Hormonal influence on renal function with particular reference to diabetes mellitus
Hoogenberg, Klaas

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CHAPTER 3

INFLUENCE OF AMBIENT PLASMA NOREPINEPHRINE ON RENAL HAEMODYNAMICS IN IDDM PATIENTS AND HEALTHY SUBJECTS

K. Hoogenberg¹, A.R.J. Girbes⁴, C.A. Stegeman², W.J. Sluiter¹, W.D. Reitsma³ and R.P.F. Dullaart¹

Imbalances in renal vasodilatory and vasoconstrictive mechanisms are responsible for the renal haemodynamic changes observed in IDDM patients. Animal experiments have shown that norepinephrine (NE) infusion increases the intraglomerular pressure by predominantly efferent arteriolar vasoconstriction. The relationships between ambient plasma NE levels and renal haemodynamics were studied in 18 healthy control subjects (group C), in 17 normoalbuminuric (albumin excretion rate (Ualb.V) <20 µg/min; group D1) and in 17 microalbuminuric (Ualb.V 20-200 µg/min; group D2) IDDM patients without overt autonomic neuropathy. Supine glomerular filtration rate (GFR (ml/min per 1.73m²)) and effective renal plasma flow (ERPF (ml/min per 1.73m²)) were determined over a 2 h period using constant infusions of ¹²⁵I-iothalamate and ¹³¹I-hippuran, respectively. The subjects were studied in the fasting state. The IDDM patients were investigated during near normoglycaemia. Data are given as means±SD. In group D1, GFR and ERPF (126±15 and 538±89, respectively) were elevated as compared to group C (108±15 and 478±73; p<0.01 and p<0.05, respectively). In group D2, GFR (124±25, p<0.05) but not ERPF (515±104) was higher than in group C. GFR and ERPF were negatively correlated with venous plasma NE in C (r=-0.61, p<0.005 and r=-0.64, p<0.001, respectively), in group D1 (r=-0.54, p<0.03 and r=-0.63, p<0.005, respectively) and in group D2 (r=-0.53, p<0.03 and r=-0.60, p<0.01, respectively). Multiple regression analysis disclosed that diabetes per se, independent from plasma NE, had a positive contribution to GFR. In contrast, ERPF was only related to plasma NE levels. In conclusion, GFR and ERPF are inversely related to venous plasma NE levels both in healthy and in IDDM subjects, supporting the hypothesis that plasma NE is a vasoconstrictive substance. The independent positive effect of diabetes as a categorial variable on GFR, suggests that concomitant vasodilating mechanisms play a role in the renal haemodynamic alterations in IDDM patients.

Introduction

In patients with insulin-dependent diabetes mellitus (IDDM) the presence of microalbuminuria does not only predict the future development of diabetic nephropathy [1], but is also associated with generalized vascular damage [2]. Microalbuminuria is thought to result from an increased glomerular leakage of macromolecules. Both changes in the glomerular permselectivity properties as well as in systemic and intrarenal haemo-dynam-
cs factors have been demonstrated to underlie elevations in urinary albumin excretion [3]. Before and during the microalbuminuric phase renal haemodynamic changes, commonly reflected by an increase in glomerular filtration rate (GFR), are frequently observed in IDDM patients [4-7]. In animal models of diabetes mellitus an increase in GFR is associated with the development of glomerulosclerosis and the progressive loss of kidney function [8]. Some clinical observations also support the notion that an elevated GFR per se might contribute to the subsequent development of diabetic nephropathy [5,9].

The elevated GFR associated with IDDM has been attributed to an increase in effective renal plasma flow (ERPF) [5-7], an increase in the glomerular filtration surface area [10] and possibly an increase in the intraglomerular pressure [5]. Many vasodilatory and vasoconstrictive substances are able to modulate renal haemodynamics by influencing the glomerular afferent and efferent arteriolar tone [6,7,11]. Glomerular arterioles contain α-adrenoreceptors which mediate vasoconstriction induced by norepinephrine (NE) released at the terminal nerve ending of the sympathetic nervous system (SNS). Intravenous infusion to reach high physiological NE levels lowers ERPF, whereas the fall in GFR is less marked [11-14]. Consequently, the filtration fraction (FF) (i.e. the quotient of GFR and ERPF) rises, reflecting a change in pressure profile along the arterioles. Recent data suggest that IDDM with microalbuminuria are hypersensitive to NE-induced vasoconstriction of dorsal hand veins which also carry α-adrenoreceptors [15]. Thus alterations in SNS activity might be implicated in the pathogenesis of diabetes-associated renal haemodynamic abnormalities. However, the relation between plasma NE and renal haemodynamic parameters is uncertain. In a small group of adolescent IDDM patients a strong negative relationship between the plasma NE level and GFR was observed [16], whereas others did not find such a relationship [17,18].

