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Cardiovascular Regulation During Administration of Co-Dergocrine to Normal Subjects

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Summary. Whether and to what extent activation of peripheral presynaptic dopamine$_2$-receptors may modulate the release of norepinephrine (NE) and so affect blood pressure (BP) in normal or hypertensive man is not clear. The hydrogenated ergotoxine derivative, co-dergocrine, given in effective antihypertensive rather than excessive experimental doses, has recently been shown to act predominantly as a peripheral dopamine$_2$-receptor agonist in several species. Accordingly, BP regulation assessed has been in 8 normal men on placebo and after 3 weeks on co-dergocrine 4 mg/day. Co-dergocrine significantly reduced urinary NE excretion from 43 to 33 µg/24 h, supine and upright plasma NE 21 to 16 and 49 to 36 ng/dl, respectively, heart rate (−8 and −5%, respectively) and upright systolic BP, 115 to 102 mm Hg; upright diastolic BP also tended to be lower. A standard pressor dose of infused NE was lowered from 131 to 102 ng/kg/min, and the relationship between NE-induced changes in BP and concomitant NE infusion rate or plasma NE concentration was displaced to the left. Exchangeable sodium and plasma volume tended to be slightly decreased. Plasma and urinary electrolytes and epinephrine, plasma renin activity and aldosterone levels, pressor responsiveness to angiotensin II, the chronotropic responses to isoproterenol, and the NE-induced rise in BP, plasma clearance of NE, glomerular filtration rate and effective renal plasma flow were not consistently modified. The findings are consistent with effective peripheral dopamine$_2$-receptor agonism by co-dergocrine in humans. Peripheral presynaptic dopaminergic activation may modulate sympathetic activity and BP in normal man.

Key words: co-dergocrine, blood pressure regulation; presynaptic dopamine receptors, dopamine$_2$-receptors, rennin-angiotensin-aldosterone system, cardiovascular responsiveness, side-effects

The release of norepinephrine (NE) from peripheral sympathetic nerve terminals may be modulated by signals received by different types of presynaptic receptors. Activation of presynaptic angiotensin II or beta-receptors may facilitate and stimulation of presynaptic alpha$_2$- or dopamine$_2$-receptors may reduce the sympathetic outflow [1, 2]. The relative importance of these mechanisms in determining the level of efferent sympathetic activity and of the blood pressure (BP) in normal or hypertensive man remains to be clarified.

Co-dergocrine contains a mixture of ergotoxine derivatives with antihypertensive properties in experimental animals [3] and in man [4, 5]. It has recently been found to act predominantly as a peripheral dopamine$_2$-receptor agonist [3]. Although excessive experimental doses of co-dergocrine cause mild central nervous system and alpha-adrenoceptor inhibition, at effective BP-lowering doses these influences have been shown to be too weak to contribute significantly to its antihypertensive action [3]. Therefore, the present study was undertaken to assess the effects of co-dergocrine on cardiovascular regulation in normal subjects. Some indices of noradrenergic and angiotensinogenic BP control, chronotropic responses to acutely increased BP or cardiac beta-receptor stimulation, levels of plasma and urinary epinephrine and circulating aldosterone, the body sodium - blood volume state, renal function and urinary prostaglandin excretion were systematically investigated before and after 3 weeks of administration of co-dergocrine.

Subjects and Methods

Eight normal healthy male volunteers (aged 23 to 42 years; mean ± SD, 28 ± 6 years) were studied. Their BP was consistently < 140/90 mm Hg. After having given their informed consent to the study, they were instructed to eat a normal diet, avoiding a

very high or low sodium intake [6], and to maintain their usual physical activity during the study. Using a single-blind approach, 1 matched placebo tablet was given every morning for 2 weeks (placebo phase). The placebo was then replaced by active co-dergocrine 4 mg (Hydergin spezial, Sandoz, Nuremberg, FRG; [7]), 1 tablet every morning for 3 weeks. No other drugs were allowed. At the end of the placebo and treatment phases, side-effects were evaluated by a standard self-administered questionaire [8]. At the same times glomerular filtration rate and effective renal plasma flow were determined by the conventional constant infusion clearance technique, using ^{51}Cr-EDTA and PAH, respectively [9, 10].

