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Sexual Dimorphisms of High-Fat or Glucose Feeding in Rats: Differences in Body Composition and the Hypertensive Response

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SEXUAL DIMORPHISMS OF HIGH-FAT OR GLUCOSE FEEDING IN RATS: DIFFERENCES IN BODY COMPOSITION AND THE HYPERTENSIVE RESPONSE

By

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ABSTRACT

SEXUAL DIMORPHISMS OF HIGH-FAT OR GLUCOSE FEEDING IN RATS: DIFFERENCES IN BODY COMPOSITION AND THE HYPERTENSIVE RESPONSE

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Female Sprague-Dawley rats resisted the hypertensive response which develops in males fed either high-fat or glucose enriched diets. After 10 weeks of diet treatment systolic blood pressure was 20% higher in males compared to females fed high-fat, and 15% higher in males compared to glucose fed females ($P<0.05$). Females fed the high-fat diet became obese(energy density = 6.21 ± 0.3) and gained a higher percentage of body fat compared to control females without exhibiting an increase in body weight. Females failed to develop hyperinsulinemia or elevated norepinephrine levels. However epinephrine excretion was elevated in females compared to males fed the high-fat diet. Anatomical preference for fat accretion differed between males and females with females depositing more fat in the interscapular and retroperitoneal regions. In both sexes inguinal depot size seemed to parallel body growth while gonadal depot size paralleled degree of adiposity. Differences in regional fat accretion and sympatho-adrenal system response to diet manipulation may participate in the female ability to resist hyperinsulinemia and hypertension. In conclusion females demonstrate a resistance to the altered physiological state that males display in response to chronic high-fat or glucose enriched diet feeding.

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INTRODUCTION

Indications of the need for hypertension studies in females

Hypertension afflicts an estimated 35 million people in the United States(1). Treatment of this disease is linked with reduced cardiovascular disease, cerebrovascular and renal disease(1,15). Universally, there is a higher percentage of hypertension in men. However, males and females develop hypertension at equal rates as the population ages(1). Both men and women receive similar recommendations for treatment hypertension, but investigative research has primarily focused on males. There is a need for data on gender, like age and ethnic influences on hypertension and associated complications(1). Research expanded to investigate hypertension in females would assist in efficient treatment of women afflicted with hypertension as well as characterize the disease process in general. This study was initiated to address the sex differences in the hypertensive response to diet in male and female Sprague-Dawley rats. The specific aim of this study was to elucidate sex differences in hemodynamic effects of macronutrients and metabolic responses to these nutrients. Specifically, this approach examined lipid accumulation, insulin sensitivity, sympathoadrenal activity, systolic blood pressure, and electrolytes.

females from hyperinsulinemia and hyperglycemia(10,19). Insulin functions in fat metabolism by promoting lipid storage in adipose tissue. Adipose tissue, however, does not react as a homogenous tissue to different hormonal stimuli(38). Specifically, androgens and progesterone in conjunction with insulin cause hyperinsulinemia, and an increase in body weight and fat(25,58). Conversely, estrogen improves peripheral insulin utilization, lowers body fat(18,58). Prenatal hormone organizational effect and activational effects of hormones later in life contribute to the sex differences in body weight and fat(6). Animal studies have shown these activational effects also include androgen or progesterone stimulation of hyperphagia and insulin resistance and estrogen suppression of food consumption as well as improved insulin sensitivity(6,33,35). Factors responsible for location of body fat accretion are not completely known, yet sex hormones appear to play an important role. Regional differences in adipocyte response to insulin and sex hormones have been studied. Postmenopausal women with a disproportionate amount of android fat show increased susceptibility to typically male metabolic disorders such as diminished glucose tolerance and hyperinsulinemia(10,48). Estrogen treatment has been shown to alleviate the effects of pharmacologically induced diabetes in male rats; testosterone treatment has been shown to worsen diabetes in female rats.

<u>Rat Models of Obesity and Fat Topography</u>

In rats, strain, age, sex and diet all have an effect on the ability to produce obesity(16,31,45,51,54). Ventro-medial hypothalamic lesions and pharmacologic manipulations are used in studies to induce obesity. Scientific investigations have continually observed that dietary factors appear to play a substantial role in increasing storage of body fat. Diet composition manipulations in rats best parallel human adiposity changes.

High-fat or carbohydrate feeding results in obesity due to increased caloric intake and feed efficiency(10,31). Increased palatability of the diet is the cause for the increased intake, and the ability to convert diet energy into weight gain constitutes improved efficiency(32,34). Animals fed diets of high energy content tend to lower consumption to compensate for increased caloric density. This compensation of intake has been demonstrated to be imperfect and animals fed high fat or glucose diets consume more kilocalories over time due to an increase in palatability(10,16). Feeding of high-fat, highly palatable diets from weaning through adulthood produces the greatest tendency toward obesity(54). In certain rat strains body weights can reach 900g and 35% fat after 20 weeks of high-fat feeding(45). During these 20 week or longer studies of ad libitum feeding, females amass a greater percentage of fat, especially in gonadal, inguinal and interscapular fat pads(31,51). Studies conducted over a shorter time period show an increase of 16-32% in body weight of high-fat fed versus chow fed rats(31).

Body weight alone is not a reliable indicator of fat deposition(31,45). As a rat ages total body lipid shows a curvilinear relationship to body weight(45). Growth of certain fat pads tightly correlate with body fat accretion, while others correlate with body growth. Retroperitoneal depots grow exponentially compared to body growth(45). The gonadal depots, on the other hand, are linearly related to body growth(45). Therefore, retroperitoneal fat pads are a good representation of total body lipid, while gonadal accumulation falls behind body lipid accretion(45). Retroperitoneal fat pad weighing in Wistar rats allows for estimating total body fat to within 3-4% due to this tight association of retroperitoneal fat deposition and body lipid(45). Specific metabolic and morphologic characteristics effect changes in fat pad size as body weight increases. Anatomical location as well as size of adipocytes are associated with differences in insulin mediated lipid metabolism(36). Adipocytes from different anatomical sites, which differ in lipid content will all adjust to one common size when transferred to the same area of the body(3).

Macronutrient Assimilation

There are disparities in energy costs for nutrient assimilation. Eight to 20% of the energy contained in a carbohydrate meal is used in the digestion and conversion to fat. Seven percent of the total energy is used in the conversion of fat into adipose tissue(21,49). Additionally, the conversion of carbohydrate and protein to fat ceases in diets containing 30% or more fat if the diet is not also high in carbohydrate. Therefore high fat diets can lead to obesity through the increased efficiency of fat assimilation. Moreover, increased adipose to lean body tissue ratio causes a decrease in basal metabolic rate,per unit body weight, since adipose tissue has a slower metabolic rate(10,21). The resulting disequilibrium between energy input and output due to efficient assimilation in obese individuals will compound weight gain. The importance of diet composition in the etiology of hypertension and related complications is realized, since the typical western diet contains approximately 43% of its energy from fat(16).

Sympathetic Nervous System

Peripheral autonomic innervation is profuse and intricate. Sympathetic and parasympathetic nerves innervate many effector organs. Sympathetic outflow to different organs has not been proven to be homogeneous(46). Norepinephrine is the major catecholamine released at the effector tissues in response to increased sympathetic tone. The adrenal medulla is the another source of peripherally released catecholamines. Medullary secretions consists primarily of epinephrine with approximately 20% norepinephrine. Plasma norepinephrine levels are generally six to seven times greater than epinephrine(52). This sympatho-adrenal system is controlled by areas of the central nervous system, including the ventromedial hypothalamus, pons, and medulla(42).

Alpha and ß-adrenergic receptors mediate the response to norepinephrine or epinephrine. Norepinephrine stimulatory effects on cardiac muscle (ß receptor), renal function(ß receptor), and smooth muscle of arterioles(α receptor) are the primary inducers of increase blood pressure(2,40,55).

Urinary catecholamine measurement is a good indicator of both central and peripheral sympathetic activity, including adrenal medullary activity(50). Central control of sympathetic activity is stimulated by diet and external influences like cold and stress(24). The sympatho-adrenal effects can be uncoupled through demedullation. The hypertensive response to high-fat or glucose feeding is significantly diminished in demedullated animals(43). Females are suggested to have higher catecholamine levels systemically than males. Uterine tissue especially is densely innervated(60). Estrogen treatment causes elevated sympathetic activity while progesterone treatment reduced the rise in norepinephrine in uterine tissue(60). These studies also demonstrated that increased adrenergic activity in an organ does not always correlate with an increase in plasma norepinephrine.

Obesity, Sympatho-adrenal Activity and Hypertension

Chronic high fat or carbohydrate feeding results in an increased systolic blood pressure in male rats. The sympathetic nervous system (SNS) is highly responsive to diet. Overfeeding induces SNS activity, while fasting suppresses it(40). High-fat and simple sugars (glucose, fructose, sucrose) are more effective than complex carbohydrates in inducing sympatho-adrenal activity and hypertension(22,24,26,34).

An increase in SNS activity is apparent in male rats fed high-fat diets only when it is associated with increased caloric intake and obesity(34,40,53). The hypertensive response and increased SNS activity is not apparent when obesity is prevented by feeding restricted amounts of a high-fat diet(34,40). This caloric restriction effect indicates the important role of increased body weight in hypertension induced by fat. Weight loss in obese, hypertensive humans lowers blood pressure and SNS activity (40,41).

Direct macronutrient effects should not be discounted as a factor involved in the development of hypertension. Male rats chronically fed diets of 66% glucose became hypertensive without obesity(22,26,34). Therefore, increased caloric intake as well as macronutrient composition are involved in eliciting the hypertensive response. The sympatho-adrenal system is thought to participate in mediating the consequence of obesity and macronutrient effects on blood pressure(26,34).

