± 0.14	8	-5.73 ± 0.04	9
ICI 118551	-5.23 ± 0.03	5	-4.20 ± 0.06	5	-4.88 ± 0.07	7	-6.66 ± 0.03	9	-9.54 ± 0.06	8
Ligands considered as dopamine or 5-HT ligands, SSRIs and antipsychotics										
amitriptyline	-8.19 ± 0.02	9	-6.22 ± 0.05	9	-6.44 ± 0.06	7	-4.36 ± 0.06	8	-4.99 ± 0.04	9
aripiprazole	-7.32 ± 0.09	5	-6.71 ± 0.03	5	-6.73 ± 0.13	7	-6.13 ± 0.05	5	-6.68 ± 0.10	5
chlorpromazine	-8.94 ± 0.06	5	-7.84 ± 0.05	5	-8.17 ± 0.11 -5.36 ± 0.07 63.2 ± 2.6% site 1	14	-4.83 ± 0.05	5	-5.11 ± 0.03	5
clomipramine	-8.16 ± 0.12	7	-6.38 ± 0.08	7	-6.26 ± 0.11	7	-4.98 ± 0.04	5	-5.30 ± 0.07	5
clozapine	-8.27 ± 0.04	5	-7.39 ± 0.07	5	-7.22 ± 0.12 -4.70 ± 0.13 74.9 ± 3.2% site 1	10	-4.30 ± 0.10	6	-5.01 ± 0.14	5
dosulepin	-7.11 ± 0.04	5	-5.28 ± 0.11	7	-5.57 ± 0.08	7	-4.43 ± 0.08	3	-4.77 ± 0.09	3
doxepin	-7.74 ± 0.04	5	-6.18 ± 0.03	5	-6.24 ± 0.12	7	-4.06 ± 0.01	5	-4.62 ± 0.02	5
dihydroergotamine	-8.62 ± 0.08	5	-6.92 ± 0.08	5	-7.28 ± 0.13[ep]	9	-4.46 ± 0.11	4	-5.25 ± 0.01	5
haloperidol	-7.70 ± 0.03	5	-7.21 ± 0.07	6	-6.57 ± 0.12	8	-4.09 ± 0.03	4	-4.97 ± 0.03	4
lisuride	-7.94 ± 0.06	5	-6.07 ± 0.04	5	-7.54 ± 0.14 -5.19 ± 0.21 64.4 ± 4.1% site 1	10	-6.03 ± 0.06	5	-7.48 ± 0.04	5
nortriptyline	-7.74 ± 0.03	6	-6.07 ± 0.07	5	-5.95 ± 0.11	9	-4.64 ± 0.13	5	-5.40 ± 0.08	5
olanzapine	-6.61 ± 0.11	7	-6.00 ± 0.10	10	-5.64 ± 0.12	9	>-3	4	-4.96 ± 0.05	4
risperidone	-8.77 ± 0.06	6	-7.81 ± 0.04	6	-7.41 ± 0.11	7	No binding	4	>-4	4
trimipramine	-7.37 ± 0.08	5	-6.10 ± 0.06	5	-5.90 ± 0.09	5	-4.16 ± 0.03	5	-4.70 ± 0.05	5
ziprasidone	-8.75 ± 0.06	6	-7.73 ± 0.07	7	-7.39 ± 0.10	8	No binding	4	No binding	4

*data from Baker (2005) *Br. J. Pharmacol.* **144:** 317-322.
data from Baker (2010) *Br. J. Pharmacol.* **160: 148-161.