Renal noradrenaline spillover correlates with muscle sympathetic activity in humans

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1. To study the relationship between indices of resting sympathetic traffic in nerves to skeletal muscles and the kidneys, simultaneous measurements were made of muscle sympathetic activity in the peroneal nerve and renal noradrenaline spillover in ten healthy normotensive males aged 18–69 years (mean 42 years).

2. Group mean levels (± S.D.) of muscle sympathetic activity and renal spillover were 22 ± 17 bursts min^{-1} and 105 ± 49 ng min^{-1}, respectively. There were significant positive correlations between individual values of muscle sympathetic activity and renal noradrenaline spillover ($r = 0{\cdot}76$, $P < 0{\cdot}01$) and similarly between muscle sympathetic activity and renal venous plasma concentration of noradrenaline ($r = 0{\cdot}79$, $P < 0{\cdot}007$).

3. The results indicate that, although the sympathetic system has the capacity for selective activation of different subdivisions, in healthy human subjects resting traffic is similar or proportional in sympathetic nerves to skeletal muscles and the kidney.

There is evidence in humans both from direct nerve recordings (Vallbo, Hagbarth, Torebjörk & Wallin, 1979) and measurements of regional noradrenaline spillover (Esler, Jennings, Korner, Blombery, Sacharias & Leonard, 1984*a*; Esler *et al.* 1984*b*; Esler, 1993) that different sympathetic subdivisions may be activated to different degrees and in different combinations depending on the functional demand. In view of such findings, it may seem surprising that at rest the forearm venous plasma concentration and total body spillover of noradrenaline correlate positively with the strength of the nerve traffic in one particular sympathetic subdivision, namely that to muscle (Sundlöf & Wallin, 1978*b*; Wallin, Sundlöf, Eriksson, Dominiak, Grobecker & Lindblad, 1981; Hjemdahl *et al.* 1989). Part of the explanation may be that skeletal muscle is a large tissue responsible for around 20% of total body noradrenaline spillover (Esler *et al.* 1984*a*, *b*) and that noradrenaline from muscle is over-represented in forearm venous blood. It is questionable, however, whether these factors alone are sufficient to explain the relationship or if, in addition, the strength of activity in other sympathetic subdivisions is similar or proportional to that of muscle. In support of this possibility it was recently found that resting noradrenaline spillover in the heart showed a significant positive correlation with the strength of resting muscle sympathetic nerve activity (MSA) in healthy subjects (Wallin *et al.* 1992).

The aim of the present study was to investigate if the strength of resting sympathetic traffic in nerves to the kidney also correlates with the strength of activity in muscle nerves. To this end we have compared interindividual differences of peroneal nerve sympathetic activity and renal noradrenaline spillover in a group of healthy normotensive men.

METHODS

Experiments were performed on ten healthy white male volunteers aged 18–69 years (mean 42 years) who were recruited from the general community by advertisement. The age range of the subjects was large, in order to have a large range of noradrenaline spillover and MSA values. A comprehensive clinical evaluation was performed on each subject, including biochemical and haematological laboratory testing, an electrocardiogram (ECG), and testing for HIV and Hepatitis B, to ensure that subjects were in good health. All subjects were non-smokers and no subject was on medication. All volunteers gave written informed consent to the study, which was approved by the Ethics Review Committee of the Alfred Hospital, Melbourne, Australia, where these experiments were conducted.

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Table 1. Data on noradrenaline, renal plasma flow and blood pressure

Plasma noradrenaline (pg ml^{-1})		Fractional extraction [^{3}H]-NA	Renal plasma flow (ml min^{-1})	Renal NA spillover (ng min^{-1})	Blood pressure (mmHg)	
Artery	Vein				Systolic	Diastolic
286 ± 105	294 ± 111	0·50 ± 0·08	750 ± 165	105 ± 49	138 ± 11	81 ± 5

Measurements

Nerve recordings. Multi-unit postganglionic sympathetic activity was recorded at rest with a tungsten microelectrode (Titronics Medical Instruments, Iowa City, IA, USA), with an uninsulated tip diameter of approximately 1 μm, inserted in a muscle fascicle of the peroneal nerve at the fibular head. A reference electrode was inserted subcutaneously a few centimetres away from the recording electrode. The neurogram was amplified (× 50 000), filtered (bandpass, 500 Hz to 2 kHz), passed through a discriminator for further noise reduction, and audiomonitored. A mean voltage (integrated) display was obtained by passing the original neurogram through a resistance–capacitance network (time constant, 0·1 s). Details of the technique and evidence for the sympathetic nature of the recorded impulses have been described previously (Sundlöf & Wallin, 1977; Thompson, Jennings, Chin & Esler, 1994).