In humans, established hypertensive subjects failed to show increased SNS activity, yet borderline hypertensive individuals showed significantly increased plasma catecholamine levels(14,28). There seems to be a point where sympatho-adrenal activation ceases to play a role once hypertension is established. Once blood pressure is established it is suggested that anatomical changes in arteriole smooth muscle override the sympathoadrenal role in hypertension(14). In animal studies increased norepinephrine levels have been demonstrated after five weeks of special diet feeding, approximately at the onset of increased blood pressure(34).

Epinephrine may facilitate the action of the peripheral sympathetic nerves(2,7,13). One hypothesis suggests that epinephrine is taken up by sympathetic nerve endings peripherally and then released with norepinephrine as a co-transmitter during sympathetic stimulation. Experiments using pharmacological doses of epinephrine have supported this co-transmitter hypothesis. Determining if physiological concentrations of epinephrine promote the same effects is less conclusive. A second hypothesis suggests that epinephrine facilitates norepinephrine release by acting on the presynaptic ß-adrenoceptor, resulting in elevated norepinephrine release(2,7,13). Additionally, the inhibitory presynaptic α-adrenergic receptor may possibly be activated by epinephrine in addition to ß receptor stimulation(13). Thus a balance exists between stimulation of these two receptors which may change due to physiological status. Furthermore, epinephrine may have trophic effects on cardiac muscle to heighten response to adrenergic stimulation(8). Investigations of hypertension during its development will lead to uncovering the role of the sympatho-adrenal system in the pathogenesis of hypertension.

Effects of Insulin on Sympathetic Activation and Hypertension

The major function of insulin is glucose homeostasis. Release of insulin from ß-cells of the pancreas is stimulated by increased concentration of circulating metabolic fuels. Overall, insulin functions at the level of the tissues to promote glucose utilization. Fat storage in adipocytes is also induced by insulin, while fat mobilization is inhibited(59). Insulin inhibits hepatic glucose production through reduced glycogenolysis and gluconeogenesis.

Obese humans have been found to have 20% less binding capacity for insulin at the level of the tissues due to a down regulation in the number of insulin receptors(47). Post receptor deficiencies also attribute to reduced insulin action in obese individuals(47). Non insulin dependent diabetics also demonstrate signal or regulatory protein defects which culminate in reduced insulin action(47). The clinical sign of hyperglycemia in NIDDM results when insulin production cannot meet high insulin needs due to reduced peripheral sensitivity to insulin. In addition, hepatic glucose output is increased due to deficient insulin effects on the liver. In NIDDM there is a positive feedback cycle of hyperglycemia stimulating insulin release which cannot efficiently function, due to receptor down regulation and postreceptor defects, thus more insulin is released and hyperinsulinemia ensues.

Insulin may be the link between diet and SNS effects on blood pressure(34,40,41,50). Insulin is also a potent stimulator of SNS activity both centrally and peripherally(37). Hyperinsulinemia has been associated with increased SNS activity in hypertensive rats(34,40). Activation of the SNS through hyperinsulinemia is suggested since plasma norepinephrine increases and clearance of circulating norepinephrine is not altered during insulin infusion(50). Insulin can enter cerebral spinal fluid and insulin receptors have been found in monkey and pig hypothalamus(39). Insulin may act as the mediator for increased SNS activity by acting centrally at the ventromedial hypothalamus to stimulate peripheral SNS activity. This central control mechanism is supported by increases in SNS activity in a dose dependent relationship during hyperinsulinemic, euglycemic clamping experiments in non diabetics humans(50). Additionally, subjects with autonomic failure or diabetics with normal autonomic function do not produce the increased response to insulin infusion or a glucose load, respectively(40).

The insulin mediated glucose hypothesis model explains the central control of SNS activity in the ventromedial hypothalamus(VMH). Interruption of glucose metabolism within the cells of the VMH, which occurs during fasting, causes inhibition of the sympathetic center within the brain stem. Conversely, excess of glucose metabolism allows sympathetic centers to increase central sympathetic outflow(37).

Insulin also acts centrally as a satiety signal to control food intake and body weight(58). SNS stimulation and satiety functions support the importance of insulin as a messenger between the brain and body metabolism.

The present investigation has attempted to compare gender differences in the effects of high-fat and glucose diets on blood pressure, SNS activity, hyperinsulinemia, energy retention and body composition. Disparities in the above parameters may assist in elucidating sexual dimorphisms in the metabolic effects of specific nutrients.

<u>Null Hypotheses:</u>

1. Systolic blood pressure will be elevated equally in male and female rats fed a high fat or refined sugar diet.
2. Occurrence of hyperphagia and hyperinsulinemia in hypertensive males will be matched in females fed the same diet.
3. The degree of SNS activity and hyperinsulinemia paralleling hypertension will be the same in males and females.
4. Energy intake and body energy accumulated throughout the experiment will be equal between the sexes fed the same diets.
5. Macronutrient handling, and body fat distribution will be equivalent in both sexes.

MATERIALS AND METHODS

General Protocol

Forty eight Spraque-Dawley rats (24 males and 24 females) were housed in a room maintained at 25° C, 70% humidity and with a 12 hour light/dark cycle. The animals were divided into 6 experimental groups consisting of eight rats per group. At the age of 10-11 weeks of age each rat was allowed ad libitum access to one of three specially formulaated diets. Protein, vitamin and mineral content were adjusted according to expected food intake in order to provide equivalent amounts. (Table 1). The rats were housed individually in order to measure individual food intake. Food intake was followed three times weekly by measuring the amount given and subtracting the amount left in cages (with corrections for moisture differences). Kilocalories of food consumed were then calculated from amount and caloric value of the diet(Table 2). Body weight was monitored three times per week.

Blood Pressure Measurements

Blood pressure(BP) was measured weekly in conscious animals using a photoelectric sensor and tail cuff sphygmomanometer(Bunag & Butterfield, 1982). This method is preferred over direct measurements of BP (via indwelling arterial catheter) for this chronic feeding type of investigation. Rats were acclimated to the restraining apparatus used for BP measurement for two weeks during which they were fed a stock diet. After the acclimation period, experimental diet feeding was initiated and weekly blood pressures for each rat were recorded between 0800 and 1200 hours. An equal number of rats from each group were taken for BP measurement each time to keep exercise and any other factors as constant as possible. A single, weekly measurement was the average of four to five successive inflation-deflation cycles.

Measurement of sympatho-adrenal activity

Urine was collected approximately 7 weeks after diet initiation. Rats were acclimated to metabolic cages for 36 hours prior to a 3 day collection period. Samples were collected every 24 hours in the presence of 4.5 mls of 3M HCl and pH adjusted to approx. 2.5 to deter catecholamine degradation. One ml aliquots where taken, prior to pH adjustment, for Na+/K+ analysis. For each animal three 24 hour samples were combined, diluted and stored at -15 C. Catecholamines were purified using cation exchange resin(Bio-Rex 70, 100-200 mesh: Bio-Rad Laboratories, Richmond, CA) and concentrated using alumina-oxide (Bioanalytical Syatems, W. Lafayette, IN). Immediate analysis followed by reverse phase column high pressure liquid chromatography (Bio-Sil, ODS-5S, 250x4mm: Bio-Rad) and electrochemical detection (LC-4A: Bioanalytical stems). Results were an average of duplicate sampling.

Biochemical and Physical Analysis

At the conclusion of the 10 week diet feedings rats were sacrificed following a 5 hour fast. Blood was collected during decapitation for glucose and insulin analysis by the glucose oxidase method(Beckman glucose analyzer) and RIA(Incstar, Stillwater, MN), respectively. The heart, liver and 5 fat pads (gonadal, retroperitoneal, inguinal, axillary and a single interscapular) were dissected and weighed to the nearest 0.0001 gram. Comparisons of right and left pads were used to assess the reproducibility of the dissection process.

Carcasses were autoclaved at 100° C for 2 hours and homogenized with the addition of water (Polytron, Brinkman Instruments, Westbury, NY). Homogenates were dried and 1 gram samples analyzed using an adiabatic calorimeter(Parr Instruments, Moline, IL). Total body energy was calculated from averaged values of repeated calorimetry trials of each rat homogenate. Fecal energy losses were also calculated from adiabatic calorimetry of a 48 hour fecal sample collected during week 7 of the experiment.

Statistical Analysis

Independent variables include diet offered, and gender. The experiment followed a mixed factorial ANOVA design. Data were statistically analyzed by two-way ANOVA(p=.05). A posteriori tests were conducted using the Student Neuman-Keuls procedure.

RESULTS

Energy intake, body weight and energy density

High-fat versus Control Feeding

Total energy intake in the female high-fat diet group exhibited no significant difference compared to their control group (Figure 1). Energy intake increased significantly by the sixth week in males fed the high-fat diet and continued to be higher than control fed male rats throughout weeks seven through ten. Male controls consumed 23% more kcals and were approximately 45% heavier than control females(Table 2). Body weight of the high-fat fed males at the end of 10 weeks of diet feeding was approximately 6% greater than control males, and total kcals consumed was 10% greater (Table 2). Energy density of the subjects at the end of ten weeks was higher in both males and females fed high-fat diets compared to rats of the same gender fed the control diet, (6% and 8%, respectively). Males and females fed high-fat did not significantly differ in energy density, though the total body energy was 40% greater in males than in females fed the high fat diet(Table 2).

High-fat males versus glucose feeding

Glucose fed male rats like the high-fat group consumed 10% more energy than the control group over the ten week period (Table 2). However, body weights of glucose and control males did not differ, (406.0 and 403.13, respectively). As shown previously, energy density and total energy of the carcass of glucose fed males were significantly lower than high-fat fed males and closely resembled control male values. (Figure 1)

Compared to female rats fed glucose, the female rats fed the high-fat diet had approximately 20% greater total body energy, and 10% greater energy density of the carcass, although body weights did not differ significantly (Table 2).

