What do beta-blockers really do? A view from both sides of the receptor

Based on the Oliver Sharpey Lecture 1992

The scene for this lecture will effectively be a cell in the heart or blood vessels, although the evidence for what happens there will be drawn more widely. Such cells bear β-adrenergic receptors in their membrane which permit the cell to interact with the β-agonists adrenaline and noradrenaline. Since the work of Landis on the rabbit 25 years ago, at least two types of β-receptor have been recognised for which noradrenaline and adrenaline differ in their so-called rank order of potency. Noradrenaline is about 20-fold less potent (that is 20-fold more noradrenaline is required) at stimulating β_2- than β_1-receptors. For a long time, and perhaps correctly for most species except man, the heart was thought to have only β_1-receptors, while lung and blood vessels had β_2-receptors.

β-blockers were developed to protect the heart from excessive increases in rate or contractility when coronary artery disease sets a fixed limit to the blood supply—a sort of reverse monetarism, in economic terms. The first blocker in clinical use, propranolol, binds with equal affinity to β_1- and β_2-receptors. Practolol, and later atenolol, were developed as β_1- selective blockers, the therapeutic rationale being that such drugs would protect the heart without risking asthma by blocking the action of endogenous or therapeutic β-agonists in the lungs. Atenolol is the best known but not now the most β_1-selective antagonist available, and in our studies presented here we have used bisoprolol and some compounds with numbers only. Beyond the receptor, inside the cell, is the cell signal to which β-receptors are coupled, namely the enzyme adenylyl cyclase, and between the receptors and their target are the GTP-binding proteins which are responsible for the coupling of receptor to enzyme.

Clinical studies with β-agonists

The work started with a clinical observation more than 10 years ago. When adrenaline was infused into healthy subjects over two hours to reproduce the plasma adrenaline concentration seen in patients after a myocardial infarction, the resultant tachycardia persisted long after the circulating adrenaline concentration had returned to normal. This persistent tachycardia occurs only after prolonged infusions of adrenaline and not after infusion of the synthetic β-agonist, isoprenaline. At the time, we considered these observations evidence for the uptake and accumulation of circulating adrenaline in sympathetic nerve endings, from where it could be re-released after it disappeared from the circulation. Isoprenaline, by contrast, is not a substrate for the neuronal uptake pump [1,2]. An alternative explanation, however, was suggested by another difference between the amines, namely that isoprenaline is relatively selective for β_1-receptors. Figure 1 shows the large fall in plasma potassium during infusion of adrenaline, but not with isoprenaline. This hypokalaemia is β_2-receptor mediated since it was abolished by low doses of the selective β_2- antagonist ICI 118551. This drug also abolished the tachycardia caused by adrenaline and some of the inotropic effect as assessed by shortening of systolic time intervals. Because of these various β_2-receptor mediated actions of adrenaline, we started to question the prevailing administration of β_1-selective blockers to patients with ischaemic heart disease. Although Minemann had already published evidence for β_2-receptors in the human heart as assessed by radioligand binding to heart membranes, studies in isolated hearts of other species were strongly against a functional β_2-receptor [3].

This view was shown to be incorrect experimentally in organ-bath studies, and clinically in six patients undergoing cardiac catheterisation [4]. Low doses of the selective β_2-agonist salbutamol infused into the right coronary artery caused tachycardia, whereas the same doses of salbutamol had no effect when injected systemically (into the aorta). This investigation was performed because of the theoretical objection to studies with intravenous β_2-agonists that tachycardia is just a reflex response to the peripheral vasodilation caused by their stimulation of vascular β_2-receptors.

Because of the importance of demonstrating a functional cardiac β_2-receptor, we also confirmed that salbutamol was acting on a β_2-receptor, in two further groups of patients pretreated with a single dose of either practolol to block only β_1-receptors, or two hours before the catheterisation with propranolol to block both β_1 and β_2-receptors. Figure 2 shows the mean rises in heart rate from these two groups and the untreated

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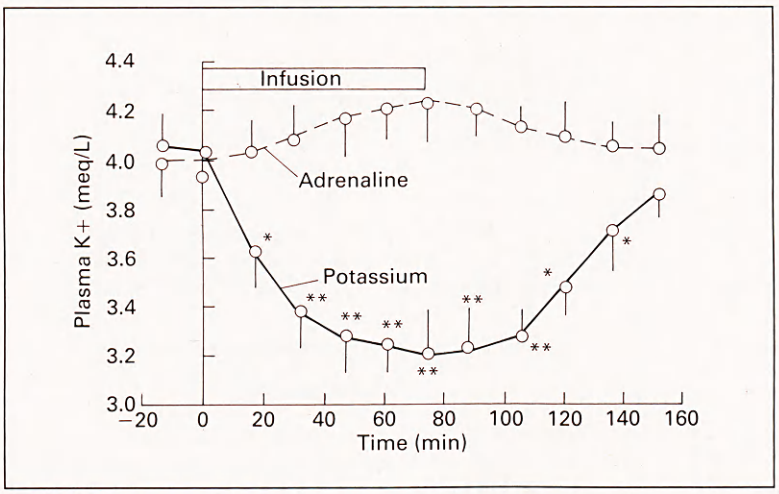