Blood pressure (BP) and ECG. BP was recorded via an intra-arterial cannula and the ECG from chest electrodes. Analog signals of the mean voltage neurogram, BP and ECG signals were recorded on an 8-channel ink recorder (Gould brush 2800; Gould Recording Systems Division, Cleveland, OH, USA) with a paper speed of 5 mm s^{-1} and stored on magnetic tape (Hewlett-Packard 3968A Instrumentation recorder; Hewlett-Packard, Palo Alto, CA, USA) for subsequent analysis.

Renal noradrenaline plasma kinetics. To measure the renal noradrenaline spillover rate, by isotope dilution, tritiated L-noradrenaline ([^{3}H]-7-noradrenaline, 12–20 Ci mmol^{-1}; New England Nuclear, USA) was infused into an antecubital vein at a rate of 0·35 μCi min^{-1} m^{-2}, to reach steady state in plasma (reached within 60 min).

Renal noradrenaline (NA) spillover measurements were calculated from the relation:

$$\text{Renal NA spillover rate} = [(R_v - R_a) + R_a E]\text{RPF},$$

where R_a and R_v are noradrenaline plasma concentrations in arterial and renal venous blood, respectively, E is the fractional extraction of tritiated noradrenaline across the renal vascular bed, and RPF is renal plasma flow (Esler *et al.* 1984*a*, *b*, 1988). Renal plasma flow was determined by p-aminohippurate clearance and extraction (Esler *et al.* 1984*a*, *b*, 1988).

Plasma noradrenaline assays. Endogenous and [^{3}H]-noradrenaline were extracted from plasma using alumina adsorption and separated by high-performance liquid chromatography as previously described (Medvedev, Esler, Angus, Cox & Eisenhofer, 1990). The concentration of endogenous noradrenaline in plasma was quantified by electrochemical detection and that of tritiated noradrenaline by liquid scintillation spectroscopy.

General procedure

Subjects were studied supine in the morning after a standardized light breakfast, caffeine and alcohol having been excluded for the previous 12 h. For plasma catecholamine sampling a brachial or radial arterial cannula and a central venous catheter were inserted percutaneously under local anaesthesia. The venous catheter was placed under fluoroscopic control into the right renal vein (to avoid contamination from adrenal medullary drainage that occurs into the left renal vein). Radiolabelled noradrenaline was infused for a minimum of 60 min prior to blood sampling so that steady state could be reached in plasma (Esler *et al.* 1979). Blood samples (5 ml) were taken at the end of a 15 min rest period after steady state had been reached and transferred immediately to ice-chilled tubes containing EGTA and reduced glutathione, centrifuged at 4 °C, then stored at −70 °C prior to assay.

Analysis

For analysis sympathetic bursts were identified by inspection of the chart and the amount of activity was expressed as bursts per 100 heart beats and bursts per minute. The analysis of sympathetic activity, BP and ECG were taken over the last 5 min of the 15 min rest period. Results are expressed as means ± S.D. Regression analysis was used to analyse the relationships between muscle sympathetic nerve activity and catecholamine measures. P values < 0·05 were considered significant.

Table 2. Correlation of skeletal muscle sympathetic activity (MSA) with noradrenaline spillover/plasma concentrations

	MSA (bursts (100 heart beats)$^{-1}$)	MSA (bursts min^{-1})
Renal NA spillover	$r = 0·77$	$r = 0·76$
	$P < 0·009$	$P < 0·01$
NA concentration		
Artery	$r = 0·54$	$r = 0·58$
	$P < 0·11$	$P < 0·07$
Renal vein	$r = 0·78$	$r = 0·79$
	$P < 0·008$	$P < 0·007$

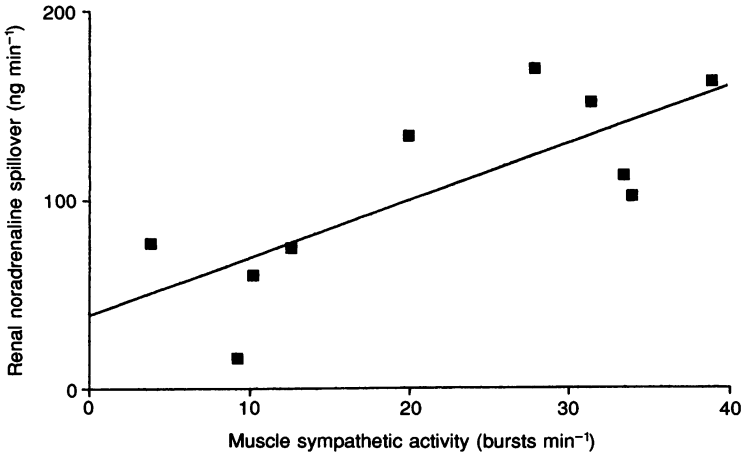

Figure 1

The relationship between muscle sympathetic activity and renal noradrenaline spillover. Each data point represents one subject ($n = 10$). $r = 0{\cdot}76$; $P < 0{\cdot}01$.