Glucose versus Control Feeding

Both gender groups showed no difference in total body energy or energy density between their respective glucose and control fed groups. Energy density of male rats fed glucose and control diets were both approximately 7% higher than female groups of the same diet (Table 2).

Fecal energy losses represented less than 9% of daily energy intake in all experimental groups(Table 2).

Fat Localization

Data discussed here as total percent body fat refers to the five fat depots that were dissected, which are: gonadal, inguinal, retroperitoneal, axillary and interscapular. Therefore, actual percent body adiposity is underestimated. In rats fed the same diet total fat weight(g) in the five fat pads was greater in males than in females(Table 5). However, when expressed as a percentage of body weight significant differences were evident between males and females on the same diet for all fat depot weights except retroperitoneal and axillary(Figure 2). Even though retroperitoneal depots were bigger in males, percent of the body weight that the two pads represented was not significantly different between males and females fed the same diet. Females fed high-fat diets actually had slightly greater representation of body fat by the retroperitoneal and interscapular pads than fat fed males(Figure 2). Rats fed high-fat had a greater percentage of fat than controls. The five pads contributed to a significantly lower percent body fat in glucose fed males or females compared to the fat fed counterparts (22% and 30% lower, respectively) Furthermore, glucose fed males had lower percentage of body fat in all depots except retroperitoneal and interscapular compared to high-fat fed males. No significant difference in depot weights existed between glucose fed rats and controls of the same sex. Glucose fed females had significantly lower percentage fat in the gonadal, retroperitoneal and inguinal pads than glucose fed males. Fat representing total body weight of glucose females were significantly lower than females sustained on a high-fat diet(Figure 2).

Blood Pressure Elevation

Baseline systolic blood pressures (wk 0) did not differ among all six groups of rats. After five weeks of diet feeding systolic blood pressure of high-fat males increased significantly when compared to male controls and females fed high-fat diets(Figure 1). Systolic pressures of male rats fed the high-fat diet continued to increased throughout the remaining five weeks. At the end of ten weeks the systolic pressure of the high-fat males were 15% higher than male controls, and 25% higher than high-fat females. On the other hand, blood pressures for females fed the high-fat diet remained constant and even slightly decreased along with other female diet groups during weeks seven through ten

(Figure 1).

Systolic blood pressure of glucose fed male rats was significantly greater than those fed the control diet between six and ten weeks of feedings. The elevation in BP of glucose sustained male rats lagged slightly behind the increases measured in high-fat males. At the tenth week of feeding systolic BP of glucose fed male rats was 15mm Hg higher than male control rats and 25mm Hg higher than glucose fed females. The systolic BP of females in all experimental groups were similar to that of control males throughout the ten week period.

Sympathetic Activation

Urinary norepinephrine levels collected during week seven tended to be higher in high-fat males (1377 ± 187) compared to glucose and control males (1212 ± 235 and 1201 ± 268, respectively), although these differences are not statistically significant at $p<.05$(Table 3). Norepinephrine excretion in all the females did not differ significantly and was similar to control and glucose male norepinephrine excretion(Table 3).

Electrolyte excretion

High-fat and control males demonstrated significantly greater urinary levels of sodium(Na) and potassium(K) compared to females fed the same diet(Table 3). However, average daily Na/K intake were approximately 30% greater in males fed high-fat or glucose diets compared to females fed the same diet, and 25% greater in control males compared to control females(Table 2). The difference between intake and output of sodium and potassium were estimated using concentrations of each electrolyte given in the specific diets and amount of food consumed, to correct for intake differences(Table 3).

Plasma insulin and glucose concentration

Fasting insulin levels in high-fat fed males, 1.95+0.11 ng/ml, were significantly higher than females fed high-fat, 1.38+0.6ng/ml. Control male fasting insulin levels of 1.73+ 0.14 ng/ml, is slightly lower than high-fat or glucose fed males, although this difference is not considered significant(Table 4).

Plasma insulin levels of glucose fed males were significantly higher than those of glucose fed females (1.94$\pm$ 0.17 and 1.44$\pm$ 0.24ng/ml, respectively, $P<0.05$)(Table 5).

Fasting plasma glucose levels did not differ among the six experimental groups at ten weeks(Table 3).

DISCUSSION

Obesity and macronutrient effects on hypertension

In an effort to broaden inquiry, I will propose two routes for macronutrient induction of sympathetic nerve activation in the development of dietary induced hypertension. In addition, I propose certain sex specific metabolic responses to dietary intake which allow females to resist hyperinsulinemia and hypertension.

As in previous experiments, this investigation has demonstrated that male Sprague Dawley rats exhibit hyperphagia, and subsequently become obese when fed a high-fat diet ad libitum for ten weeks. Both males sustained on fat and glucose diets consumed more energy(Figure 1). These rats develop hypertension with mean systolic blood pressure levels of 181 and 169 mm Hg, respectively. Obesity, however, was absent in the hyperphagic, hypertensive glucose sustained male rats (406g vs 403g for controls). Incomplete compensation for increased energy content of diet as well as high efficiency of dietary fat assimilation undoubtedly function to promote obesity from chronic high-fat feeding. This energy efficiency is exhibited by females fed the same high-fat diet. (Table 2). This study suggests the hypertension in male rats can develop due to the obese state or peripheral influences of the macronutrient glucose. Elevated systolic blood pressure in male rats was induced through obesity as well as some direct or indirect influence of the macronutrient glucose.

A possible scenario to account for the uncoupling of hyperphagia and obesity observed in glucose fed males is increased energy expenditure due to the highthermogenic effect of carbohydrate, discussed above. Less weight gain would result from glucose feeding if this thermogenic disparity actually occurs. A second possibility implements direct effects of glucose on sympathetic nervous activity and energy expenditure in brown adipose tissue(BAT). A shift or increase in sympathetic activity to the densely innervated brown adipose tissue(BAT)is suggested. If a shift of SNS activity originates due to glucose rather than fat feeding, more energy would be dissipated in glucose feeding leading to less weight gain. The shift in metabolic pools resulting from chronic glucose intake may function in the in shunt of SNS activity.

In contrast to males, females failed to exhibit hyperphagia in response to the palatable diets. However, females fed high-fat in this experiment demonstrated obesity through energy density of the carcass(Table 2). High feed efficiency is suggested to be functioning here to increase body fat in females, and compensation of intake of the caloric dense diet does seem to be more in-tune in these females. This indicates a sexual dimorphism in the energy balance mechanism. Additionally, an uncoupling of obesity and hypertension occurs in these females. Subsequently, no elevation of plasma insulin was observed(Table 3). There seems to be a tendency in males toward altered metabolic action of fat or glucose. The altered physiological state causing males to be hyperinsulinemic.

Insulin stimulation of the sympathetic nervous system; indications of glucose induction of a shift in sympathetic activity

The onset of hypertension in glucose fed rats lagged behind the rise in systolic blood pressure of obese males(Figure 1). This suggests fats have a greater effect or more direct route in the pathogenesis of hypertension. In this study insulin mediated sympathetic promotion of increased blood pressure is less evident in the glucose fed males. Norepinephrine excretion in high-fat males was slightly elevated although the increase was not considered significant(34). In contrast to previous findings norepinephrine excretion in glucose rats were unaffected(34).

Elevation of insulin in males fed glucose like males fed high-fat were slightly elevated, although not considered significantly higher than compared to controls(Table 3). However, male and female fed controls failed to exhibit differences in insulin levels while levels were significantly higher in males compared to females fed high-fat or glucose. With this in mind, it would seem that both glucose and fat postingestively induce insulin secretion as a consequence of increased circulating metabolic fuels or endocrine facilitation.

The non-significance of the elevation in insulin levels may be due to a limitation in the method of taking one sample, rather than measurements of glucose and insulin throughout a 24 hour period via indwelling catheterization. I suspect insulin resistance in high-fat fed and glucose males would intensify if feeding was continued. The peripheral state of hyperinsulinemia, I propose is functioning to stimulate sympatho-adrenal norepinephrine release. Obesity compounds the peripheral pressor effects primarily by promoting the insulin receptor down regulation/ insulin release cycle of insulin resistance. Males fed glucose do not exhibit the protective uncoupling of dietary intake and increased blood pressure mechanism of females. Direct or indirect effect through insulin may function in glucose induced hypertension. Furthermore, a redistribution of SNS activity, selectively stimulating the heart, blood vessels and kidney may be caused by glucose effects and lead to hypertension in spite of reduced overall norepinephrine excretion measured(Table 3).

Whether hyperinsulinemia precedes obesity is unclear. Obesity is necessary to induce the hypertensive response in males, but not require in glucose induced hypertension. It seems that increased anabolism of fat and increased circulating insulin function synergistically, allowing a greater divergence of blood pressure from controls. Furthermore, the sensitivity of the body to increased caloric intake and this positive feedback cycle seems gender related(Figure 4). Females seem able to compensate energy intake for energy dense diets as well as uncouple the insulin resistant effects of glucose or high-fat feeding.

