Mediating the sympathoexcitatory effects of insulin. We compared the neurons and blockade of central melanocortin-4 receptors (MC-4R) in the a-MSH precursor pro-opiomelanocortin in hypothalamic have not been reported. Recently, insulin was shown to stimulate expres-
sion of the a-MSH precursor pro-opiomelanocortin in hypothalamic neurons and blockade of central melanocortin-4 receptors (MC-4R) in-
hibit the feeding response to insulin. We examined the role of MC-4R in mediating the sympathoexcitatory effects of insulin. We compared the effects of intracerebroventricular (ICV) administration of insulin in MC-4R knockout and wild-type mice (C57BL/6J). The effects of ICV administration of MC-4R agonist (MTIII), insulin or corticotrophin releasing factor (CRF) were recorded during 4 hours under anesthesia (Xylazine/Ketamine). As expected, ICV administration of MT II (2 mcg) increased RSNA in wild-type mice by 299±48% (n=6, P<0.001), but not in the homozygous MC-4R knockout mice (n=5). The RSNA re-
ponse to MTIII in the heterozygous MC4R mutant mice was intermediate between the wild type and homozygous mutant sibs (153±31%, n=9, P<0.001). Insulin (20 mcU) induced a significant rise in RSNA in the wild-type mice (190±30%, n=7, P<0.001), but not in the homozygous MC-4R knockout mice (4±11%, n=6). The RSNA response to insulin in the heterozygous MC4R mutant mice was also intermediate between the wild type and homozygous MC4R mutant mice (95±22%, n=11, P<0.01). However, renal sympathoactivation induced by CRF (5 mcg) was comparable in wild type, heterozygous and homozygous MC4-R knockout mice (209±52, 200±57 and 250±52%, respectively, P=0.78). Our data demonstrate that the rise in renal sympathetic nerve outflow induced by insulin is mediated by the melanocortin-4 receptors because the sympathoexcitatory effect of insulin was absent in homozygous mice and attenuated in the heterozygous melanocortin-4 receptor knockout mice.

Key Words: Insulin, obesity, melanocortin system

P-505
CAROTID AUTONOMIC FUNCTION IN 422 PATIENTS WITH ORTHOSTATIC SYMPTOMS
Simona Maule, Edouardo Catalfamo, Sara Del Colle, Giannina Loetta, Mimma Caserta, Mirko Tredici, Franco Rabbia, Franco Veglio.
Autonomic Laboratory, University of Turin, Turin, Italy; Hypertension Unit, University of Turin, Italy.

The objective of the study was to evaluate retrospectively the prevalence of orthostatic hypotension (OH) and supine hypotension of patients referred to our Autonomic Laboratory with suspected autonomic dys-
function (AD). Standard cardiovascular tests (deep breathing, lying to standing, Valsalva manoeuvre, postural blood pressure) were performed to quantify autonomic function. According to their clinical presentation, 422 patients (221 males, median age 60 years, range 21-79 years) were classified into 4 groups: without neurological features (n=122), with parkinsonian features (n=145), with peripheral neuropathy (n=100) and with other neurological features (n=55). AD was mild in 9% and moderate to severe in 20% of the population. OH was isolated in 14% and associated with AD in 16% of the patients. Supine hypotension was present in 45% of the patients. Cardiovascular function was normal in 57% of the population. Prevalence of OH (isolated and with AD) was higher in patients with supine hypertension (43%) than with normal blood pressure (19%) (P<0.001). Prevalence of isolated OH and AD increased with age (OH: 0% before 40 years, 14% over 40 years; P=0.01; AD: 7% before 40 years, 21% over 40 years; P=0.02). Patients with peripheral neuropathy and parkinsonian features showed the highest prevalence of AD, 36% e 27% respectively. In conclusion, supine hyper-
tension was very frequent in our patients; its presence may impair baroreceptor function and worsen orthostatic tolerance. OH, both isolated and with AD, was also a common feature. Autonomic assessment and identification of OH and supine hypertension, especially in the elderly, is necessary for determining the prognosis and for appropriate therapeutic intervention.

Key Words: autonomic function, orthostatic hypotension, supine hyper-
tension

P-506
RENAL SYMPATHOACTIVATION TO INSULIN IS MEDIATED BY MELANOCORTIN-4 RECEPTORS
Kamal Ruhmouni, Donald A Morgan, William G Haynes.
Hypertension Genetics SCOR, CV Center and Department of Internal Medicine, University of Iowa, Iowa City, IA.