A plastic cannula was inserted into an antecubital vein, and an intravenous priming dose of 25 μCi ^{51}Cr-EDTA and 6 g PAH in 50 ml NaCl (0.9%) was administered, followed by infusion of a maintenance solution (15 μCi ^{51}Cr-EDTA and 8 g PAH in 200 ml NaCl) at a rate of 3 ml/min. For blood sampling a vein on the contralateral arm was used. Urine samples were obtained by catheter. Results are the mean of 3 clearance periods.

Thereafter, the subject rested in the supine position. After 30 min bolus i.v. injections of 0.2, 0.4, 0.8, 1.6 μg isoproterenol in 5% dextrose were given, and the increase in heart rate did not reach 25 beats/min, 3.2 μg isoproterenol hydrochloride was administered [12].

Three to 5 days later, a 24-h-urine was collected for determination of sodium, potassium, creatinine, NE, epinephrine and prostaglandin E_2 and $F_{2\alpha}$ excretion rates; on completion of the urine collection, body weight, BP, heart rate, exchangeable body sodium, haematocrit, plasma and blood volumes, potassium, chloride, calcium, creatinine, renin activity (PRA), aldosterone, NE and epinephrine levels were measured between 08.00 and 10.00 a.m., after an overnight fast of at least 12 h and 1 h of rest in the supine position, as described previously [6, 11]. Blood was always collected through an intravenous cannula inserted into an antecubital vein at least 30 min before the initial sampling. BP, heart rate, PRA, aldosterone, NE and epinephrine were measured again after 1 hour of being up and about.

Two to 4 days later NE and angiotensin II were infused intravenously [13, 14]. After an overnight fast and an equilibration period of 1 hour in the supine position, with a slow i.v. infusion (6 ml/h) of 5% dextrose solution, basal BP and heart rate were measured. Blood was collected from the arm contralateral to the infusion through an intravenous cannula (inserted 30 to 60 min previously) for determination of basal PRA, plasma NE and epinephrine levels. The basal samples were collected between 08.30 and 09.00 a.m. The dextrose solution was then replaced by an infusion of l-NE bitartrate in 5% dextrose, which was infused in stepwise increasing doses of approximately 20, 40 and 100 ng/kg body weight/min and, if the NE-induced increase in mean BP did not reach 20 mm Hg, at a rate of 200 ng/kg/min, each for 20 min. During the last 10 min of each infusion step, BP was recorded every minute and heart rate was measured 3 to 5 times. At the end of each infusion step, blood was sampled from the arm contralateral to the infusion for determination of plasma NE. The NE solution was then replaced by 5% dextrose, which was infused for 45 to 50 min at a constant rate (6 ml/h). At the end of the second equilibration period, basal BP and heart rate were measured and blood was taken for determination of basal PRA, AII and aldosterone levels. The dextrose infusion was then replaced by a solution of AII (Hypertension Ciba) in 5% dextrose, which was infused at the increasing rates of approximately 2, 4 and 10 ng/kg/min and, if the AII-induced increase in diastolic BP did not reach 20 mm Hg, at the rate of 20 ng/kg/min, each for 20 min. BP and heart rate were monitored as described above; at the end of each AII infusion step, blood was collected for determination of plasma AII and aldosterone levels.

BP was measured with a standard cuff and sphygmomanometer; the mean of three readings was used for analysis. During the infusion studies, BP was monitored with an automatic recorder (Physiometrics SR 2); the mean of 9 to 11 measurements was used for analysis. Mean arterial pressure was calculated as the sum of the diastolic and one-third of the pulse pressure. During the isoproterenol sensitivity test, heart rate was monitored by electrocardiography; after 30 min in the supine position, resting heart rate was calculated from the R-R intervals as the mean resting rate over 1 minute. The heart rate after insoproterenol was obtained from the shortest R-R interval after injection [12, 14].

Cardiovascular responsiveness was analyzed as follows. Increases in mean BP (NE infusion) or diastolic BP (AII infusion) were related to plasma NE or AII levels, respectively, obtained before and during infusions [14]. The pressor doses of NE or AII necessary to increase mean (NE infusion) or diastolic (AII infusion) BP by 20 mm Hg were calculated from dose-response curves [11, 13]. To estimate baroreceptor function, the negative chronotropic effect of a 20 mm Hg increase in mean BP was assessed from BP-heart rate response curves [11, 15]. The chronotropic dose of isoproterenol was determined from dose-heart rate response curves [12]; it was defined as the dose increasing the supine heart rate by 25 beats/min.

