Modulation of neurohumoral effector gain as a novel mechanism for the long term regulation of blood pressure

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There is increasing evidence for the importance of the sympathetic nervous system in a number of disease states such as hypertension, congestive heart failure and renal failure. While it is recognised that the sympathetic nervous system consists of differentially regulated outflow to a variety of organs, perhaps the most relevant to the long term regulation of blood pressure (BP) and also to hypertension is renal sympathetic nerve activity (RSNA). By regulating renal hemodynamics, tubular function, and renal renin release, RSNA has the potential to contribute to the initiation, development and maintenance of hypertension. DiBona and colleagues suggest that renal sympathetic activity at low frequencies affects renin release, moderate frequencies inhibits sodium excretion and only at high stimulation frequencies reduces renal blood flow (RBF) (DiBona & Kopp, 1997). They suggest that in conscious animals resting RSNA is too low to affect RBF. We developed a combined nerve electrode and flowprobe for conscious rabbits and examined the relationship between RSNA and RBF. Initial studies showed that RSNA can influence RBF especially when activated by physiological stimuli (Janssen *et al.*, 1997). In further studies we examined the effect of acute sympathetic inhibition with rilmenidine, and acute angiotensin converting enzyme inhibition with captopril. Rilmenidine produced hypotension but no change in renal vascular conductance in normal rabbits, renal vasodilatation in barodenervated rabbits and some renal vasoconstriction in renal denervated rabbits. By contrast captopril produced similar renal vasodilatation whether the RSNA increased or was absent. These results suggest that while RSNA can influence short term fluctuations in RBF, the renin angiotensin system is the major influence on RBF and can override the influence of RSNA. From these studies we might expect there to be little role for RSNA in conditions where there is elevated plasma renin such as in renovascular hypertension. However, there is a large body of evidence to suggest an important role of the sympathetic nervous system and the central nervous system in this form of hypertension (Fink, 1997). We assessed the contribution of the sympathetic nervous system using acute and chronic sympathetic inhibition with rilmenidine in 2K1C hypertensive rabbits. After establishing a stable level of hypertension, rilmenidine or vehicle (saline) was infused by osmotic minipump. After a further 2 weeks, an electrode for recording renal sympathetic nerve activity (RSNA) and a RBF probe was implanted under halothane anaesthesia. Five weeks after renal artery clipping, mean arterial pressure (MAP) was 34% higher and renin was elevated 5 fold, but rabbits treated with rilmenidine were normotensive with less elevated renin. RSNA, heart rate and blood flow to the unclipped left kidney were similar in both groups of rabbits. The acute response to rilmenidine was greater in the hypertensive group with a lesser fall in RSNA such that the change in BP per change in RSNA was 5 fold greater than in normotensive rabbits. Also the relative renin release in response to increased RSNA was increased 3 fold in 2K1C rabbits. By contrast the pressor response to airjet stress was similar in hypertensive and chronic rilmenidine treated (normotensive) rabbits indicating that vasoconstrictor neuroeffector mechanisms were not altered by high renin states. These studies suggest that in the long term the RSNA may make an increasing contribution to the maintenance of BP in renovascular hypertension, possibly though an amplification of the neural release of renin. The long term modulation of the renin neuroeffector mechanism which in our case took at least 4 weeks may be an important way in which the sympathetic nervous system contributes to the long term setting of BP.

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