Experimental Physiology – *Introduction*

Neurogenic hypertension

This issue contains five symposium papers on ***Neurogenic hypertension*** originating from the workings of two major international meetings. The first was on ***Neurovascular inflammation and neurogenic hypertension***, held at the Physiological Society's main annual meeting in Dublin, Ireland (7–10 July 2009) and the second, entitled ***Neurogenic hypertension***, at the XXXVI International Union of Physiological Sciences congress in Kyoto, Japan (27 July–1 August 2009). These meetings were organized by Eric Lazartigues (Louisiana State University Health Science Centre, New Orleans, LA, USA), Julian F. R. Paton (University of Bristol, Bristol, UK) and Mohan K. Raizada (University of Florida, Gainesville, FL, USA).

The focus of these two symposia was to provide a forum for debate and scientific exchange between the basic and clinical scientist, to highlight important issues and chart future direction in the field of neurogenic hypertension. This was deemed timely because of the current trend towards translational science but, importantly, 'reverse translation', whereby observations made in human patients can be studied at great detail to reveal putative mechanistic insight in animal models. Indeed, the clinical problem of essential hypertension is ripe for both translation and reverse translation.

Despite the intense research activity in the area in the last two decades, hypertension remains a major health problem worldwide, with devastating economic and financial impact to society. With numbers growing (expected to hit 1 billion in 2025), one in three people worldwide are likely to suffer from it. By far the most depressing statistic is that despite the armory of antihypertensive agents, approximately 30% of patients are drug resistant and so-called refractory hypertensive. With this alarming figure, our symposia were timely since it now becomes clear that blood pressure control in patients with hypertension is altered and complex. The papers in this *Symposium Issue* summarize the state of our understanding, provide new revelations concerning the mechanisms underpinning neurogenic hypertension and, importantly, provide novel clues for future therapeutic intervention.

The prevalence and dangers of high blood pressure are well summarized by Fisher & Fadel (2010). This report and that by Grassi *et al.* (2010) emphasize the phenotype of neurogenic hypertension, that being elevated sympathetic activity destined for skeletal muscle vasculature as recorded from the peroneal nerve in humans, and raised levels of circulating catecholamines. Both these papers make an important point that increased sympathetic nerve activity is associated with other disease states (obesity, diabetes, left ventricular hypertrophy and arrhythmias) as well as with elevated plasma levels of leptin, insulin and angiotensin II. Fisher & Fadel (2010) also emphasize the dangers of excessive sympathetic nerve activity in terms of end organ damage. Alarmingly, they provide evidence that some conventional antihypertensive medications (e.g. calcium channel and angiotensin type 1 receptor antagonists) raise sympathetic nerve activity that could, potentially, exacerbate end organ failure. They go on to discuss human data where centrally acting drugs (e.g. imadazoline) have been used to successfully lower sympathetic activity as well describe the effects of antioxidant and anti-inflammatory medications (e.g. statins) on sympathetic activity. They review the effects of exercise on raised sympathetic traffic, indicating the intriguing, calming cross-talk between physical activity and sympathetic motor outflow.

Grassi *et al.* (2010) review human and animal data, again indicating excessive sympathetic activity in hypertension, and demonstrate the power of artificially manipulating autonomic activity as a therapeutic strategy for controlling, at least in part, high blood pressure and sympathetic activity. They discuss the recent clinical trials on refractory hypertensives where carotid sinus baroreceptors have been stimulated chronically as well as renal nerve ablation. These first two papers make it clear that sympathetic activity is elevated in hypertensive patients,

DOI: 10.1113/expphysiol.2009.047282

but the degree to which this is responsible for the development and maintenance of this condition is less clear. Addressing the issue of causation is not easy, but it is evident that a major goal for high blood pressure research is to protect against end organ damage by targeting elevated sympathetic activity.

