on insulin sensitivity. However, the relatively high serum leptin in obese subjects suggests that humans may be resistant to the weight-reducing actions of leptin.

A basic understanding of the leptin signal pathway has been achieved; however, the mechanisms that regulate leptin production are not understood. Hexosamine biosynthesis is a mechanism through which cells “sense” the influx of nutrients. Hexosamines appear to regulate leptin production in human adipocytes.

In summary, leptin provides a coordinating signal to the central mechanisms regulating body energy balance. The adipocyte utilizes the hexosamine biosynthetic pathway to determine the amount of leptin to release.

Key Words: Leptin; neurotransmitters; hexosamines

ROLE OF NEUROPEPTIDES IN LINKING OBESITY, SYMPATHETIC ACTIVITY AND HYPERTENSION
William G. Haynes, M.D.

Leptin is almost exclusively produced by adipose tissue and acts in the central nervous system (CNS) to decrease appetite and increase energy expenditure. We have demonstrated that systemic or CNS administration of leptin markedly increases sympathetic nerve activity (SNA) to brown adipose tissue, kidney, skeletal muscle and adrenal glands. Acute administration of leptin does not increase arterial pressure, although chronic leptin infusion does have a modest pressor effect. Leptin also has actions that oppose sympathetically mediated vasoconstriction, including natriuresis, insulin sensitization and simulation of endothelial nitric oxide generation. These diverse actions have made it difficult to assess the overall role of leptin in control of arterial pressure. Recent studies from our laboratory have shown the obese leptin-deficient ob/ob mice have lower arterial pressure than lean littermates. These data suggest that endogenous leptin contributes to the physiological maintenance of arterial pressure.

The hypothalamic melanocortin system, via activation of melanocortin-4 receptors, decreases appetite and weight. The leptin and melanocortin systems appear to have independent and additive actions on body fat content. The melanocortin system acts to increase SNA to thermogenic and other tissues. Interestingly, obesity in the agouti mouse strain, due to genetic antagonism of melanocortin receptors, is associated with elevated arterial pressure. This may represent a non-specific effect of obesity or a purative hypertensive effect of melanocortinergic underactivity.

Altercations in leptin and melanocortin activity may contribute to the adverse cardiovascular consequences of obesity. Contrasting blood pressure responses to obesity in ob and agouti mice suggests that the cardiovascular response to obesity depends critically on the underlying genetic and neuroendocrine mechanisms.

Thursday, May 20, Broadway Ballroom South, 5:00 PM to 7:00 PM
Theme II: New Drugs
NEW DRUG ABSTRACTS: SUMMARY
N.K. Hollenberg*, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA

As this abstract is being written before the abstracts have been reviewed, the specifics of their content cannot be discussed. Of substantial interest is the fact that early in this decade the conventional wisdom—both in many companies and in academe—was that antihypertensive therapy was now so good that there was little point in investing time and effort in further development. Many companies, some of them substantial, closed their hypertension research programs and turned elsewhere. At the moment, the development of antihypertensive treatments is more active than at any time in history. The abstracts will cover angiotensin II antagonists, aldosterone antagonists, and vasopeptidase inhibitors. Once again, conventional wisdom was incorrect.

Key Words: Antihypertensive therapy; vasopeptidase inhibitors; angiotensin II antagonists; eplerenone

Friday, May 19, Broadway Ballroom North, 10:30 AM to 11:30 AM
Theme I: Hypertension and Atherosclerosis
MICROVASCULAR AND INFLAMMATORY RESPONSES TO HYPERCHOLESTEROLEMIA
D. Neil Granger. Mol & Cellular Physiology, LSU Health Sciences Center, Shreveport

While the inflammatory manifestations of hypercholesterolemia (Hch) are generally assumed to occur exclusively in major arterial vessels, recent studies suggest that the inflammatory cell-mediated pathology may also extend to the arterial and venous segments of the microcirculation. Hch is known to result in an impaired endothelium-dependent relaxation of arterioles and to produce responses in capillaries and venules that are characteristic of an acute inflammatory response, including leukocyte-endothelial cell adhesion and increased vascular permeability and capillary fluid filtration. The accompanying oxidant stress appears to initiate the recruitment of inflammatory cells in postcapillary venules. These inflammatory cells appear to amplify the microvascular and inflammatory responses to Hch and cause greater vulnerability of tissues to the deleterious effects of ischemia and reperfusion.

Key Words: Leukocytes; ischemia; endothelium

Friday, May 19, Broadway Ballroom North, 11:30 AM to 12:30 PM
Theme I: Mechanisms of Diabetes Mediated Cardiovascular Disease
ENDOTHelial DYSFUNCTION AND ARTERIAL PRESSURE CONTROL IN DIABETES
Michael W. Brands. University of Mississippi Medical Center

Endothelial dysfunction, defined as impaired endothelial-dependent vasodilation, generally is ascribed to abnormalities in the synthesis or action of nitric oxide (NO). There is considerable evidence for endothelial dysfunction in diabetes...
tes, and because NO is a major factor in normal arterial pressure control, dysfunction of this system in diabetes could have significant hemodynamic impact. However, it has been difficult to demonstrate a relationship between NO and chronic blood pressure control in diabetes. One potential explanation for this may be the time at which the NO system has been studied. This is because there is growing evidence that NO synthesis is not impaired at the onset of diabetes, and that diminished vasodilatory responsiveness is due to inactivation of NO by free radicals. Later in the disease, when virtually all studies have been conducted, impaired NO synthesis develops and it is possible that other factors such as prostaglandins acquire a greater role in the vasodilatory function of the endothelium. In support of this hypothesis, we have shown, in chronically instrumented and monitored rats, that endothelial function is not impaired during the first week of diabetes. To test the role of NO in blood pressure control at this early stage, we induced diabetes in rats that were pre-treated with the NO synthase inhibitor, L-NAME. The induction of diabetes gradually increased mean arterial pressure over 21 days to approximately 60 mmHg greater than arterial pressure in control diabetic rats and 20 mmHg above normal rats treated with L-NAME. Thus, it appears that a pressor system is activated following induction of diabetes, and that the normally functioning, or perhaps activated, NO system is important to prevent hypertension. Additional studies have provided clues for the pressor mechanism and for the time-dependence of NO activity.

ACTIVATION OF PROTEIN KINASE C PATHWAY, A COMMON PATHWAY FOR HYPERGLYCEMIA TO CAUSE VASCULAR PATHOLOGIES

George L. King, MD. Joslin Diabetes Center, Harvard Medical School, Boston, MA

Hyperglycemia is a major cause of vascular diseases in diabetic patients. Multiple theories have been proposed to explain the adverse effects of hyperglycemia. Recent studies have focused on the intracellular mechanisms by which hyperglycemia are mediating their toxic effects. One key intracellular signal transduction mechanism is activation of protein kinase C (PKC) which is activated by glucose directly or indirectly via oxidants and glycation products. Activation of PKC and its β and δ isoforms has been shown to cause vascular dysfunctions in the retinal, renal, and cardiovascular systems in diabetic patients and animals. Using specific inhibitors to PKC and gene transfer techniques, we have shown that overexpression of PKC β isoform can cause cardiomyopathy, nephromegaly, acceleration of restenosis, and retinopathy in animals. Preliminary data in clinical trials using PKC β inhibitor have suggested early changes in diabetic vascular abnormalities can be reversed. These results have provided supportive evidence that activation of PKC could be a common pathway by which the metabolites of glucose are causing vascular pathologies in diabetes.

Key Words: Diabetes; protein kinase C; gene transfer; cardiovascular complication