Possible mechanisms of action of beta blockers on the coronary circulation

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Abstract

Beta adrenoceptor blockers are widely used in the treatment of angina and hypertension. It is suggested that beta blockers relieve angina by reducing the myocardial oxygen demand. Many groups of investigators have demonstrated that beta blockers are likely to cause a generalised vasoconstriction at least in the short term and even a cardioselective beta blocker can reduce the coronary blood flow (CBF). It was shown in many animal models and also in humans, both healthy and those suffering from ischaemic heart disease, at rest and during exercise that beta blockers reduced the basal CBF and blunted the coronary active hyperaemia. It has been observed that all beta blockers exert their beneficial effects on the heart by their negative chromotropic and inotropic effects. Therefore, with beta blockers therapy, the endogenous adenosine production by the heart is likely to be reduced, resulting in the attenuation of the increase in CBF during exercise. The likely beneficial effects of beta blocker therapy could be the net result of the difference between decrease in oxygen demand by the heart induced by beta blockade and the reduction in CBF.

Introduction

Beta adrenoceptor blocking drugs (beta blockers) block the beta adrenoceptors in the heart and peripheral vasculature, bronchi, liver etc[1]. They are used in the treatment of hypertension and angina as well as in many other disorders. Many beta blockers are now available and they differ by their cardioselective properties and the duration of action. All beta blockers slow the heart rate thereby reducing the metabolic demands of the heart and also lower the blood pressure[1].

Beta blockers such as propranalol and atenalol have been used for over a quarter of a century in the treatment of angina and hypertension. It has been observed that all beta blockers exert their beneficial effects on the heart by their negative chronotropic and inotropic effects[2]. When under treatment with beta blockers, the endogenous ADO production is likely to be reduced, and is therefore likely to result in a reduction in CBF.

Background

It is well established that coronary blood flow (CBF) is regulated by many factors such as myogenic, neural, humoral and metabolic factors. While neural and myogenic factors may be more important in the regulation of CBF under basal conditions[3,4], metabolic factors seem to be more important in the mediation of vasodilation under more demanding conditions such as exercise[5]. It appears that under normal conditions, there is a constant competition between metabolic vasodilation and alpha receptor mediated vasoconstriction[6]. During increased activity, metabolic vasodilation overcomes sympathetic mediated vasoconstriction[6].

Berne in 1963[7] proposed in his adenosine hypothesis that adenosine (ADO) is one such metabolic vasodilator, which was important in the regulation of coronary blood flow. It has been demonstrated that ADO plays a more important role in the mediation of active hyperaemia in the heart than in the skeletal muscle[8,9,10]. The rate of ADO production at least in the short term appears to be related to the intensity of myocardial activity and is inversely related to the oxygen supply to the myocardium[11].

Beta adrenoceptors and cardioselectivity

The anti angina effects of beta 1 blocking agents are based on intrinsic negative inotropic and chronotropic properties. Some beta blockers such as propranalol are non selective, and have both beta 1 and beta 2 effects. Beta 1 receptor blockade leads to vasoconstriction. In addition, some cardioselective beta blockers such as metaprolol and epanalol have partial beta 1 agonistic activity, which may counteract beneficial effects of beta 1 receptor blockade[12]. It has also been found that there is a resting alpha adrenoceptor mediated vasoconstriction tone in the coronary circulation and that daily exercise or stellate gangliotectomy increased the CBF in adult mongrel dogs by reducing the alpha receptor mediated vasoconstriction[13].

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Mechanisms of action

There seems to be multiple mechanisms involved in the action of beta adrenoceptor blockade on the coronary circulation and the outcome is the net result of the interactions of these mechanisms. It has been found that autoregulation in the coronary vascular bed is partly responsible for the favourable changes produced by propranalol in the ischaemic myocardium in anaesthetized dogs[14]. Bund et al observed that the effect of beta blockers on the coronary vessels would differ according to the branching order or the caliber of the vessels in porcine coronary arteries, which suggests evidence for regional heterogenecity of vascular responses in the porcine coronary vasculature to vasoconstrictor and vasodilator agents[15].