RESULTS

Muscle sympathetic activity had its usual pulse synchronous character, with stable resting levels in each subject but fairly large interindividual differences (mean, 32 bursts (100 heart beats)$^{-1}$ (range, 7–56); and mean, 22 bursts min^{-1} (range, 4–39)). Mean data on blood pressure, renal blood flow, renal noradrenaline spillover and plasma concentrations of arterial and renal venous noradrenaline are summarized in Table 1. Individual values for muscle sympathetic activity correlated significantly with corresponding values of both renal noradrenaline spillover and the renal vein plasma noradrenaline concentration (Table 2). The degree of correlation with arterial plasma noradrenaline concentrations was less and did not reach statistical significance. This suggests that sympathetic nervous activity in some organs, which contributed importantly to arterial plasma noradrenaline concentrations, was dissimilar to that in skeletal muscle, unlike the case for the renal sympathetic outflow. The relationship between muscle sympathetic activity and renal noradrenaline spillover is illustrated in Fig. 1. The relationship with the plasma concentration of noradrenaline in renal venous plasma is shown in Fig. 2. All correlation coefficients and P values are summarized in Table 2.

There was an increase in MSA at rest with increasing age; older subjects also had higher renal noradrenaline spillover measurements (Fig. 3). There was no correlation between MSA and resting diastolic blood pressures. There appeared to be a rise in renal noradrenaline spillover with increasing

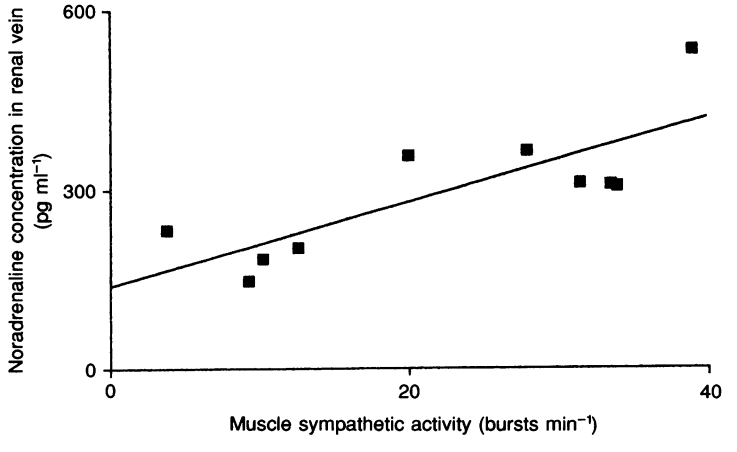

Figure 2

The relationship between muscle sympathetic activity and the plasma concentration of noradrenaline in renal venous plasma. Each data point represents one subject ($n = 10$). $r = 0{\cdot}79$; $P < 0{\cdot}007$.