Toney and colleagues (2010) review the impact of salt and angiotensin II on blood pressure control and highlight the central autonomic actions. They remind us that angiotensin II is a major conspirator in neurogenic hypertension. This of course includes circulating angiotensin II, but most relevant to neurogenic hypertension is overactivity of the brain renin–angiotensin system. They provide evidence in an animal model that angiotensin infusion and a high-salt diet cause marked hypertension through actions on the central nervous system. This provides a unique sympathetic signature of raised activity to the splanchnic vascular bed but not to the kidney or hindlimb, at least in the anaesthetized rat. Their evidence shows that the elevated sympathetic activity in this model appears to be due to an increase in coupling strength with the central respiratory pattern generator located within the ventral medulla oblongata. Why these changes come about remains unclear, but the finding that angiotensin II and salt harness the respiratory oscillator to provide greater sympathetic drive is a fascinating observation.

Waki *et al.* (2010) shed light on a potential mechanism for heightened sympathetic activity and explore potential genetic and molecular changes occurring within the hypertensive brainstem. Using gene array on brainstem samples from the spontaneously hypertensive rat, they describe two genes that may be responsible for the novel finding of inflamed brain microvasculature. Both these genes express proteins that are well known for attracting leukocytes to the luminal wall of capillaries. Indeed, leukocyte binding is suggested as the prompt for subsequent release of chemokines, which are discussed as a mediator of vascular–neuronal signalling that modulate blood pressure and alter baroreceptor reflex function. In this regard, new data are presented revealing a role for Ccl5 (or RANTES). The suggestion proposed is that signalling across the blood–brain barrier appears to play a major role in blood pressure regulation and that this is disrupted in the hypertension condition, perhaps because of vascular inflammation. This ties in well with the human statin data discussed by Fisher & Fadel (2010).

Finally, the issue of increased activity of the central renin–angiotensin system and hypertension is discussed by Feng *et al.* (2010). They show that angiotensin-converting enzyme 2 (ACE2), known to be present within heart, kidney and blood vessels, is also present within autonomic control nuclei of the brain. Angiotensin-converting enzyme 2 plays a counterregulatory role to angiotensin II. It is described that ACE2 counteracts angiotensin II effects by decreasing the expression of angiotensin type 1 receptors and increases production of angiotensin (1–7), which is vasoprotective; the latter also increases production of nitric oxide, triggering alterations in blood flow and presumably neuronal integration. Feng *et al.* (2010) show that blocking ACE2 activity in the brain causes disruption to normal cardiovascular control, yet its activity appears suppressed in conditions of hypertension, since overexpression lowers blood pressure in a hypertensive animal model; the latter has obvious clinical relevance.

All told, this series of papers provides the reader with up-to-date viewpoints on the current major issues concerning hypertension, some novel therapeutic approaches being trialed presently, the latest in potential central nervous mechanisms driving up blood pressure and some possible new therapeutic strategies to exploit in the future.

Julian F. R. Paton and Mohan K. Raizada
Email: julian.f.r.paton@bristol.ac.uk, mraizada@phys.med.ufl.edu

References

Grassi G, Seravalle G & Quarti-Trevano F (2010). The 'neuroadrenergic hypothesis' in hypertension: current evidence. *Exp Physiol* **95**, 581–586.

Feng Y, Xia H, Santos RA, Speth R & Lazartigues E (2010). Angiotensin-converting enzyme 2: a new target for neurogenic hypertension. *Exp Physiol* **95**, 601–606.

Fisher JP & Fadel PJ (2010). Therapeutic strategies for targeting excessive central sympathetic activation in human hypertension. *Exp Physiol* **95**, 572–580.

Toney GM, Pedrino GR, Fink GD & Osborn JW (2010). Does enhanced respiratory–sympathetic coupling contribute to peripheral neural mechanisms of angiotensin II–salt hypertension? *Exp Physiol* **95**, 587–594.

Waki H, Gouraud SS, Maeda M & Paton JFR (2010). Evidence of specific inflammatory condition in nucleus tractus solitarii of neurogenic hypertension. *Exp Physiol* **95**, 595–600.