METABOLIC EFFECTS OF BETA-ADRENOCEPTOR BLOCKADE. PART II.

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In "Metabolic effects of beta adrenoceptor blocking drugs. Part I", we reviewed the effects of this group of drugs (beta blockers) on glucose homeostasis, lipolysis and serum potassium [1]. We concluded by considering some of the ways in which these actions and others might modify the metabolic responses to exercise.

This paper is part II and it completes our review. It consists of three sections, two of which relate to potentially therapeutically relevant functions as opposed to ways in which beta blockers may produce unwanted effects. The first section reviews our current understanding of the effects of beta-blockers on thyroid hormones and the clinical implications of these observations. The second section considers briefly the way in which beta blockers may modify plasma renin activity and the possible relevance of this to their blood pressure lowering actions. Finally, we shall consider the possible effects of beta blockers on other hormones and endocrine fuctions. Insulin, the renin angiotensin system and thyroid hormones have already been considered and most is known about these. However there are other ways in which beta receptor stimulation may modify endocrine function; these will be documented in the final section.

BETA-BLOCKERS AND THE THYROID

The clinical picture of thyrotoxicosis - palpitations, tachycardia, agitation, sweating and tremor - closely resembles sympathetic overactivity. In the early part of this century, the disease was still regarded as a disorder of the autonomic nervous system and early treatment comprised surgery to the sympathetic outflow tracts and later the use of catecholamine-depleting drugs such as reserpine [2]. The introduction of beta-blockers in the 1960's provided a logical extension to this approach. In recent years the contribution of excessive sympathetic activity to the thyrotoxic state has been questioned and attention has turned to adrenoceptor number and function, although with contradictory results. However, since their introduction beta-blockers have proved very effective in the prompt relief of many of the manifestations of thyrotoxicosis and have established a place in the management of this condition.

Changes in circulating thyroid hormones

Initially, beta-blockers were thought to have no effect on thyroid hormone levels. Roszkowska et al first reported that propranolol lowered total serum triiodothyronine (T3) [3]. Other authors have since confirmed this observation [4-6]. Reductions in serum T3 of between 10 and 40% have been reported, a variability which is explained, at least in part, by the variability of the pharmacokinetics, and hence plasma concentrations, of propranolol in hyperthyroid patients [7]. These studies have also demonstrated a concomitant rise in reverse T3 [5,6], a metabolically inactive analogue of T3. By contrast propranolol has little effect on total thyroxine T4 concentrations in hyperthyroid patients.

Perhaps the best model for studying the effects of beta-blockers on circulating thyroid hormones is the euthyroid subject, as here there is no primary disturbance of thyroid homeostasis to modify or overshadow the effects of the drugs per se. Fewer studies have been done in this area, not all have been comprehensive in the thyroid hormones measured and attention has been confined to the effects of propranolol. Lotti et al [8] and Faber et al [5] noted a fall total T3 with propranolol 40 to 120mg daily given to euthyroid patients. The latter group also recorded a rise in reverse T3. Neither group found a change in total T4 levels. On the other hand Kristensen and Weeke [9] and Cooper et al [10] have reported raised total T4 levels in patients receiving propranolol (80 to 1280 mg daily) for essential hypertension and angina pectoris respectively; five of the six patients described by Cooper et al also had raised reverse T3 levels but both groups of patients maintained normal T3 levels. These studies differ in their overall finding but where a change in thyroid hormone concentration has been demonstrated, the direction of change is consistent between reports. Thus, although not demonstrated in one study, the composite picture from these reports is that propranolol may lower total T3, elevate reverse T3 and, particularly in higher doses, may raise total T4 concentrations.

