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COMMENTARY

The 'state' of β-adrenoceptors

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Abbreviations: BRL 37344, (*RR* + *SS*)[4-[2-[[2-(3-chlorophenyl)-2-hydroxy-ethyl]amino]propyl]phenoxy]acetic acid; CGP 12177, 4-(3-t-butylamino-2-hydroxypropoxy)benzimidazol-2-one; CGP 20712A, 2-hydroxy-5(2-((2-hydroxy-3-(4-((1-methyl-4-trifluoromethyl) 1H-imidazole-2-yl) -phenoxy) propyl) amino) ethoxy)-benzamide monomethane sulphonate; CL 316243, disodium (*R*,*R*)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl-amino]propyl]-1,3-benzodioxole-2, 2-dicarboxylate; ZD 2079, (±)-1-phenyl-2-(2-(4-carboxymethylphenoxy)-ethylamino)-ethan-1-ol

'Atypical' β-adrenoceptors have emerged as receptors for compounds with known β-adrenoceptor agonist or antagonist activity, but display pharmacology that differs from existing descriptions of β_1-, β_2- or β_3-adrenoceptors. The use of the term 'atypical' as a prefix to 'β-adrenoceptor' does not necessarily imply or require demonstration of the function of the endogenous β-adrenoceptor agonists, noradrenaline or adrenaline. The number of 'atypical' β-adrenoceptor descriptions exceeds the number of cloned β-adrenoceptors (β_1-, β_2-, β_3-). Therefore, in the absence of cloning information, to extend the current classification of β-adrenoceptors beyond the three β-adrenoceptor subtypes, is it possible for 'atypical' β-adrenoceptor pharmacology to be accommodated within them?

Recently, the concept of β-adrenoceptor 'states' emerged (Konkar *et al*., 2000; Kaumann *et al*., 2001) to account for the observation that one receptor can interact with a single compound with two distinctly different modes of action, namely, blockade and stimulation (Kaumann, 1989; Pak & Fishman, 1996). Such compounds, termed 'nonconventional' partial agonists (Kaumann, 1989), exemplified by CGP 12177 cause blockade of β_1- and β_2-adrenoceptors at low (nano- or subnanomolar) concentrations, but activation at considerably higher (~2–3 log units) concentrations. The effects attributed to activation by CGP 12177 were mostly studied in the heart, where it causes increases in force and rate of contraction (Kaumann & Molenaar, 1996; Malinowska & Schlicker, 1996), and in brown adipose tissue where it causes thermogenesis and activation of adenylyl cyclase (Preitner *et al*., 1998; Konkar *et al*., 2000). The requirement for the involvement of the β_1-adrenoceptor in these effects was not immediately obvious because stimulatory effects of CGP 12177 were relatively resistant to β_1- and β_2-adrenoceptor blockade by propranolol (Kaumann & Molenaar, 1996) or selective β_1-adrenoceptor blockade with CGP 20712A (Malinowska & Schlicker, 1996). The property of propranolol resistance was more typical of pharmacology associated with β_3-adrenoceptor-mediated effects; however, the involvement of β_3-adrenoceptors for CGP 12177-evoked cardiostimulation was discounted on the basis of several lines of evidence, including the preservation of effects in mice lacking β_3-adrenoceptors (Kaumann *et al*., 1998). Although functional β_3-adrenoceptors exist in brown adipose tissue, stimulatory effects of CGP 12177 were also conserved in mice lacking β_3-adrenoceptors (Preitner *et al*., 1998, Konkar *et al*., 2000). An obligatory role of β_1-adrenoceptors for the stimulatory effects of CGP 12177 in brown adipose tissue and the heart was deduced from mice lacking β_1-adrenoceptors (adipose tissue, Konkar *et al*., 2000) or both β_1- and β_2-adrenoceptors (heart, Kaumann *et al*., 2001). In brown adipose tissue from β_1-adrenoceptor knockout mice, the high-affinity component of the CGP 12177 effect attributed to β_1-adrenoceptor activation was abolished (Konkar *et al*., 2000) while in the heart, the cardiostimulant effects of (−)-CGP 12177 were abolished from double β_1-/β_2-adrenoceptor knockout mice, but preserved in β_2-adrenoceptor knockout mice (Kaumann *et al*., 2001). On this basis, the concept of separate states of the β_1-adrenoceptor was proposed.