This investigation supports evidence of an overall correlation between hyperphagia and hyperinsulinemia. Correlation of insulin and systolic blood pressure is relevant, and stronger than norepinephrine, systolic blood pressure correlation,p=.38 and .33, respectively(Figure 3& 4). It should be recalled that specific organ norepinephrine turnover is not accurately measured by urinary means. Failure to measure increased norepinephrine excretion in glucose stimulated hypertensive rats above controls may be due a limitation the technique used to assess SNS activity. Urinary catecholamine excretion is a final end pathway to central and peripheral(including adrenal medullary)sympathetic activity. If glucose induced hypertension is mediated through increased sympathetic turnover in a specific effector organ, this would explain the absence of increased norepinephrine excretion. In the case of high percent glucose ingestion, norepinephrine turnover would give a better indication of specific organ sympathetic activation. These measurements would elucidate the possibility of a shift in sympathetic activation to organs involved in response to glucose intake. Additionally, at seven weeks of experimental feeding sympatho-adrenal activity proposed in the high-fat inducement of hypertension may not be at peak function. Therefore, underestimation of sympathetic activity in correlation to the blood pressure response observed.

High-fat induction of central and peripheral activation

The results of this experiment supports the theory that insulin is the link between diet and the pathological state of high blood pressure, either through direct effects on peripheral organs or indirectly through stimulation of the sympatho-adrenal system.

Dietary fat may have a two fold effect on SNS activity by inducing central sympathetic outflow and peripheral sympathetic activity. A mechanism that is suggested involves differences in peripheral utilization of fats and glucose and the stimulation of SNS outflow by the aforementioned insulin-glucose model of central control. It is recalled that diets greater than 30% fat prevent the assimilation of carbohydrate to fat, since ingested fat conversion to adipose is energetically favored. It can be assumed this excess of fat is the physiological state of males sustained on high-fat in this study(Table 1). The carbohydrate that is ingested along with fat is subsequently free to be utilized at the ventromedial hypothalamus to increase SNS outflow, rather than used for energy peripherally. The increase in central outflow through insulin-mediated glucose oxidation(discussed above) augments peripheral sympathetic activity. Overall, the diet induced hyperinsulinemia state and central SNS activation result in an additive hypertensive effect of increased cardiac output, vaso- and veno constriction and renal sodium retention.

Female resistance to hyperinsulinemic effects

The maintenance of female blood pressure below 150 mm Hg, despite increased body fat, shows a gender specific protection to the high-fat and glucose hyperinsulinemic effects. Females fed high-fat diets in this experiment demonstrated obesity, increased energy density of the carcass, without increased insulin levels. This maintenance of insulin sensitivity suggests that the protective mechanism involves a shielding to insulin resistance and insulin stimulated SNS activity. Overall, it seems females do not change insulin sensitivity in response to increased obesity. Gonadal hormones undoubtedly play a role indirectly and/ or directly on these physiological parameters. Sex hormone influence may increase insulin sensitivity of tissues in females, allowing insulin elevation to be avoided. Norepinephrine levels in females feed high-fat or glucose diets did have slightly elevated norepinephrine compared to controls, although the difference was not significant.(Table 3). This may be due to the aforementioned central stimulation of the SNS by high-fat ingestion.

Elevated epinephrine levels of high-fat and glucose females compared to males fed the same diet indicates a possible antihypertensive ability of this catecholamine in females. In contrast to the ability of norepinephrine to induce pressor effects this study suggest epinephrine is especially active(Table 2). The elevation in epinephrine could be a consequence of an increased ratio of β to α-adrenergic receptors in peripheral organs. Antihypertensive effects by the action of β-adrenergic stimulation may be functioning in the gender protection from increased blood pressure, specifically gonadal effects on α : β receptor ratio or affinity for catecholamines. The sympathetic stimulatory actions of progesterone or inhibitory actions of estrogen would be a reasonable start point for further investigation. Overall, a balance between the anabolic effects of insulin and lipolytic effects of epinephrine may function in the uncoupling of dietary induced hypertension in females. Determination of epinephrine correlation to sex hormones would clarify the function of epinephrine in promoting or protecting the body from pressor effects.

Indications of catecholamine and gonadal effects on fat topography

Protection from the effects of obesity gives indication of sex specific disparities in macronutrient sensitivity and handling. Location of fat accretion in the female may be a contributing factor to the inability to induce hyperinsulinemia and obesity. The retroperitoneal and interscapular areas seem to be a preferential area for fat deposition in females (Figure 2). The correlation of epinephrine levels and retroperitoneal fat weight is especially strong in females, $p=.60$(Figure 5). Males seem prone to accumulation in the gonadal, inguinal and axillary regions. Estrogen and progesterone effects of fat metabolism may allow fat topography consistent with reduced risk for insulin resistance.

It is suggest that certain anatomical areas in males the adipocytes are especially sensitive to the anabolic effects of insulin. Thus fat accumulates easily, initially in the inguinal area and sets the stage for obesity and subsequent insulin resistance. It would be interesting to measure lipogenic enzyme activity in the inguinal depots in males. Increased insulin sensitivity of adipocytes in the inguinal or gonadal area due to proximity to gonadal blood flow is a possibility.

From this investigation it seems that the insulin sensitivity in females does not change with obesity as easily as in males. Females demonstrate increased insulin sensitivity compared to males throughout studies. The female physiological status may be able to avoid the hyperphagic and hyperinsulinemic response by differential control of insulin's anabolic effect on adipose and other tissues of the body. Females may be able to preferentially reduce adipose accumulation in high risk anatomical locations without reducing sensitivity for insulin in other tissues of the body.

Gonadal and other neuroendocrine mechanisms undoubtedly participate in fat topography differences between males and females. The characterization of gonadal facilitated insulin mediated anabolism in different fat depots would delineate the particular sex disparities in the mechanisms of lipid metabolism. Studies of gonadal effects on SNS would assist in characterizing the mechanisms involved in cardiac, smooth muscle and renal stimulation.

Inguinal depot size seem to parallel body growth best, while gonadal depot accretion paralleled body lipid changes. Specifically, gonadal depot size followed carcass energy increases, therefore, this fat pad was largest in the most obese rats and was progressively smaller as body fat percentage declined(Figure 2). Inguinal pads were largest in the heaviest (total body weight) animal and declined as weight of the animal declined regardless of body lipid content. The interscapular area is the anatomical area for lipid accretion in females regardless of diet composition in comparison to males which were at least 37% heavier and had at least 30% more body fat. Notably, the percent fat in retroperitoneal and axillary pads did not differ between sexes on the same diet. This indicates, especially in high-fat fed animals, regional disparities in metabolic activity of adipose tissue.

The preference for interscapular fat accumulation in females fed high energy diets correlates with the Schemmel studies (51). The increased percent of fat in the retroperitoneal rather than gonadal areas in females sustained on fat is in disagreement with the Schemmel studies. Theses discrepancies may be due to a time factor. Rats in the Schemmel study were sustained on the experimental diets approximately six times longer than in the present study. Total fat from the five pads in this study representing 8% or less percentage of body fat(Figure 2). This is in contrast to the high percentage of body fat(30-40%) attained in the Schemmel study. This time factor may indicate a threshold response. For example, it is possible that females at a certain percent body fat will cease fat deposition in the retroperitoneal depot and increase deposition in another. Additionally, changes in deposition occur since females demonstrate a higher percentage of body fat as obesity increases. The present study also indicates females may preferentially accumulate subcutaneous or fat in another areas. This is suggested since while fat fed females were equal to males in obesity, the percentage of body fat in the five depots measured was about 1.5% less, indicating fat deposition elsewhere.

From this study it is interesting to note that energy density of the carcass parallels percentage of fat attributed to the five pads dissected. Therefore it is suggested that in Sprague-Dawley rats total weight of the retroperitoneal, gonadal, inguinal, axillary and interscapular fat pads is a good indicator of carcass obesity, although total percentage of fat will be underestimated.

Insulin, sympathetic nervous system and electrolyte handling

Insulin's effect on renal sodium and potassium handling may function to induce hypertension(17,35). Renal sympathetic innervation allows SNS stimulation and subsequent renin secretion,. Additionally the SNS can increase sodium reabsorption by direct action on renal tubules(41). Disparities in Na/K excretion may be related to differences in body weight and percentage fat or dietary intake of sodium and potassium. From estimations of daily sodium intake, adjusted for differences in daily intake and specific diet content, differences between males and female sodium excretion can be attribute to differences in intake(Table 2 & 3). Within gender groups the differences in corrected excretion amounts of the studied electrolytes are negligible. Between gender groups, however, males seem to excrete more sodium and potassium relative to females indicating gender specific differences in electrolyte handling dispite changes in blood pressure elevation(Table 3).

SUMMARY AND CONCLUSIONS

In summary the present study describes a female physiological state which protects them from diet induced hyperinsulinemia and hypertension. Gonadal influences are most likely the basis for improved insulin sensitivity demonstrated in females. High-fat or glucose feeding in females seem to have a disparate action on sympath-adrenal system stimulation with which indicate different physiological states between males and females fed these experimental diets. Preference for interscapular and retroperitoneal fat accretion in females in this study contrast the findings in other investigation. This contrast of results may be due to differences in the degree of adiposity; other studies achieved body fat percentages of 40% and above, typifying gross obesity. In this study the five measured fat pads represented no greater than 7% of the total body weight. Additionally, in Sprague-Dawley rats weights of five fat depots; retroperitoneal, inguinal, gonadal, axillary and interscapular can be considered a good indicator of adiposity. Further investigation is needed to characterize the hormonal protection of insulin sensitivity in females in one of three hormonal conditions: ovariectomy with subsequent hormone replacement, the hyperestrogenic state of pregnancy and chronic exposure to androgens. Characterization of estrogen and progesterone effects on insulin receptor action in different tissues and sympathetic action at specific tissues through studies in females will lead to an understanding of the pathogenesis of cardiovascular disease and associated diseases as well as improved treatment of these diseases in both sexes.

Conclusions:

1. Sex hormones are most likely the mediator of improved insulin sensitivity in females and intensified insulin resistance in male Sprague-Dawley rats.

