METABOLIC EFFECTS OF BETA ADRENOCEPTOR BLOCKADE

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Beta adrenoceptor blocking drugs (beta blockers) are used chiefly to treat hypertension, to control arrhythmias and angina and to try to prevent recurrences in patients who have recovered from a myocardial infarct. Using the Lands classification [1], these effects are mediated by their actions on beta, receptors. The major adverse effects of beta blockers are produced by their blockade of beta receptors in the bronchi and in the peripheral arteries where they may cause asthma or cold ischaemic peripheries respectively[2]. However there are other beta receptors which are presented in table I and by their action on some of these, beta blockers may exert a number of metabolic effects. In this paper we shall review the ways in which beta blockers affect glucose homeostasis, fat metabolism and potassium concentrations in plasma. In addition, the possible relevance of these actions on a patients ability to take exercise will be considered. In a second paper we shall consider the endocrine changes which may occur during beta blockade.

Table I - Alpha and beta adrenoceptors.

Organs, Tissues and Functions	Main Adrenoceptor type
Muscular Functions	
Heart - Rate	B_1
- Force	B_1
- Excitability	B_1
Bronchi	B_2
Blood vessels - Proximal	B_2
- Distal	α
Metabolic Functions	
- Muscle glycogenolysis	B_2
-Hepatic Glycogenolysis	α (B_2)
Gluconeogenesis	B_2
- Insulin release	
Inhibition	α
Stimulation	B_2
Lipolysis - Stimulation	B_1 (B_2)
- (Inhibition)	(α)
Cellular uptake of potassim	B_2

This is a guide to the predominant receptor types. Most tissues contain more than one type of receptor. Brackets indicate less important or less well documented receptor mediated function.

BETA BLOCKERS AND BLOOD SUGAR

There are 3 main ways in which being on a beta blocker may influence a person's response to changes in blood glucose. They impair insulin release; delay the recovery from hypoglycaemia; and modify the haemodynamic response to hypoglycaemia.

The last of these, the hemodynamic response which may occur when people on beta blockers become hypoglycaemic, has been described elsewhere 3,4 and will not be considered here since it is a vascular rather than metabolic consequence of beta blockade.

Insulin release and hyperglycaemia

Insulin is released normally in response to a rise in blood glucose, but it is also secreted in response to stress and catecholamines. This is perhaps surprising since it has been known for many years that the overall effect of catecholamines is to cause a rise in blood glucose. When insulin assays became available it was anticipated that suppression of insulin release might contribute to the hyperglycaemic response to stress. In fact, Porte in 1967 5 showed that stimulation of alpha receptors inhibited, whereas stimulation of beta receptors promoted insulin release. Subsequently Loubatieres and colleagues[6] performed some infusion studies on dogs which showed that non selective beta stimulation with isoproterenol increased insulin secretion and that this was effectively blocked by propranolol but not by the beta, selective practolol. This suggested that insulin release was mediated via beta receptors, a concept supported by the finding that insulin levels increase in response to the beta selective agents salbutamol [6,7] and terbutaline [8].

The finding that beta receptors are involved in insulin release raises 3 important questions in relation to the clinical use of beta blockers: 1) Will long term beta blockade provoke the development of diabetes mellitus? 2) Will beta blockade adversely affect blood sugar control in diabetes? 3) Would a selective beta blocker be less likely to adversely affect blood sugar control in diabetics?

It is difficult to be absolutely sure about question one. However there have been many fairly long term studies of beta bloker therapy particularly in relation to secondary prevention following myocardial infarction and no tendency for diabetes to develop has been reported. Since beta blockers are widely used and

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diabetes mellitus is relatively common, it must be anticipated that from time to time diabetes will be first diagnosed soon after starting beta blocker therapy. Anecdotal reports of such coincidences have occurred but scientific evidence of a causative link between beta blocker therapy and diabetes is lacking.