Therefore, the present cross sectional study was conducted to establish the relationships between circulatory NE levels and renal haemodynamic changes in normo- and microalbuminuric IDDM patients as compared with matched healthy subjects.

**Subjects and methods**

**Subjects**

All participants consented to the procedure after explanation of the purpose of the study, which was approved by the local medical ethics committee. Eligible subjects had an age between 21 and 50 years, a serum creatinine ≤120 µmol/l, a urinary protein excretion ≤ 500 mg/day, and a body mass index <27 kg/m². Subjects with hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg), using antihypertensive or anti-inflammatory drugs were excluded from participation. The IDDM were considered to be insulin-dependent since their glucagon stimulated C-peptide levels were <0.2 nmol/l. They had a disease duration of at least 5 years. Autonomic function was assessed with beat-to-beat variation (abnormal if variation less than 10 beats per minute), valsalva manoeuvre (abnormal if lower than 1.11) and systolic blood pressure response to standing (abnormal if exceeding 30 mmHg) [19]. None of the
Table 1. Clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=18)</th>
<th>Group D1 (n=17)</th>
<th>Group D2 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.8 ± 7.7</td>
<td>32.0 ± 8.3</td>
<td>35.8 ± 8.0</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td></td>
<td>14.8 ± 6.0</td>
<td>18.8 ± 5.3</td>
</tr>
<tr>
<td>Sex (males/females)</td>
<td>13 / 5</td>
<td>15 / 2</td>
<td>14 / 3</td>
</tr>
<tr>
<td>Ualb.V (µg/min)</td>
<td>n.d.</td>
<td>9.1(6.4-11.5)</td>
<td>34.4(22.9-105.3)</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>92 ± 9</td>
<td>95 ± 7</td>
<td>100 ± 8d</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.6 ± 2.3</td>
<td>22.5 ± 2.0</td>
<td>23.7 ± 2.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>n.d.</td>
<td>8.6 ± 1.4</td>
<td>8.3 ± 1.0</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>182 ± 76</td>
<td>156 ± 63</td>
<td>203 ± 82</td>
</tr>
<tr>
<td>Urinary urea excretion (mmol/day)</td>
<td>425 ± 108</td>
<td>435 ± 127</td>
<td>384 ± 113</td>
</tr>
<tr>
<td>Insulin dose (U/kg per day)</td>
<td>-</td>
<td>0.74 ± 0.23</td>
<td>0.79 ± 0.22</td>
</tr>
<tr>
<td>Retinopathy (O/B/P)</td>
<td>-</td>
<td>11/4/2</td>
<td>8/5/4</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>n.d.</td>
<td>1.57 ± 0.26</td>
<td>1.62 ± 0.38</td>
</tr>
<tr>
<td>Beat-to-beat variation during deep breathing</td>
<td>n.d.</td>
<td>29 ± 13</td>
<td>28 ± 10</td>
</tr>
<tr>
<td>Change in systolic blood pressure in response to standing (mmHg)</td>
<td>-5 (-10 to 5)</td>
<td>-4 (-8 to 2)</td>
<td></td>
</tr>
</tbody>
</table>

Group C: control subjects; group D1: IDDM patients with UalbV <20 µg/min; group D2: IDDM patients with UalbV > 20 µg/min and <200 µg/min. n.d. denotes not determined; Ualb.V: urinary albumin excretion rate; Retinopathy: O: absent; B: background; P: proliferative. Values are given in mean ± SD, except for Ualb.V and blood pressure response to standing which are given in median (interquartile range). c denotes p<0.001 from group D1; d denotes p<0.01 from groups C and D1

subjects suffered from overt autonomic neuropathy defined as at least 1 abnormal test. Because of the high variability of urinary albumin excretion [20], three timed overnight urine collections were obtained to measure urinary albumin excretion rate (Ualb.V). Microalbuminurina was defined as Ualb.V ranging 20 to 200 µg/min in at least two urine samples [1].