2. Anatomical site of fat accretion may be a factor in the ability of females to maintain insulin sensitivity. Female hormonal environment may influence insulin affects at these anatomical sites.

3. Increased adrenal medullary secretion of epinephrine in females suggests a need for investigations in comparing adrenergic receptor ratios in specific tissues.

4. Females display a more efficient ability to balance energy intake and output which allows for obesity and a higher percentage fat to occur without increased energy intake.

5. Insulin is associated with obesity and hypertension in male rats fed high-fat diets.

6. Insulin is associated with glucose induced hypertension in male rats.

7. Two routes of diet induced hypertension may involve direct effects of macronutrients on sympatho-adrenal activating mechanisms and indirect effects through obesity.

8. The uncoupling of increased intake and obesity demonstrated in males fed glucose enriched diets indicate glucose induction of an alternate physiological process which dissipates the extra energy intake.

9. High-fat and glucose diet feeding may shift sympathetic activity to separate peripheral organs to elicit the hypertensive response.

10. Glucose diets in both males and females tend to result in a deposition of less energy in the body during chronic feeding compared to high-fat and starch fed animals

Table 1 Composition of Experimental Diets

	HIGH-FAT	GLUCOSE	CONTROL
Caloric Density (kcal/g)	6.10	4.02	4.02
Methionine	4.00	3.00	3.00
AIN-76 Vitamin Mix	13.50	10.00	10.00
AIN-76 Vitamin Mix*	47.30	35.00	35.00
Choline Chloride	2.70	2.00	2.00
Cellulose	57.50	50.00	50.00
Casein**	317.00	210.00	224.00
Corn Starch	151.00	0.00	625.00
Glucose	0.00	642.00	0.00
Corn Oil	73.00	48.00	51.00
Lard	423.00	0.00	0.00
Protein (% of energy)	21.50	21.50	21.50
Carbohydrate (% of energy)	12.00	66.40	66.50
Fat (% of energy)	66.50	12.10	12.00

*Values for nutrients are g/kg. *Because of the differences in caloric density and anticipated food intake, high-fat diet contains 3.02mg NaCl and 6.09mg elemental calcium/g, while glucose and control diets contain 2.85mg NaCl and 5.20mg elemental calcium/g. **Vitamin Free Casein, ICN Nutritional Biochemicals, Cleveland, OH*

TABLE 2. Effects of experimental diets on food consumption, body weight and carcass energy, and fecal energy loss.

MALE				FEMALE		
HIGH-FAT	**GLUCOSE**	**CONTROL**		**HIGH-FAT**	**GLUCOSE**	**CONTROL**
*^ 6424.00 ± 95	*^ 6486.00 ± 126	* 5814.00 ± 142	**Total intake (kcals)**	4455.00 ± 105	4343.00 ± 95	4294.00 ± 95
52.70	56.90	50.50	**NaCl Intake (mg /day)**	36.60	38.10	37.50
*^+ 431.00 ± 6	* 406.00 ± 13	* 403.00 ± 11	**Body Weight(g)**	256.00 ± 4	239.00 ± 5	243.00 ± 6
*^+ 891.00 ± 24	* 784.00 ± 27	* 762.00 ± 25	**Total Body Energy(kcals)**	^+ 530.00 ± 21	417.00 ± 11	424.00 ± 13
^+ 6.40 ± 0.3	6.13 ± 0.3	6.04 ± 0.30	**Energy Density (kcal/g)**	^+ 6.21 ± 0.3	5.70 ± 0.2	5.60 ± 0.2
7.67 ± 0.73	6.44 ± 0.62	5.11 ± 0.23	**Fecal Energy (kcal/day)**	5.48 ± 0.49	3.64 ± 0.2	4.50 ± 0.25
8.5	7.0	6.2	**% of Daily Energy Intake**	8.7	5.9	8.1

*Values are means ± SE of measurements on eight rats in each group. Values for NaCl intake are approximations from daily food intake over the ten week feeding period and NaCl content of each diet. Value for Fecal Energy % are approximations from daily food intake averages and daily fecal energy losses. *Significant difference between males and females fed the same diet. ^Differs significantly from same sex controls. + Differs significantly from glucose fed rats of the same sex. $P<0.05$, using ANOVA with Newman-Keuls test.*

TABLE 3. Effects of experimental diets on urinary catecholamines, sodium and potassium, and fasting plasma insulin and glucose.

MALE High-fat	MALE Glucose	MALE Control		FEMALE High-fat	FEMALE Glucose	FEMALE Control
1377 ± 66	1215 ± 89	1201 ± 95	NE(ng/day)	1219 ± 61	1198 ± 75	1133 ± 61
186 ± 9	153 ± 17	166 ± 20	E(ng/day)	*^+ 269 ± 13	* 189 ± 16	197 ± 35
* 1.95 ± 0.11	* 1.94 ± 0.17	1.73 ± 0.14	**Insulin** (ng/ml)	1.38 ± 0.06	1.44 ± 0.14	1.46 ± 0.09
133.90 ± 3.70	133.10 ± 0.80	129.40 ± 2.50	**Glucose** (mg/dl)	135.10 ± 2.80	137.90 ± 2.40	132.80 ± 3.20
* 0.41 ± 0.16	0.37 ± 0.04	* 0.38 ± 0.03	**Sodium** (mmol/24hr)	0.30 ± 0.02	0.32 ± 0.0	0.27 ± 0.03
0.46	0.57	0.45	#(mmol/dl)	0.30	0.32	0.38
*^+ 0.81 ± 0.02	0.68 ± 0.06	* 0.66 ± 0.05	**Potassium** (mmol/24hr)	0.55 ± 0.04	0.57 ± 0.04	0.49 ± 0.04
0.98	1.27	1.07	#(mmol/dl)	0.70	0.76	0.85

Values are means ± SEM of measurements on eight animals in each group. * Denotes significant differences between males and females fed the same diet. ^ Differs significantly from same sex controls. + Differs significantly from same sex glucose fed. P< .05, using ANOVA with Newman-Keuls test. Norepinephrine(NE), epinephrine(E), sodium and potassium measurements are from urine, insulin and glucose from plasma. # Values are estimated excreted concentrations based on different intake amounts.

TABLE 4. Percent differences in weights of right and left retroperitoneal, gonadal, inguinal, and axillary fat pads from the same animal.

	High-fat	Glucose	Control	
Retroperitoneal	10.50 $\pm$ 0.01	6.80 $\pm$ 0.02	5.30 $\pm$ 0.02	Male
	5.60 $\pm$ 0.05	9.00 $\pm$ 0.05	8.20 $\pm$ 0.02	Female
Gonadal	6.30 $\pm$ 0.03	1.80 $\pm$ 0.30	5.10 $\pm$ 0.20	Male
	10.1 $\pm$ 0.06	7.20 $\pm$ 0.05	8.50 $\pm$ 0.05	Female
Inguinal	6.30 $\pm$ 0.06	5.00 $\pm$ 0.02	7.90 $\pm$ 0.03	Male
	8.60 $\pm$ 0.04	5.70 $\pm$ 0.04	13.40 $\pm$ 0.05	Female
Axillary	5.70 $\pm$ 0.09	18.80 $\pm$ 0.09	12.50 $\pm$ 0.06	Male
	10.40 $\pm$ 0.05	8.60 $\pm$ 0.07	15.30 $\pm$ 0.07	Female

Values are average differences expressed as percent for eight rats in each group.
Values are expressed as means $\pm$ SEM.

TABLE 5. **Effect of experimental diets on heart and liver weight and total fat weight from five body fat depots.**

MALE High-fat	MALE Glucose	MALE Control		FEMALE High-fat	FEMALE Glucose	FEMALE Control
3.04 ± 0.05	* 3.12 ± 0.11	* 3.04 ± 0.09	**LIVER**	2.95 ± 0.11	2.87 ± 0.03	2.79 ± 0.06
0.33 ± 0.01	* 0.34 ± 0.01	* 1.35 ± 0.01	**HEART**	+ 0.35 ± 0.01	0.38 ± 0.01	0.38 ± 0.01
*^+ 34.82 ± 2.25	* 25.07 ± 1.44	* 21.65 ± 1.43	**TOTAL FAT (g)**	^+ 17.60 ± 1.17	11.15 ± 0.44	9.83 ± 0.55

Values for heart and liver are % of total body weight. Total fat is measured in grams. Values are means ± SEM for eight animals in each experimental group. * Denotes significant difference between males and females fed the same diet. ^ Differs significantly from same sex controls. + Differs significantly from same sex glucose fed. $P<0.05$, by ANOVA and Newman-Keuls test.

