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Effect of metoprolol on 24-hour urinary excretion of adrenal steroids and kallikrein in patients with essential hypertension

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1 Treatment of fifteen patients with essential hypertension over four weeks using the β_1-adrenoceptor blocking agent, metoprolol, resulted in a decrease in 24 h urinary excretion of kallikrein and aldosterone along with a decrease in plasma renin activity.

2 There was no significant change in 24 h excretion rates of the free adrenal steroids deoxycorticosterone, 18-OH-deoxycorticosterone, corticosterone, cortisol or 18-OH-corticosterone during treatment, which were not significantly different from excretion rates of normal males, thus excluding inhibitory effects of adrenal steroids on urinary kallikrein activity.

3 A positive correlation was found between plasma renin activity and urinary excretion of kallikrein during the control period and after 2 weeks on metoprolol, supporting the assumption of a preserved link between the renin-angiotensin-aldosterone system and the renal excretion of kallikrein in these patients.

4 The decrease in kallikrein excretion during β_1-adrenoceptor blockade in patients with essential hypertension may be explained by a reduction in sympathetic tone and by reduced activity of the renin-aldosterone system.

Introduction

Urinary kallikrein excretion has been found to be decreased in patients with essential hypertension (Elliot & Nuzum 1934; Margolius *et al.*, 1971; 1974; Abe *et al.*, 1976; Carretero & Scicli, 1978; Overlack *et al.*, 1980b). This finding may reflect altered intrarenal activity of the kallikrein-kinin system (Nustad, 1970 a,b), since kidney kininogenase activity has been demonstrated in kidney cortex homogenate (Nustad, 1970a) and in urine of rat isolated kidneys (Roblero *et al.*, 1976), and it appeared chemically similar to urinary kininogenase activity (Nustad, 1970b). These observations have been supported by *in vitro* experiments which demonstrated that kidney slices from two-kidney one-clip hypertensive rats excreted less active kallikrein than normotensive controls (Nolly & Lama, 1981). Kallikrein excretion has also been found to be subnormal in spontaneously hypertensive rats *in vivo* (Keiser *et al.*, 1976). Recent results have indicated that the quantity of urinary kallikrein excreted by renal transplant recipients is possibly linked to the transplant recipient's blood pressure as well as to the state of renal function (O'Connor *et al.*, 1982).

The physiological significance of altered urinary kallikrein excretion in human essential hypertension is at present unclear. A variety of physiological regulators of the renal kallikrein-kinin system have been proposed in normal man. Briefly, correlations between urinary kallikrein activity and renal blood flow (Levy *et al.*, 1977), sodium excretion (Adetuyibi & Mills, 1972; Marin-Grez *et al.*, 1972; Levy *et al.*, 1978), urinary potassium and urinary creatinine (Zinner *et al.*, 1976), glomerular filtration rate (Martinéz-Seeber, *et al.*, 1982), and water excretion and urinary osmolarity (Mills & Ward, 1975) have been reported.

Changes in sodium and potassium intake cause variations in urinary kallikrein excretion in man (Margolius *et al.*, 1974; Horwitz *et al.*, 1978) and experimental animals (Marin-Grez *et al.*, 1972). These findings relate the renal kallikrein-kinin system to the renin-angiotensin-aldosterone system. In support of this concept, kallikrein excretion is increased in primary aldosteronism in man (Margolius *et al.*, 1974; Lechi *et al.*, 1978) and Bartter Syndrome (Lechi *et al.*, 1976; Halushka *et al.*, 1977; Vinci *et al.*,

1978) or upon aldosterone administration (Rapelli *et al.*, 1982), whereas adrenalectomy reduces kallikrein excretion in rats (Geller *et al.*, 1972).

The present study was conducted in order to evaluate the effect of β_1-adrenoceptor blockade, which is known to lower the activity of the renin-angiotensin system, on urinary excretion of kallikrein in patients with essential hypertension.