Fig 1. *Comparison of hypokalaemia during adrenaline and isoprenaline infusion.* Adrenaline (0.1 μg/kg/min) was infused over 80 minutes into six healthy volunteers. The infusions caused a similar tachycardia, but only the adrenaline caused a fall in plasma potassium. (Reproduced with permission from *New England Journal of Medicine* [1]).

patients. Only when the β_2-receptor was blocked by propranolol was the dose-response curve shifted.

The therapeutic implication is also clear from this study. Patients receiving β-selective antagonists like practolol or its modern descendants are not protected against tachycardia caused by β_2-agonists, including the endogenous agonist, adrenaline. And with tachycardia goes the threat—in patients with ischaemic heart disease—of increased oxygen demand, angina and arrhythmias.

Organ bath studies

Further dissection of the roles and interactions of the β-receptors in heart had to be carried out in organ bath studies to construct complete dose-response curves and employ highly selective antagonists which cannot be administered to patients.

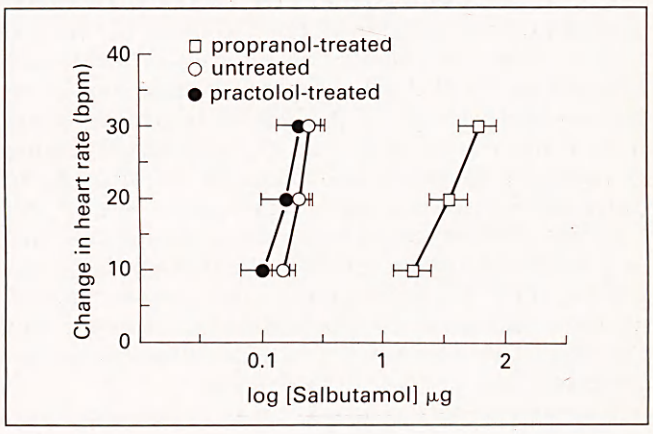
Kaumann had already shown in studies on human papillary muscle strips that the inotropic response achieved with β_2-receptor stimulation amounted to about 40% of that achieved with β_1-receptor stimulation [5]. Atrium was potentially even more interesting because ligand binding studies had shown a higher proportion of β_2 binding sites in atrium. In Figure 3, redrawn from the autoradiographic study of Buxton *et al*, the receptors are seen as silver grains in pieces of atrial appendage which have been incubated with the ligand radiolabelled iodocyanopindolol [6]. Neither β_1- nor β_2-antagonists fully displace the silver grains resulting from bound radiolabel, whereas non-selective blockade displaces the radioligand virtually entirely.

We used the highly selective β_1- and β_2-antagonists CGP20712A (CGP) and ICI118551 (ICI) to investigate the responses of noradrenaline and adrenaline selectively on the remaining non-blocked receptor. At the end of each dose response curve, we added a maximal concentration of the non-selective β-agonist isoprenaline to the organ bath so that results could be expressed as a percentage of the maximal (isoprenaline) response. Two patterns of response began to emerge. The mean dose-response curves for one pattern are shown in Figure 4. The features to note are:

- that adrenaline starts to contract the atrium at concentrations (around 1 nM) well within the range seen during stress;
- that this contraction is β_2-mediated, since the β_1-blocker CGP has no effect; and
- this β_2-mediated contractile response in atrium achieves the maximum possible through β-receptors (unlike the 40% of maximum in healthy ventricular muscle).

But the most interesting feature of this Figure proves to be the title. This pattern of response was

Fig 2. *Heart rate responses to intracoronary salbutamol.* Three groups of six patients each received incremental doses of salbutamol into the right coronary artery at the end of a diagnostic catheterisation. These doses had no effect when injected into the aorta. The graph shows the interpolated doses determined to increase heart rate by 10, 20 and 30 beats per minute (bpm) in the three groups of patients. (Reproduced with permission from *Circulation Research* [4]).