Though beta blockers do not appear to precipitate diabetes mellitus, there is adequate data to suggest that these drugs do cause some deterioration in blood sugar control in patients with the disease. Wright and colleagues[9] for example followed a group of maturity onset diabetics whilst on placebo, metoprolol and propranolol using a double blind cross over design. Both beta blockers tended to cause a rise in blood sugar levels both when fasting and after food. However, the effects were not striking when seen against a background of fairly considerable intra, subject variation which is a feature of most patients followed in diabetic clinics. In this study[9], the blood sugars on metoprolol were not so high as those on propranolol, which tended to confirm an earlier observation of Waal Manning[10] who demonstrated that glucose tolerance was better on a selective rather than on a non selective beta blocker. More recently Holm and colleagues have again shown some benefit conferred by selectivity in relation to diabetic glucose tolerance tests. Here again the differences were not great and only of clinical relevances in two of their ten patients.

In conclusion it would seem that beta blockers are not dangerous for diabetics and are not contraindicated. They do, however, tend to cause some deterioration in glucose tolerance which may require some adjustment of diet or hypoglycaemic agents in perhaps 5-10% of patients. In this situation relative cardioselectivity must be considered to confer some benefit, but the advantages of this property are marginal.

Metabolic response to hypoglycaemia

Following an injection of insulin the blood sugar falls to a low point after about 25-30 minutes and then starts to rise. The elevation in blood sugar is not caused by disappearance of the insulin which is still well above basal levels 12 but is probably caused by a rapid and marked increase in catecholamines in the blood L . The catecholamines promote glucose release from the liver, initially by glycogen breakdown (glycogenolysis) and subsequently by new glucose formation from amino acids, lactate and other substrates (gluconeogenesis). Glycogenolysis is sometimes quoted as being an alpha adrenoceptor mediated process 3,13, although the evidence that this is true in man is not good. Gluconeogenesis, on the other hand, is said to be mediated by beta receptors. In this instance there is more evidence for a beta[2] hyperglycaemic effect, though the exact mechanism[2]. is more often inferred than proven. Garber and colleagues [12] performed kinetic studies on glucose production and uptake and thereby defined the effects of insulin and the contributions of glycogenolysis and gluconeogenesis. They also investigated many different hormones during insulin induced hypoglycaermia and showed that only epinephrine concentrations in the plasma increased markedly in response to hypoglycaemia and preceded the recovery phase. Subsequently a number of studies [14,15] have shown that pretreatment with beta blockers tends to delay the second part of the recovery phase in subjects with insulin induced hypoglycaemia. Beta, selective agents interfere much less and this is considered to be an advantage of this type of beta blocker and also to confirm that beta2 receptors are involved in gluconeogenesis. As further support, data from studies using beta,2 stimulants such as terbutaline may be quoted [16]. However, although terbutaline can be shown to raise blood sugar levels, the rapid rate of onset (within a few minutes) suggests that either glucose synthesis is achieved rapidly or that beta stimulation also provokes glycogenolysis.

The fact that beta receptor stimulation is a potentially important mechanism in the prevention of or recovery from hypoglycaemia, raises specific questions about the possible unwanted effects of betablocking drugs. These are: 1) Will diabetics on insulin react differently or abnormally if they are on beta blockers? 2) Is the ability to tolerate starvation likely to be affected by beta blockers? 3) What happens to glucose production during exercise when patients are on beta blockers?

There does not appear to be good evidence to suggest that diabetics on insulin come to any harm because they are on beta blockers [17]. Presumably an effect on the hypoglycaernic action of therapeutic doses of insulin given subcutaneously would be marginal, difficult to demonstrate in clinical practice and of doubtful relevance.

The ability to tolerate starvation requires that the individual can mobilize glucose from body stores or synthesise it. In a few instances patients on beta blockers starved for various reasons have developed severe hypoglycaemia [18,19]. In addition, neonates born to mothers on beta blockers [2O,21] and small children after taking an overdose22 have become severely hypoglycaemic. Propranolol induced hypoglycaemia has also been reported in a patient after gastrectomy2-1. The whole subject of drug induced hypoglycaemia has been discussed by Seltzer24 and the possible role of beta blocker-induced reduction in glucagon release (to be described in a second review) has been discussed in a letter by Lawrence and Hagen[25]. The occurrence of beta blocker-induced hypoglycaemia is therefore well documented and because of its seriousness those who prescribe beta blockers must be aware of it. However, compared with the overall use of these drugs, the risks are extremely small. There is usually some underlying predisposition and the patient has been fasting.