Insulin acts in the central nervous system to increase sympathetic nerve activity. The pathways by which insulin affects sympathetic nerve traffic have not been reported. Recently, insulin was shown to stimulate expres-
sion of the a-MSH precursor pro-opiomelanocortin in hypothalamic neurons and blockade of central melanocortin-4 receptors (MC-4R) in-
hibit the feeding response to insulin. We examined the role of MC-4R in mediating the sympathoexcitatory effects of insulin. We compared the

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P values (stim vs sham): 0.008†; 0.000†; 0.000†

Key Words: medulla, sympathetic, neurogenic hypertension

P-507
PLASMA CATECHOLAMINES AND RESPONSES TO MENTAL STRESS IN YOUNG, BORDERLINE HYPERTENSIVE MEN. CONTRAST BETWEEN LEAN AND OVERWEIGHT INDIVIDUALS
Henrik M Reim, Egel Fossom, Aud Heiegen, Ivar Eide, Sverse E Kjeldsen. Department of Cardiology, Ullevaal University Hospital, Oslo, Norway; Department of Nephrology, Ullevaal University Hospital, Oslo, Norway.

1. We studied body mass index (BMI) and plasma catecholamine levels in borderline hypertension (BH), and tested the hypothesis that overweight subjects have lower levels than lean.
2. Males (age 20-24 years) with BH (screening BP 140/90 mmHg), and normotensive (NT) controls were divided into lean and overweight NT (LN, n=36; ON, n=7) and BH (LH, n=62; OH, n=29) groups (cut-off: BMI>25 kg/m²). Venous plasma epinephrine (E) and norepi-
nephrine (NE) (radioenzymatic method) levels were averaged during a hyperinsulinemic glucose clamp (rest) and a mental arithmetic stress test (MST) (both 4 samples).
3. Resting E (E0) and NE (NE0) (both P<0.01), and E and NE during stress (E1 and NE1) (both P<0.001) were higher in BH than in NT. In BH, E and E1 correlated negatively with waist circumference (WC) (r=-0.35, P<0.001 and r=-0.26, P<0.05), BMI (0.43, P<0.001 and r=0.35, P<0.001), and smokers had lower E1 (P<0.001), E0 and NE0 (both P<0.01), compared to non-smokers.

Plasma Catecholamines and Responses to Mental Arithmetic Stress

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<tr>
<th>LN</th>
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<th>OH</th>
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<tr>
<td>Rest</td>
<td>E0 (pg/ml)</td>
<td>175 (89)</td>
<td>204 (167)</td>
</tr>
<tr>
<td>NE0 (pg/ml)</td>
<td>0.95 (0.39)</td>
<td>1.07 (0.51)</td>
<td>1.30 (0.61)**</td>
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<tr>
<td>Mental Stress</td>
<td>E1 (pg/ml)</td>
<td>264 (129)</td>
<td>313 (324)</td>
</tr>
<tr>
<td>NE1 (pg/ml)</td>
<td>89 (93)</td>
<td>109 (158)</td>
<td>252 (275)**</td>
</tr>
<tr>
<td>*ΔE (pg/ml)</td>
<td>1.18 (0.43)</td>
<td>1.43 (0.79)</td>
<td>1.75 (0.80)**</td>
</tr>
<tr>
<td>*ΔNE (pg/ml)</td>
<td>0.21 (0.19)</td>
<td>0.36 (0.35)</td>
<td>0.45 (0.30)**</td>
</tr>
</tbody>
</table>

Means (SD). * P<0.05, ** P<0.01, *** P<0.001 vs. LN; † P<0.05, †† P<0.01 vs. OH (Bonferroni)

In stepwise multiple regression analysis with BH, BMI, WC, and smoking as explanatory variables, BH was independently related to higher E0 (P=0.004), E0 (P=0.001), NE0 (P=0.003), and NE1 (P=0.0009), BMI to lower E0 (P<0.01) and E (P=0.003), and smoking to lower E0 (P=0.0007), E (P=0.002), and NE0 (P=0.02).
4. Increased peripheral venous plasma catecholamine levels in borderline hypertensives are mainly accounted for by lean subjects. Plasma epinephrine levels are lower in overweight than in lean borderline hypertensives, at rest and during mental stress, while smoking seems to lower plasma norepinephrine as well as epinephrine levels.