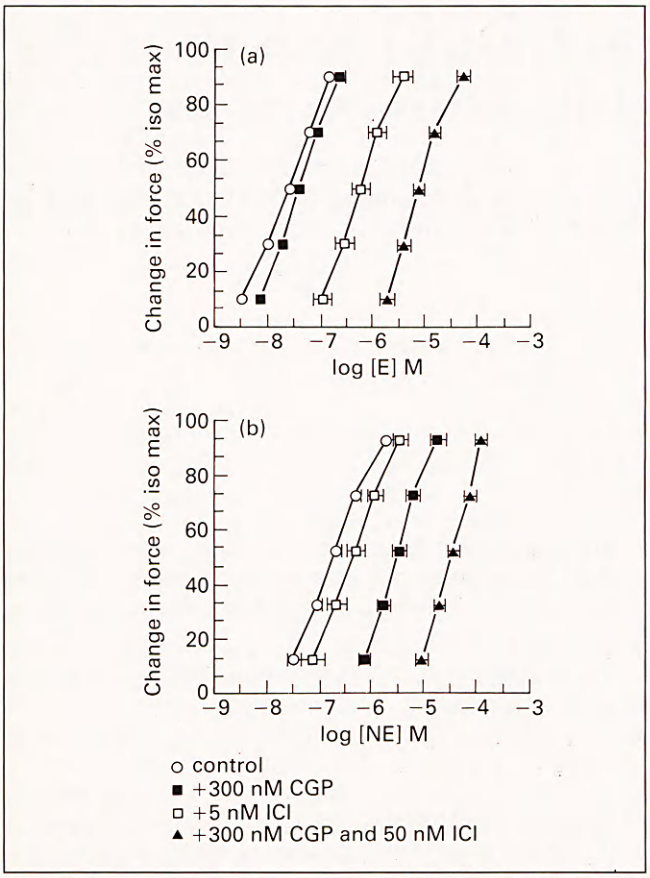


Fig 3. *Concentration-effect curves for (a) adrenaline (E) and (b) noradrenaline (NE) on tissues from atenolol-treated patients.* Responses are the developed contractile force expressed as a percent of the maximum response of the tissue to 0.2 mM isoprenaline (iso). (Reproduced with permission from *Circulation Research* [7]).

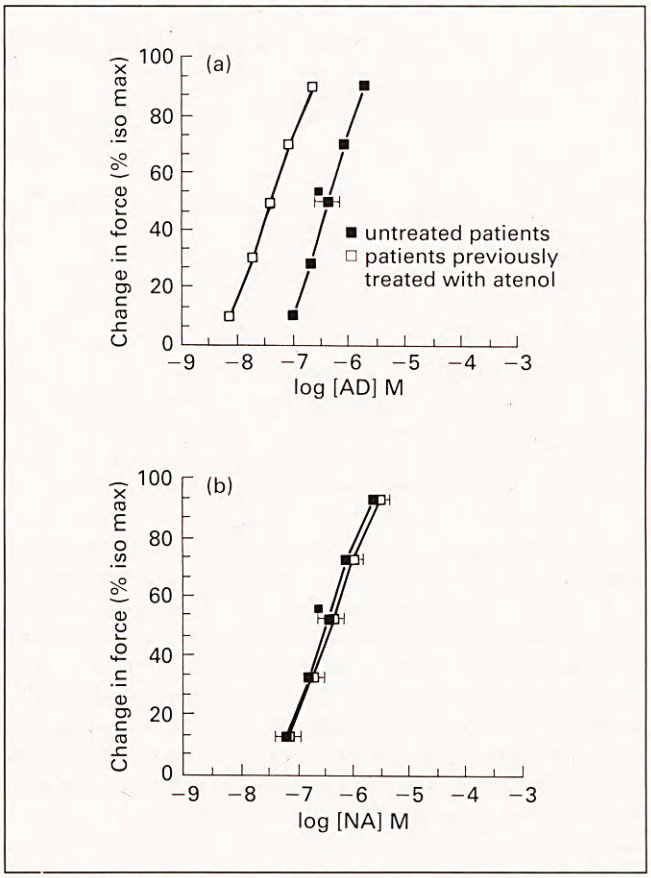


Fig 4. *Effect of beta$_1$-blockade on (a) adrenaline and (b) noradrenaline responses in human atrial strips.* Responses are the developed contractile force expressed as a percent of the maximum response of the tissue to 0.2 mM isoprenaline (iso).

seen only in patients receiving β_1-blockers—mainly atenolol—for at least a month prior to surgery. When we looked at the responses of atrium from non-β–blocked patients, quite a different pattern was observed. These two responses are summarised in Figure 5, in which adrenaline is seen to have a ten-fold greater potency in the β_1-blocked patients. In order to confirm that, the potentiation induced by β-blockade is paradoxically of the β_2-receptor, we undertook a further prospective study of β_1-blockade in patients awaiting coronary artery-vein graft (CAVG) surgery, using the selective β_2-agonist salbutamol in the organ bath. Since salbutamol is a partial agonist, the results this time (Fig 6) were even more dramatic because not only is the potency increased in the β-blocked patients (that is, there was a reduction in the concentration of agonist which achieved a half maximal response), but the efficacy, or maximal response, to salbutamol is also increased [7].