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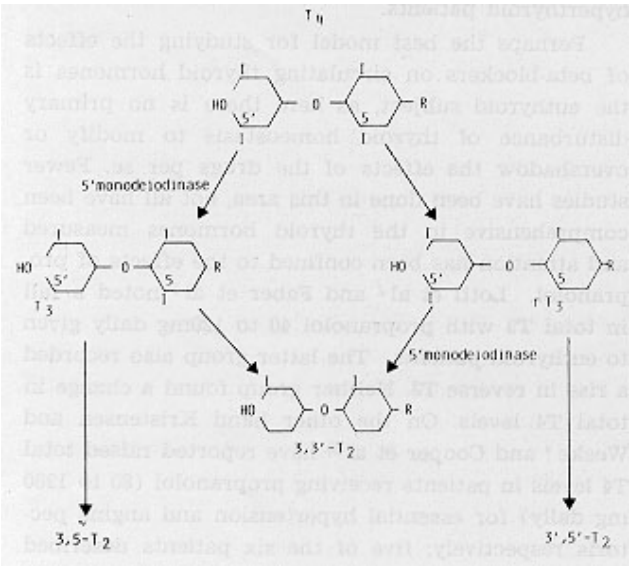
Mechanism

Most T3 and reverse T3 is produced by monodeiodination of T4 (figure 1) in the liver and kidney rather than by the thyroid [11]. To explain the fall in T3, the current hypothesis is that propranolol exerts an inhibitory effect on 5' deiodinase, the enzyme responsible for the peripheral conversion of T4 to T3. Metabolism of T4 is diverted to reverse T3 production whose clearance is reduced as the same enzyme, 5'deiodinase, degrades revers T3 to T2. Hence reverse T3 concentrations rise. The mechanism by which propranolol exerts this inhibitory effect remains unknown. It does not appear to be mediated through beta-blockade. Heyma et al have shown that D-propranolol, which is devoid of beta-blocking activity, also reduces serum T3 [12]. This compound does possess membrane-stabilising (local anaesthetic) activity and it was suggested that only those beta-blockers with this property would have a similar effect on T3 concentrations. However, it has been argued that the membrane stabilising effect only becomes manifest at very high doses [13]. Furthermore, nadolol [14], sotalol [15] and alprenolol [6], none of which possess this property, have since been shown to lower T3 levels in thyrotoxic subjects.



METABOLISM OF CIRCULATING THYROID HORMONES
Fig. 1 - Pathways of peripheral metabolism of circulating T4.

Perrild et al have studied a number of beta-blockers in relation to their effect on total T4, T3 and reverse T3 levels in hyperthyroid patients [6]. Alprenolol, a non-selective beta-blocker, had the same effect as propranolol, reducing serum T3 and increasing reverse T3 concentrations. On the other hand atenolol and metoprolol, both cardioselective beta-blockers, reduced both T3 and reverse T3. The authors suggest that selectivity might be important to the mechanism by which beta-blockers effect thyroid hormone concentrations. Clearly, further studies are required to clarify this issue.

Clinical significance

In the final analysis, the important question is what is the effect of beta-blockers on thyroid homeostasis? Or, to put the question another way, what do the reported changes in thyroid hormone concentrations mean in clinical terms? Only a small fraction of total circulating T4 and T3 - 0,3 and 0.03% respectively - is in a free (unbound) and metabolically active form [16]. Moreover, it is now generally accepted that most if not all the biological activity of thyroid hormones is attributable to T3. Until recently, the technology for emasuring free T3 has not been widely available. Not surprisingly then, studies of the effects of beta blockers on thyroid hormones have concerned themselves with measuring total T3. A study of the response of free T3 to treatment with beta-blockers has become fundamental to our understanding of the effect of beta-blockers on thyroid homeostasis. Such a study has become all the more important as a result of a report by Wilkinson et al showing that thyroxine binding globulin (TBG), a major carrier protein for thyroid hormones, falls in euthyroid subjects taking nadolol [17], and may therefore contribute to the changes in total T3 observed during beta-blocker therapy.

