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.

Key Words: Renal Denervation, Carotid Body, Hypertension, Sympathetic Nervous System

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.

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 10mmHg rise in blood pressure doubles the risk of death from cardiovascular disease, and each 2 mmHg 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 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 et al., 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 et al., 2016). In some countries, β-adrenoceptor blockers are prescribed to block sympathetically mediated release of renin from the kidney (Wong et al., 2016). Calcium channel blockers and α_1-adrenoceptor antagonists reduce vascular resistance (Cubeddu, 1988; Tocci et al., 2015), while centrally-acting sympatholytic drugs such as the α_2-adrenoceptor agonist clonidine and the imidazoline receptor agonist moxondine, 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; Mancia 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.

Current Problems with Renal Denervation

Despite considerable promise in early studies (Esler et al., 2012; Krum et al., 2014), the recent SYMPLICITY 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 SYMPLICITY 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 et al., 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; Booth et al., 2015b; 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.

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 et al., 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 hyper-sensitivity and aberrant tonicity 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 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 acompanied by a profound (50%) reduction in renal sympathetic nerve activity, improved baroreceptor reflex function and renal function, and reduced systemic inflamamtion (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 abberant chemoreflex activity is unqiue 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 not normotensive subjects (Sinski et al., 2014). The volume of the carotid bodies have been reported to be significantly larger in patients with essential hypertension (Heath et al., 1985), with size correlating with indirect measures of autonomic function (Jazwiec et al., 2015). Bilateral surgical resection of the carotid bodies to relieve symptoms in obstructive airway disease has been noted to reduce blood pressure acutely (Winter et al., 2004), with others observing that this effect persisted for at least 6 months in a hypertensive sub-group (Nakayama, 1961). A recent retrospective analysis of patients undergoing unilateral carotid body tumour removal, found sustained blood pressure reductions in 12 out of 20 hypertensive patients (Fudim et al., 2015). Similarly, recent preliminary data from our research team shows that unilateral carotid body removal is associated with prolonged (12 month) reductions in arterial pressure and sympathetic activity, in ~60% of resistant hypertensive patients (Hart et al., 2016). While the proportion of resistant hypertensive patients who may benefit from carotid body ablation is similar to the ~50% of patients seen to respond to renal denervation, the ventilatory response to hypoxia appears to be a simple method able to discriminate responders from non-responders (Hart et al., 2016). Thus, unlike renal denervation, there is the potential to pre-screen for patients most likely to benefit from carotid body targeted treatment.

Taken together, these studies make a compelling case that the carotid bodies play a fundamental role in the pathogenesis of essential hypertension. Thus, exploiting the carotid bodies in order to reduce sympathetic overactivity in cardiovascular disease has attracted considerable scientific interest (Andrade et al., 2015; Kara et al., 2003; Niewinski et al., 2013; Paton et al., 2013a; Paton et al., 2013b; Ratcliffe et al., 2014; Schultz et al., 2015). We have recently published a safety and feasibility trial examining unilateral carotid body resection in human resistant hypertensive patients, which found a >10mmHg reduction in arterial pressure, accompanied by a fall in muscle SNA, in patients with indicators of increased carotid body drive (Narkiewicz et al., 2016). Although these preliminary findings clearly require verification in a larger, prospectively-identified patient cohort, these early indications hold promise.

Carotid body ablation after renal denervation

Over 10’000 hypertensive patients worldwide have undergone renal denervation procedures, in many cases as a last resort after the failure of multi-drug therapy to control their blood pressure. If, as we propose, the carotid bodies are a viable therapeutic target for hypertension, is this of any relevance to the growing body of patients who have previously undergone renal denervation but

remain hypertensive? We have shown that prior renal denervation does not attenuate the reduction in arterial pressure to carotid sinus nerve denervation in the spontaneously hypertensive rat (Figure 1). This indicates that the presence of renal nerves is not required in order for the removal of carotid body input to have a beneficial effect on arterial pressure, supporting our notion of distinct afferent drives causing hypertension (Koeners et al. 2016). Importantly, the combined effect of severing nerves to the kidneys and carotid bodies was additive. Thus, carotid body denervation could potentially provide therapeutic benefit in human hypertensive patients who have failed to respond to renal denervation.