Table 1. Effect of co-dergocrine on certain clinical and endocrine parameters (Mean ± SEM)

	Placebo	Co-Dergocrine
Supine blood pressure (mm Hg)		
systolic	110 ± 5	106 ± 3
diastolic	64 ± 3	63 ± 3
Upright blood pressure (mm Hg)		
systolic	115 ± 5	102 ± 4[a]
diastolic	80 ± 3	76 ± 3
Heart rate (beats/min)		
supine	59 ± 3	54 ± 2[c]
upright	77 ± 3	73 ± 2
Plasma renin activity (ng/ml/h)		
supine	2.3 ± 0.3	2.4 ± 0.4
upright	4.5 ± 0.6	5.0 ± 1.0
aldosterone (ng/dl)		
supine	4.9 ± 1.3	5.1 ± 1.2
upright	13.1 ± 2.4	15.5 ± 2.4
norepinephrine (ng/dl)		
supine	21.4 ± 2.7	15.9 ± 2.1[a]
upright	48.8 ± 3.6	36.3 ± 5.6[b]
epinephrine (ng/dl)		
supine	2.1 ± 0.6	2.2 ± 0.6
upright	3.0 ± 0.7	4.2 ± 0.9[a]
Urinary excretion rate		
norepinephrine (µg/24 h)	43.3 ± 5.4	32.5 ± 5.9[b]
epinephrine (µg/24 h)	11.4 ± 1.6	11.7 ± 1.9
prostaglandin E_2 (µg/24 h)	652 ± 200	449 ± 45
prostaglandin $F_{2\alpha}$ (µg/24 h)	891 ± 190	921 ± 149

[a] $P<0.05$; [b] $P<0.025$; [c] $P<0.005$ versus placebo

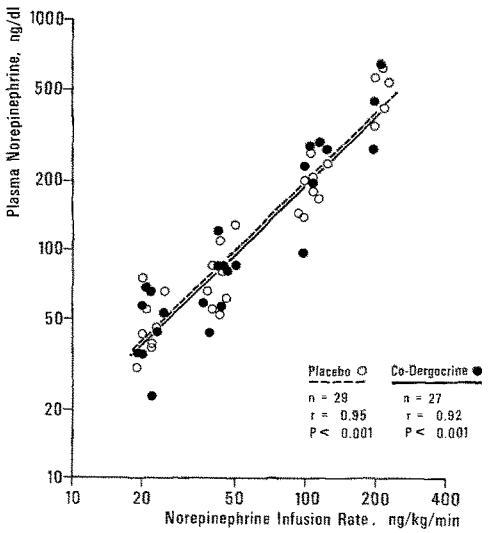

Fig. 1. Relationship between plasma norepinephrine concentration and norepinephrine infusion rate in normal subjects on placebo and after co-dergocrine. Mean ± SEM

Table 2. Effect of co-dergocrine on electrolyte - blood volume state and renal function (Mean ± SEM)

	Placebo	Co-Dergocrine
Body weight (kg)	70.6 ± 2.3	70.3 ± 2.2
Plasma concentration (mmol/l)		
sodium	141 ± 0.5	140 ± 0.5
potassium	4.1 ± 0.1	4.0 ± 0.1
chloride	104 ± 1	104 ± 1
calcium	2.28 ± 0.02	2.26 ± 0.03
creatinine	88 ± 3	91 ± 2
Urinary excretion rate (mmol/24 h)		
sodium	176 ± 18	145 ± 18
potassium	71 ± 8	79 ± 9
Hematocrit (%)	42 ± 1	43 ± 1
Plasma volume (ml)	2810 ± 133	2740 ± 139
Blood volume (ml)	4720 ± 217	4660 ± 213
Exchangeable sodium (mEq)	3080 ± 90	2970 ± 89[a]
Renal function		
24-h-creatinine clearance (ml/min/1.73 m^2)	109 ± 6	105 ± 5
^{51}Cr-EDTA clearance (ml/min/1.73 m^2)	110 ± 5	109 ± 6
PAH clearance (ml/min/1.73 m^2)	616 ± 26	605 ± 58
Filtration fraction	0.18 ± 0.01	0.19 ± 0.01

[a] $P<0.01$ versus placebo

Table 3. Effect of co-dergocrine on cardiovascular responsiveness to norepinephrine, angiotensin II and isoproterenol (Mean ± SEM)

