



## Review

## Evaluating the carotid bodies and renal nerves as therapeutic targets for hypertension

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## ABSTRACT

Despite the plethora of current treatment options, hypertension remains a difficult condition to adequately control, and there is a pressing need for novel therapeutic strategies. The carotid body has recently become the focus of considerable interest as a potential novel treatment target in essential hypertension. Herein, we appraise the current literature suggesting that the carotid body plays an important causative role to generate sympathetic overactivity and drive increases in arterial pressure, in animal models of hypertension. We also review evidence from human studies showing cardiovascular benefits to the transient inactivation, or surgical removal of carotid bodies, and evaluate the potential benefits of pre-screening to identify patients likely to respond to carotid body-targeted therapy. Finally, given that a high proportion of patients who have undergone renal nerve ablation procedures remain hypertensive, we examine whether the renal nerves are necessary for the drop in blood pressure seen with carotid body removal.

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## 1. Introduction

High blood pressure is of pandemic proportions with between 25–33% of the world's population affected (Go et al., 2014). Its asymptomatic characteristic and multiple potential causes make this syndrome notoriously difficult to treat clinically. Interventions to control blood pressure are of high importance, as sustained hypertension is a major risk factor for stroke, heart disease, atherosclerosis and renal damage (Lewington et al., 2002). Here we compare interventional approaches

for the treatment of hypertension with our focus on a novel anti-hypertensive target.

## 2. Do we need new treatments for hypertension?

Despite the armoury of anti-hypertensive medications currently available, only around 50% of treated patients have adequate blood pressure control (Go et al., 2014), an alarming statistic given that a 10 mm Hg rise in blood pressure doubles the risk of death from cardiovascular disease, and each 2 mm Hg rise in blood pressure increases the risk of stroke by 10% (Lewington et al., 2002). Several possible factors may underpin this failure to control blood pressure, including white coat hypertension, sub-optimal treatment regimens and poor patient compliance. When other causes are excluded, true multi-drug resistant

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hypertension has been estimated to account for ~10% of all cases (de la Sierra et al., 2011; Persell, 2011). Poor adherence to anti-hypertensive medication is seen in a large proportion of patients – up to 40% of patients with newly diagnosed hypertension choose to discontinue their medication within 12 months (Mazzaglia et al., 2005), and 25% of patients enrolled into specialist hypertension clinics were non-adherent to treatment (Tomaszewski et al., 2014). This is undoubtedly related to the relatively high rate of side effects, which affect over one third of patients being treated for an otherwise largely asymptomatic condition (Benson and Britten, 2003). In order to address patient compliance, intolerance and drug-resistance, there is a pressing need for a wider range of treatment options to control blood pressure.

At present, pharmacological treatments for hypertension are dominated by drugs targeting the renin-angiotensin aldosterone system, such as ACE-inhibitors, angiotensin receptor blockers, diuretics and aldosterone antagonists targeting the mineralocorticoid receptor (Romero et al., 2015; Roush and Sica, 2016). In some countries,  $\beta$ -adrenoceptor blockers are prescribed to block sympathetically mediated release of renin from the kidney (Wong et al., 2016). Calcium channel blockers and  $\alpha_1$ -adrenoceptor antagonists reduce vascular resistance (Cubeddu, 1988; Tocci et al., 2015), while centrally-acting sympatholytic drugs such as the  $\alpha_2$ -adrenoceptor agonist clonidine and the imidazoline receptor agonist moxonidine, lower sympathetic activity (Sica, 2007). The clinician will typically follow a nationally-agreed protocol for drug type, dose and sequence/combinations (James et al., 2014; Mancía et al., 2007; Whitworth et al., 2003). In most cases blood pressure can be reduced, although not always to target levels (Go et al., 2014).

Aside from the release of the renin inhibitor aliskiren in 2007 (Brown, 2008), there have been no truly novel anti-hypertensive medications released in over 20 years. Instead, in recent years a series of device-based and surgical interventions have been trialled with varying degrees of success, including renal denervation (e.g. (Krum et al., 2009)), electrical stimulation of carotid baroreceptors (Heusser et al., 2010), deep brain stimulation (Patel et al., 2011) and arterial venous anastomosis (Lobo et al., 2015). For the treating physician, device-based or surgical approaches may offer a greater degree of control over patient compliance/intolerance when compared to conventional drug therapies.

