

Editorial

Muirhead's syndrome and medullipin

A new syndrome and a unique hypotensive agent

The era of the eponymous syndrome is well-high past. Nevertheless a report earlier this year in a new journal, *Blood Pressure*, of a patient with persistent hypotension caused by a renal medullary tumour should be recognised as the first case of Muirhead's syndrome.^{1,2} For 40 years Eric Muirhead, working in Memphis, Tennessee, has carried out a remarkable series of experiments demonstrating that the interstitial cells of the renal medulla secrete a remarkably potent non-prostanoid vasodepressor lipid.³ Originally Muirhead was inspired by Grollman's observation that hypertension associated with bilateral nephrectomy could not be explained solely by sodium and water retention. Thus blood pressure did not become raised in the presence of a single kidney rendered non-excretory by diversion of the ureter into the vena cava.⁴ Subsequently he was able to show that transplanted renal medullary cells lowered blood pressure in Goldblatt hypertension and that lipid granules within these cells were discharged when blood pressure was lowered by renal artery deconstriction.⁵ In tissue culture these cells secreted both prostanoid and non-prostanoid lipids.⁶ One of these was a neutral lipid (subsequently termed medullipin I) that was activated by a cytochrome P-450 dependent mono-oxygenase system in the liver to the active compound medullipin II.⁷ Medullipin II reduces peripheral resistance and blood pressure probably by decreasing sympathetic tone.⁸ The release of medullipin II is critically dependent on renal perfusion pressure. Folkow and his colleagues in Gothenburg showed that perfusion of an isolated kidney at high pressure resulted in the release of a substance (now believed to be medullipin I) that profoundly lowered the blood pressure of a recipient rat.⁹ The one pathophysiological situation so far in which the renomedullary medullipin system seems to play a major part is the major fall in blood pressure that occurs in Goldblatt hypertension within a few hours of renal artery deconstriction.¹⁰ None of the classic regulatory systems can explain this fall which is not influenced by blockade of the renin-angiotensin system, prostaglandin, kallikrein-kinin, or opioid systems.^{10,11} Further the fall is much too rapid to be explained by reversal of trophic changes in the resistance vessels. In an exhaustive search for means of inhibiting this fall in blood pressure the only manoeuvre which we found to be effective was chemical removal of the renal medulla.^{10,11} "Chemical medullectomy" induced by the selective toxic agent bromethylamine hydrobromide produced a moderate increase in blood pressure in rats¹² but substantially reduced the fall in blood pressure observed when renal artery constriction is relieved.^{10,11}

Unfortunately, the chemical structure of medullipin is still unknown and this has undoubtedly held back progress. Had the lipid been a peptide the world would have beaten a path to Muirhead's door and no doubt would now be treating patients with medullipin and its agonists. Remarkably medullipin seems to be active when given by mouth.¹³

The other factor that has limited interest in the medullipin system is the lack of evidence of clinical relevance. This has been resolved by a recent case report.¹ A woman of 46 underwent chronic dialysis treatment for renal failure caused by nephrolithiasis for which she had had a left nephrectomy 19 years before. Though during the course of her renal disease she had been hypertensive she later became progressively hypotensive with blood pressures ranging from 39/27 mm Hg to 71/39 mm Hg. There was no postural element to her hypotension and it could not be attributed to either fluid depletion or cardiac disease. Her venous plasma induced substantial blood pressure lowering when injected into spontaneously hypertensive rats. The animals' response pharmacologically resembled that observed with injections of medullipin. This case report is suggestive, but a follow up

report, also published in *Blood Pressure* this month, is even more persuasive.² The patient died of peritoneal infection and at necropsy a small renal medullary tumour was found consisting of renal interstitial cells and adipocytes. Extraction yielded high concentrations of medullipin I. Medullipin I could not be identified in renal tissue outside the mass. Muirhead *et al* conclude that the patient had a lipomedullipinoma and that this had produced her hypotension.

The clinical implications of this observation in the diagnosis of patients with histories of short-lived hypotension are self-evident. Unfortunately imaging these relatively inaccessible tumours may be difficult and diagnosis will have to be based upon a fairly crude bioassay until the structure of medullipin is identified. We have little idea of the physiological role of the renomedullary vasodepressor system apart from its involvement in the fall in blood pressure that occurs when renal blood flow is restored after renal artery constriction.^{5,10,11} Chemical medullectomy inhibits the blood pressure fall induced by angiotensin converting enzyme (ACE) inhibitors^{14,15}: on these and other grounds it has been suggested that pharmacological inhibition of angiotensin II formation stimulates the system, which may therefore play an important part in antihypertensive drug treatment.^{14,15} We know nothing of the medullipin receptors or even indeed the tissue in which they are situated, though the brainstem seems to be a prime candidate. It is even more surprising that the pharmaceutical industry has taken so little interest in medullipin. The existence of a physiological compound that is active when given by mouth and which lowers blood pressure largely if not entirely by a novel mechanism raises possibilities which are in urgent need of exploration.

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