The third situation in which individuals need to be able to mobilize glucose is during physical exercise. During exercise carbohydrate and lipid stores have to be metabolized to provide energy rich subs-

trates. These processes will be considered later in this review, but at this point we should note that: a) during exercise blood sugars may fall a little; b) they fall rather more during beta blockade; c) this effect of beta blockade is less marked if the beta blocker being taken is relatively cardioselective.

BETA BLOCKERS AND LIPIDS

The possible effects of beta blockers on plasma lipid concentrations must be one of the most confusing and difficult areas of beta blocker pharmacology. This is firstly because the subject of cholesterol fractions is complicated and seems to present some methodological problems and secondly, and more important for the non-expert, the literature is full of conflicting reports. This confusion may be partly due to the difficulties in understanding and measuring lipids but must also be due to the fact that different groups study differing types of beta blockers, at different doses for varying periods of time.

An attempt to review the subject in detail would only serve to add to the confusion. Instead we will briefly examine the role of catecolamines in lipid metabolism, the acute effects of beta blockers which may reduce the body's ability to produce energy with substrates for exercise and the limited conclusions which can be drawn about the chronic effects of beta blockade which may be relevant because they may increase the patients coronary risk factors.

Catecholamines are the most important. hormones acutely stimulating the degradation of stored triglycerides to fatty acid and glycerol [26,27]. This is achieved by the stimulation of camp which leads to phosphorylation and activation of triglyceride lipase. Although the receptors involved are predominantly beta$_1$, beta$_2$ receptors do also play a role. This is supported by the finding that the adrenaline induced rise in free fatty acids is significantly smaller following pre-treatment with the non-selective drug pindolol than following the beta, selective drug atenolol[28]. There are also inhibitory alpha receptors but these play a minor role in the regulation of lipolysis[27].

Since beta receptors are involved in lipolysis, beta blockers will inhibit lipolysis. This means that during stress or exercise and when a person becomes hypoglycaemic the ability to mount a normal metabolic response which involves lipolysis will be adversely affected. During exercise, for example, blood sugar concentrations in the plasma fall more rapidly if the person is on beta blockers[29]. There are several possible mechanisms (see later) but it seems that lipolysis normally prevents serious hypoglycaemia developing in two ways. Firstly the free fatty acids, produced by lipolysis, are themselves an important source of energy so that their production has a glucose sparing effect. Secondly glycerol, also released during lipolysis, is used in gluconeogenesis to provide more glucose. Beta blockers by reducing the supply of fatty acids and glycerol may make the person who takes prolonged exercise liable to develop hypoglyeaemia [30].

Studies on the long term effect of beta blockers on plasma lipids have failed to produce a clear picture 31. However most studies suggest that plasma triglycerides tend to rise, total cholesterol remains unchanged or rises, but HDL cholesterol may fall [23-34]. These changes might be interpreted as indicating that beta blocker therapy increases the patients burden of risk factors in relation to coronary artery disease. However the changes tend to be modest in amount, and have to be seen against the background of the potential benefits of beta blockade, particularly the evidence for a reduction in reinfarction and deaths resulting from chronic beta blockade given after a myocardial infarction [35].

BETA BLOCKERS AND POTASSIUM

The involvement of beta receptors, specifically beta, receptors in the cellular uptake of potassium is well documented. Studies in the 1930s by D'Silva[36] showed that the serum potassium fell in cats when adrenaline was injected and subsequent studies in pancreatectomised and nephrectomised animals demonstrated that this hypokalaemic effect was independent of insulin, and aldosterone and also not due to a change in the renal elimination of potassium [37]. Since a fall in potassium can be achieved not only by the non-selective stimulant isoproterenol but also by the selective beta, agonists salbutamol and terbutaline [16,38,39] the mechanism would seem to involve beta2 receptors. Finally since it can be inhibited by ouabain[40], the fall in serum potassium can probably be ascribed to increased cellular uptake achieved by activation of the Na-K ATPase pump. Since beta$_2$ receptors are involved in the cellular uptake of potassium,[2] patients with asthma who are given beta$_2$ stimulants may be at risk of developing hypokalaemia [4l,42] and conversely patients on beta$_2$ blockers will tend not to show a normal fall at times of pathological or physiological stress, and indeed may show a rise.

