Endothelin Antagonists and Hypertension: A Question of Dose?

To the Editor:

We read with interest the recent report in Hypertension from Martin et al.1 on the effects of intra-arterial administration of the endothelin ET_{A/B} receptor antagonist, SB 209670, on forearm blood flow in hypertensive subjects and matched controls. Their finding of forearm vasodilation to intra-arterial SB 209670 in healthy controls suggests a role for endothelin-1 (ET-1) in regulation of basal vascular tone and is consistent with our own work.2-4 and that of some,5,6 but not all other groups,7-9 with both ET_{A} receptor selective and ET_{A/B} receptor antagonists. Also, contrary to some earlier work,5,6 they find no difference from controls in the in vivo response of the resistance vessels of hypertensive subjects to ET receptor antagonism.

Our early intra-arterial studies were undertaken with the ET_{A} selective antagonist, BQ-123, at a dose of 100 nmol/min.2 We have since undertaken pharmacodynamic and kinetic dose-ranging systemic studies with BQ-123 and find that this dose of BQ-123 has modest systemic effects, more on vascular resistance than blood pressure.5,9 Maximum plasma concentrations of BQ-123 at 100 nmol/min were 585±158 nmol/L,8 and IC_{50} values for BQ-123 at the ET_{A} and ET_{B} receptors in vitro are 9 to 24 nmol/L and 10 to 18 000 nmol/L, respectively, depending on cell type.10 Hence, when given locally into the forearm (blood flow ≈50 mL/min) rather than the systemic circulation (≈5 000 mL/min), this dose of BQ-123 will achieve concentrations (≈60 000 nmol/L) that may have functionally important inhibitory effects at the ET_{A} receptor. On this basis, our laboratory has more recently delivered BQ-123 in forearm studies at a dose of 10 nmol/min, with which, if anything, greater effects on local blood flow have been seen.4 This may be explained by the major role of the vascular ET_{A} receptor being to mediate vasoconstriction,11 such that combined ET_{A/B} inhibition may, by blocking ET_{B} mediated effects, attenuate the vasodilation associated with selective ET_{A} receptor antagonism.4 We have also used BQ-788 intra-arterially (at 1 nmol/min) as an ET_{B} selective antagonist, here based on systemic studies showing that 30 nmol/min, but not 3 nmol/min, increases systemic vascular resistance.11 However, a key issue arises for the published body of work using intra-arterial administration of ET receptor antagonists. These investigations have generally used high doses that are likely to be both nonselective and systemically active, conditions that interfere with a clear interpretation of these studies. Cardillo and colleagues gave BQ-123 (at 100 nmol/min) and BQ-788 (at 50 nmol/min) by intra-arterial coadministration to hypertensives and controls to achieve dual ET receptor blockade.6 However, it would now appear that both of these agents were given at systemically active doses. A similar problem of using a systemically active dose at the ET_{B} receptor may account for a rather modest effect on vascular tone in healthy subjects in one study7 and the lesser effect of a greater dose of TAK-044 in another.3 By giving systemic doses of the pharmacological probes, responses in the infused forearm may have been influenced directly by changes in systemic vascular resistance or indirectly by the activation of reflex neurohormonal mechanisms.12 In this regard, there must remain some uncertainty about interpretation of work examining the role of endothelin in hypertension and other vascular diseases using drug administration via the brachial artery until these studies are repeated with doses of drugs that are demonstrably confined to a local action.


Response

We thank Doctors Goddard and Webb for their comments regarding intra-arterial infusion of endothelin (ET) antagonists. Goddard and Webb raise a number of relevant issues. They reiterate the importance of using subsystemic doses of vasoactive substances to test hypotheses regarding direct effects on the vasculature. The key issue is how to establish that doses are indeed subsystemic. The usual approach includes careful assessment of systemic blood...
pressure and heart rate responses and/or measurement of forearm blood flow and vascular resistance in the contralateral limb. This is really a general issue of the technique itself and not limited to endothelin blockade as the vasoactive substance.

Specific to endothelin blockade, however, is the issue of selectivity of the receptor antagonist. Goddard and Webb suggest that doses of the ET_{A}−“selective” antagonist BQ-123, assumed to be subsystemic in a number of studies, may indeed be systemically active and also block ET_{B}-mediated vasodilation. However, this still does not explain differences in vascular responses to this agent given at the same dose and at the same infusion rate over similar periods of time. We used SB209670 in our study specifically because it is nonselective, and we wished to test the impact of blockade of all major ET receptor subtypes on the vasculature, between normal subjects and patients with cardiovascular disease.

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