In addition, the question was asked whether, in this group of patients, a correlation of urinary kallikrein activity with the excretion rate of unconjugated adrenal steroids (deoxycorticosterone, 18-OH-deoxycorticosterone, corticosterone, cortisol, and 18-OH-corticosterone) was present, since the possibility had been raised that, in these patients, steroid precursors could be linked to the renal kallikrein excretion rate by preventing a stimulatory effect of aldosterone, thus causing subnormal urinary kallikrein activity in essential hypertension (Marin-Grez, 1982).

Methods

Fifteen patients with a mean age of 37 ± 3 (s.e.mean) years were diagnosed as suffering from sustained benign essential hypertension (WHO 1–2) on the basis of a standardized clinical work-up in our outpatient clinic, including rapid sequence intravenous pyelography, x-ray of the chest, determination of vanillylmandelic acid in 24 h urine specimens, and routine biochemical tests. None of the patients had congestive heart failure, diabetes or renal insufficiency. Patients were included in the study after informed consent had been obtained. Blood pressure measurements were performed in a sitting position on the right arm with a manual sphygmomanometer after 5 min of rest. Diastolic blood pressure was taken as 5-phase Korotkoff sound (disappearance).

Study design

A control period of 2 weeks without any medication was followed by 4 weeks treatment with metoprolol (Beloc). After 2 weeks on 100 mg metoprolol, the dose was doubled in all patients with diastolic blood pressures above 95 mmHg. A complete physical examination was done after each 2 week period.

Analytical procedures

The 24 h excretion of kallikrein and aldosterone, as well as the excretion of the 5 unconjugated steroid hormones deoxycorticosterone (DOC), 18-OH-deoxycorticosterone (18-OH-DOC), corticosterone, cortisol, and 18-OH-corticosterone (18-OH-B) were measured after 2 weeks on placebo as well as after 2 and 4 weeks on metoprolol. Plasma renin activity and urinary excretion of kallikrein were estimated at the same time intervals. Urinary excretion of sodium, potassium, and creatinine was estimated in parallel.

The hydrolysis of the chromogenic substrate S2266 by urinary kallikrein (AB Kabi, Mölndal, Sweden) yields P-nitroaniline (PNA), which is cleaved from the substrate and which was determined photometrically at 405 nm. One esterase unit (EU) equals the amount of enzyme which catalyzes the hydrolysis of 1 μmol substrate per min at 37°C and pH 8.2. The procedure was a modification of the method of Claeson *et al.* (1978) and was adopted from Overlack *et al.* (1980b). The kallikrein excretion of 10 male volunteers (mean age 34 years) was 1.28 ± 0.15 EU $24\,h^{-1}$.

Plasma renin activity was estimated by a modification of the method of Haber *et al.* (1969), which was adopted from Oelkers *et al.* (1974). For the determination of plasma renin activity, blood was withdrawn from patients in a standing position. The specific determination of the unconjugated steroid hormones was performed after extraction from 2 ml urine samples by a solid-phase technique using the automatic high performance liquid chromatography (h.p.l.c.) method of Schöneshöfer & Weber (1983), where the steroid hormones were finally quantitated by radioimmunoassay.

Statistics

Statistical procedures were performed at the Institute of Statistics of the Free University Berlin. Results are reported as mean values ± s.e.mean. Statistical comparison of results was performed using the two-tailed Student's *t* test for paired and unpaired observations, respectively, where appropriate, and $P < 0.05$ was considered significant. The experimental data were subjected to linear least square curve fitting. Significant values of *r* and *t* were estimated using the tables reproduced by Steel & Torrie (1960).

Results

Blood pressure

Systolic arterial pressure decreased during 2 weeks (Table 1) of metoprolol treatment from initially 167 ± 6 (mmHg) to 145 ± 4 (s.e.mean) ($P < 0.001$) and was 144 ± 5 after 4 weeks of treatment. Diastolic pressure was initially 114 ± 3 after the placebo period, decreased to 98 ± 4 after 2 weeks, and was 96 ± 4 after 4 weeks on metoprolol ($P < 0.001$).