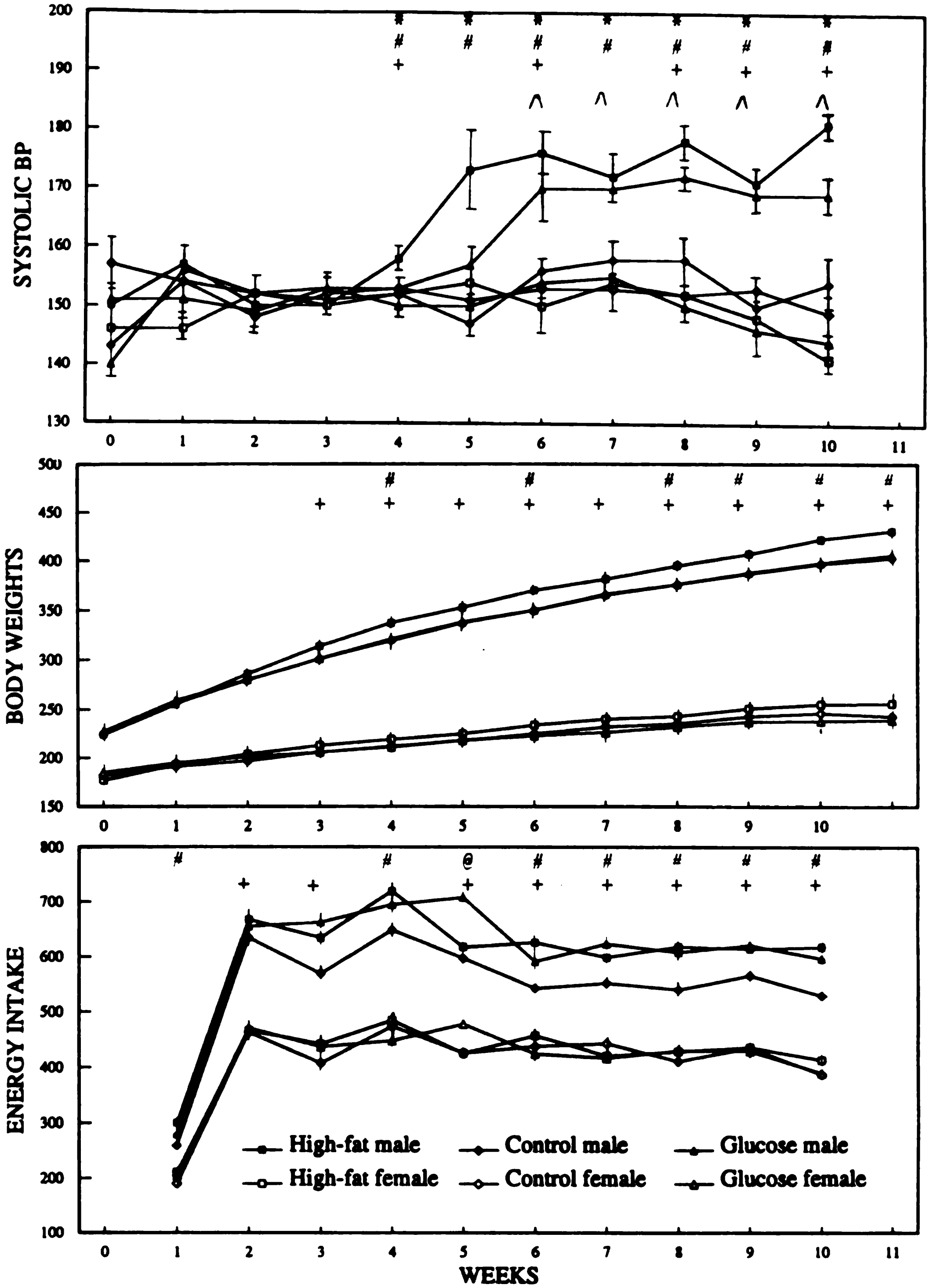

Figure 1. Effects of high-fat or glucose feeding on systolic blood pressure, body weight, and energy consumption.
Data are expressed as means±SEM for eight animals in each diet group. * Indicates significant difference between high-fat male and high-fat female, # significant difference between high-fat and control males, + significant difference between glucose and control males, ^ significant differences between glucose male and glucose female. *@ indicates significant differences between both high-fat and glucose males; significant differences between high-fat and gluocose or control females.* P< 0.05 by ANOVA with Newman-Keuls test.

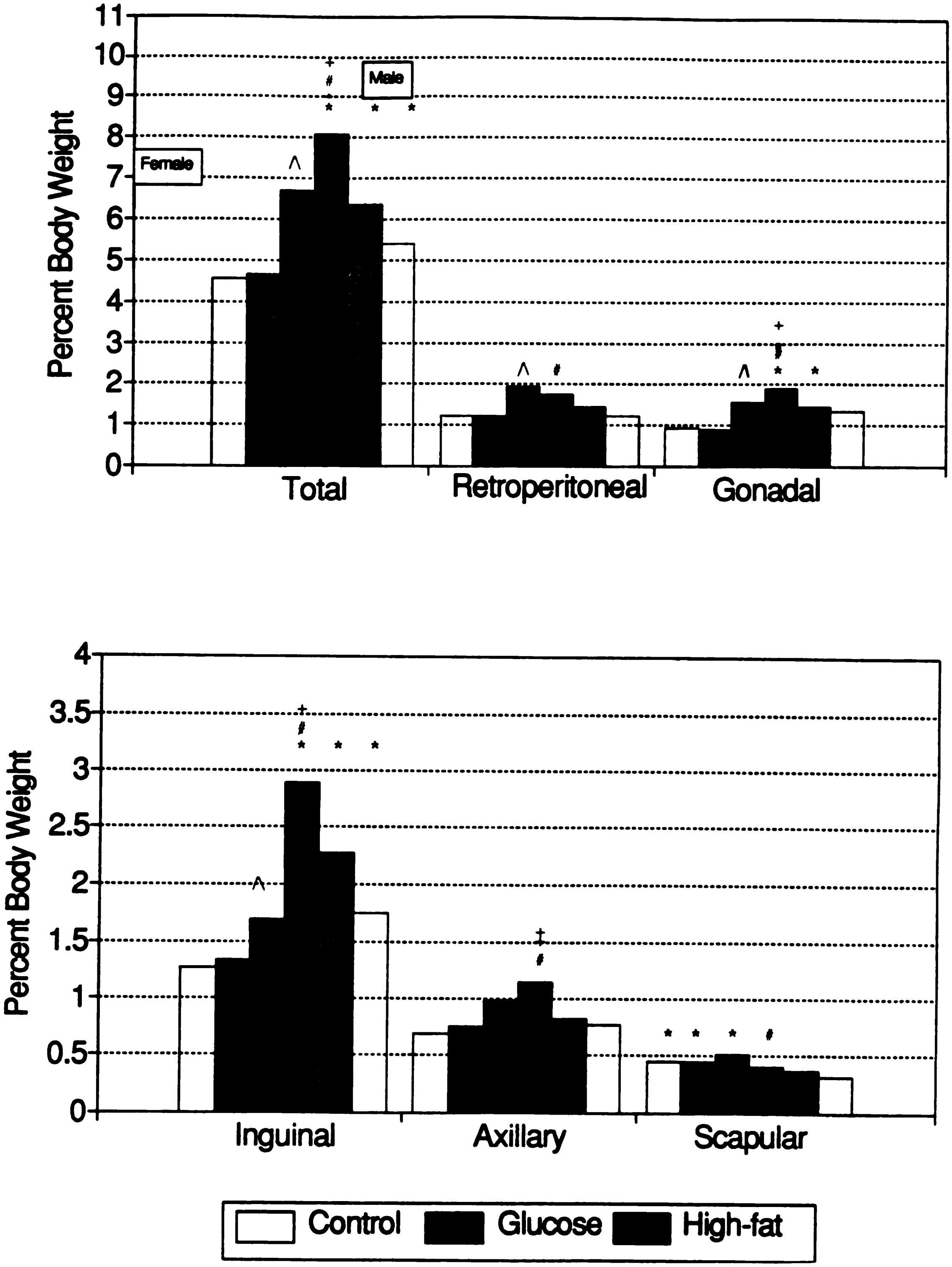

Figure 2. Effects of high-fat or glucose feeding on percentage of body fat in five regional fat depots.
Females are represented on the left half of each bar graph cluster, males represented on the right. "Total" indicates percentage fat represented by the five depots shown. * Indicates significant differences between males and females fed the same diet. # significant difference between high-fat and control males, + significant difference between high-fat and glucose males, ^ significant differences between high-fat and glucose or control females. P< 0.05 by ANOVA with Newman-Keuls test.