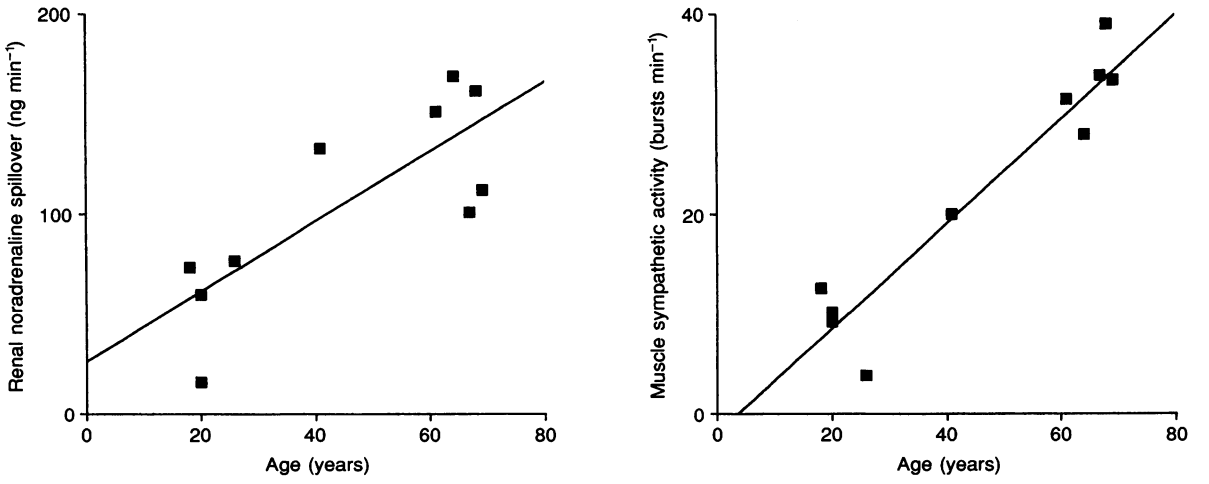

Figure 3

The relationship between renal noradrenaline spillover ($r = 0{\cdot}79$; $P < 0{\cdot}01$), muscle sympathetic activity ($r = 0{\cdot}95$; $P < 0{\cdot}001$) and age. Each data point represents one subject ($n = 10$).

diastolic blood pressures. However, this did not reach statistical significance (Fig. 4).

DISCUSSION

Regional spillover of noradrenaline is an indirect measure of sympathetic nerve traffic to the region (Bradley & Hjemdahl, 1984; Noshiro, Saigusa, Way, Dorward & McGrath, 1991) and therefore the present results provide evidence of a coupling between the strength of resting sympathetic neural outflows to the skeletal muscles and the kidney. Although our recordings were made in a nerve innervating lower leg muscles, the result should apply to other extremity muscles since simultaneous double recordings from arm and leg nerves in resting subjects reveal a high degree of coherence between the two neurograms (Sundlöf & Wallin, 1977; Wallin, Victor & Mark, 1989; Wallin, Burke & Gandevia, 1994). A similar coupling has been found previously between the sympathetic nerves to skeletal muscles and the heart, based on a comparison of muscle sympathetic activity and cardiac noradrenaline spillover measurements in healthy resting men (Wallin *et al.* 1992). Since skeletal muscles and the kidneys together account for approximately 40% of total body noradrenaline spillover at rest (Esler *et al.* 1984*b*), the concordance between muscle sympathetic activity and renal noradrenaline spillover probably provides an important additional (see the Introduction) explanation for the

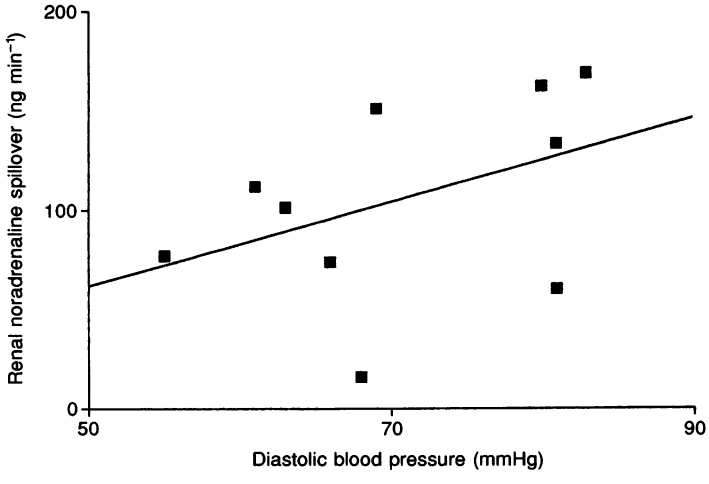

Figure 4

The relationship between renal noradrenaline spillover and diastolic blood pressure. Each data point represents one subject ($n = 10$). $r = 0{\cdot}42$; $P < 0{\cdot}2$.

correlation between the strength of muscle sympathetic activity and plasma concentrations of noradrenaline in forearm venous blood.

Possible underlying mechanisms

The strength of nerve traffic in a sympathetic subdivision is a product of an inherent central sympathetic drive and modulatory influence from different reflex mechanisms. In the cat the central sympathetic drive has been suggested to be represented by coupled rhythm generators (Gebber & Barman, 1980), but there is no information on differences between individual animals concerning the relative strength of sympathetic traffic in nerves to different organs. A common or proportional central sympathetic drive to kidney and skeletal muscle, which displays interindividual differences, would be a possible explanation for the present results.