Key Words: Borderline Hypertension, Plasma catecholamines, Overweight

P-508
ASSOCIATION BETWEEN SUPINE HYPERTENSION AND ORTHOSTATIC HYPOTENSION IN CHRONIC AUTONOMIC FAILURE
David S Goldstein, Sandra Brentzel, Courtney Holmes, Basil Eldadah, Yehonatan Sharabi. Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD.

Background: Supine hypertension occurs commonly in primary chronic autonomic failure. This study explored whether supine hypertension in this setting is associated with orthostatic hypotension (OH) and, if so, what mechanisms underlie this association.

Methods: Supine and upright blood pressure, hemodynamic responses to the Valsalva maneuver, and plasma norepinephrine levels were measured in pure autonomic failure (PAF), multiple system atrophy (MSA) with or without OH, and Parkinson’s disease (PD) with or without OH. Controls included age-matched normal volunteers and patients with essential hypertension (EH) or referred for dysautonomia.

Results: PAF, MSA+OH, and PD+OH all featured supine hypertension equivalent in severity to that in EH, regardless of fludrocortisone treatment for OH. Patients with MSA or PD lacking OH did not have supine hypertension. Individual values for supine mean arterial pressure correlated negatively with orthostatic changes in mean arterial pressure (r = -0.40, p < 0.0001). Baroreflex-cardiovagal gain and orthostatic increments in plasma norepinephrine levels were markedly decreased in all groups with OH. In both MSA and PD, norepinephrine levels during supine rest were lower in the subgroups with than without supine hypertension.

Conclusions: In chronic primary autonomic failure, supine hypertension accompanies OH. Decreased baroreflex-cardiovagal gain correlates with and therefore might play a pathophysiologic role in both abnormalities of blood pressure regulation. Increased delivery of norepinephrine to its receptors does not adequately explain supine hypertension in patients with primary chronic autonomic failure and OH, suggesting a hypertensive mechanism independent of the sympathetic nervous system.

Key Words: Sympathetic nervous system, Baroreflex, Orthostatic hypotension

P-509
EFFECT OF ET-A RECEPTOR ANTAGONIST ON SYSTEMIC SYMPATHETIC NERVOUS ACTIVITY IN HYPERTENSIVE PATIENTS
Isabella Sudano, Stefano Taddei, Daniele Versari, Antonio Salvetti. Department of Internal Medicine, University of Pisa, Pisa, Italy.

It is well documented that essential hypertension is characterized by an increased ET-1 vasoconstrictor tone. Since experimental evidence indicates that endothelin-1 (ET-1) exerts a potentiating activity on central and peripheral control of sympathetic nervous system (SNS), an effect exerted by the activity of ET-A receptor subtype in the present study we assessed the possible role of endogenous ET-1 in modulating SNS activity.

In 9 patients with essential hypertension (EH) (age: 47 ± 3.9 years BP: 151.7 ± 13.1/95.8 ± 5.8 mmHg) we evaluated the modification of systolic (S) and diastolic (D) blood pressure (BP; measured by Finapress), heart rate (HR, EKG) and muscle sympathetic nervous activity (MSNA; measured by microneurography) induced by 20-min infusion of BQ123 (0.1 mg/Kg/h), a selective ET-A receptors antagonist, or sodium nitroprusside (SNP 2.4 μg/Kg/h). Drugs were infused for 20 minutes and the infusion sequence was randomised.

BP was similarly reduced by BQ123 (SBP -2.9±0.6% and DBP -3.8±0.9% vs baseline) and SNP (SBP -2.9±0.9 mmHg; DBP -3.6±0.7 mmHg vs baseline). Under SNP, HR increased up to a maximum of 14.5±3.7% above baseline in 10 minutes while BQ123 induced a slower increase in HR reaching a maximum of 14.7±4.1% after 20 minutes. Moreover, BQ123 induced MSNA increase (21.3 to 30.2 bursts/min, 43.4% vs baseline) resulted significantly lower than SNP induced MSNA increase (19.4 to 29.4 burst/min; 54.5% vs baseline). Results do not change when MSNA is expressed as bursts/100 HR beats or burst area under the curve (data not shown). The results seems to confirm that in essential hypertension endogenous ET-1 potentiates SNS activity.

Key Words: sympathetic nervous system, endothelin, essential hypertension