SYMPATHETIC NEURAL CONTROL OF RENAL BLOOD FLOW

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ABSTRACT

Renal sympathetic nerve activity (RSNA) plays an important role in the control of renal hemodynamics and function. It achieves this control by changing the mean levels of activity and/or changing the power of the distinct frequencies that comprise this mean activity. My studies, presented in four parts, investigate how total renal blood flow (RBF) and intrarenal blood flow are controlled by these changes in RSNA.

While RSNA and RBF both show oscillations at various frequencies, the functional significance and regulation of these oscillations is not well understood. To establish whether the strength of these oscillations is under differential control I measured the frequency spectrum of RSNA and RBF following volume expansion in conscious rabbits. At least 6 days prior to experiments animals underwent surgery to implant an electrode for recording renal nerve activity and a flow probe for recording RBF. Volume expansion resulted in a 25 ± 5% decrease in mean RSNA, paralleled by an increase in RBF. Renal denervated rabbits did not show an increase in RBF with volume expansion. Spectral analysis of the different frequencies in RSNA showed oscillations in RSNA between 0.2 to 0.4 Hz were selectively decreased following volume expansion (14 ± 3 to 6±1% of total power in RSNA at < 3Hz). A corresponding decrease in the strength of oscillations in RBF at this frequency was also seen (20 ± 6 to 8 ± 2%). In contrast the strength of respiratory (0.8 to 2.0 Hz) and cardiac (3 to 6 Hz) related rhythms did not change with volume expansion. These results show that selective changes in the different frequency components of RSNA can occur.

While RSNA plays a significant role in the regulation of RBF, little is known about the role renal nerves may play in the control of regional kidney blood flows i.e. cortical and medullary blood flow (CBF and MBF respectively). This is an important question as the control of blood flow to the renal medulla has been shown to be critical in the long-term control of arterial pressure, chiefly through its influence on tubular reabsorption of salt and water. If renal nerves are involved in the control of medullary blood flow then they may also have a role in long-term arterial pressure regulation. My aim was to investigate the role RSNA may have in the regulation of both CBF and MBF.

In a series of experiments, using pentobarbitone anaesthetized rabbits, I electrically stimulated the renal nerves whilst simultaneously recording RBF, CBF, and MBF. Three sequences of stimulation were applied, 1) varying the amplitude of stimulation, 2) varying the frequency of stimulation and 3) stimulation with a modulated sinusoidal pattern which allows determination of the frequency response characteristics of each flow. Increasing amplitude or frequency of stimulation progressively decreased all flow variables. RBF and CBF responded similarly, but MBF responded less. For example, 0.5 V stimulation decreased CBF by 20 ± 9% but MBF fell by only 4 ± 6%. The amplitude of oscillations in all flow variables was progressively reduced as the frequency of sinusoidal stimulation was increased. An increased amplitude of oscillation was observed at 0.12 and 0.32 Hz in MBF, and to a lesser extent RBF, but not CBF. MBF therefore appears to be less sensitive than CBF to the magnitude of RSNA, but more able to respond to these higher frequencies of

neural stimulation. These results show that regional renal blood flows may be differentially regulated by RSNA and indicate a role for RSNA in the control of MBF.

To further investigate the effects of RSNA on intrarenal blood flow I performed another series of experiments in which I reflexly increased RSNA while simultaneously recording CBF and MBF. I exposed pentobarbitone anesthetized, artificially ventilated rabbits to graded reductions in inspired O_2 content. A separate group of animals with denervated kidneys underwent the same protocol. Graded hypoxia (16, 14, 12 and 10% inspired O_2) progressively reduced arterial O_2 partial pressure and increased RSNA (by 8 ± 3, 44 ± 25, 62 ± 21 and 76 ± 37% respectively compared with air) without affecting MAP. This was accompanied by progressive reductions in CBF (by 2 ± 1, 5 ± 2, 11 ± 3 and 14 ± 2% respectively) in intact but not denervated rabbits. MBF was unaffected by hypoxia in either group. Thus, reflex increases in RSNA cause renal cortical vasoconstriction, but not at vascular sites regulating MBF.