	Placebo	Co-Dergocrine
Norepinephrine infusion		
Pre-infusion mean supine blood pressure (mm Hg)	77 ± 3	74 ± 3[a]
plasma norepinephrine (ng/dl)	20.2 ± 2.9	16.1 ± 1.9[a]
plasma renin activity (ng/ml/h)	2.6 ± 0.3	2.2 ± 0.3
Pressor dose (ng/kg/min)	131 ± 16	102 ± 21[b]
Plasma norepinephrine clearance (l/min/1.73 m^2)	5.1 ± 0.5	4.6 ± 0.5
Angiotensin II infusion		
Pre-infusion, plasma angiotensin II (pg/dl)	25.3 ± 5.6	15.8 ± 4.5[b]
plasma renin activity (ng/ml/h)	2.9 ± 0.3	2.2 ± 0.3[b]
Pressor dose (ng/kg/min)	8.5 ± 0.8	7.8 ± 1.0
Plasma angiotensin II clearance (l/min/1.73 m^2)	4.1 ± 0.4	3.9 ± 0.7
Isoproterenol		
Chronotropic dose (µg)	1.82 ± 0.44	1.25 ± 0.32

[a] $P<0.05$; [b] $P<0.02$ versus placebo

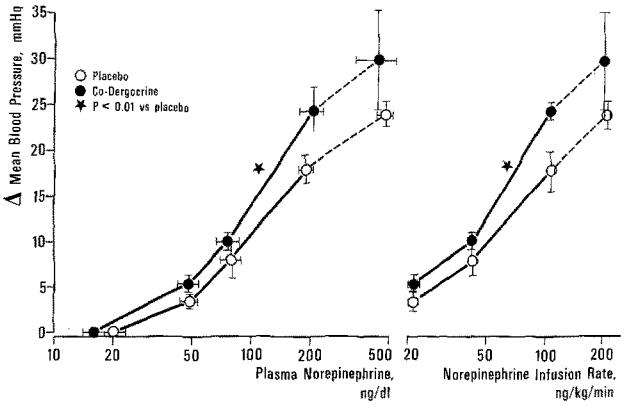

Fig. 2. Relationships between norepinephrine infusion rate or concomitant plasma norepinephrine concentration and accompanying changes in mean blood pressure in normal subjects on placebo and after co-dergocrine. P-values indicate significant shift during co-dergocrine treatment as compared to placebo

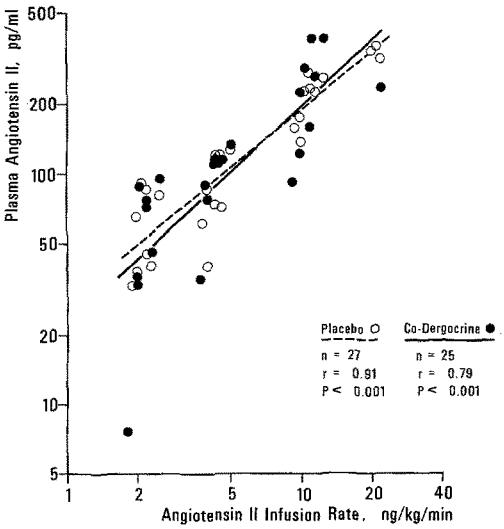

Fig. 3. Relationship between plasma angiotensin II concentration and angiotensin II infusion rate in normal subjects on placebo and after co-dergocrine

The total plasma clearances of NE and AII were calculated [13] by the formula

$$\text{clearance (l/min)} = \frac{\text{NE (or AII) dose/min}}{\text{corresponding plasma NE (or AII)} - \text{basal plasma NE (or AII)}}$$

Each clearance value consisted of the mean of 2 to 3 single clearances obtained with the different infusion rates.

Plasma and urinary sodium and potassium were measured by flame photometry, chloride, calcium and creatinine by Autoanalyzer, plasma and blood volumes and exchangeable sodium by isotope dilution methods [16], PRA [18], plasma AII [18], aldosterone [19] and urinary prostaglandin E and F_2 alpha [20] by radioimmunoassay, plasma and urinary NE and epinephrine by a radioenzymatic method [21], as previously reported [6, 14, 16].