Table 1 Effect of metoprolol on arterial pressure, creatinine clearance, urinary and serum electrolytes, plasma renin activity, and urinary kallikrein excretion

	Placebo (2 weeks)	*Metoprolol* (2 weeks)	$P<$	*Metoprolol* (4 weeks)	$P<$
Blood pressure:					
systolic (mmHg)	167± 6	145± 4	0.001	144± 5	0.001
diastolic (mmHg)	114± 3	98± 4	0.001	96± 4	0.001
Creatinine clearance (ml min^{-1})	114± 9	120± 7	NS	122± 10	NS
Urinary sodium excretion (mmol $24\,h^{-1}$)	167± 14	172± 13	NS	193± 16	0,05
Urinary potassium excretion (mmol $24\,h^{-1}$)	73± 4	80± 8		74± 7	
Urinary volume (ml $24\,h^{-1}$)	1582±158	1519±199	NS	1509±142	NS
Serum sodium (mmol l^{-1})	141±0,76	141±0,57	NS	140±0,51	NS
Serum potassium (mmol l^{-1})	4,3±0,11	4,4±0,10	NS	4,4±0,10	NS
Upright plasma renin activity (ng $ml^{-1}\,h^{-1}$)	3,93±0,73	2,52±0,55	0,05	1,71±0,34	0,01
Urinary kallikrein excretion (EU $24\,h^{-1}$)	0,98±0,15	0,78±0,11	0,02	0,65±0,12	0,01

Values are mean from 15 patients ± s.e.mean.
The comparisons refer to the differences between control values (1st column) and treatment (2 and 4 weeks, respectively) with metoprolol. NS = not significant.

Renin activity

Plasma renin activity measured with the patient standing was 3.93 ± 0.73 (ng $ml^{-1}\,h^{-1}$) after the control period (Table 1) and decreased significantly to 2.52 ± 0.55 ($P < 0.05$) after 2 weeks on metoprolol ($n = 15$). After 4 weeks on metoprolol, renin activity was 1.71 ± 0.34 ($P < 0.01$).

Twenty four hour excretion of free aldosterone

Twenty four hour excretion of aldosterone was 0.79 ± 0.15 (nmol $24\,h^{-1}$) after the control period and decreased slightly to 0.68 ± 0.13 after 2 weeks of treatment (Table 2). After 4 weeks on metoprolol, urinary excretion of aldosterone was found to be significantly decreased ($P < 0.05$) to 0.53 ± 0.13 ($n = 15$). The 24 h excretion rate of aldosterone from 32 normal male subjects (range) was found to be 0.29 to 0.74 (median: 0.46) nmol $24\,h^{-1}$ (Schöneshöfer & Weber 1983).

Adrenal steroids

The 24 h excretion of the adrenal steroids, DOC, 18-OH-DOC, corticosterone, cortisol, and 18-OH-B, remained unchanged throughout the study (Table 2). The normal values for these steroids using the method of Schöneshöfer & Weber (1983) are shown in Table 3. There was no significant difference be-

Table 2 Effect of metoprolol on excretion of adrenal steroids in 24 h urines of 15 patients with essential hypertension

	Placebo (2 weeks)	*Metoprolol* (2 weeks)	*Metoprolol* (4 weeks)
DOC (nmol $24\,h^{-1}$)	0,40± 0,04	0,37± 0,05	0,32± 0,03
18-OH-DOC (nmol $24\,h^{-1}$)	4,26± 0,51	4,13± 0,82	3,51± 0,49
Corticosterone (nmol $24\,h^{-1}$)	1,29± 0,10	1,21± 0,11	1,18± 0,19
Aldosterone (nmol $24\,h^{-1}$)	0,79± 0,15	0,68± 0,13	0,53± 0,13*
Cortisol (nmol $24\,h^{-1}$)	129,58±12,70	128,46±17,06	125,38±20,56
18-OH-B (nmol $24\,h^{-1}$)	7,71± 1,05	8,55± 1,37	7,99± 1,76

DOC, deoxycorticosterone; 18-OH-DOC, 18-OH-deoxycorticosterone; 18-OH-B, 18-OH-corticosterone.
Values are mean ± s.e.mean.
Comparisons are made between control values (1st column) and treatment (2 and 4 weeks of metoprolol, respectively). There were no significant changes in 24 h excretion rates of adrenal steroids except for the decrease in free aldosterone after 4 weeks of metoprolol (* $P < 0.01$).