Taken together results from both these studies provide strong evidence that MBF is less sensitive to the vasoconstrictor influence of RSNA than is CBF. However, larger, chronic increases in RSNA, such as occur in heart failure, could be associated with decreases in MBF. This may implicate RSNA in the long-term control of arterial pressure.

The 0.3 Hz oscillation in RSNA, and thus MAP, is intermittent in its presence. In a final series of experiments I studied the underlying reasons for the presence or absence of the 0.3 Hz oscillation. Using conscious animals I studied the oscillation under a range of sympathetic stimulants. I was unable to induce an oscillation in MAP at 0.3 Hz and propose reasons for this. To allow further analysis, I performed a second set of experiments in which I induced the oscillation in RBF by electrical stimulation of the aortic depressor nerve. I found that large amplitude oscillations in baroreceptor stimulation were required to induce oscillations in RBF and MAP. I speculate on what this may tell us about the nature of the slow oscillation.

PREFACE

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JOURNAL PUBLICATIONS

Leonard BL, Malpas SC, Denton KM, Madden AC and Evans RG. Differential control of intrarenal blood flow during reflex increases in sympathetic nerve activity. *Am. J. Physiol.* 280: R62-R68, 2001

Leonard BL, Evans RG, Navakatikyan MA and Malpas SC. Differential neural control of intrarenal blood flow. *Am. J. Physiol.* 279: R907-R916, 2000

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The research described in this thesis was co-authored. I performed all animal surgeries, postoperative animal care, experimentation, data analysis and written presentations. The co-authors contributed in the following ways:

- Dr. Michael Navakatikyan wrote the data acquisition and analysis programs used in these experiments.
- Dr. Simon Malpas, as my doctoral supervisor, advised on the development of methodologies, experimentation, and interpretation of results.
- Dr. Roger Evans advised on the development of methodologies, experimentation, and interpretation of results. He also assisted in recording of intrarenal blood flows. The laser Doppler validation experiments described in Chapter 3 were also performed by Dr. Evans.
- Dr. Kate Denton provided technical advice on renal nerve recordings
- Anna Madden performed the plasma and urine measurements of sodium, inulin and para-aminohippurate.

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LIST OF FIGURES

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ABBREVIATIONS

To aid ease of reading, less common abbreviations are reiterated at their first use in each chapter.

AAG	autoradiographic grains
ADN	aortic depressor nerve
Ang II	angiotensin II
ANOVA	analysis of variance
CBF	cortical blood flow
dB	decibel
ERBF	effective renal blood flow
F_E	fractional excretion
FE_{Na+}	fractional excretion of sodium
FE_{vol}	fractional excretion of urine
Fig.	figure
GFR	glomerular filtration rate
h	hour
HR	heart rate
Hz	Hertz
i.c.v.	intracerebroventricular
Inc.	incorporated
i.v.	intravenous
kg	kilogram
L	liter
L-NAME	N^G-nitro-L-arginine methyl ester
Ltd	limited
mg	milligram
min	minute
ml	milliliter
mm	millimeter
mmHg	millimeters of mercury
mOsmol	milli osmole
NaCl	sodium chloride
ng	nanogram
Pa_{CO_2}	arterial partial pressure of CO_2
PAH	para-aminohippurate
Pa_{O_2}	arterial partial pressure of O_2

PVN	paraventricular nucleus
RBF	renal blood flow
RVLM	rostral ventrolateral medulla
RSNA	renal sympathetic nerve activity
s	second
SEM	standard error of the mean
SNA	sympathetic nerve activity
$U_{Na+}V$	urinary sodium excretion
USA	United States of America
U_V	urine flow
v	versus
V	volt
w/v	weight to volume
µg	microgram
µl	microliter
µmol	micromole
<	less than
>	greater than
≤	less than or equal to
≥	greater than or equal to
~	approximately
°C	degrees Celsius
%	percentage