We have had the opportunity to study the effects of propranolol therapy 80 to 160 mg daily on free T3 concentrations in thyrotoxic and euthyroid healthy volunteers [14,18]. In the thyrotoxic group total T3 fell but there was no significant change in free T3 [14]. This would suggest that changes in circulating thyroid hormones contribute little to the therapeutic effect of beta-blockers in thyrotoxicosis. This conclusion is supported by the published data on total T3 - the reported reductions still leave T3 levels above the normal range. It is also supported by the observation that the clinical efficacy of beta-blockers such as oxprenolol that have not been shown to reduce serum T3 is similar to those that do [7]. When the same techniques were used to study the euthyroid subjects there was an 18% fall in free T3 [18]. Free T4 rose by 20%, but in view of the relative biological activities of the two hormones the net effect was a fall in biological activity. In health an individuals free T3 level is kept within a very narrow range; an 18% reduction then is unphysiological. However, the significance of such a fall at the cellular level is difficult to assess. At present the two most sensitive indicators of "adequacy" of circulating thyroid hormone levels are the serum TSH and its response to TRH. In our study there was no significant change in TSH levels Cooper et al [10] included TRH-tests in their assessment of six patients on high-dose propranolol; they obtained normal or blunted rather than exaggerated TSH responses to TRH. Thus there is no evidence at the moment to suggest that the pituitary appreciates treatment with propranolol as drug-induced hypothy-

roidism but the definitive test awaits the discovery of a sensitive assay of thyroid status at the tissue level.

In conclusion, beta-blockers may: 1) reduce total and free T_4 and reverse T_3; 3) reduce TBG.

These effects are most easily demonstrated by longitudinal studies using euthyroid subjects. However, the clinical significance of these changes in euthyroid patients is unknown. Furthermore, whilst there is no doubt that beta-blockers are very effective in relieving symptoms of hyperthyroidism, reducing heart rate, sweating and tremor, it is unlikely that this is mediated to any significant extent by an effect on circulating thyroid hormones.

BETA BLOCKERS AND THE RENIN-ANGIOTENSIN

The renin angiotensin system represents one of the body's mechanisms for maintaining blood pressure; this is well known and accepted. There is less agreement about its role in the aetiology of hypertension. Sympathetic stimulation increases plasma renin activity and it has been suggested that beta blockers may, at least in part, lower blood pressure by reducing plasma renin activity. The subject is complicated and the situation is made worse because of methodological difficulties in determining accurately the active, relevant component of plasma renin. In an attempt to make a difficult subject as simple as possible we shall pose and try to answer three questions: (a) What is the function of the renin-angiotensin system in health and disease? (b) What is the role of beta stimulation on renin production and which receptor(s) is(are) involved? (c) What do beta blockers do to plasma renin activity and what is the relevance of this to their antihypertensive activity?

The role of the Renin-Angiotensive System

Renin is a proteolytic enzyme which is stored in and released from the juxta medullary apparatus in the kidney. In the circulation it cleaves off two amino acids from the inactive peptide, angiotensin I, to produce angiotensin II (AII). AII is a very powerful vasoconstrictor which increases blood pressure directly. It is also the main stimulator of the release of the hormone aldosterone, secreted by the zona glomerulosa of the adrenal medulla, which acts within the kidney to provoke salt and water retention and potassium loss [19,20]. All have other functions, including vasopressing release, which tend to increase blood volume [21,22]. These various actions would help to restore to normal the blood pressure of a person who was hypotensive following fluid loss or haemorrhage. However they might also contribute to the maintenane of an elevated blood pressure in a hypertensive patient.

The evidence available does not suggest that increased renin activity is an important factor in the aetiology of essential hypertension. These patients may have high, low or normal plasma renin and some authors have attributed, particular characteristics to each group [23]. Thus for example it has been suggested that low renin hypertensives are older, more likely to respond to thiazide diuretics and less prone to develop vascular complications than those with high renin [23,24]. However if a large enough group is studied the renin activities of hypertensive patients are distributed in a smooth unimodal skewed fashion [25]. Furthermore most values obtained outside the "normal range" can be explain on the basis of the haemodynamic effects of raised blood pressure or the consequences of its treatment.

In conclusion it would seem that although the renin angiotensin system is important in maintaining normotension in health, its relevance in the aetiology of essential hypertension remains uncertain.