In this issue, Kozłowska *et al*. (2003) propose the existence of an 'atypical' β-adrenoceptor in rat isolated mesenteric artery, which has many features that appear to differentiate it from β_3-adrenoceptors and the 'state' of the β_1-adrenoceptor activated by (−)-CGP 12177 and cyanopindolol in the heart (Kaumann *et al*., 2001). As was the case in rat heart for CGP 12177 and cyanopindolol (Kaumann & Molenaar, 1996; Malinowska & Schlicker, 1996), these compounds caused activation of the mesenteric artery 'atypical' β-adrenoceptor, but with considerably lower potencies (CGP 12177 ~3-log units; cyanopindolol ~2-log units) than in the heart. One of the many intriguing aspects of the description of the mesenteric artery 'atypical' β-adrenoceptor is that ZD 2079 aligns itself alongside CGP 12177 and cyanopindolol as a full agonist with similar sensitivity to blockade by high concentrations of CGP 20712A and bupranolol. It would be interesting to know whether other selective β_3-adrenoceptor agonists also have the same sensitivity to blockade by high concentrations of CGP 20712A and bupranolol or whether ZD 2079 distinguishes itself also on the basis of sensitivity to β-blockers, but the other selective β_3-adrenoceptor agonists used by Kozłowska *et al*. (2003), CL 316243 and BRL 37344 had relatively low potency and intrinsic activities and were therefore excluded from

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further investigation. It is also interesting to make comparisons between the pharmacology of ZD 2079 in the rat mesenteric artery and other rat tissues. In rat colon ZD 2079 is a full agonist at β_3-adrenoceptors with very similar pharmacology to other β_3-adrenoceptor agonists such as BRL 37344, SR 58611 and CL 316243 (Kaumann & Molenaar, 1996), while it has no effect on the β_1-adrenoceptor state stimulated by CGP 12177 and cyanopindolol in the heart (Kaumann & Molenaar, 1996; Malinowska & Schlicker, 1996). Unlike CGP 12177 and cyanopindolol, ZD 2079 is not a nonconventional partial agonist, at least not in the heart (Kaumann & Molenaar, 1996). Unlike the CGP 12177-activated state of the β_1-adrenoceptor described in the heart (Kaumann & Molenaar, 1996; Malinowska & Schlicker, 1996), where all known activators block β_1- and β_2-adrenoceptors with high affinity and cause activation at much higher concentrations, the effects of ZD 2079 suggest that this may not always be the case for the mesenteric artery 'atypical' β-adrenoceptor. If the pharmacology of the rat mesenteric artery 'atypical' β-adrenoceptor is reproducible in mice, it could then provide the opportunity to use genetically engineered mice that lack β_1-, β_2- or β_3-adrenoceptors to determine which, if any, of these receptors play a critical role and whether the rat mesenteric artery 'atypical' β-adrenoceptor can then be considered to be another distinct 'state' of a β-adrenoceptor.

The next phase of 'atypical' β-adrenoceptor research will be expected to elucidate the molecular requirements that confer 'atypical' β-adrenoceptor pharmacology. Several approaches may prove necessary. For example, investigations of β-adrenoceptors with site-specific mutagenesis may provide information about critical amino acids that are crucial for interactions between the ligand and receptor such as those required for the antagonist and agonist properties of nonconventional partial agonists, or are responsible for the divergent activities for ZD 2079 and CL 316243, such as that seen in the study of Kozłowska *et al*. (2003). Detailed analysis of structure activity relationships of compounds may determine the requirements for 'atypical' β-adrenoceptor activity. So, finally, can 'atypical' β-adrenoceptor pharmacology be explained within the context of the three cloned β-adrenoceptors? Do specific compounds, such as nonconventional partial agonists including CGP 12177 and cyanopindolol and other compounds such as ZD 2079, induce specific activated 'states' of β-adrenoceptors corresponding to 'atypical' behaviour? The observation that receptors, including β_1- and β_2-adrenoceptors can also form homo- or heterodimers (Mercier *et al*., 2002), raises the opportunity to explore whether these entities may be responsible for divergent ligand-β-adrenoceptor interactions and what we now term, 'atypical' β-adrenoceptors; however, this hypothesis remains to be investigated.

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