Experiments with partial agonists permit the receptor occupancy to be estimated. This confirmed that β-blockade does not alter the number of receptors occupied but that the potentiation must occur at a later stage in the cell signalling pathway.

Further pharmacological experiments pointed to an effect of β_1-blockade not only on the coupling of the β_2-receptor to its effector, adenylyl cyclase, but also on the coupling of other receptors to adenylyl cyclase. We had found that 5HT stimulates an inotropic response in isolated human atrial (but not ventricular) strips, and that this response—through what is now called the $5HT_4$ receptor—is associated with a rise in cyclic AMP and PKA* [8]. Compared to isoprenaline, 5HT was only a partial, albeit highly potent, agonist and, as with salbutamol, we found that atrial strips from patients receiving β_1-blockers showed a marked increase in the maximal response to 5HT (Fig 7) [9]. Since 5HT is presumably released during clot forma-

* Cyclic AMP dependant protein kinase

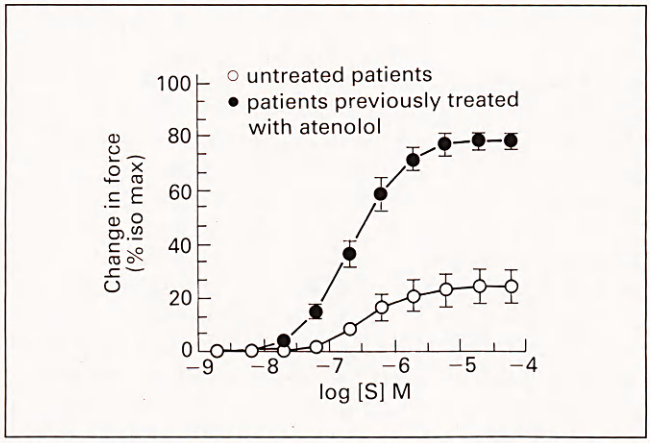


Fig 5. *Inotropic responses to salbutamol* (S). Responses are developed contractile force expressed as a percent of the maximum response of the tissue to 0.2 mM isoprenaline (iso).

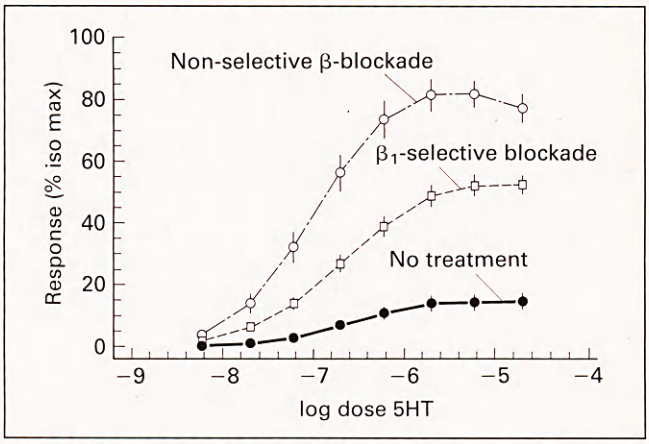


Fig 6. *Effect of prior beta-blockade on inotropic response to 5HT in isolated human atria.* Responses are the developed contractile force to increasing concentrations of 5HT expressed as a percent of the maximum response of the tissue to 0.2 mM isoprenaline (iso).

tion in a coronary artery, this potentiation of 5HT's response by β-blockade may also be of clinical interest, and the question now arises whether 5HT responsiveness is greater when one or both β-receptors have been blocked. We have not often obtained atrium from patients receiving non-selective blockers, but in five patients non-selective β-blockade has raised the intrinsic activity of 5HT to 80% of maximum, compared to only 60% in the strips from β-blocked patients. I shall speculate about the clinical meaning of this observation later. Its mechanistic implication is that all receptors coupled to adenylyl cyclase share a limited pool of some critical factor which in heart muscle is normally 'hogged' by the β_1-receptors, since these are under a high degree of tonic stimulation by neuronal noradrenaline. We shall see later that in blood vessels, where sympathetic innervation is much poorer than in the heart, β-blockade does not potentiate β_2-responsiveness.

