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Novel genomic clues to the central origins of hypertension in animal models of hypertension

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Human essential hypertension is a complex polygenic trait with underlying genetic components that remain unknown. Since the brainstem structure - the nucleus of the solitary tract (NTS) - is a pivotal region for regulating the set-point of arterial pressure, we proposed a role for it in the development of primary hypertension. In this study, we screened for hypertension-related genes expressed in the NTS of spontaneously hypertensive rats (SHR). Three- and 18-week-old male SHR and their progenitor strain, Wistar-Kyoto rats (WKY) (all humanely killed), were used. cDNA microarray analysis was performed to find differentially expressed genes in the NTS between SHR and WKY. Signals exhibiting >2 difference between these strains were selected for further analysis using real-time RT-PCR.

From 14,815 genes, 22 genes showed a greater expression in young (pre-hypertensive) and adult (hypertensive) SHR relative to WKY, whereas two other genes were down-regulated. So far, 4 genes have been proven to be differentially expressed using real-time PCR. One of these is junctional adhesion molecule-1 (JAM-1), which is highly expressed in both pre-hypertensive (n=4) and hypertensive SHRs (n=6) compared to WKY (young, n=4; adult, n=6).

In the NTS of adult WKY (n=5), JAM-1 protein was exogenously expressed by using a recombinant adenoviral vector and cardiovascular variables were chronically measured using an automated computer analysis package (Waki et al. 2004). 7 days after viral injection, systolic pressure was significantly increased (119±4 vs 133±4 mmHg, $p<0.01$) while spontaneous baroreflex gain did not change (1.18±0.15 vs 1.56±0.30 ms $mmHg^{-1}$, $p=0.21$).

Our data suggest that gene expression in the NTS is inherently different between SHR and WKY and that these differences are not secondary to the hypertension. One of differentially expressed genes - JAM-1 - appears important for controlling set point of arterial pressure. We conclude that over expression of JAM-1 may contribute to the hypertensive phenotype of the SHR.

Waki H et al. (2004). J Physiol 555P, PC11.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

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NEUROADRENERGIC MECHANISMS AND PATHOPHYSIOLOGY OF HYPERTENSION

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Information drawn from a number of sources, mainly utilizing electrophysiological and neurochemical techniques, provide compelling evidence that overactivity of the sympathetic nervous system characterizes a substantial proportion of patients with essential hypertension. Nerve firing rates in postganglionic sympathetic fibres in skeletal muscle circulation are increased in hypertensive patients, the degree of activation being directly related to the severity of the hypertensive state. Essential hypertension is also characterized by an increased spillover of the adrenergic neurotrasmitters from the heart and the kidney, thereby participating to a considerable extent at the development and progression of the target organ damage characterizing high blood pressure states. All these neuroadrenergics alterations result to be potentiated when hypertension is associated with obesity, heart failure, renal insufficiency, obstructive sleep apnea, diabetes or metabolic syndrome, making the hypertensive patients particularly exposed to the adverse effects of a sympathetic activation (cardiac arrhythmias, coronary heart disease and sudden death).

Although investigated since several years, the mechanisms responsible for the neurogenic abnormalities characterizing hypertension remain largely unknown. Evidence has been provided, however, that alterations in cardiovascular reflex control (baroreceptor, chemoreceptor and/or cardiopulmonary receptor impairment) take place in hypertension, thereby contributing, together with humoral (Angiotensin II) or metabolic (insulin-resistance, leptin, etc.) mechanisms, at enhancing sympathetic cardiovascular drive. This enhancement however appears to be at least in part reversible. This because both non pharmacological (physical training, body weight reduction) and pharmacological (treatment with Ace-inhibitors, Angiotensin II receptor blockers and Central sympatholitic agents) interventions have been shown to exert symapthoinhibitory effects, thereby reducing the overall cardiovascular risk profile of the hypertensive patient.

Grassi G (2004). Counteracting the sympathetic nervous system in essential hypertension. Curr Opin Nephrol Hypertens 13, 513-519.

Grassi G et al. (2004). Neurogenic hypertension: is the enigma of its origin near the solution? Hypertension 43, 154-155.

Grassi G et al. (2003). Effects of hypertension and obesity on the sympathetic activation of heart failure patients. Hypertension 42, 873-877.

Grassi G et al (1999). How to assess sympathetic activity in humans. J Hypertens 17, 719-734.

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