Since natural logarithmic tranformed rather than absolute values followed a Gaussian distribution [6, 8, 11, 13-16], for statistical analysis the natural logs were used of PRA, AII, NE, epinephrine and aldosterone levels, doses of infused NE, AII or isoproterenol, pressor doses of NE or AII, chronotropic doses of isoproterenol, and prostaglandin excretion rates. Statistical analysis included paired and unpaired (two-tailed) Student's *t*-tests, regression analysis and analysis of co-variance.

Results

Blood Pressure, Heart Rate, Certain Biochemical and Pressor Factors, and Renal Function

Compared to placebo conditions, BP in the supine position was only minimally decreased (Table 1). However, upright systolic BP was significantly lower (-11%, $P<0.05$) and a similar tendency was noted for the upright diastolic BP (-5%). Heart rate was reduced significantly in the supine (-8%, $P<0.005$) and slightly in the upright (-5%) positions. Supine and upright plasma NE as well as the urinary NE excretion rate were distinctly lower (-25.7, -25.6 and -25.1%, $P<0.05$ to <0.025), while upright plasma epinephrine concentration was slightly increased ($P<0.05$) and supine plasma epinephrine and the urinary epinephrine excretion rate were unchanged. Supine or upright plasma renin and aldosterone levels, urinary prostaglandins E_2 and F_2 alpha excretion rates (Table 1), plasma and urinary electrolytes (Table 2), whole blood volume, and glomerular filtration rate and effective renal plasma flow measured by clearances of ^{51}Cr-EDTA or PAH, respectively, were not consistently changed. Body weight, plasma volume and exchangeable sodium tended to be minimally decreased (Table 2).

Norepinephrine Infusion

Plasma NE concentration measured at the end of each NE infusion step was closely correlated with the corresponding NE infusion rate, and this relationship remained unaltered during co-dergocrine treatment (Fig. 1).

Compared to placebo conditions, mean supine pre-infusion BP tended to be slightly decreased dur-

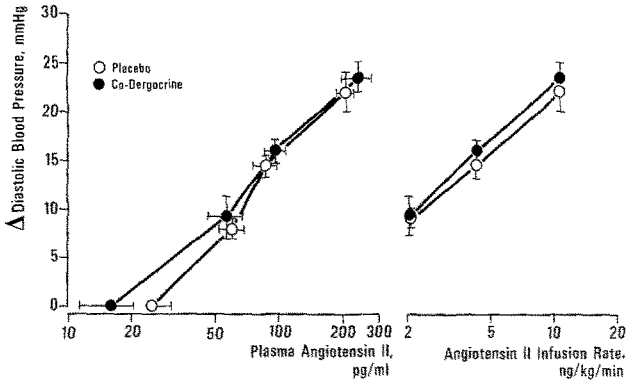

Fig. 4. Relationships between angiotensin II infusion rate or concomitant plasma angiotensin II concentration and accompanying change in diastolic blood pressure in normal subjects on placebo and following co-dergocrine. Mean ± SEM are depicted

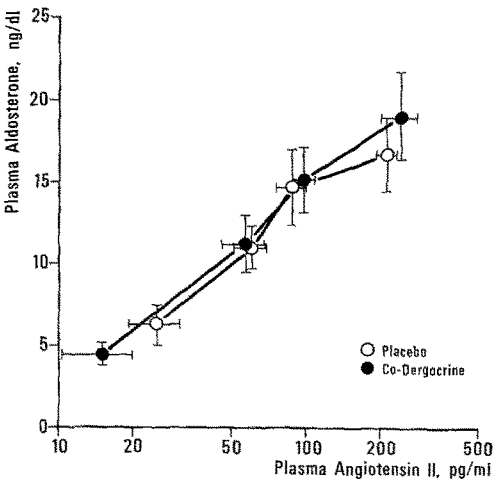

Fig. 5. Relationship between plasma angiotensin II and aldosterone level before and during angiotensin II infusion in normal subjects on placebo and after co-dergocrine. Mean ± SEM

ing co-dergocrine treatment ($P<0.05$; Table 3). It also lowered supine pre-infusion plasma NE as well as the pressor dose of NE (−20 and −22%; $P<0.05$ and <0.02, respectively), while the relationship between NE-induced changes in mean BP and the concomitant NE infusion rates or plasma NE concentrations were displaced to the left ($F=8.81$ and 7.12, respectively; $P<0.01$; Fig. 2). The total plasma clearance of NE was not significantly modified.