Table 3 Mean values and ranges of the 24 h urinary excretion of kallikrein and 6 adrenal steroids from normal males

Kallikrein		1.28±	0,15	EU 24 h^{-1}	(mean ± s.e.mean)[1]
		1,26±	0,14	EU 24 h^{-1}	(mean ± s.e.mean)[2]
Aldosterone	0,29 –	0,46 –	0,74	nmol 24 h^{-1}	(median + range)[3]
		0,63		nmol 24 h^{-1}	(mean)[4]
DOC	0,21 –	0,35 –	0,59	nmol 24 h^{-1}	(median + range)[3]
	0,41 –	0,12 –	0,23	nmol 24 h^{-1}	(mean + range)[5]
18-OH-DOC	1,10 –	2,11 –	4,03	nmol 24 h^{-1}	(mean + range)[3]
		2,48		nmol 24 h	(mean)[4]
Corticosterone	0,85 –	1,49 –	2,62	nmol 24 h^{-1}	(median + range)[3]
Cortisol	35,10 –	68,30 –	133,00	nmol 24 h^{-1}	(median + range)[3]
18-OH-corticosterone	3,62 –	5,41 –	8,10	nmol 24 h^{-1}	(median + range)[3]
	1,50 –	4,00 –	6,50	nmol 24 h^{-1}	(mean + range)[4]

[1] This study.
[2] Overlack *et al.*, (1980b).
[3] Schöneshöfer & Weber (1983).
[4] Conolly *et al.*, (1978).
[5] Cope & Loizou (1975).

tween the 24 h excretion of adrenal steroids from normal males ($n = 32$) and male hypertensives ($n = 15$).

Urinary kallikrein excretion

Urinary excretion of kallikrein decreased from 0.98 ± 0.15 (EU 24 h^{-1}) to 0.78 ± 0.11 ($P < 0.02$) after 2 weeks of treatment (Table 1). Urinary kallikrein excretion decreased further after 4 weeks on metoprolol to 0.65 ± 0.12 ($P < 0.01$, $n = 15$) when compared with the excretion rate on placebo treatment.

There was a weak correlation between plasma renin activity and 24 h excretion of kallikrein ($n = 15$) prior to treatment ($r = 0.57$, $P < 0.05$). The 24 h excretion of kallikrein also correlated significantly with plasma renin activity after 2 weeks on metoprolol ($r = 0.69$, $P < 0.01$). However, after 4 weeks on metoprolol, there was no longer a statistically significant correlation between the two variables ($n = 15$). The plot showing the mean kallikrein values of each period and the mean plasma renin activity values of each period shows a correlation ($r = 0.999$; $P < 0.05$) between kallikrein excretion and renin activity (Figure 1).

The correlation of 24 h excretion of kallikrein with 24 h excretion of aldosterone did not reach statistical significance during any of the periods ($n = 15$).

Kallikrein excretion correlated significantly with potassium excretion per 24 h after 2 weeks on metoprolol ($r = 0.59$, $P < 0.05$) and after 4 weeks on metoprolol ($r = 0.51$, $P < 0.05$). However, the correlation of kallikrein excretion with potassium excretion did not reach statistical significance during the control period ($r = 0.43$, $n = 15$, $P < 0.1$).

There was no statistically significant correlation between 24 h excretion of kallikrein and sodium excretion per 24 h. Likewise, there was no significant correlation between 24 h excretion of kallikrein and diastolic blood pressure.