Catecholamines play a major role during initiation and propagation of myocardial ischaemia and beta blockers such as propranalol and pindalol were found to restrict the extent of the myocardial damage in isolated rabbit hearts subjected to ischemia[16]. The growth of the myocardial infarction might be caused by oxygen free radicals generated from noradrenaline by autoxidation. However, it has not been demonstrated that beta blockers such as pindalol or propranalol exert their cardioprotective effects through a free radical scavenging action in isolated rabbit hearts under similar ischaemic conditions[17].

It has also been shown that beta adrenergic blockade with timolol helped uniform contraction of the heart in anaesthetized cats leading to improved contraction efficacy[18]. Another possible cardioprotective effect of beta blockers could be their membrane stabilizing action, thus preventing electrolyte depletion from ischaemic myocardial cells[19].

Effect of beta blockers on coronary arteries

Several groups of investigators have found that beta blockers such as propranalol reduce the CBF in both experimental animals and humans under varying conditions[20,21,22]. Sekiguchi et al observed that beta blockade with propranalol completely abolished the vasodilator effect of phentolamine and also constricted the coronary arteries in all vessel groups under their study in the beating hearts of anaesthetized dogs[20]. During treadmill exercise in conscious chronically instrumented dogs, propranalol administration (1 mg/kg) significantly attenuated the CBF at rest and also attenuated the coronary active hyperaemia[22]. This could be partly due to the unmasking effect of alpha adrennergic tone at rest, but other mechanisms may also be involved during exercise. Other workers also observed similar results on the effect of beta adrenoceptor blockade on the CBF in anaesthetized dogs[23].

The effect of bet blockers on the coronary vasculature at rest and during exercise was also investigated in humans. The effect of propranalol on CBF at rest and during exercise in patients with ischaemic heart disease was examined using biplane quantitative coronary angiography[21]. It has been oberved that patients with exercise induced angina had significantly more vasoconstriction than patients without angina and intravenous administration of propranalol was accompained by a significant decrease in coronary luminal area of both normal and stenotic vessel segments at rest, which is overridden by dymanic exercise, further supporting the coronary vasoconstrictor effect of beta blockers and the metabolic mediated vasodilation, which opposes it.

In healthy humans with angiographically normal coronary arteries and cardiac transplanted patients at rest, the beta blockade with propranalol decreased the CBF and increased the coronary vascular resistance[24]. However, the coronary vascular resistance did not increase in healthy human hearts or transplanted hearts after selective beta 1 blockade with metaprolol, suggesting that the increase in vascular resistance after non selective beta blockade is the result of direct beta 2 vascular effects.

Interaction of beta blockade and adenosine mediated vasodilation

The increase in the metabolic activity of the heart produces more vasodilator metabolites including adenosine (ADO) which produces coronary active hyperaemia during exercise[9,10]. The Beta blockers through their negative inotropic effects reduce the work of the heart, thereby reducing the ADO production. Therefore, it can be expected that beta blockers may attenuate the exercise induced coronary active hyperaemia, leading to at least a restriction of the coronary active hyperaemia[25,26]

Adenosine is produced in significant quantities during hypoxia, which leads to coronary vasodialation. Beta blockade with propranalol blunted the release of ADO and attenuated the hypoxia induced coronary vasodilation in anaesthetized dogs[25,26]. Even in concious dogs, similar reduction in the coronary active hyperaemia during treadmill exercise was observed in the

presence of beta blockade[22]. Even the coronary reactive hyperaemic flow response was found to be significantly attenuated in the presence of beta blockers in some animal studies[27], which is evidence in support for the attenuation of the increase in CBF in both animal and humans under varying conditions in the presence of beta blocker therapy. Any beneficial effect of the use of beta blockers in the treatment of angina would therefore be the result of the beta blocker mediated reduction in oxygen demand of the myocardium and the reduction in the CBF, which may occur with beta blocker therapy.

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