The response of heart rate to a 20 mm Hg rise in mean BP induced by NE-infusion was quite similar on co-dergocrine (−8 ± 3 beats/min = −25%) and on placebo (−11 + 4 beats/min = −19%). No correlation was found between co-dergocrine-induced changes in supine pre-infusion BP and those in NE pressor dose ($r=0.17$); a tendency for such a relationship with the pre-infusion supine plasma NE-levels ($r=0.66$) did not reach statistical significance.

Angiotensin II Infusion

Plasma AII concentrations measured at the end of each infusion step were closely correlated with the corresponding AII infusion rates, and this relationship did not alter during co-dergocrine treatment (Fig. 3). Compared to placebo conditions, supine pre-infusion plasma renin activity and AII levels were slightly decreased ($P<0.02$) during co-dergocrine treatment (Table 3). However, the relationship between AII-induced changes in diastolic BP and the concomitant AII infusion rate or plasma AII concentration was unchanged (Fig. 4), as was the total plasma clearance of AII (Table 3).

Plasma aldosterone levels measured before and at the end of each AII infusion step were correlated ($P<0.01$) with the corresponding plasma AII concentrations, and this relationship did not differ significantly during the placebo and co-dergocrine treatment periods (Fig. 5).

No significant correlation existed between co-dergocrine-induced changes in pre-infusion supine BP and concomitant variation in plasma AII level ($r=0.30$).

Isoproterenol Testing

The responsiveness of heart rate to isoproterenol did not differ significantly between placebo and co-dergocrine treatment (Table 3).

Side-Effects

As elicited by the self-administered questionnaire, subjective symptoms on placebo were subtracted from those on co-dergocrine. Five subjects reported effects during co-dergocrine treatment; they were always mild and included fatigue in 3, orthostatic lightheadedness in 2 and palpitation, stuffy nose or itching each in 1 subject.

Discussion

Certain hydrogenated ergotoxine derivatives developed almost 40 years ago were among the first drugs used in the treatment of hypertension. Their antihypertensive mechanism could not be entirely clarified by the methods available at that time. Although the medulla oblongata was assumed to be the main site of action [22], recent re-assessment using modern pharmacological methods may necessitate a revised concept. Interest in this type of drug has been revived by the observations of antihypertensive efficacy and good tolerance of a new galenic formulation of co-dergocrine [7], particularly in elderly hyperten-

sive patients [4, 5]. In the experimental animal, the decrease in blood vessel tone induced by co-dergocrine was antagonized by the selective dopamine receptor blocking agent, SCH 23390 [23]. In a series of studies co-dergocrine was characterized as a peripheral presynaptic dopamine$_2$-receptor agonist [3]; this mechanism seemed largely to account for the antihypertensive action in various animals, and central nervous or alpha-adrenoceptor inhibiting effects became relevant only at excessive experimental rather than effective BP-lowering doses.

Based on these considerations, co-dergocrine (4 mg/day) was administered for 3 weeks to study its impact on cardiovascular regulation in normal subjects. The efficacy of the pharmacological intervention is well apparent from the significant ($P < 0.05$ to < 0.005) reductions in supine and upright plasma NE concentrations, urinary NE excretion rate, upright heart and upright systolic BP. Upright diastolic BP and supine HR also tended to be slightly decreased, while supine BP was not consistently changed. The reduction in NE outflow during treatment with co-dergocrine was accompanied by a distinct increase in the responsiveness of supine BP to NE. The beta-receptor mediated response of the heart rate to isoproterenol on average was slightly but not significantly enhanced. The changes in noradrenergic regulatory parameters and BP after 3 weeks of co-dergocrine treatment cannot be explained by familiarization of the subjects with the test. In fact, using a similar study design, pharmacological agents that do not interfere directly with sympathetic function failed to lower NE level, heart rate and upright diastolic BP, or to augment cardiovascular NE responsiveness in normal man [11, 13, 24, 25]. Thus, a mild decrease in NE levels under the sympatholytic influence of co-dergocrine was accompanied by increased sensitivity at least of the vascular alpha-receptors. This adaptive change may well have blunted the impact of reduced sympathetic tone on BP.