There was no significant change in creatinine clearance, urinary volume, or urinary potassium excretion during the study. Urinary sodium excretion was slightly elevated after 4 weeks on metoprolol ($P < 0.05$, $n = 15$) (Table 1). There was no significant change in serum sodium or serum potassium.

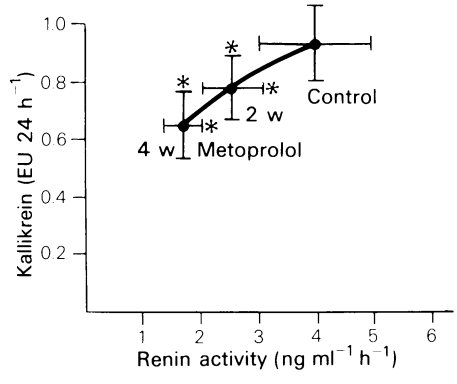

Figure 1 Effect of metoprolol on plasma renin activity. A significant (*) decrease in renin activity was found in plasma after 2 and 4 weeks of metoprolol treatment. This was paralleled by a significant decrease in 24 h urinary kallikrein excretion after 2 and 4 weeks of treatment. Each point represents the mean of 15 patients. The formula $y = 0.5x^{0.494}$ ($r = 0.9997$; $P < 0.05$) predicts urinary kallikrein excretion with great accuracy when compared to the experimental results. * $P < 0.05$: significant changes compared to placebo treatment.

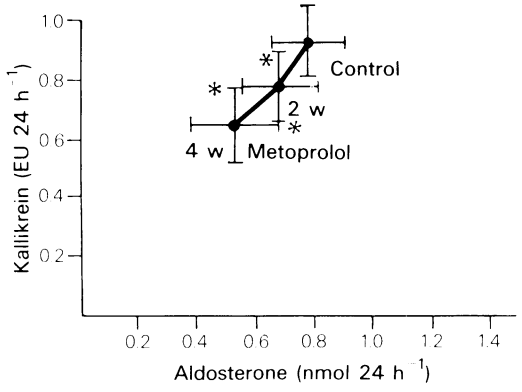

Figure 2 Effect of metoprolol on excretion of free aldosterone: 24 h excretion of aldosterone was decreased (*) after 4 weeks of metoprolol treatment. The formula $y = 1.2x^{0.998}$ ($r = 0.998$; $P < 0.05$) may be used to predict urinary kallikrein excretion from 24 h urinary excretion of free aldosterone. Each point represents the mean of 15 patients. * $P < 0.05$: significant changes compared to placebo therapy.

A comparison of patients requiring only 100 mg metoprolol for adjustment of blood pressure ($n = 6$) with those requiring 200 mg metoprolol per day revealed no significant difference in 24 h excretion of aldosterone. However, in patients requiring only 100 mg metoprolol per day, there was a clear correlation between kallikrein and aldosterone during the control period ($P < 0.01$) and also after 4 weeks on metoprolol ($P < 0.01$). In contrast, the correlation of urinary kallikrein excretion with urinary excretion of aldosterone was not significant in patients requiring 200 mg metoprolol per day, suggesting that, in patients with higher blood pressure, the correlation of aldosterone with urinary kallikrein excretion is disturbed. The plot of the mean kallikrein values of each period against the mean aldosterone excretion values of each period shows a correlation ($r = 0.998$; $P < 0.05$) between kallikrein excretion and aldosterone excretion (Figure 2).

Discussion

This study demonstrates an inhibitory effect of metoprolol on urinary kallikrein excretion, suggesting that, in patients with essential hypertension, renal kallikrein activity may be impaired by β-adrenoceptor blockade, hence relating the kallikrein-kinin system to the activity of the sympathetic nervous system and, ultimately, to the activity of the renin-aldosterone system.

