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Recent research

High blood pressure (hypertension) is a major risk factor for heart disease, kidney disease and strokes. Its cause remains unclear in the majority of people affected. Lowering blood pressure in hypertension reduces the risk of heart disease and slows the progression of kidney disease. Recent studies have suggested that the immune system, and a particular cell within the immune system called the macrophage (Mϕ), is involved in the development and progression of hypertension. Endothelin-1 (ET-1) is a chemical produced in the body and which raises blood pressure and causes hypertension.

The focus of my recent research has been the interactions between the ET and immune systems and their role in the development, progression and clinical consequences of hypertension. I have developed considerable experience of the *in vivo* and *in vitro* characterisation of Mϕ, and have initiated a programme of studies addressing the role of Mϕ in regulating the effects of ET-1. Determining the mechanisms whereby Mϕ regulate the effects of ET-1 will provide a new understanding of blood pressure control and, through modulation of Mϕ number and/or phenotype, may lead to new approaches to the treatment of hypertension.

Details and utility of grant

I am grateful to the Myre Sim Committee for awarding me £1,538. These funds allowed me to attend the annual meeting of the *American Society of Nephrology* (ASN, see www.asn-online.org/), one of the world's leading renal organisations. I presented our recent data (outlined in the abstract and figures below) to leading researchers, experts in their fields and potential peer reviewiers. Our data were well received and sparked a lively discussion between a number of individuals about the potential mechanisms for our findings. However, all agreed the data were novel and of significnat scientific and potentially clinical interest. We have gone on to submit a manuscript for publiaction in the journal *Circulation Research*. The reviewers comments were positive and the paper is currently under revision. Furthermore, the opportuntiy the Myre Sim grant has afforded me has also allowed me to set up a number of new collaborations that should generate interesting data in the near future.

Abstract of Research

Macrophage endothelin-B receptors clear endothelin-1 & regulate blood pressure

Introduction

Hypertension is common. However, its cause remains unclear in the majority of those affected. Recent data suggest that macrophages (Mϕ)/monocytes contribute to, and protect from, hypertension. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor with additional pro-inflammatory properties. However, the effects of ET-1 on Mϕ biology are not well studied.

Methods & Results

Here we show that systemic depletion of Mϕ results in an augmented pressor response to ET-1 (**Figure 1**). We conclusively demonstrate that murine bone marrow derived macrophages (BMDM) and human monocytes express *both* ET_A and ET_B receptors and display chemokinesis to ET-1. However, stimulation of Mϕ with exogenous ET-1 does not polarize Mϕ phenotype. Importantly, we show a novel clearance mechanism for ET-1 through ET_B receptor mediated dynamin-dependent endocytosis present in both murine and human Mϕ. We confirm our *in vivo*

and *in vitro* findings through the generation of mice lacking ET_B receptors solely on myeloid cells (*LysMET*$_B^{-/-}$) (**Figure 2**). Finally, in patients receiving Mϕ depleting immunotherapy we show that BP is higher and the ET system more activated than in those receiving non-depleting therapies.

Conclusions

Overall, these data suggest that Mϕ and ET-1 may play an important role in BP control and potentially have a critical role as a therapeutic target in hypertension.

Figure 1

Acute blood pressure (BP) response to 3 incremental doses of endothelin-1 (ET-1) following acute depletion of circulating monocytes and resident Mϕ (DTR+DT+), and in controls (those with the diphtheria toxin receptor (DTR) construct but given saline, DTR+DT, and mice given diphtheria toxin (DT), DTR-DT+). (n=10 mice for each group). (A) Baseline BP between the 3 groups of animals (B) Example of the differences seen between the 3 groups in the acute pressor response to ET-1. The black arrow defines the time at which intravenous ET-1 was administered. The dotted and dashed lines represent baseline and maximal mean arterial pressure (MAP), respectively. (C) Maximal change in MAP, and (D) Overall magnitude of the BP response defined by the area under the BP curve for a period of 1200s.