Beta Receptors and Renin Production

It has been known for many years that a number of different factors are capable of modifying plasma renin concentrations or plasma renin activity (PRA). In 1965 Vander [26] using dogs produced a rise in PRA by renal nerve stimulation and by giving catecholamines. Subsequently Gordon and colleagues [27] in 1967 showed that sympathetic stimulation either by an infusion of catecholamines or by exposure to cold could increase PRA in man. Michelakis and McAllister [28] continued the investigation into the mechanisms of sympathetically stimulated renin release by using phenoxybenzamine and propranolol as tools to determine whether the renin response was mediated by alpha or beta receptors or both. Alpha blockade had little effect on the increase in PRA induced by the upright posture and by sodium depletion, whereas beta blockade with propranolol consistently blocked the rise in PRA. These studies and others [29] therefore indicate that beta adrenoceptor stimulation is capable of increasing PRA and beta blockade of reducing it.

The relative importance of β_1 and β_2 receptors in relation to renin release was more difficult to determine. There is good evidence that the two relatively cardioselective (β_1 selective) antagonists atenolol [30] and metoprolol [31] do reduce the increase in PRA in response to a variety of stimuli. This suggests that β_1 receptors are involved because these drugs have little effect on β_2 receptors. The study by Harms and colleagues [32] in which the effects of a number of different beta blockers on renin release (and other metabolic responses to sympathetic stimulation) suggested that non selective beta blockers had a greater effect and they postulated that whereas β_1 receptors may be the maim mediator β_2 receptors are also involved. This concept is supported by the finding that salbutamol, a selective β_2 agonist, will increase PRA [33,34].

It would seem therefore that the answer to the second question must be that both β_1 and β_2 receptor stimulation may increase PRA, with perhaps the former being the more important.

Is blood pressure reduction by beta blockers related to their effects on PRA?

A major early study by Buhler and colleagues [35] in 1972 strongly suggested that the response to beta blockade was determined by whether the hypertensive patient had initially high normal or low PRA. Those with high PRA responded well, those with low PRA did less well. Furthermore the fall in blood pressure achieved appeared to correlate closely with the extent to which PRA was reduced. However since that time most investigators have come to completely the opposite conclusion, namely that although beta blockers do lower PRA there is no relationship between this and their effect on blood pressure. Since current views are significantly different from those proposed 10-12 years ago it seems important to be sure that the lack of correlation between BP reduction and PRA reduction is well documented. The table I gives some of the publications which have made this point.

Table I - Studies showing no correlation between response to beta blockade and change in renin activity

Beta blocker	Country of study	Journal	Ref. N.º
Propranolol	Australia	British Medical Journal	36
Propranolol and Pindolol	Australia	British Journal of Clinical Pharmacology	32
Propranolol	Italy	Clinical Science and Molecular Medicine	38
Metoprolol	Sweden	Clinical Pharmacology and Therapeutics	39
Alprenolol	Denmark	European Journal of Clinical Pharmacology	40
Metoprolol	USA	Clinicial Pharmacology and Therapeutics	41
TirnoloI	Italy	International Journal of Clinical Pharmacology Therapy and Toxicology	42

In conclusion, beta blockers have consistently been shown to reduce PRA probably through their effects on both beta[1] and beta[2] receptors. This may be one of the ways in which these drugs exert their antihypertensive effect but it is difficult to believe that it is an important mechanism. This view is based on the lack of evidence for a definite role of increased PRA in essential hypertension and the lack of a good correlation between the effects of beta blockers on renin activity and their effects on blood pressure.

THE EFFECTS OF BETA ADRENERGIC BLOCKADE ON OTHER HORMONES

The effects of beta adrenergic blockade on a variety of other hormones have also been studied. These hormones include the catecholamines, growth hormone, cortisol, glucagon, and parathyroid hormone.