So far, there is no unequivocal confirmation of a direct effect of the sympathetic nervous system on urinary kallikrein-kinin activity on the basis of studies in experimental animals. Renal denervation or noradrenaline infusion experiments in rats had no effect on urinary excretion of kallikrein (Diz *et al.*, 1981). In dogs, intra-arterial infusion of noradrenaline in subpressor doses yielded a stimulatory effect on kallikrein activity (Mills & Obika, 1977). Again, high doses of infused noradrenaline (Mills & Newport, 1979) as well as stimulation of the efferent nerves in cats (Albertini *et al.*, 1981) resulted in a suppression of kallikrein excretion. Further studies in rats demonstrated a dose-dependent decrease in urinary kallikrein activity after clonidine treatment, which was antagonized by phenoxybenzamine (Olsen, 1982). Unopposed α-adrenoceptor stimulation could therefore be considered as a possible mechanism by which metoprolol decreases urinary kallikrein activity. This assumption is, however, rendered unlikely by data obtained in humans demonstrating that phenoxybenzamine decreases urinary kallikrein activity after one week of treatment (Overlack *et al.*, 1980). This suggests that species differences may be present. Furthermore, experimental evidence points to a reduction of sympathetic nervous activity as a mechanism of the antihypertensive effect of propranolol (Lewis & Haeusler, 1975). This is also supported by the demonstration of a decreased adrenal dopamine content after metoprolol, suggesting that a reduced rate of catecholamine synthesis may reflect a reduced rate of discharge through the adrenergic system during metoprolol treatment (Ljung *et al.*, 1979). A delayed reduction in sympathetic activity has also been concluded from significant reductions in tyrosine hydroxylase and dopamine β-hydroxylase activities in the superior cervical ganglia of rabbits after prolonged treatment with β-adrenoceptor antagonists including metoprolol (Raine & Chubb 1977). While, therefore, increased α-adrenergic activity does not readily explain the effect of metoprolol on kallikrein excretion, one of the most attractive remaining explanations for the observed impact on kallikrein excretion is the effect of metoprolol on renal β_1-adrenoceptors which has been demonstrated by *in vitro* inhibition of ^{125}iodocyanopindolol binding to membranes from rat kidneys by metoprolol (Brodde, 1982). Further *in vivo* results in showing that metoprolol blocks the isoprenaline-induced increase in plasma renin activity, whereas the β_2-selective agonist, fenoterol, fails to change plasma renin activity (Weber *et al.*, 1983) confirm that the decreases in plasma renin activity after metoprolol (Attman *et al.*, 1975; von Bahr *et al.*, 1976; Velasquez *et al.*, 1979; Karlberg *et al.*, 1979;) may be mediated by renal β_1-adrenoceptors. The correlation of plasma renin activity with urinary kallikrein activity (Sealey *et al.*, 1979), which was

also confirmed in this study in essential hypertensive patients, suggests again that β-adrenoceptor activity is not only related to renin release (Atlas *et al.*, 1977) but also to renal kallikrein activity. At present it is unclear whether the impact of metoprolol on kallikrein activity is directly conveyed by renal β_1-receptors which may also be located at the distal nephron (Gavendo *et al.*, 1980), where morphological and physiological studies have demonstrated the major activity of the kallikrein-kinin system (Scicli *et al.*, 1976; Omata *et al.*, 1982; Erdös & Yamada, 1982; Proud *et al.*, 1983). It is also conceivable that the suppressed kallikrein excretion after metoprolol is a consequence of a change in the state of activity of the renin-aldosterone system. There are several known interrelationships between the kallikrein and the renin systems: these include the activation of prekallikrein and prorenin by serine proteases such as plasmin and the demonstration of the presence of prekallikrein, kallikrein, renin and converting enzyme of kininase II in the same membrane fraction of the distal tubular cells, suggesting interactions between hypertensive and hypotensive enzyme systems (Erdös & Yamada, 1982). Kallikrein activity tends also to be lower in low-renin hypertensives than in normal-renin patients and the slope of the regression line between urinary kallikrein quantity and activity has been reported to be significantly less steep in low-renin hypertensives (Ura *et al.*, 1983), supporting a link between the renin and the kallikrein system also in chronic hypertension.