Moving Forward

Given the multi-factorial nature of essential hypertension, it is hardly surprising that optimizing patient treatment often requires an individualized, 'trial and error' approach, especially when our ability to phenotype symptoms remains so limited. However, it is apparent that new and effective interventional approaches are needed in some cases, to compliment current pharmacological treatment options. It will become essential to better diagnose the blood pressure controlling mechanisms in individuals in order to prescribe the most effective treatment strategy, whether pharmacological and/or interventional. Preclinical animal and a small number of human studies have confirmed the importance of the carotid bodies in mediating sympathetic over-activity and hypertension, and have built a strong case to investigate therapeutic targeting of carotid bodies in cardiovascular disease. To date, the only option to reduce carotid body activity long-term has been the surgical removal of one or both carotid bodies, although an ablation catheter is currently being trialled. While these procedures may have benefits in terms of guaranteeing patient compliance, approaches which do not permanently disable carotid body function may be more desirable in the long term. Thus, it may be attractive to also seek novel pharmacological compounds to selectively inhibit aberrant carotid body afferent signalling, while sparing its ability to respond to physiological cues. We have recently published a study evaluating the use of a selective purinergic antagonist to target the P2X3 receptor, present in the carotid body (Pijacka et al., 2016). We found that P2X3 inhibition was able to successfully reduce sympathetic nerve activity and arterial pressure in spontaneously hypertensive rats. If proven to be successful, such a compound would be the first new class of anti-hypertensive drug in over 15 years.

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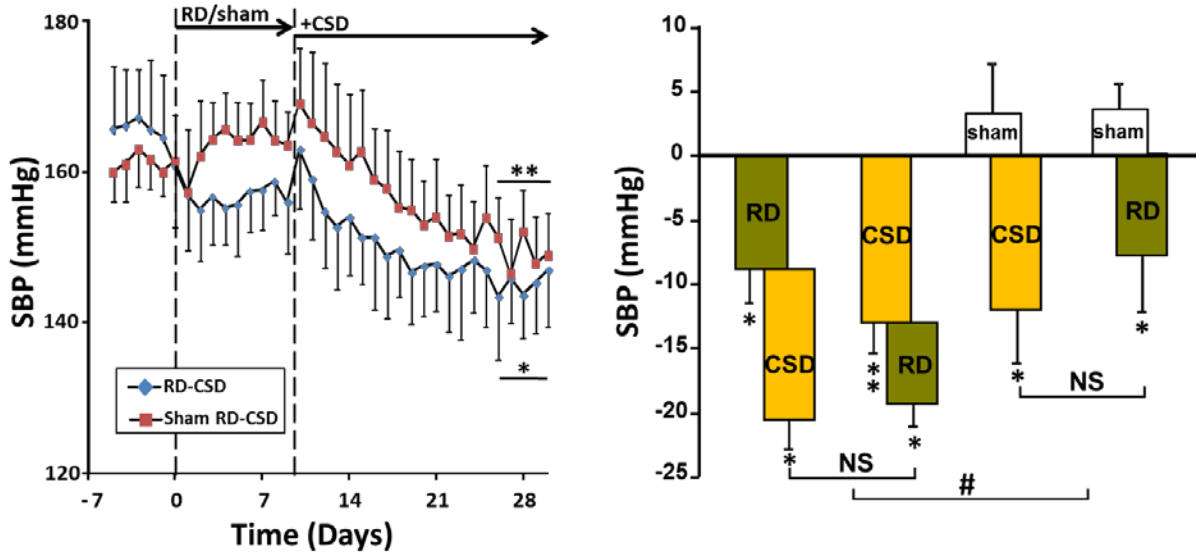

Figure 1 – Prior Renal Denervation (RD) does not prevent the reduction of arterial blood pressure with Carotid Sinus Denervation (CSD) in the spontaneously hypertensive rat. Panel A: Systolic blood pressure (SBP) before and after RD/sham, followed by CSD. Note the similar fall in SBP with CSD, regardless of the presence or absence of renal nerves. Panel B: Change in SBP with combined RD and CSD, compared to RD and CSD alone. The additive response regardless of whether CSD or RD is performed first suggests an independent mechanism of action. Within-subject comparisons: *p<0.05, **p<0.001, repeated measures ANOVA with Holm-Sidek posthoc comparisons: CSD vs RD or sham. Between Group Comparisons: NS = not significant, #p<0.05, two way ANOVA with Holm-Sidek posthoc comparisons: RD+CSD vs CSD+RD vs sham+CSD vs sham+RD. Redrawn from (McBryde et al., 2013).

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