Assessing the potential clinical relevance of the above observations is still at an early stage. Long term treatment with beta blockers may produce a small rise in serum potassium which is believed to be the result of a redistribution from the intra- to the extracellular compartment [43,44]. The relevance of this is not great since the increase is small but it may be of some importance when combined with diuretics if the fall in potassium which occurs with these agents is counteracted. This is of some interest since diuretics alone given to hypertensive patients have failed to reduce the mortality from ischaemic heart disease and may be associated with a slightly increased risk [45,46]. The effect of beta blockade in this context would be advantageous. It might also be an asset during the stress of a myocardial infarction when catecholamines are produced which may not

only increase myocardial excitability but also lower the serum potassium. In pharmacological studies, beta blockers have been shown to counteract these effects [47,48].

The role of beta blockers is also of interest in patients undergoing cardiopulmonary by-pass operations. Petch and colleagues49 compared the changes in potassium when two groups of 10 patients treated with either metoprolol (B, selective) or propranolol underwent by-pass surgery. The operative procedures were the same but those on propranolol showed a rise of 1.2 mmol/l in serum potassium whilst those on metoprolol had a fall of 0.08 mmol/l. There was no difference in urinary potassium loss between the two groups. It is possible that the greater rise on propranolol might be a disadvantage but evidence on this question is not available.

Exercise is a physiological stress. Normally during exercise potassium from muscle cells is 'released' and the serum potassium rises, returning to normal at the end of exercise. In a study by Carlsson and colleagues on 6 healthy volunteers a rise in serum potassium was demonstrated but this group also showed that pretreatment with either metoprolol or propranolol caused a greater rise in potassium concentrations,50. After exercise the potassium fell rapidly when the subjects were on placebo and metoprolol but more slowly when they were on propranolol. The implication of this study was that non-selective beta blockade impaired beta2 mediated cellular reuptake of potassium. In a second study involving a more severe exercise test and following two days pretreatment with the same two beta blockers or placebo the findings during exercise were similar but on both drugs the fall in potassium towards normal was delayed[29]. In this latter study a significant reduction in the duration of exercise occurred on the beta blockers, but no correlation between the increase in serum potassium and the reduction in exercise tolerance was demonstrated.

A further study involving only four subjects but in which there was continuous monitoring of arterial potassium has confirmed the potentially serious rise in serum potassium (between 6.3 and 7.8 mmol/D which may occur when exercising whilst beta blocked5l. The relevance of these observations on the effects of beta blockade to muscle fatigue and the possible risks of hyperkalaemia, during jogging or exercising as part of a cardiac assessment, merit furthe revaluation.

BETA BLOCKER AND EXERCISE

Many patients on beta blockers want to take exercise and perhaps they should be encouraged to do so as part of a programme designed to reduce the risk of suffering from ischaemic heart disease [52]. However beta blockers have been blamed for causing fatigue[53] and reducing exercise performance [54,55], thereby perhaps making it less easy for patients on these drugs to exercise and perhaps even to perform moderately strenuous physical work. Since the metabolic effects of beta blockade as described above may be in part responsible it seems relevant to discuss these and to consider briefly the other ways in which beta blockers may alter the body's ability to make the necessary physiological adaptations for exercise.

The body's responses to physical exertion, particularly to prolonged periods of exercise, are complicated and involve many inter-related processes. Broadly the changes may be classified as haemodynamic, metabolic, endocrine and psychological. Of these the first two categories are probably most important in relation to beta adrenoceptor blockade. We shall therefore briefly consider the effects of beta blockade during exercise on blood flow, substrate production and metabolite disposal.

Blood flow

During exercise there is an increased demand for oxygen and energy rich substrates and an increased production of breakdown products. These require changes in the rates of production, delivery and disposal. An increase in the blood supply to muscles is necessary to provide nutrients and to remove metabolites. This is probably achieved largely by increased adrenergic activity which produces a tachycardia, an enhanced cardiac output and, by stimulating the beta, receptors, dilatation of the limb arteries. Beta blockers will counteract all these physiological responses though relatively cardioselective agents should have less effect on the arteries[2]. A number of studies have shown that exercise during acute[56] and chronic[57] beta blockade is associated with reduced muscle blood flow though others have failed to show any effect of locally administered beta blockers[58]. This latter observation suggests that the main haemodynamic effect of beta blockers may be on cardiac output. However the lack of evidence for a good correlation between any haemodynamic effect and impaired exercise performance suggests that other mechanisms, in particular the metabolic effects of beta blockade, may be more important.