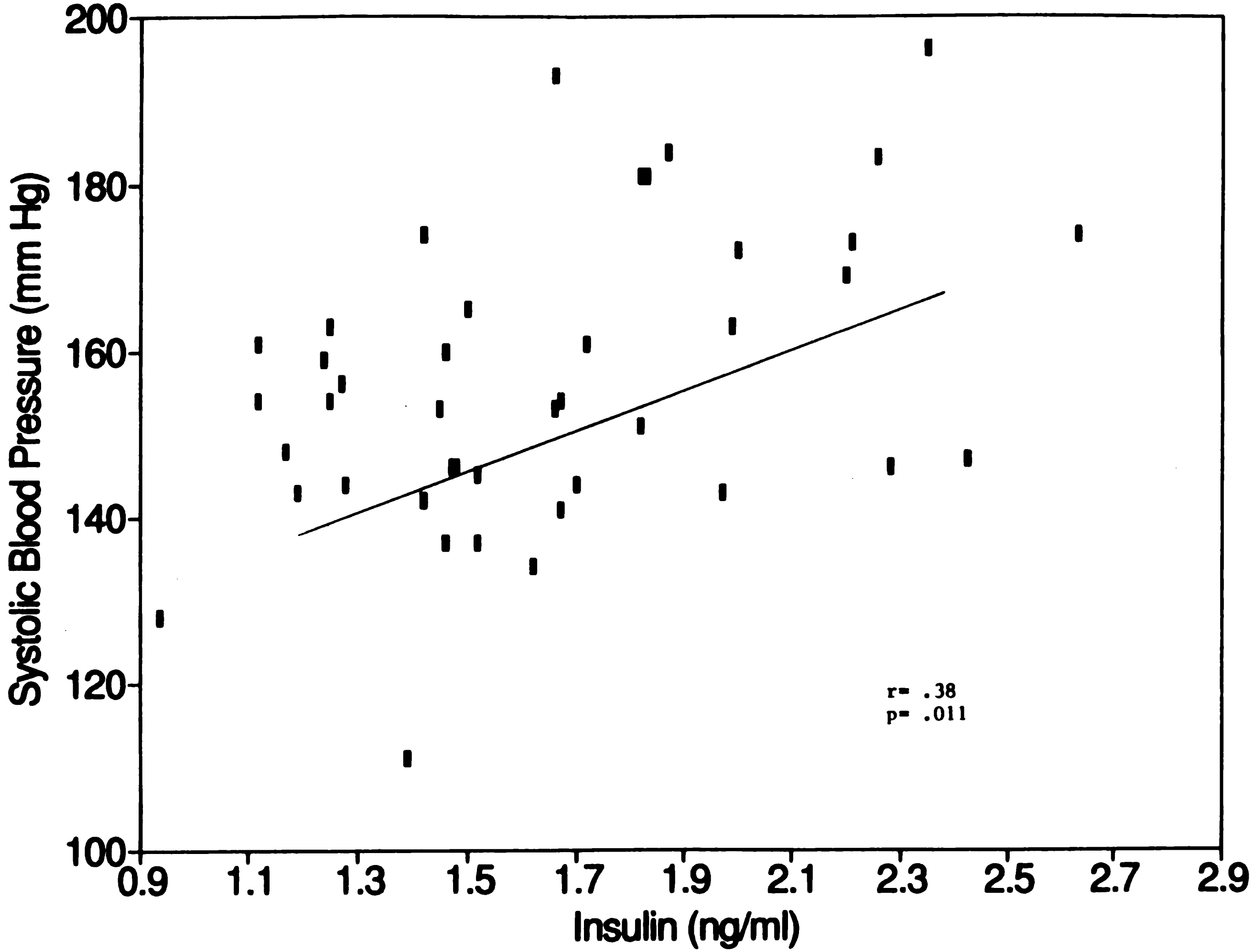

Figure 3. Relationship between fasting plasma insulin and systolic blood pressure during the tenth week of diet feeding. Squares represent values for individual rats from each of the six experimental groups.

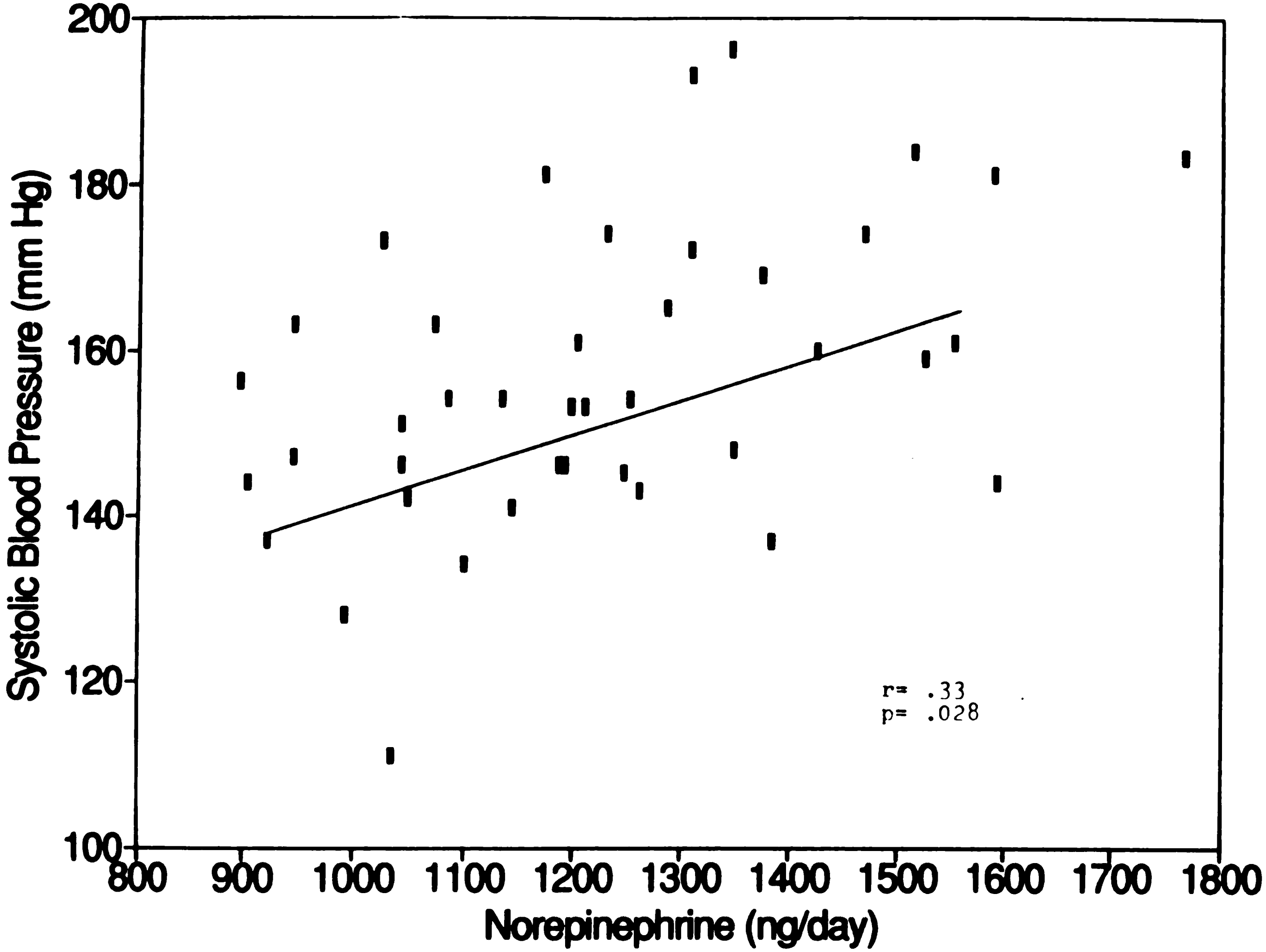

Figure 4. Relationship between norepinephrine levels and systolic blood pressure. Squares represent values for individual rats from each of the six diet groups (high-fat, glucose, starch).

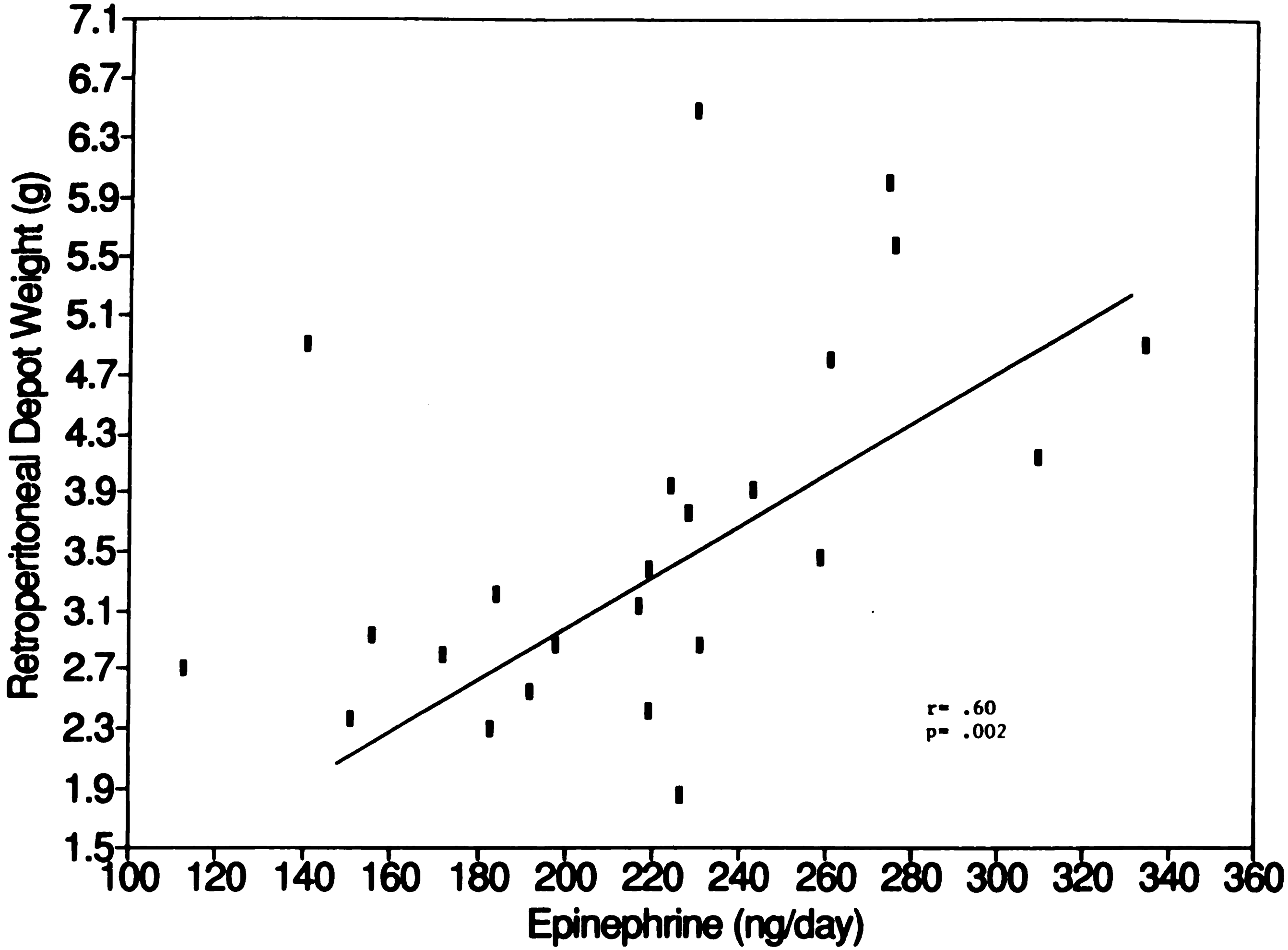

Figure 5. Relationship between epinephrine levels and retroperitoneal fat depot size in female rats. Squares represent values for individual female rats from each of the three diet groups (high-fat, glucose, starch).