Three groups of subjects were included in the study: 18 healthy controls (group C); 17 IDDM patients with normoalbuminuria (group D1), 17 IDDM patients with microalbuminuria (group D2). Table 1 shows the clinical characteristics of the study groups and data of the autonomic function tests. The groups were closely comparable with respect to age and there was no difference in sex distribution. Mean urinary sodium and urea excretion was similar in the groups and none of the subjects used a protein (<0.8 g/day per kg bodyweight) or a sodium restricted (<50 mmol/day) diet. The two IDDM groups did not differ in diabetes duration and metabolic control. The proportion of patients with retinopathy was similar in each IDDM group.

Procedure of the renal haemodynamic measurements
All participants were studied after an overnight fast and remained fasting during the procedure. Starting at 0800 h, the subjects were studied in the supine position and were only allowed to stand on voiding. Diuresis was promoted by a waterload of 300 ml/h, and no other liquids than water were permitted to drink. The IDDM patients received their last regular insulin dose 8 to 12 h before the start of the study.

The IDDM patients were studied during near normoglycaemia to minimize the possible effects of actual glycaemia on GFR and ERPF [21]. Thus, a 5% glucose solution was initially infused at a rate 1 ml (0.28 mmol)/h per kg bodyweight together with regular acting insulin (Velosulin H.M., Novo-Nordisk, Bagsvaerd, Denmark). The amount of insulin infused was 1% of the total daily requirements per hour. Blood glucose was measured at 30 min intervals. If blood glucose exceeded 8.3 mmol/l extra insulin was given intravenously until one hour before the start of the renal haemodynamic measurements. Further insulin boluses were not given since insulin can acutely stimulate catecholamine release [22]. After a stabilisation period of at least 2 h the renal clearance studies were carried out.

GFR and ERPF were measured simultaneously during a 2 h clearance period, using primed infusions of $^{125}$I-iothalamate and $^{131}$I-hippuran, respectively [23]. $^{125}$I-iothalamate and $^{131}$I-hippuran were infused at a constant rate of 4.8µCi/h (178 kBq/h) and 12 µCi/h (444 kBq/h), respectively. The clearances were calculated using the formulas U.V/P and I.V/P, respectively. U.V represents the urinary excretion rate of the tracer, I.V represents the infusion rate of the tracer, P represents the mean tracer value of 2 plasma samples taken at the beginning and at the end of the clearance period. Errors in the estimation of the GFR due to incomplete bladder emptying and dead space were corrected by multiplying the clearance of $^{125}$I-iothalamate with the formula: clearance of $^{131}$I-hippuran (I.V/P) / clearance of $^{131}$I-hippuran (U.V/P). The coefficients of variation for GFR and ERPF are 2.2% and 5.0%, respectively [23]. The GFR and ERPF were corrected to 1.73m$^2$ of body-surface area. The FF was calculated as the ratio of the GFR and the ERPF.

Blood pressure was recorded every hour, using a sphygmomanometer. Korotkoff phase I and V were taken as the systolic and the diastolic blood pressure, respectively. At the beginning and the end of the clearance period venous blood was drawn from a catheter inserted into an antecubital vein (kept patent with 0.9% NaCl 20 ml/h).

Laboratory methods

Blood glucose was measured using a Yellow Springs glucose Analyser (Model 23A, Yellow Springs Inc., Yellow Springs, Ohio, USA). HbA1c was determined by colorimetry (24) (reference values: 4.5 to 5.8%). Serum creatinine, albumin, and urinary sodium and urea were measured on SMA(C) autoanalysers (Technicon Instru-ments Inc. Tarrytown, N.Y., USA). Urinary albumin was measured by radioimmuno-assay (Diagnostic Products Corporation, Apeldoor, The Netherlands; coefficient of variation 8%). Plasma insulin and plasma C-peptide concentrations were measured by radioimmuno-assay. Plasma epinephrine and NE concentrations were determined by high-performance liquid chromatography (coefficient of variation 4%) [25].