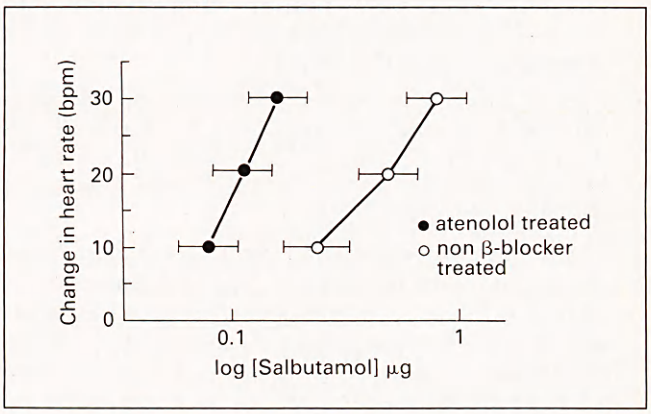
G-proteins

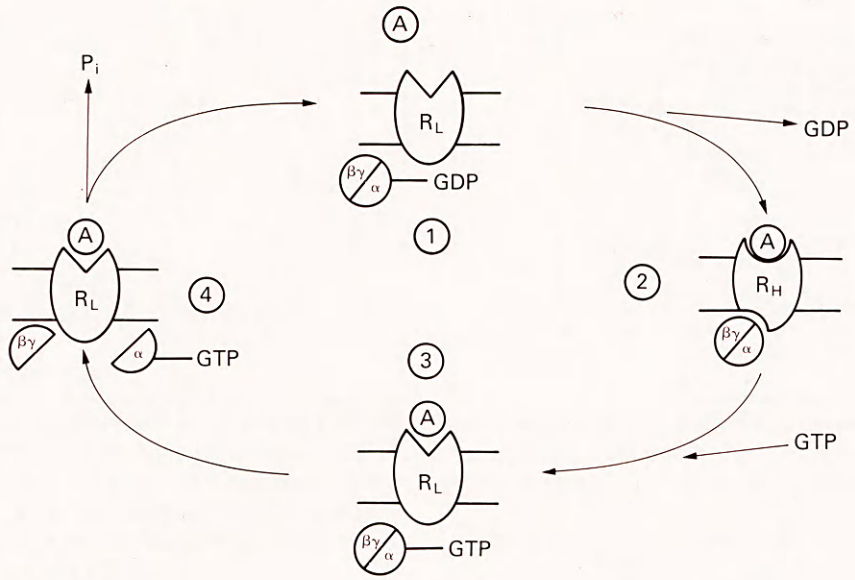
A high affinity receptor, such as the growth factor receptor, binds its agonist too long to permit the rapid on-off rates for the response necessary for most neurotransmitters. Nature has solved this problem by providing molecules which can continue talking to the cell after the receptor and agonist have parted company, leaving the receptor free to be stimulated once again (Fig 8). The G-proteins are trimeric, consisting of α, β and γ subunits. Each time a β-receptor is occupied by an agonist, the stimulatory G-protein (G_s) coupled to the receptor binds GTP and releases the α subunit with its bound GTP. It is this $G_s\alpha$-GTP complex which activates adenylyl cyclase.

The possibilities of the coupling system are further enhanced by adding an inhibitory G-protein (G_i) whose activation opposes the effect of the stimulatory G-protein, G_s. These G_s and G_i proteins differ in their alpha subunit, but share common subunits which themselves have an inhibitory action by mopping up alpha subunits of G_s. This improves signal-to-noise ratio by requiring a higher degree of receptor occupation before enough $G_s\alpha$ is generated. But even $G_s\alpha$ and $G_i\alpha$ are not single proteins. There are three variants of $G_i\alpha$, coded on different genes, and four splice variants of $G_s\alpha$, coded by the same gene.

We considered at least three ways in which β_1-blockade may alter coupling.

Fig 7. *Heart rate response to intracoronary salbutamol.* Increase in heart rate in beats per minute (bpm) plotted against log concentration of salbutamol (S). The doses to increase heart rate by 10, 20, and 30 beats per minute (bpm) have been determined for each individual by linear interpolation. Points are mean dose; bars are SEM. (Reproduced with permission from *Circulation Research* [21]).





1 *Basal state:* the receptor (R) is in a low affinity state (R_L) towards its agonist (A). The three subunits, αβγ, of the trimeric G-protein are associated with each other but not the receptor.

2 *Agonist binding:* spontaneous release of GDP from the G-protein promotes association of the G-protein with the receptor, changing this into a high affinity state (R_H) towards its agonist (A), which now binds to the receptor.

3 *GTP binding:* agonist binding to the receptor promotes the binding of GTP by the G-protein, which in turn causes the receptor to revert to a low affinity state (R_L) towards the agonist.

