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COMMENTARY

Defying the economists: a decrease in heart rate improves not only cardiac but also endothelial function

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Ivabradine has proven therapeutic efficacy for cardiac ischaemia and, until proved otherwise, is a very specific inhibitor of the cardiac sinoatrial node I_f current. In the current issue of the *British Journal of Pharmacology*, Drouin *et al.* demonstrated that chronic treatment of the human apoB-100 transgene dyslipidaemic mouse with ivabradine significantly improved endothelium-dependent vasodilatation to ACh in renal and cerebral arteries and that the beneficial effects of ivabradine result secondarily to the lowering of heart rate. These data suggest that drugs that target the I_f current have potential benefits not only as anti-ischaemics but also as agents for the treatment of endothelial dysfunction.
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Economists tell us that the raising of interest rates is a very efficacious medicine that slows the heart beat of the economy and corrects all manner of economic ills. When it comes to our health, however, several reports have indicated that raising the heart rate elevates the risk for not only cardiovascular defects but also the mortality rate (for instance, see Benetos *et al.*, 1999). It is therefore not surprising that there has been considerable interest in developing drugs that selectively lower heart rate. Two widely used groups of drugs do directly lower heart rate—namely certain (L-type) calcium channel antagonists and β-adrenoceptor antagonists. Although both groups of drugs are widely used therapeutically for the treatment of cardiovascular diseases, neither group of drugs is cardio-selective in its actions. Heart rate is determined by the pacemaker activity of the sinoatrial node cells and, in particular, the activity of the hyperpolarization-activated cyclic nucleotide-gated channels (HCNs), or *f* channels, that are responsible for the I_f current. The I_f current, activated by cyclic AMP (and hence, indirectly, inhibited by β-adrenoceptor blockade), is turned on during repolarization, inhibited by ACh and is a key determinant for the slope of diastolic depolarization. The I_f current was first described by Brown *et al.* (1979) and has been referred to as the '*funny*' current based, in large part, on the very slow kinetics and that the current is carried by both Na^+ and K^+ ions. Ivabradine is the only drug currently in clinical use that is specific for the *f* channel (see Difrancesco and Borer, 2007). In this issue of the *British Journal of Pharmacology*, Thorin and colleagues from the Montreal Heart Institute and the Institut de Recherches Internationales Servier (Drouin *et al.*, 2008) showed that a 3-month treatment of young dyslipidaemic mice with ivabradine, but not with the β_1-adrenoceptor selective antagonist, metoprolol, improved both ventricular and endothelial functions. These data may help provide an understanding about the basis for the association among elevated heart rate, coronary disease and overall mortality.

In previous studies with ivabradine, no direct effects of this drug on the vasculature were observed (Simon *et al.*, 1995). In the study from Drouin *et al.*, chronic treatment with ivabradine did not affect lipid levels and acute treatment had no direct effects on endothelial function. Seemingly, then these endothelial protective effects of ivabradine must be secondary to the reduction, albeit a modest 17%, of heart rate. Why, however, was comparable protection not seen in the metoprolol-treated group? The authors suggest that the inhibitory effects of a β-adrenoceptor antagonist on endothelial cell β-adrenoceptor-mediated activation of endothelial NO synthase, arguably a β_2-mediated process, may counter the protective actions mediated by a metoprolol-induced reduction in heart rate. Metoprolol has only sixfold selectivity for β_1- over β_2-adrenoceptors (Smith and Teitler, 1999) and thus the use of a highly selective β_1-adrenoceptor antagonist may help answer this question.

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However, β-blockade with metoprolol has been found to reduce behavioural stress-induced tachycardia and coronary artery endothelial dysfunction in cynomolgus monkeys (Strawn *et al*., 1991), thus raising the question of whether there are organ- or species-specific protective effects of β-blockade on vascular function.

Chronic treatment with ivabradine may affect oxidative stress. Drouin *et al*. did demonstrate that ivabradine treatment restored the contribution of hydrogen peroxide to endothelium-dependent vasodilatation in cerebral vessels. In their previous studies with the dyslipidaemic human apoB-100 transgene mouse, Krummen *et al*. (2005) showed that, despite elevated lipids, endothelium-dependent vasodilatation is maintained in young (3 month) mice. However, with ageing, endothelial dysfunction develops considerably more rapidly than in wild-type mice and was attributed to elevated free radical production in the dyslipidaemic mice. Thus, additional studies to determine whether ivabradine treatment results in changes in endothelial NO synthase, superoxide dismutase and NADPH oxidase subunit expression and oxidative stress may further our understanding of the mechanisms responsible for the endothelial protective actions of ivabradine.

The normal basal heart rate for humans is <100 and for mice $\geqslant 600$ and the question thus arises as to whether the role of the I_f current and the actions of ivabradine differ between the two species? Harzheim *et al*. (2008) demonstrated, using a knock-in mouse model wherein cyclic AMP binding to the HCN (*f*) channel was abolished, that the cardiac pacemaker role of the HCN4 channel, the major isoform in the sinoatrial node, is only evident in the embryonic mouse. In adult mice, Harzheim *et al*. (2008) propose that the HCN4 channel serves to regulate heart rate only during and after stress. Embryonic mice have heart rates considerably lower than adult mice and closer to the range seen in humans and thus data obtained from adult mice chronically treated with ivabradine may not be directly comparable to data obtained from humans.

The anti-ischaemic properties of ivabradine have been extensively investigated in animals and humans and the preclinical work in this area has been reviewed (Berdeaux, 2007). The INITIATIVE (INternatIonal TrIAl on the Treatment of angina with IVabradiE) study compared ivabradine with atenolol, and ivabradine was shown to be as effective as the β-blocker. Two additional studies involving, in total, 16 000 patients are also underway and designed to investigate anti-angina, anti-ischaemic and efficacy in heart failure: The BEAUTIFUL (morBidity–mortality EvAlUaTion of the I(*f*) inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) and the SHIfT (Systolic Heart failure with the I_f inhibitor ivabradine Trial) studies involve patients with heart failure. Endothelial dysfunction is an early indicator of cardiovascular disease and thus additional studies are required in humans to determine whether treatment with ivabradine can also improve endothelial function in a comparable manner to that reported by Drouin *et al*. for mice. Furthermore, whether the benefits to endothelial function are specific for a particular vascular bed (that is, coronary) or of global benefit to the circulation needs to be determined. In conclusion, ivabradine, a drug with reported high specificity for the cardiac sinoatrial node I_f current, shows promise as an agent that also improves endothelial-dependent vasodilatation and, hence, is potentially beneficial in the treatment of macro- and microvascular diseases.

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