BIBLIOGRAPHY

1. Anastos, K., et al. Hypertension in women: what is really known? Ann Intern Med. 115: 287-293, 1991.

2. Adler-Graschinsky, epinephrine. & Langer, SZ. Possible role of a ß adrenoreceptor in the regulation of noradrenaline release by nerve stimulation through a positive feedback mechanism. Br J Pharmacol. 53: 43-50, 1975.

3. Ashwell, M., et al. The use of the adipose tissue transplantation techniqueto demonstrate that abnormalities inthe adipose tissue of genetically obese mice are due to extrinsic rather than instrinsic factors. Int J Obesity. 9(1): 77-82, 1986.

4. Astrup, A., et al. Impaired glucose-induced thermogenesis in skeletal muscle in obesity. The role of insulin and the sympathoadrenal system. Int J of Obesity. 11(1): 51-66, 1987.

5. Baskin, et al. Insulin in the brain. Ann Rev Physiol. 49: 335, 1987.

6. Bell, DD., Zucker, I. Sex differences in body weight and eating: Organization and activation by gonadal hormones in the rat. Physiol. Behav. 7: 27-34, 1971.

7. Bereck, KH. & Brody, MJ. Evidence for neurotransmitter role of epinephrine derived from the adrenal medulla. Am J Physiol. 242: H593-601, 1982.

8. Beran, RD. Trophic effects of peripheral adrenergic nerves on vascular structure. Hypertension. 6(suppl. III): 9-26, 1984.

9. Bjorntorp, P. Classification of obese patients and complications related to the distribution of surplus fat. Am J Clin Nutr 45: 1120-5, 1987.

10. Bjorntorp, P. Adipose tissues in obesity. Recent advances in obesity research: IV. London, UK: John Libby, 1985: 163-70.

11. Bunag, RD., Butterfield, J. Tail-cuff blood pressure measurements without external pretreating in awake rats. Hypertension 4: 898-903, 1982.

12. Bray, GA. Hypothalamic and genetic obesity: an appraisal of the autonomic hypothesis and the endocrine hypothesis. International J. of Obesity 8(suppl.1): 119-137, 1984.

13. Brown, MJ., et al. Hypokalemia from ß-receptor stimulation by circulating epinephrine. N Engl J Med. 309: 1414-19, 1983.

14. Brown, MJ., et al. Urinary catecholamines in essential hypertension: results of 24-hour urine catecholamine analyses from patients in the Medical Research Council Trial for Mild Hypertension and from matched controls. Quart J Med. 57: 637-51, 1985.

15. Castelli, WP., Epidemiology of coronary heart disease: the Framington study. Am J Med. 76(2A): 4-12, 1984.

16. Danforth, E., Jr. Diet and obesity. Am J Clin Nutr. 41: 1132-45, 1985.

17. Defronzo, RA., et al. The effect of insulin on renal handling of sodium, potassium, calcium and phosphate in man. J Clin Invest. 55: 845-55, 1975.

18. Eldon, SD. et al. Divergent correlations of circulating dehydroepiandrosterone sulfate and testosterone with insulin levels and insulin receptor binding. J Clin Endocrinol Metab. 66(6): 1329-1331, 1988.

19. Evans, JE, et al. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab 57: 304-309, 1983.

20. Hennes, MI. et al. Synergistic effects of male sex and obesity on hepatic insulin dynamics in SHR/Mcc-cp rat. Diabetes 39: 789-95, 1990.

21. Hill, JO., et al. Nutrient balance in humans: effects of diet composition. Am J Clin Nutr. 54(1): 10-17, 1991.

22. Hwang, IS., et al. Fructose-induced insulin resistance and hypertension in rats. Hypertension 10(5): 512-16, 1987.

23. Finch, L., Hauesler, G. & Thoinen, H. Failure to induce experimental hypertension in rats after intraventricular injection of 6-hydroxydopamine. Br J Pharmacol. 44: 356-57, 1972.

24. Frankenhauser, M. Behavior and circulating catecholamines. Brain Res. 31: 241-62, 1971.

25. Foley, JE., et al. Sex differences in insulin-stimulated glucose transport in rat and human adipocytes. Am J Physiol 246: E211-25, 1984.

26. Fournier, RD., et al. Refined carbohydrate increases blood pressure and catecholamine excretion in SHR and WKY. Am J Physiol. 250: E381-385, 1986.

27. Fujioka S., et al. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 36: 54-59, 1987.

28. Goldstein, DS. Plasma catecholamines and essential hypertension. An analytical review. Hypertension 5: 86-99. 1983

29. Hennes, MMI., et al. Synergistic effects of male sex and obesity on hepatic insulin dynamics in SHR/Mcc-cp rat. Diabetes 39: 789-95, 1990.

30. Kannal, WB., et al. Obesity, lipids and glucose intolerance in the Framington study. Am J CLin Nutr. 32: 1238, 1979.

31. Kanarek RB., Hirsch epinephrine., Dietary-induced overeating in

experimental animals. Federation Proceedings 36:2, 154-57, 1977.

32. Kai-Lin CJ., et al. Sex differences in the effects of high-fat feeding on behavior and carcass composition. Physiol Behav. 27: 161-66, 1981.

33. Kakolewski JW., Cox VC., Valenstein ES. Sex differences in body-weight change following gonadectomy of rats. Psychol Reports 22:547-54, 1968.

34. Kaufman, LN., Peterson, MM., Smith, SM., Hypertension and sympathetic hyperactivity induced in rats by high-fat or glucose diets. Am J Physiol E95-99, 1991.

35. Kava RA., et al. Sexual dimorphism of hyper glycemia and glucose tolerance in wistar fatty rats. Diabetes 38: 159-163, 1989.

36. Kissebah, AH et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 54: 254-260, 1982.

37. Kriegar, DR., Landsberg, L. Neuroendocrine mechanism in obesity-related hypertension: the role of insulin and catecholamines. Endocrine Mechanisms in Hypertension. Laragh, JH., Brenner, BM., Kaplan, NM.(eds). Raven Press, New York. V.2:105-123, 1989.

38. Krotkiewski, M. et al. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 72: 1150-62, 1983.

39. Landau et al. Binding of insulin by monkey and pig hypothalamus. Diabetes 32: 284, 1983.

40. Landsberg, L. Diet, obesity and hypertension: An hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Quart J Med. 61(236): 1081-1090, 1986.

41. Landsberg L., Insulin and hypertension: Lessons from obesity. N Engl J Med 317: 378-9, 1987.

42. Landsberg L., & Young, JB. Catecholamines and the adrenal medulla. Williams Textbook of Endocrinology. Wilson, JD. and Foster DW(eds), Philadelphia: WB Saunders Co. p662, 1992.

43. Li, HY. The effects of the adrenal medulla on the development of diet-induced hypertension. Thesis for the degree of masters of science. Michigan State University, 1990.

44. McDonald RB., et al. Effect of gender on the response to a high fat diet in aging fisher 344 rats. J Nutr 119: 1472-77, 1989.

45. Newby DF., et al. Model of spontaneous obesity in aging male wistar rats. Am Physiol Soc R1117-25, 1990.

46. Nisimaru, N. et al. Comparison of gastric and renal nerve activity. Am J Physiol. 220: 1303-1308, 1987

47. Olefsky, JM., MD. Insulin action and insulin resistance in non-insulin dependent diabetes mellitus. Recent Advances in Insulin Action and its Disorders. Elsevier Science BV., 1991.

48. Peiris, AN., et al. Splanchnic insulin metabolism in obesity. Influence of body fat distribution. J Clin Invest 78: 1648-57, 1986.

49. Reed, DR., et al. Enhanced acceptance and metabolism of fats by rats fed a high-fat diet. Am J Physiol. 261(5pt2):R1084-1088, 1991.

50. Rowe, JW., et al. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 30: 219-224, 1981.

51. Schemmel, R., Mickelsen, O., Mostosky, U. Influence of body weight, age, diet and sex of fat depots in rats. Anat Rec 166: 437-46, 1970

52. Scheurink, AJW., et al. Adrenal and sympathetic catecholamines in exercising rats. Am J Physiol. 256: R155-160, 1989

53. Schwartz, JH., et al. Effect of dietary fat on sympathetic nervous system activity in normal man. J CLin Invest. 72: 361-370, 1983.

54. Sclafani, A. Dietary Obesity. Recent Advances in Obesity Research:II. Proceedings of the 2nd International Congress on Obesity, 123-32, 1977.

55. Schmidt, HW., et al. Local modulation of noradrenaline release in vivo. Presynaptic ß-adrenoceptors and endogenous adrenaline. J Cardiovasc Pharmacol. 6: 641-649, 1984.

56. Shoup, RE., et al. LCEC: A powerful tool for biomedical problem solving. American Laboratory, 1981.

57. Terry, RB., et al. Contributions of regional adipose tissue depots to plasma lipoprotein concentrations in overweight men and women: possible protective effects of thigh fat. Metabolism. 40(7): 733-40, 1991.

58. Wade, GN., Gray, JM. Gonadal effects on food intake and adiposity: A metabolic hypothesis. Physiol Behav 22: 583-93, 1979.

59. Woods, et al. Insulin: its relation to the control of food intake and body weight. Am J Clin Nutr. 42: 1063, 1985.

60. Zuspan, FP. & O'Shaughnessy, R. The uteroplacental bed: its anatomic and neuroendocrine alterations. Endocrine Mechanisms in Hypertension. Laragh, JH., Brenner, BM., Kaplan, NM.(eds). Raven Press, New York. V.2:105-123, 1989.