4 *Release of GTP-α-subunit complex, activation of adenylyl cyclase, and GTP hydrolysis:* the complex of αβγ with GTP is unstable, causing dissociation of the α-subunit with its bound GTP; it is this α-subunit-GTP complex which acts on the effector, eg adenylyl cyclase.

Return to the basal state occurs when the GTP is hydrolysed by the GTPase activity of the free α-subunit. This GTPase activity is slow relative to the cycle of receptor occupation and release by the receptor. Hence amplification is achieved because several effector molecules are acted upon for each cycle of receptor occupation.

Fig 8. *Schema of G-protein/receptor interaction.*

- The simplest is an increased level of G_s or reduced level of G_i, the latter being half expected from considerable data showing that a chronic increase in β-receptor stimulation—both in cultured cells, and *in vivo* in patients with heart failure—leads to increased levels of G_i [10,11].
- The second is that β-receptor stimulation or blockade regulates a modification of G_s or G_i that affects their function $G_s\alpha$ has recently been shown to be phosphorylated at a serine residue present in two of the splice variants [12,13].
- Third, but more difficult to detect, there may be no change in total levels of G_s or G_i, but a limiting pool of G_s for different receptors to share, so that blockade of one receptor leaves more available for the remaining receptors. Alternatively, the sensitivity of all receptors coupled to G_s may normally be damped by βγ subunits tonically released from a dominant receptor's coupled G_s, as already believed to be the case for βγ subunits released from G_i. Again, blockade of the β_1-receptor would help the remainder by reducing the ambient concentration of βγ.

Any explanation has to provide for the failure of β_1-sensitivity itself to increase, and the time course of hours to days over which sensitisation seems to occur. One possibility, which intrigued us at the beginning, stemmed from the known variants for $G_s\alpha$, the alpha subunit of $G_s\alpha$. These are sometimes known as long and short $G_s\alpha$, since the latter lack 15 amino acids, expressed by exon 3.

How could we determine whether β-blockade affects the proportion of these variants, and more generally the proportion of G_s to G_i.

Techniques for measuring G-proteins

G-proteins can be studied either at the level of the whole protein, or the alpha subunits which define the different G-proteins, or the mRNA encoding them. We have used each of the available techniques to compare the levels of G_s and G_i in atria from β_1-blocked and untreated patients.

For protein detection, the proteins are separated by polyacrylamide gel electrophoresis, and detected either by a specific antibody (immunoblotting), or by enzymatically radiolabelling the protein (prior to running the gel) in a reaction for which the G-protein of interest is a semi-specific substrate. This enzyme activity is present in the bacterial toxins from cholera and pertussis, catalysing the transfer of ^{32}P-ADP-ribose from NAD to G_s or G_i, respectively. Neither assay has demonstrated a difference in G_s: G_i ratio in the two groups of patients. However, the immunoblot which detects only the $G_s\alpha$ subunit has demonstrated an eight-fold greater level of the long $G_s\alpha$ splice variant than of the shorter variant; whereas the enzymatic assay, which detects only intact trimeric G_s, demonstrates a two-fold greater level of the shorter variant [14,15]. Since β-receptor stimulation, as explained already, leads to dissociation of the $G_s\alpha$ subunit, we suspect that the low level of long G_s detected by the ADP ribosylation (enzymatic) assay is due to the high sympathetic drive at the stage of the bypass operation when the atrial strip is removed for insertion of the bypass cannula. This is interesting since in the β_1-blocked patients only the β_2-receptor is available for stimulation; therefore the lack of difference between β_1-blocked and untreated patients would highlight the functional importance of the β_2-receptor in human atrium during high rates of sympathetic discharge. If we are correct in our explanation of the low level of long $G_s\alpha$ detected by ADP ribosylation, the interesting further implication is that there must be preferential activation of the longer variant of G_s following stimulation of the human atrial β_2-receptor. Direct investigation of this has been inconclusive. Our own rather circumstantial evidence for such selectivity comes from two coincidental findings of species variation in $G_s\alpha$ and adenylyl cyclase activity. The first finding is that the longer variant of $G_s\alpha$ is the predominant form detected by immunoblot or at mRNA level in human atrium, which is unlike our findings in other species (eg guinea-pig, dog, and rat); and second, we have found that approximately three-fold more adenylyl cyclase is coupled to β_2- than β_1–adrenoceptors in human atrial membranes [5,14].