Statistical analysis

Results are expressed as mean±SD for parametrically distributed data and as median
Ambient plasma noradrenaline and renal haemodynamics

... (interquartile ranges) for non-parametrically distributed data. Comparisons of variables between groups were carried out using analysis of variance for parametrically and non-parametrically distributed data as appropriate. Changes of variables within groups were assessed by paired Student’s t-tests or Wilcoxon tests. Adjustment for multiple comparisons was carried out using Duncan’s method [26]. Differences in prevalence of clinical variables were analysed by chi-square statistic. Correlations were studied using Spearman’s rank analysis. Multiple stepwise regression analysis was used to disclose the independent contribution of the hormonal and metabolic parameters to GFR and ERPF. Two-sided p-values less than 0.05 were considered to be significant.

Results

Blood glucose, plasma insulin and renal haemodynamic parameters

During the 2-h clearance period, insulin and blood glucose concentrations were not different between the two IDDM groups and did not change significantly (Table 2).

GFR was significantly higher in both IDDM groups as compared to group C (p<0.01 and p<0.05 for groups D1 and D2, respectively, Table 2), whereas ERPF was only higher in group D1 than in group C (p<0.05, Table 2). FF was significantly elevated in group D2 as compared to group C (p<0.05) (Table 2). In the combined IDDM groups, ERPF as well as FF were higher than in group C (p<0.05, for both, Table 2).

Plasma norepinephrine and epinephrine.

Plasma NE levels were higher in group C than in groups D1 and D2 at the beginning (p<0.05 for both, Table 3) but not significantly so at the end of the 2 h clearance period (Table 3). The differences in averaged plasma NE levels did not reach significance (p=0.08 for group C compared with groups D1 and D2, Table 3). Plasma epinephrine concentrations were not significantly different between the groups. No significant changes were observed in plasma NE and epinephrine during the 2 h study period.

Correlation analysis

The averaged values of plasma NE and epinephrine were used for the correlation analysis. GFR and ERPF were negatively correlated with plasma NE levels in group C (r=-0.61, p<0.005 and r=-0.64, p<0.001, respectively), in group D1 (r=-0.54, p<0.03 and r=-0.63, p<0.005, respectively) and in group D2 (r=-0.53, p<0.03 and r=-0.60, p<0.01, respectively, Figure 1A,B). In the combined IDDM groups, a positive correlation was found between FF and plasma NE (r=0.34, p<0.05, Figure 1C) which was not present in group C (r=0.11, NS, not shown). GFR was significantly related to HbA1c (r=0.34, p<0.05) in the combined IDDM groups, whereas no significant relation existed between HbA1c, ERPF (r=0.24, p=0.17) and FF (r=0.02, NS). Plasma epinephrine was not correlated with renal haemodynamics.
### Table 2. Renal haemodynamics and corresponding plasma glucose and insulin levels.

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=18)</th>
<th>Group D1 (n=17)</th>
<th>Group D2 (n=17)</th>
<th>IDDM all (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate (ml/min per 1.73m²)</td>
<td>108 ± 15</td>
<td>126 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>124 ± 25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>125 ± 20&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Effective renal plasma flow (ml/min per 1.73m²)</td>
<td>478 ± 73</td>
<td>538 ± 89&lt;sup&gt;b&lt;/sup&gt;</td>
<td>515 ± 104</td>
<td>527 ± 96&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.22 ± 0.02</td>
<td>0.23 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.24 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.24 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fractional sodium excretion</td>
<td>0.95 ± 0.53</td>
<td>0.78 ± 0.31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93 ± 0.42</td>
<td>0.88 ± 0.33&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08.00 h begin</td>
<td>4.6 ± 0.4</td>
<td>12.2 ± 5.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.6 ± 4.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.9 ± 4.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>08.00 h end</td>
<td>n.d.</td>
<td>6.6 ± 1.1</td>
<td>6.9 ± 1.4</td>
<td>6.7 ± 1.1</td>
</tr>
<tr>
<td>Free plasma insulin (mU/l)</td>
<td>n.d.</td>
<td>28 (23 - 49)</td>
<td>26 (18 - 35)</td>
<td>28 (19 - 35)</td>
</tr>
<tr>
<td>08.00 h begin</td>
<td>n.d.</td>
<td>6.5 ± 1.1</td>
<td>6.5 ± 1.2</td>
<td>6.5 ± 1.1</td>
</tr>
<tr>
<td>08.00 h end</td>
<td>n.d.</td>
<td>32 (19 - 43)</td>
<td>23 (13 - 34)</td>
<td>26 (17 - 40)</td>
</tr>
</tbody>
</table>

