G-PROTEIN-COUPLED RECEPTORS

Better beta-blockers

A new study has shown that the majority of β-adrenoceptor antagonists (beta-blockers) currently in clinical use for hypertension, heart disease and, more recently, heart failure have poor selectivity between adrenoceptor subtypes β_1 and β_2 in whole-cell assays. The report by Jillian Baker in the *British Journal of Pharmacology* suggests that the development of existing, more selective, β-adrenoceptor antagonists as beta-blocker drugs should be considered as an alternative to those already in clinical use.

The clinical rationale for using beta-blockers to treat most cardiovascular disorders is to antagonize β_1-adrenoceptor signalling to reduce the rate and force of cardiac muscle contraction. However, the beneficial mode of action in heart failure is still not understood. Although highly selective β_1-antagonists do exist, most of the beta-blockers available for clinical use also antagonize β_2-adrenoceptors, which are expressed at high levels in the airways, causing bronchospasm, a major side-effect of this therapeutic class.

One of the challenges when comparing the subtype-specificity of different β-adrenoceptor antagonists is the method by which the selectivity was originally determined. Initially, drugs were screened for selectivity by observing changes in heart rate or contraction of cardiac muscle (β_1-selective) or bronchial smooth muscle (β_2-selective) using animal or human tissue. However, these measurements are subject to great variation caused by differences in cellular context and between individuals and species, as well as the effects of underlying disease or of previous medication, such as exposure to β-adrenoceptor drugs. Results obtained by this method therefore more accurately reflect tissue-binding specificity, rather than the receptor-binding specificity of the drug.

The study by Baker measured the binding of a wide range of β-adrenoceptor antagonists to stably expressed β_1-, β_2- and β_3-adrenoceptors in an identical mammalian cell culture environment. Using a competitive binding assay, K_D values (the concentration at which half the receptors are bound by the competing ligand) were determined for each drug. The values showed that although there is great variation in the potency of clinically used beta-blockers for all receptor subtypes (from nanomolar to micromolar affinity), they showed little selectivity between β_1 and β_2 subtypes, and only one drug was found to be selective for the β_3-adrenoceptor. Some drugs (for example, metoprolol, bisoprolol and atenolol) thought to be β_1-adrenoceptor-selective and currently used to treat cardiovascular disorders are poorly β_1-selective, whereas others (for example. carvedilol, sotalol and timolol) actually have higher affinities for the β_2-adrenoceptor subtype.

It is becoming clear that the clinical benefit of beta-blockers in heart failure cannot be attributed to receptor affinity alone, and other factors, such as longevity of action at the receptors, must also play a part. Indeed, this study comes at a controversial time for beta-blockers — the paradoxical hypothesis that beta-blockers might actually be beneficial in asthma is now being tested in clinical trials after it was shown that long-term exposure can reduce lung sensitivity in a mouse model of asthma. As more is learnt about the complex pharmacology of adrenoceptors, there is clearly potential for the development of drugs with greater selectivity and less side-effects for a range of indications.

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References and links

ORIGINAL RESEARCH PAPER Baker, J. G. The selectivity of β-adrenoceptor antagonists at the human β_1, β_2 and β_3 adrenoceptors. *Br. J. Pharmacol.* **144**, 317–322 (2005)

FURTHER READING Callaerts-Vegh, Z. *et al.* Effects of acute and chronic administration of beta-adrenoceptor ligands on airway function in a murine model of asthma. *Proc. Natl Acad. Sci. USA* **101**, 4948–4953 (2004) | Abbott, A. Beta-blocker goes on trial as asthma therapy. *Nature* **432**, 7 (2004)