The most sensitive assay for RNA uses the polymerase chain reaction (PCR) to amplify cDNA transcribed from the RNA. This assay also permits differentiation of mRNA species only slightly different in size. In particular, the principle of what is now called 'competitive PCR' allowed us to demonstrate that there is similar or slightly greater expression of the long than short variants of $G_s\alpha$. This similarity at mRNA level supports the thesis that the difference in the protein assays is due to selective activation of the long variant. However, once again we have found no difference between the β_1-blocked and untreated patients.

To achieve more accurate quantification, the PCR products are used to generate long cRNA probes labelled with digoxigenin-UTP to permit a sensitive non-radioactive Northern blot in which the RNA can be measured without amplification by detecting the chemiluminescent product of an anti-digoxigenin-enzyme conjugate. Once again, we have found no difference by this technique in expression of $G_s\alpha$ or $G_i\alpha$ between the two groups of patients.

In summary, the G-protein measurements point indirectly to a change following β-blockade not in absolute levels, but of functional—or available—G_s. The simplest model at present regards the inhibitory βγ subunits as the critical shared intermediate of all G-proteins—both G_s and G_i. The release of βγ subunits during activation of the dominant β_1-receptor will tend to mop up $G_s\alpha$ subunits around other receptors coupled to G_s, hence damping their sensitivity. This will be tested in the functional assays of G_s on which we are now concentrating. On the other hand, recent reports point to more functional heterogeneity than previously suspected among the subtypes of both βγ subunits and of adenylyl cyclase; therefore we cannot be confident that we have excluded a relevant change in G-protein or adenylyl cyclase expression following β_1-blockade [16–18].

Organ bath predictions

The remaining experiments were designed to test the predictions which we now felt able to make from our working model of β-blocker-induced supercoupling.

The first prediction was that the phenomenon could not be seen in a tissue where β_1-receptors were not the dominant receptors regulating adenylyl cyclase activity *in vivo*, for in that case β_1-blockade would not be expected to affect available G_s. This important negative would also exclude the possibility that the potentiating effect of β_1-blockade was systemic—for example, through increased production of thyroxine—rather than at the level of the cardiomyocyte itself.

For our experiments we used internal mammary artery where the density of both β_1-receptors and sympathetic nerve endings releasing noradrenaline is many-fold lower than in the heart.

First, we showed that functional β_2-receptors and—less expected—β_1-receptors, mediating relaxation, are present. Increasing concentrations of noradrenaline or adrenaline caused increasing relaxation up to 60% of the maximal relaxation achieved by nitrate. There was a striking similarity between the pattern of response to adrenaline in the artery and that seen in the heart strips from β_1-blocked patients. The relaxation of the artery was initiated by less than 10

nmol of adrenaline, and was not blocked by adding a β_1-blocker to the organ bath. The major difference from heart was that there is no difference between the groups of patients [19]. This is consistent with the first prediction that β_2- potentiation is tissue specific. Even the unexpected presence of a small number of functional β_1-receptors is insufficient to enable potentiation if they are not a major contributor to cyclase activation *in vivo*.

This leads to our second prediction, or question, that, in the language of Malvolio, tissues not born to respond to β-blocker induced potentiation, could have this thrust upon them *ex vivo* by stimulating the β_1-receptor with a much higher concentration of noradrenaline than obtains *in vivo* so that (in our model) the β_1-receptor starts to 'hog' more of the available G_s. We used human coronary artery for this experiment, where the β_1-receptors have a slightly greater functional role. The coronaries always come from transplant recipients in end-stage cardiac failure, and such patients never receive β-blockers.

As in the mammary artery, increasing concentrations of noradrenaline or adrenaline caused increasing relaxation of the artery. Strips of coronary artery were incubated overnight with either noradrenaline or atenolol, or both in combination. Noradrenaline, at the concentration of 10^{-6}M (modest compared to likely intrasynaptic concentrations *in vivo)* markedly reduced sensitivity of the coronary artery to β_2-receptor stimulation by adrenaline without altering β_1-receptor sensitivity to noradrenaline itself. Is this desensitisation mediated through the β_1- or β_2-receptor? Atenolol, at the very low concentration of 100 nmol/L to ensure selective β_1-blockade, completely prevented the desensitisation caused by noradrenaline when the artery was incubated overnight with agonist and antagonist together. Subsequently, the between-receptor nature of this desensitisation has been confirmed, using the highly β_1-selective blocker CGP to block the β_2-desensitisation caused by noradrenaline.

Thus we have reproduced in the organ bath over about 18 hours the potentiating effect of atenolol, but only stimulating β_1-receptors to the level likely to obtain normally in the heart (but not arteries).

Clinical predictions

Our second and final predictions from the model bring us back to clinical studies. Mechanistically, we wished again to induce β_2-hyperresponsiveness, but of greater clinical interest is the question whether such hyperresponsiveness is present in patients receiving long-term β-blockade, and who are at risk of adrenaline release during a myocardial infarction.