Group C: control subjects; group D1: IDDM with Ualb.V <20µg/min; group D2: IDDM patients with UalbV >20 µg/min and <200 µg/min. IDDM all: combined IDDM groups; n.d. not determined; Values are given in mean±SD, except for free insulin which is given in median (interquartile range).<sup>a</sup> denotes p<0.01 and <sup>b</sup> denotes p<0.05 from group C.

### Table 3. Plasma norepinephrine and epinephrine concentrations during the renal haemodynamic measurements.

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=18)</th>
<th>Group D1 (n=17)</th>
<th>Group D2 (n=17)</th>
<th>IDDM combined (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma norepinephrine (nmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Begin</td>
<td>1.56 ± 0.45&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.32 ± 0.56</td>
<td>1.28 ± 0.40</td>
<td>1.29 ± 0.48</td>
</tr>
<tr>
<td>End</td>
<td>1.52 ± 0.53</td>
<td>1.30 ± 0.50</td>
<td>1.33 ± 0.49</td>
<td>1.31 ± 0.49</td>
</tr>
<tr>
<td>Mean</td>
<td>1.54 ± 0.50</td>
<td>1.31 ± 0.45</td>
<td>1.30 ± 0.44</td>
<td>1.31 ± 0.44</td>
</tr>
<tr>
<td><strong>Plasma epinephrine (nmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Begin</td>
<td>0.15 ± 0.10</td>
<td>0.20 ± 0.14</td>
<td>0.19 ± 0.10</td>
<td>0.19 ± 0.12</td>
</tr>
<tr>
<td>End</td>
<td>0.13 ± 0.10</td>
<td>0.18 ± 0.13</td>
<td>0.20 ± 0.10</td>
<td>0.19 ± 0.11</td>
</tr>
<tr>
<td>Mean</td>
<td>0.14 ± 0.11</td>
<td>0.18 ± 0.12</td>
<td>0.22 ± 0.10</td>
<td>0.19 ± 0.11</td>
</tr>
</tbody>
</table>

Group C: control subjects; group D1: IDDM patients with Ualb.V <20 µg/min; group D2: IDDM patients with Ualb.V >20 µg/min and <200 µg/min. Values are given in mean ± SD. <sup>a</sup> denotes p<0.05 from groups D1 and D2.
Multiple regression analysis was carried out to evaluate whether renal haemodynamics were independently related to the plasma NE level and to establish if plasma NE contributed to the differences in GFR and ERPF between the IDDM and the non-diabetic subjects. In the analyses plasma NE as well age, diabetes duration, HbA1c, sodium and urea excretion, and blood pressure were the independent variables. In the combined groups (n=52), ERPF was only related to plasma NE \( (r=-0.61, P<0.001) \). The model was not improved by including the presence of IDDM as a categorical variable \( (p=0.30, \text{ multiple } r=0.59) \). Thus IDDM per se did not influence ERPF, independently from the level of NE. GFR was related to ERPF both in the combined groups \( (r=0.79, P<0.001) \) as well as in IDDM groups \( (r=0.86, P<0.001) \). However in the combined groups, IDDM, included in the model as a categorical variable, had an independent effect on GFR \( (r=0.22, P<0.01; \text{ multiple } r=0.88) \), indicating that diabetes associated vasodilation influenced GFR. The other covariates did not contribute to either ERPF or GFR in a model including plasma NE and IDDM.