Catecholamines

Since beta blockers counteract beta adrenergic receptor mediated responses it is perhaps not surprising that considerable attention has been directed towards the effects of these drugs on the hormones that stimulate beta receptors physiologically. Many studies of hypertensive patients covering a variety of beta-blockers have demonstrated that plasma catecholamine levels rise during therapy with these drugs [43,44,45]. An extensive review of this aspect has been provided by Man in't Veld and Schalekamp [43]. A further increase in plasma catecholamine levels occurs when beta-blocked patients are exercised [46-49]. In contrast to other beta-blockers however, pindolol, a non-selective drug with partial agonist activity, consistently lowers basal plasma noradrenaline levels [50-53]. It is tempting to postulate a compensatory increase in sympathetic activity to explain the rise in plasma noradrenaline levels seen with agents lacking partial agonist activity. However, an alternative explanation is a reduced clearance of noradrenaline from the circulation. In one study in which normal subjects were infused with adrenaline, its clearance was reduced when propranolol was simultaneously administered [54], and in another the plasma clearance of noradrenaline was reduced in patients taking propranolol for essential hypertension leading to a small rise in plasma noradrenaline levels [55]. Noradrenaline is cleared mainly by the liver and lungs and it is possible that the reduced rate of clearance seen with beta blocking drugs lacking partial agonist activity is due to a reduction in cardiac output. It has been shown for example that the clearance of lignocaine, a drug with a high hepatic extraction ratio, is significantly impaired by propranolol which reduces the splanchnichepatic blood flow by about 20% [56]. This contrasts with pindolol, which has less effect on cardiac output or hepatic blood flow, has no effect on the clearance of lignocaine [56].

Hormonal Responses to Hypoglycaemia

Another area of interest has been the influence of beta blockade on the hormones that are instrumental in the recovery from insulin induced hypoglycaemia. This includes all of the "diabetogenic" hormones, such as growth hormone and ACTH released from the pituitary, glucagon from the pancreas and cortisol as well as the catecholamines from the adrenals. Each of these plays a part in raising the blood sugar to normal. The potentially adverse effects of beta blockade on a number of compensatory metabolic responses to hypoglycaemia, including gluconeogenesis and lipolysis have already been discussed in part I of this review [1]. With regard to the hormonal responses to hypoglycaemia however, it appears that beta blockade if anything enhances the mechanisms involved in correcting glucose homeostasis. For example, intravenous propranolol has been shown to increase the plasma ACTH response to insulin induced hypoglycaemias [57]. Also hypertensive patients showed a more marked rise in cortisol and growth hormone, as well as adrenaline in response to insulin induced hypoglycaemia after treatment with metro-

prolol compared to before starting treatment. There was no difference in the noradrenaline or glucagon responses [58]. Larger and colleagues [59] showed similar results in diabetics treated with either propranolol or metoprolol during hypoglycaemia except that glucagon levels were also higher than when treated with placebo. Thus it seems that release of key hormones which influence the glycogenolytic and gluconeogenic pathways is augmented rather than inhibited by beta blockade during hyperglycaemia. This may be a consequence of increased sympathetic activity or again the result of reduced hormone clearance.

Parathyroid hormone

The influence of beta adrenergic blockade on parathyroid hormone (PTH) secretion has also received attention over recent years. In 1975, Kukreja and colleagues [60] showed that intradermal injection of isoprenaline or adrenaline in man produced a prompt rise in PTH levels and that propranolol infusion significantly inhibited basal secretion of PTH. They concluded that beta adrenergic stimulation probably plays an important role in the basal PTH secretion in man. These findings have therapeutic implications and suggest that beta blockade may sometimes protect from the unwanted effects of PTH. For example, in a study of patients on chronic haemodialysis nine subjects taking propranolol for hypertension or angina had lower serum levels of PTH and alkaline phosphatase and less radiological evidence of renal osteodystrophy than 25 patients not taking beta blockers [61]. It has also been shown that infusion of propranolol into patients with secondary hyperparathyroidism reduces serum PTH to the same degree as in normal subjects showing that the responsiveness of PTH to beta adrenergic blockade remains intact under these conditions [62].

Conclusions

This second part of the review of the metabolic endocrinology. In many cases however alteration in influence of these drugs on almost all facets of en-effects of beta blockade illustrates the wide ranging hormone levels by beta blockers are probably of limited clinical relevance although their effects need to be borne in mind when interpreting laboratory data.

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