The mechanistic question was tackled in a prospective trial in six healthy subjects who received, in randomised, crossover fashion, two weeks' treatment with bisoprolol, the most selective β_1-antagonist available, or placebo. Three days after each period, when β_1-responsiveness assessed by exercise testing had returned to baseline, we measured β_2-responsiveness with incremental doses of the β_2-agonist, salbutamol. The results mirrored closely the differing effect of β_1-blockade in the heart and arteries in the organ bath. In the heart, salbutamol caused a dose-related increase in heart rate which was significantly greater after bisoprolol than after placebo; β_2-sensitivity, measured from the dose of salbutamol required to increase heart rate by 30 beats per minute, was increased by about 50%. By contrast, there was no difference between the two occasions in the fall in diastolic BP that results from vasodilation of arteries. We studied subjects three days after withdrawal of the β-blocker, partly to show (by exercise testing) that, as in the organ bath, there is no change in β_1-receptor sensitivity, and partly to offer our finding as a mechanism for the clinical syndrome of β-blocker withdrawal. However, three days after β-blockade we will be underestimating the degree of β_2-hyperresponsiveness. This was confirmed in a recent study in which salbutamol and exercise testing were undertaken two weeks after either non-selective β-blockade or placebo, and on this occasion no β_2-receptor potentiation was induced. It appears that only if the β_2-receptor can be stimulated can its responses be potentiated.

The final study, performed by Dr Jim Hall at Papworth, was similar in design to our first clinical study, involving intra-coronary infusion of salbutamol, except that on this occasion he deliberately compared matched groups of patients receiving or not receiving atenolol.

Figure 8 shows that, indeed, not only does β-blockade fail to protect the heart against β_2-stimulated tachycardia, but it markedly potentiates the response—six-fold less salbutamol being required in the atenolol treated patients to increase their heart rate by 30 beats per minute [20].

I have regarded adrenaline as an emergency hormone, with little functional importance in normal people or even most diseased patients. The surprising importance of the β_2-adrenoreceptor in human heart might have given man a slight survival advantage in the fight–and–flight response over other species which can achieve the same very high circulating levels of adrenaline but provide no extra receptors on which these levels can usefully act (beyond those already activated by the noradrenaline released locally from sympathetic nerve endings). It would be ironic if one of the great drug discoveries of modern times, the β-blockers, were once again giving these cardiac β_2-adrenoreceptors a functional role, but this time, a deleterious one, by increasing the risk of arrhythmias in patients who have sustained a myocardial infarction. The finding that β-blockade also potentiates another cardiac receptor coupled to adenylyl cyclase, the novel $5HT_4$-receptor, means that a return to using non-selective β-blockade cannot be assumed to be preferable, and we are now formally comparing outcome in

patients randomised to non-selective or β_1-selective β-blockade while awaiting cardiac bypass surgery, or following a myocardial infarction. But the potentiation of cardiac adenylyl cyclase may not all be harmful. The anecdotal evidence from the paradoxical benefit from β-blockade in heart failure receives some theoretical backing from our experiments; and at a more everyday level, the maintenance of cardiac output on chronic β-blockade might be one of the factors that help to avoid tiredness with the most selective β_1-blockers.

The exact mechanism of the receptor cross–talk remains uncertain, but is likely to involve the coupling of receptor to its cell signal, cyclic AMP production. We have eliminated the possibility of a simple change in proportion of stimulatory to inhibitory GTP-binding proteins. It seems likely that blockade of the dominant receptor either prevents a cyclic AMP dependent modification of a G-protein subunit, or simply leaves more functional G-protein available for other receptors. In either case, the fascinating and unsuspected aspect of receptor cross–talk is its long duration of action, providing the human heart with a memory of its recent drug history which lasts several days.

There are also some speculative consequences of a change in the proportion of functional G_s to G_i, which may explain some of the mysterious therapeutic effects of β-blockade. Might benefit in migraine, for instance, be due to enhanced 5HT sensitivity? And how do β-blockers lower blood pressure . . .?

So what do β-blockers really do?

As an erstwhile classicist, I am not sufficiently up to date with modern literature to find an apt quotation from Shakespeare, and turn instead to a passage in Aristotle's *Metaphysics*. Aristotle tells us that a good actuality is better than a good potentiality, but a good potentiality is better than a bad actuality. For a thing can become both better and worse but cannot be both good and bad—health and disease are cited as examples. So, the best is to have kinetic energy with a healthy heart and no β-blocker. But if the heart is unhealthy, it is better to preserve its potential—and shall we add, potentiating—energy with β-blockade.

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