Substrate production

As indicated in the sections on carbohydrate and lipid metabolism, both may be affected by beta blockers and both are involved in producing energy for exercise. The actual processes are complicated and depend on the subjects physical fitness, the severity of the exercise, its duration and whether or not it is continuous or intermittent 59,60. In simple terms, it is possible to suggest that some energy comes from glycogen and triglycerides in muscle cells, but rather more from free fatty acids derived from lipolysis of serum lipids and fat stores. Glucose is derived by glycogenolysis and gluconeogenesis in the liver. When exercise takes place, glucose is metabolized and the levels

fall. Normally this provokes an outpouring of cal cholamines which stimulate hepatic glucose release and lipolysis. The latter not only provides a direct energy source in the form of free fatty acids but an indirect contribution in the form of glycerol which can be metabolized to glucose. Beta blockers by moderating these steps may be associated with a more marked fall in glucose [3,9] and an associated lack of energy. Relative beta, selective antagonists by having somewhat less effect on glucose metabolism may tend to cause a less serious hypoglycaemic effect [3,29].

The study by Lundberg and colleagues [29] indicates the importance of beta blocker induced metabolic effects of exercise. In a double blind randomised study they compared the effects of placebo, metoprolol and propranolol given for two days on a fairly demanding exercise test. The mean duration of exercise on placebo was 152 minutes, on metoprolol 117 minutes and on propranolol 88 minutes. A relationship between the ability to increase free fatty acid and exercise duration was shown. In addition they demonstrated that the fall in blood glucose was greater on propranolol, less on metroprolol and showest on placebo. This study may therefore be quoted as suggesting that the effects of beta blockade on exercise are to a significant extent due to their effects on substrate production. Whether this means that beta blocker induced muscle fatigue, a less clearly defined entity, is caused in the same way, is not known.

Metabolite disposal

Another factor which might contribute to the development of fatigue is the accumulation of metabolic products such as lactate and ammonia during exercise. During beta adrenergic blockade, lactate release from working muscle is reduced [57,61] and therefore the possibility arises that lactate accumulation in the muscles could give rise to muscular fatigue. However recent studies have not supported this contention[62]. An increase in blood ammonia concentration accompanying high-intensity muscular work has also been implicated in fatigue development and physical exhaustion 63,64. Ammonia is removed from the circulation by the liver and beta blockers by reducing cardiac output will influence liver blood flow. It is tempting to speculate that beta blockade might in some way impair removal of ammonia which in turn could contribute to the increased fatiguability seen in patients taking beta blockers.

Conclusion

Beta blockers are used to treat or prevent a variety of cardiovascular disorders and their best known unwanted effects are asthma and peripheral vascular disorders. However there are beta receptors in many other organs other than the heart, the blood vessels and the bronchi. Blockade of these other receptors may produce metabolic effects which are less well known. In this review the consequences of beta blockade on glucose and lipid homeostasis, serum potassium concentrations land the ability to take exercise have been reviewed. Our conclusions are that beta blockers:

1) May cause a deteriation in diabetic control but probably do not cause diabetes mellitus.
2) Do impair the recovery from insulin induced or other forms of hypoglycaemia. This has not been shown to be important in relation to the treatment of diabetics with insulin but is clinically relevant in relation to glucose mobilisatlon during starvation and physical exercise.
3) Do have effects on lipid metabolism which are complicated. The short term effects by impairing energy production during stress and exercise are fairly well documented. The long term consequences of taking beta blockers, which may cause a small rise in triglycerides and a fall in HDL cholesterol, are not known. The relatively n-dnor changes observed are probably of doubtful clinical relevance.
4) Reduce cellular uptake of potassium so that plasma concentrations may be higher at times of stress, including cardiac surgery, and during exercise.
5) Do modify exercise performance. There are probably many reasons for this. Reduction of lipolysis and delayed removal of metabolites may be two of the important factors.

In most of the above, the potentially adverse effects of beta blockers may be less marked if a relatively cardioselective agent is used.

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