The decrease in 24 h urinary aldosterone excretion after metoprolol along with a reduced kallikrein excretion, is consistent with earlier findings suggesting that mineralocorticoids may serve as the major link between the renin and the kallikrein systems. Treatment of normal subjects with fludrocortisone resulted in increased kallikrein excretion (Margolius *et al.*, 1974, Vinci *et al.*, 1979), and the increased kallikrein excretion in patients with primary aldosteronism was decreased by spironolactone (Margolius *et al.*, 1974b). Our results also support the suggestion (Margolius *et al.*, 1974b) of a decreased responsiveness of the kallikrein system to aldosterone in patients with essential hypertension: patients requiring only 100 mg metoprolol presented a better correlation between aldosterone and kallikrein excretion than patients with more marked hypertension requiring 200 mg metoprolol for treatment. Since parenteral administration of aldosterone to normal volunteers induces a marked rise in urinary kallikrein excretion in the presence of decreased active and inactive renin without changes in the proportion of each component (Rappelli *et al.*, 1982), renin itself does not appear to affect renal kallikrein activity markedly; nor does renal kallikrein seem to be a significant *in vivo* activator of inactive renin in man, thus again emphasizing the importance of aldosterone as a physiological link between the renin-aldosterone and kallikrein systems. Specific receptor binding of aldosterone to distal isolated tubules of the rabbit has been demonstrated (Vandewealle *et al.*, 1981), and kallikrein activity increased upon aldosterone administration in rat cortical cell suspensions (Kaizu & Margolius, 1975) after *in vitro* incubation. Since adrenalectomy significantly decreases active kallikrein in urine of rats (Geller *et al.*, 1972), it is likely that the decrease in 24 h urine excretion of aldosterone after metoprolol is causally related to the suppressed urinary kallikrein activity.

In contrast to the activation of the renal kallikrein system by mineralocorticoids, it appears that pharmacological doses of glucocorticoids inhibit the conversion of prekallikrein to active kallikrein, thus decreasing urinary kallikrein excretion in normal rats (Bönner *et al.*, 1981; Handa *et al.*, 1983) and increasing the ratio of prekallikrein to active kallikrein in adrenalectomized rats without a change in the decreased active kallikrein level (Noda *et al.*, 1983). A change in the mineralocorticoid/-glucocorticoid ratio could therefore impair the balance between these steroids in the control of renal kallikrein activity. It has therefore been suggested that the subnormal kallikrein excretion of essential hypertensive patients, which has also been found in this study, may be due to the preponderance of an inhibitory effect of glucocorticoids or glucocorticoid precursors over the stimulatory effect of the renin-aldosterone-system on renal kallikrein activity (Marin-Grez, 1982). However, we found no difference between the 24 h urinary adrenal excretion patterns (aldosterone, DOC, 18-OH-DOC, corticosterone, cortisol, 18-OH-B) of normal males and essential hypertensives. With the exception of aldosterone, there was also no change in the 24 h excretion of these steroids after metoprolol, thus excluding additional inhibitory effects of these compounds on urinary kallikrein excretion. Inhibitory effects of other variables can be rejected because of a lack of correlation with urinary kallikrein excretion (sodium excretion) and because of a lack in changes during metoprolol treatment (potassium excretion, creatinine clearance, urine flow).

In conclusion, it appears that renal kallikrein activity is linked to renal β_1-adrenoceptors, as has been previously shown for plasma renin activity.

It is likely that metoprolol suppresses urinary kallikrein activity by its effect on the β-adrenoceptor-mediated control of the renin-aldosterone system, although a direct effect of a decreased sympathetic nervous activity on renal kallikrein turnover cannot be excluded. There was no change in the urinary adrenal excretion pattern after metoprolol, except for aldosterone excretion, rendering inhibitory ef-

fects of glucocorticoid compounds on urinary kallikrein activity unlikely. Furthermore, there was no change in the mineralocorticoid/glucocorticoid ratio in patients with essential hypertension compared to normotensive controls. We therefore found no support for the suggestion that glucocorticoid compounds may be responsible for the decrease in urinary kallikrein activity in essential hypertension.

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