Apart from a reduced sympathetic outflow, other mechanisms theoretically could also contribute to the observed changes. However, the plasma clearance of NE, which can modulate the concentration of circulating NE als well as the pressor effect of a given rate of infusion of NE, was not significantly modified during co-dergocrine treatment in the present normal subjects. The baroreflex function which co-determines the pressor response to an acute increase in plasma NE or AII also appeared unaltered, as indicated by the similar negative chronotropic influence of an NE-induced rise in BP, and the stable pressor effects of infused AII during co-dergocrine treatment as compared to placebo conditions. Body sodium-fluid volume retention, which could potentially elevate BP and pressor responsiveness [14, 26], did not occur after 3 weeks of co-dergocrine treatment; in fact, the mean exchangeable sodium, plasma volume and body weight if anything tended to be slightly decreased. The latter trend could not be explained by changes in circulating aldosterone, effective renal plasma flow, glomerular filtration rate or excretion of prostaglandins E and $F_{2\alpha}$. Slight dietary modifications have not been excluded.

These findings are consistent with the concept [3] that the administration of co-dergocrine to normal subjects stimulated peripheral pre-synaptic dopamine receptors, with a consequential decrement in sympathetic outflow and blood pressure. In contrast, no evidence of an important role of a central nervous mechanism or peripheral alpha-receptor blockade was obtained. The intact chronotropic response to an acute rise in BP during co-dergocrine treatment militates against a relevant alteration in the vasomotor and/or vasodilator centre in the medulla oblongata [22]. In fact, the pharmacological constellation described earlier [3, 22, 27], namely, a) blunted BP or vasoconstrictor responses to manoeuvres causing sympathetic reflex stimulation (e.g. cold pressure test, Valsalva test, assumption of upright posture), b) intact responses to intravenous catecholamines, and c) dependence of the action of co-dergocrine on the presence of a medulla oblongata and spinal cord, is not necessarily indicative of a central nervous mechanism, but may now be explained by the stimulation of peripheral presynaptic dopamine receptors.

From the clinical viewpoint, there was a lack of specific central nervous side effects in the normal subjects and in hypertensive patients treated by others with co-dergocrine [4, 5]. A blocking effect on peripheral alpha-receptors would tend to reduce the pressor responsiveness to NE and perhaps to increase circulating NE-levels [1, 28]. The opposite effect occurred in the co-dergocrine treated normal subjects, thus confirming that clinical doses of this agent do not cause important alpha-receptor inhibition [3, 22].

Adrenomedullary function is probably not affected by co-dergocrine per se. 24-h urinary epinephrine excretion rate and supine plasma epinephrine concentration were not significantly modified during treatment of the normal subjects. The rise in upright plasma epinephrine may well be a reaction to the observed tendency for an orthostatic decrease in BP. The latter was not unexpected, since reduced sympathetic outflow usually also leads to some venous pooling [14, 29].

The mechanism whereby a reduced NE-outflow affects BP control may also involve the angiotensin-

ergic regulation. Renal renin secretion is partly influenced by the adrenergic system [30], while AII may possibly activate the sympathetic system centrally and by facilitation of NE release or inhibition of NE re-uptake at nerve endings [31, 32]. Marked sympathetic inhibition with more conventional agents, such as methyldopa, or the postganglionic neuron blocker debrisoquine, had no apparent suppressive effect on the renin-angiotensin system in normal man [14, 33, 34]. In our normal subjects, plasma renin activity and AII levels were unchanged or were slightly decreased following intervention with co-dergocrine. More importantly, AII pressor doses and the relationship between AII-induced increases in BP and concomitant plasma AII concentrations during AII infusion were stable, while the patients received either co-dergocrine or debrisoquine [14]. Thus, there is no evidence for an important role of the angiotensinogenic control mechanism in the cardiovascular adjustment to a pharmacological reduction in sympathetic outflow.

Considering the probable concomitant roles of increased sympathetic activity and/or exaggerated vascular reactivity to NE in the pathogenesis of essential hypertension [11, 15, 36–38], further clarification of the physiological mechanisms that determine the neuronal release of NE in man is deemed necessary. Stimulation of peripheral dopamine$_2$-receptors has recently been shown to lower neurogenic discharge, BP and heart rate in the dog [2] and anaesthetized rhesus monkey [35]. The observation of a similar constellation following interaction with co-dergocrine in the present study may, therefore, reflect a pre-synaptic dopaminergic modulation of cardiovascular control in normal humans.

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