***p <0.001 and ****p <0.0001 for DTR+DT+ *vs.* both DTR-DT+ and DTR+DT-.

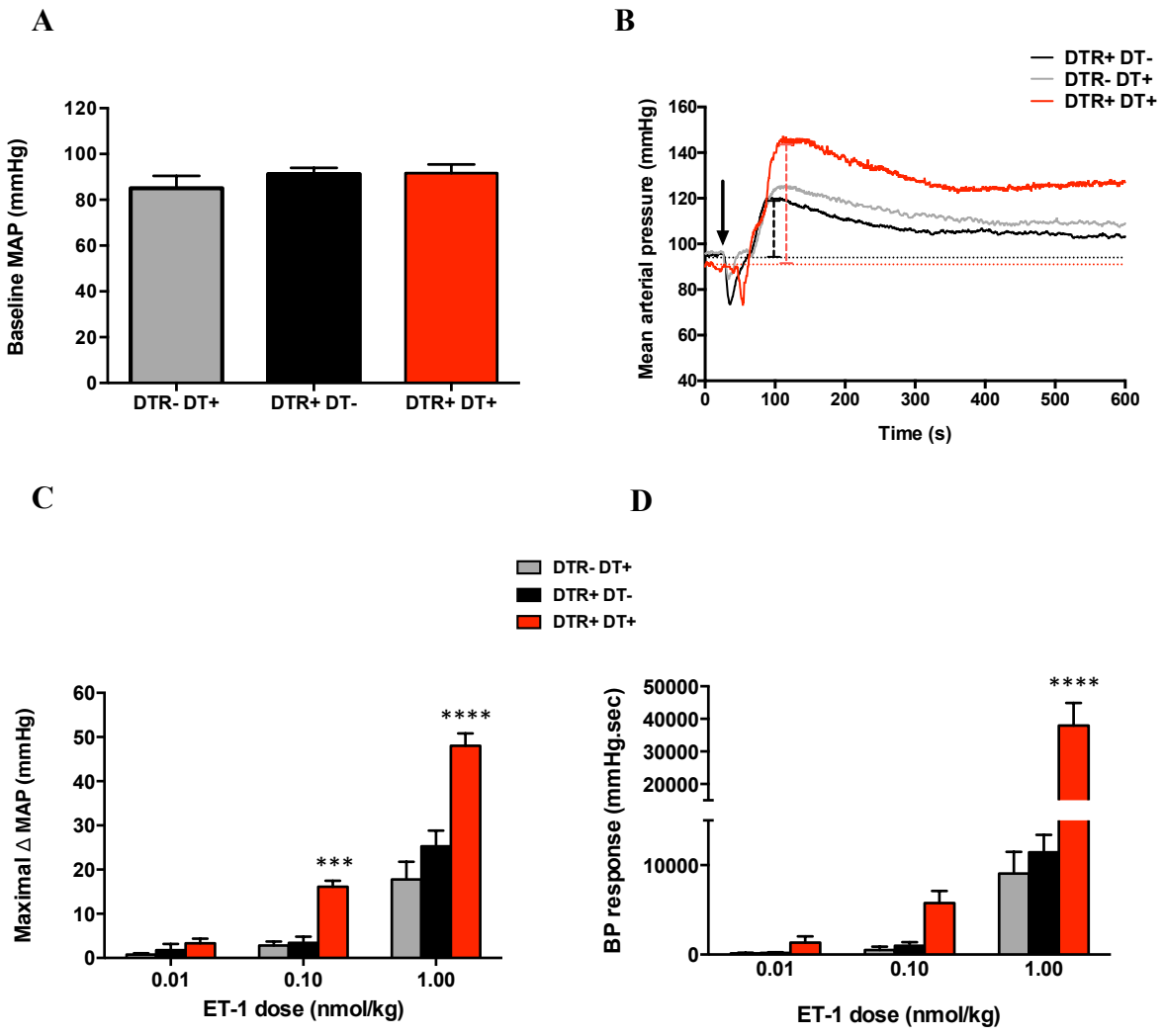

Figure 2

Acute blood pressure response to 3 incremental doses of endothelin-1 (ET-1) in wild type (WT) and *LysMET$_B^{-/-}$* mice (A) Baseline mean arterial pressure (MAP) of the 2 groups of animals (B) Maximal change in MAP, (n=6 mice for each group). *p <0.05 for WT v*s. LysMET$_B^{-/-}$* (C) WT and *LysMET$_B^{-/-}$* BMDM were exposed to ET-1 10pg/ml *in vitro* in the presence or absence of selective antagonism of the ET_B receptor (BQ788). ET-1 was measured in the supernatant at 24h. (mean ± SEM, n=7 in triplicate). (D) BMDM chemokinesis in response to varying doses of ET-1 and MCP-1 for WT and *LysMET$_B^{-/-}$* (mean ± SEM, Mϕ / high power field (hpf), n=6 mice for each group in triplicate). *p <0.05 for WT v*s. LysMET$_B^{-/-}$*.