Several reflexes influence the vascular beds of both the kidney and the skeletal muscles and this could, in theory, contribute to the proportionality between the two sympathetic outflows. Unloading of arterial baroreceptors increases muscle sympathetic activity in humans (Wallin & Eckberg, 1982; Sanders, Ferguson & Mark, 1988) and renal sympathetic activity in the dog (Kezdi & Geller, 1968) and the cat (Ninomiya, Nisimaru & Irisawa, 1972) and therefore an *arterial baroreflex* effect could contribute. Another alternative would be a *low pressure baroreflex*, since unloading of cardiopulmonary (low pressure) receptors also leads to increases of both muscle (Sundlöf & Wallin, 1977) and renal sympathetic activity (Thoren, 1979). A third possibility is a *chemoreceptor reflex*, since chemoreceptor activation is known to increase muscle (Blumberg, Jänig, Rieckmann & Szulzyk, 1980; Saito, Mano, Iwase, Koga, Abe & Yamazaki, 1988; Somers, Mark, Zavala & Abboud, 1989) and renal (Linden, Mary & Weatherill, 1981) sympathetic nerve traffic.

Implication of the results

The present findings indicate that in humans there are interindividual differences in the strength of resting sympathetic outflow, which are similar (or proportional) in nerves to skeletal muscle and kidney. We have demonstrated that resting renal noradrenaline spillover and MSA also rise in proportion to increasing age. Thus, even if the sympathetic system has the capacity for highly selective activation or inhibition of individual subdivisions (Vallbo *et al.* 1979; Esler *et al.* 1984*a*, *b*, 1988; Esler 1993), the resting nerve traffic may nevertheless be similar in many nerves. The findings probably apply primarily to vasoconstrictor neurones, which dominate multi-unit recordings of muscle sympathetic activity and also are likely to be the major source of the noradrenaline liberated in the kidney. It seems unlikely that a similar strength of resting activity should be present in, for example, non-vascular sympathetic nerve fibres, which may have very varying functions.

Approximately 40% of resting cardiac output passes the skeletal muscles and the kidneys (Rushmer, 1972; Rowell, 1974; Rothe & Friedman, 1976), and with the similarity between vasoconstrictor drives to these tissues the question arises whether subjects with high resting sympathetic activity have higher blood pressures or are more likely to develop hypertension than subjects with low levels of activity.

To date there is little evidence to suggest that, in humans, chronically high renal noradrenaline spillover contributes to the development of hypertension. However, there has recently been a study examining the sympathetic activity in normotensive offspring of hypertensive parents, looking for an explanation for the genetic predisposition to hypertension in some families. Ferrier, Cox & Esler (1992) found that total noradrenaline spillover was increased in these subjects compared with age-matched normals. In essential hypertension, noradrenaline spillover studies have shown evidence of elevated sympathetic nerve traffic in nerves to the kidneys and the heart in young hypertensives only (Esler *et al.* 1988). This suggests that elevated renal sympathetic activity may be involved in the initial stages of the develoment of hypertension. In microneurographic recordings muscle sympathetic activity was found to be normal in some studies of hypertensive patients (Mörlin, Wallin & Eriksson, 1983; Rea & Hamdan, 1990) and increased in others (Yamada, Miyajima, Tochikubo, Matsukawa & Ishii, 1989; Anderson, Sinkey, Lawton & Mark, 1989). This raises the possibility that, in subjects with high levels of sympathetic activity, blood pressure does not increase because the vasoconstrictive effects of the nerve traffic are counteracted by some other mechanism, such as a low cardiac output, downregulated vascular receptors or a circulating dilating factor. Although the data are limited, no correlation was found between levels of blood pressure and muscle sympathetic activity in resting normotensive subjects (Sündlof & Wallin, 1978*a*).

Limitations of the study

Among a study population which included a large proportion of elderly members, some of these relationships between measures of regional sympathetic function no longer hold (Esler *et al.* 1995*b*). In the elderly, cardiac noradrenaline is increased, apparently owing to impairment with ageing of neuronal reuptake of the transmitter (Esler *et al.* 1995*a*, *b*). In a population sample which includes similar numbers of older and younger members, although renal noradrenaline spillover, total body noradrenaline spillover and MSA values are correlated with each other, cardiac noradrenaline spillover values are correlated with none (Esler *et al.* 1995*b*). The mechanism presumably is that the cardiac noradrenaline spillover value is not representative of cardiac sympathetic nerve firing in the elderly (Esler *et al.* 1995*a*, *b*). Transmitter disposition in the kidney is much less dependent on neuronal reuptake, and noradrenaline spillover from the kidney is more closely

related to nerve firing rates than to the capacity for noradrenaline reuptake (Esler *et al.* 1984*a*, *b*); therefore, such an error is unlikely to influence our results in a major way.

Summary

Our results indicate that, although the sympathetic nervous system in humans has the capacity for selective activation of different subdivisions, resting traffic is normally similar or proportional in sympathetic nerves to skeletal muscles and the kidney. This may be due to a common central sympathetic drive and/or similar degrees of peripheral reflex modulation.

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