**Discussion**

The elevations in GFR and ERPF associated with IDDM are considered to reflect an imbalance between glomerular vasodilatory and vasoconstrictive mechanisms [5-7,11,17]. This study demonstrates that GFR and ERPF are inversely related to plasma NE levels in normo- and microalbuminuric IDDM patients as well as in healthy subjects. Our results extend recent observations in a small group of adolescent IDDM patients showing a negative correlation between plasma NE and GFR [16] and the possibility arises that plasma NE is a determinant of renal haemodynamics.

No differences were observed in the inverse correlations between plasma NE and ERPF in the IDDM patients as compared to the control subjects. This raises the possibility that the presently observed slightly lower plasma NE levels in the IDDM subjects could contribute to the elevations in ERPF. Clearly, our study design does not permit a conclusion with respect to potential differences in renal NE sensitivity in association with IDDM or microalbuminuria [15].

Both animal and human studies indicate that renal blood flow is an important determinant of GFR [5-7,27]. Our data support this view since GFR was strongly related to ERPF. However, the elevated GFR cannot be fully accounted for by an increase in ERPF, since the filtration fraction was higher in the IDDM patients, particularly in those with microalbuminuria. GFR is also determined by the intraglomerular pressure, the oncotic pressure and the ultrafiltration coefficient and any of these factors or a combination of them might explain the IDDM related increase in filtration fraction [5]. Indeed, the intraglomerular pressure is elevated in experimental diabetes [8] and capillary hypertension has been documented in IDDM patients [28]. In addition, the glomerular filtration surface area is increased in IDDM [10] which will influence the ultrafiltration coefficient. The present study did not differentiate between these mechanisms but multiple regression analysis disclosed an independent effect of the diabetic state per se on GFR, thus suggesting that concomitant vasodilating mechanisms are present in IDDM patients.
Figure 1. Relationships between renal haemodynamics and plasma norepinephrine levels (NE). ○ Control subjects, ○ IDDM patients with Ualb.V<20 µg/min, ● IDDM patients with Ualb.V>20 µg/min and <200µg/min. A: plasma NE and GFR in ○ $r=-0.61$, $p<0.005$; in ○ $r=-0.54$, $P<0.03$; in ● $r=-0.53$, $p<0.03$; B: plasma NE and ERPF in ○ $r=-0.64$, $p<0.001$; in ○ $r=-0.63$, $p<0.005$; and in ● $r=-0.60$, $p<0.01$; C: plasma NE and FF in the combined IDDM groups $r=0.34$, $p<0.05$. 
NE constricts renal vasculature via stimulation of $\alpha_1$-adrenoreceptors, which are located along afferent and efferent renal arterioles [11,14,29]. As compared with other isolated renal vessels, efferent glomerular arterioles from the rabbit have the highest sensitivity to the vasoconstrictive action of NE [30] and micropuncture studies in the rat have shown that NE lowers glomerular blood flow and increases the transglomerular pressure [13]. In humans NE infusion results in a decrease in ERPF and a rise in filtration fraction [12]. Moreover, an increase in plasma NE appears to contribute to exercise-induced changes in microalbuminuria possibly by a renal haemodynamic mechanism [31].

The pathophysiological mechanisms responsible for the relation between the basal plasma NE level and renal haemodynamics are unknown. NE, present in venous forearm blood, is derived both from local skeletal muscular nerve activity and from the arterial circulation [32]. The forearm venous plasma NE concentration is the net result of these sources minus local neuronal uptake. Thus, the peripheral venous forearm NE concentration is influenced by other factors than SNS activity alone. NE acts both locally as a neurotransmitter and distantly as a hormonal factor [33]. It cannot be discriminated whether the relationship between plasma NE and renal haemodynamics indicates a distant effect or reflects a generalized or local neurotransmitter spillover of the SNS. To study the role of SNS activity in diabetes related renal haemodynamic abnormalities it would be necessary to obtain arterial and venous renal blood samples simultaneously with GFR and ERPF determinations.

In conclusion, GFR and ERPF are inversely correlated with the venous plasma NE level in healthy subjects as well as in IDDM patients with normo- and microalbuminuria, supporting the hypothesis that circulatory NE can be a renal vasoconstrictive factor. The positive contribution of IDDM per se to GFR, independently from the negative effects of plasma NE, suggests that concomitant vasodilating mechanisms play a role in the renal haemodynamic alterations in IDDM patients.

References
Chapter 3


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