### 3. Current problems with renal denervation

Despite considerable promise in early studies (Esler et al., 2012; Krum et al., 2014), the recent SYMPPLICITY HTN-3 trial has raised important questions about the broad use of renal denervation to treat essential hypertension (Bhatt et al., 2014). Since 2014, over 70 articles have been published discussing and debating the methods, design, results and implications of the SYMPPLICITY trials. A particular problem is that when renal denervation is applied clinically to a diverse hypertensive cohort, the procedure only appears to benefit ~50% of patients (Brinkmann et al., 2012; Hart et al., 2013), and there is at present no clear process by which ‘BP responders’ can be pre-screened. Microneurography studies have suggested that muscle sympathetic nerve activity (SNA) tends to decrease after renal denervation, however both we and others have failed to find a correlation between either the baseline level or change in muscle SNA, and subsequent changes in blood pressure (Hart et al., 2013; Hering et al., 2014). Zuern et al. found that cardiac baroreflex sensitivity could prospectively discriminate patients who would respond to renal denervation, although the degree of baroreflex impairment did not predict the size of the fall in blood pressure (Zuern et al., 2013). It has been recently suggested that the efficacy of renal denervation should be examined in different models of hypertension, as a way to match efficacy of procedure with causal mechanisms of the hypertension (Esler, 2015; Fink and Osborn, 2014; Kandzari et al., 2015; Schlaich et al., 2014). Although small subgroups of patients have been shown to have a ~50% reduction in renal NE

spillover after catheter ablation (Krum et al., 2009), unfortunately there is currently no methodology that allows an easy routine assessment of the degree of renal nerve ablation achieved in the clinic, either on- or off- table. It is therefore difficult to reconcile the reported long-acting effects of renal denervation in human patients, with animal studies showing that functional afferent and efferent re-innervation of the kidney takes place in the months following renal denervation (Booth et al., 2015a,b; Grisk et al., 2001; Mulder et al., 2013). Additionally, given that most antihypertensive drugs on the market already target renal mechanisms (see above), the discovery of a truly novel therapeutic target would be appealing. Below, we discuss recent studies identifying the carotid body chemoreceptors as a putative target for antihypertensive treatment.

### 4. Introducing the carotid body in hypertension and cardiovascular disease

We have recently proposed an afferent activation hypothesis for hypertension where hypoperfusion of an organ triggers sensory afferent discharge eliciting sympathoexcitation; the latter may worsen organ perfusion and positively feedback to further activate the afferent source (Koeners et al., 2016). One such organ considered is the carotid body. The carotid bodies are placed strategically at the carotid bifurcation to sample the composition of blood as it enters the brain, and act as guardians of cerebral perfusion (Ponte and Purves, 1974). The activation of the carotid bodies by hypoxia drives excitation in medullary pre-sympathetic pathways (Guyenet, 2000; King et al., 2012), giving rise to a sympathetically-mediated increase in arterial pressure, ultimately aimed at improving cerebral perfusion (Marshall, 1994; Narkiewicz et al., 2006; Paton et al., 2006; Somers et al., 1989). Interestingly, Ding et al. have shown that the chronic partial occlusion of both carotid arteries results in a reduction in carotid body blood flow, an increase in resting renal SNA and hypersensitivity of the chemoreflex-mediated sympathetic response to hypoxia (Ding et al., 2011). This demonstrates that a prolonged challenge to carotid body and/or cerebral perfusion may drive a chronic increase in sympathetic outflow, although whether there was any concurrent impact on blood pressure in this model is not reported.

An extensive body of evidence published by ourselves and others demonstrates that the peripheral chemoreceptors show both hypersensitivity and aberrant tonic activity in animal models of hypertension, activating the sympathetic nervous system and driving increases in arterial pressure. In the young spontaneously hypertensive rat, an increased sensitivity to chemoreceptor reflex stimulation is seen before the onset of hypertension (Tan et al., 2010), and transection of the carotid sinus nerve to disconnect the carotid bodies from the brain post-natally ameliorates the developmental rise in arterial pressure (Abdala et al., 2012), suggesting that peripheral chemoreceptor overactivity plays a causal role in the development of hypertension. In the adult spontaneously hypertensive rat, we have shown that carotid sinus nerve denervation produces a sustained fall in arterial pressure in conscious rats for many weeks (McBryde et al., 2013). These effects are rapid (2–3 days post-surgery) and are accompanied by a profound (50%) reduction in renal sympathetic nerve activity, improved baroreceptor reflex function and renal function, and reduced systemic inflammation (McBryde et al., 2013). Recently published work has identified a possible role of the carotid body in other forms of neurogenic hypertension, such as renovascular hypertension (Campos et al., 2015; Oliveira-Sales et al., 2016; Oliveira-Sales et al., 2014) and the hypertension induced by chronic intermittent hypoxia (Iturriaga et al., 2015; Marcus et al., 2010). Normotensive rats do not show a reduction in sympathetic drive or arterial pressure after removal of carotid body input (McBryde et al., 2013), supporting the notion that aberrant chemoreflex activity is unique to the hypertensive setting. This is echoed in parallel human studies, where transient inactivation of the carotid bodies with hyperoxia caused a reduction in blood pressure in hypertensive, but

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