Autonomic nervous system activity in weight gain and weight loss

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Aronne, Louis J., Ronald Mackintosh, Michael Rosenbaum, Rudolph L. Leibel, and Jules Hirsch. Autonomic nervous system activity in weight gain and weight loss. *Am. J. Physiol.* 269 (*Regulatory Integrative Comp. Physiol.* 38): R222–R225, 1995.—Studies in both animals and humans indicate that the autonomic nervous system (ANS) responds to changes in systemic energy balance. In the present study, ANS response to weight change was examined by sequential blockade of cardiac autonomic innervation with parasympathetic (atropine) and sympathetic (esmolol) blockers. Change in heart period (interbeat interval) from baseline after atropine defined the amount of parasympathetic control (PC), and the subsequent change after esmolol defined the amount of sympathetic control (SC). In nonobese subjects, weight gain to 10% above initial body weight resulted in a decrease in PC and an increase in SC, and conversely, weight loss to 10% below initial weight resulted in an increase in PC and a decrease in SC. In obese subjects, weight loss resulted in the same pattern of changes in PC and SC. The major changes were in the parasympathetic arm of the ANS. These findings support the hypothesis that the ANS acts to oppose weight change.

parasympathetic activity; sympathetic activity; obesity; energy metabolism

DESPITE WIDE FLUCTUATIONS in physical activity and caloric intake, body weight remains remarkably stable over time in animals and humans. In humans, changes in body weight of more than 1% per year are unusual, and in most cases are related to exogenous factors, such as voluntary changes in diet, illness, stress, or medications. An integrated regulatory system, which maintains constant energy storage by coupling energy expenditure and food intake has been proposed, and it has been suggested that the autonomic nervous system may be central in coordination of this system (2). Experimental observations support this point of view. A decrease in calorie intake can produce a prompt decline in sympathetic autonomic activity despite an increase in sympathoadrenal activity (8, 9). In studies using cardiac catecholamine turnover rates, animals overeating a palatable diet show evidence of increased sympathetic activity, the result of which might be mitigation of further weight gain (9). Changes in parasympathetic nervous system tone have been implicated in the obesity of the Zucker rat (4) and the ventromedial hypothalamus-lesioned rat (2).

To examine the response of the autonomic nervous system to overfeeding and underfeeding in humans, we have investigated the utility of heart rate variability as a measure of autonomic activity (3). The role of the parasympathetic nervous system in human energy metabolism has been difficult to determine because no direct measurement of parasympathetic activity exists in humans at the present time, a result of the fact that the parasympatheic system is completely neuronally based and has no humoral factors on which measurements could be made. Animal studies have depended on invasive techniques such as counting the rate of firing of the vagus nerve, which cannot be done easily in humans. Spectral and power analysis of heart rate variability, the second-to-second variation in heart rate, has been assessed since it was described in 1981 as an indirect measure of autonomic activity (1). Our early work demonstrated that heart rate increased during a 10% weight gain and was accompanied by a significant decrease in heart rate variability attributable to a decline in parasympathetic power. Following a 10% weight loss, heart rate decreased, but the heart rate variability did not change significantly. The intrasubject and intersubject variability of the spectral analysis techniques used is high, however, and the present study was undertaken to confirm these findings by utilizing a more direct pharmacological approach.

The RR-interval, or interbeat interval of heart rate, is determined by the net effect of sympathetic and parasympathetic inputs. It has been shown in animal studies that vagal firing rate is linearly proportional to measures of parasympathetic control such as RR-interval (5). Thus the cardiac sympathetic and parasympathetic effects can be dissected out pharmacologically by first blocking the parasympathetic influence with atropine or other muscarinic blocker. The sympathetic input can then be blocked using a relatively cardiospecific β-blocker such as the short-acting drug esmolol. The heart rate that results after both drugs are given is considered to be the intrinsic heart rate; i.e., the heart rate without parasympathetic nervous system (PNS) or sympathetic nervous system (SNS) input. Thus vagal firing rate or "tone" can be estimated by measuring RR-interval before and after the administration of atropine. Similarly, SNS tone can be estimated by measuring RR-interval before and after administration of esmolol.

In the present study, we used sequential parenteral administration of atropine and esmolol to assess PNS and SNS in lean and obese subjects before and during experimental weight perturbation. Our results corroborate our previous findings by spectral analysis with regard to the parasympathetic system and extend our work into the sympathetic domain.

METHODS

Adult subjects were studied while hospitalized at the Clinical Research Center at the Rockefeller University Hospital as part of a larger investigation to determine the metabolic effects of weight loss and weight gain on energy metabolism. *Group 1* comprised seven individuals (6 male, 1 female) of normal body weight who were studied at usual body weight, during but close to the end of a 10% weight gain, and during maintenance of that increased body weight. *Group 2* comprised nine individuals (6 male, 3 female) of normal weight who were studied at usual body weight, during but close to the end of a 10% weight loss, and during maintenance of that decreased body weight (Table 1). Other details of the protocol have been described in an earlier publication (3). Figure 1 is a scheme summarizing the weight changes of the subjects. In brief, patients randomized to weight gain had studies performed first at usual baseline weight, then during a dynamic phase of weight gain, and finally, at a 10% weight gain plateau. Patients randomized to weight loss were similarly studied at baseline weight, during weight loss on an 800 calorie per day formula diet, and finally at the 10% weight loss plateau. Studies performed during weight plateaus were done after the patient had been on an isocaloric (weight maintaining) diet for at least 2 wk. If 100% represents the mean weight of a group of subjects at baseline weight, then the mean weights of the subjects studied at the respective plateaus are as follows: 10% weight gain plateau = 110.3 ± 0.6% (SE) and 10% weight loss plateau = 89.6 ± 0.4%. Weight gain was achieved by feeding a wide assortment of solid foods to promote rapid weight gain. But, during all periods of weight loss and during isocaloric weight maintenance plateaus, a fluid formula made in the Rockefeller University Diet Kitchen was used as the sole source of calories. The formula contained 40% of calories as corn oil, 45% carbohydrate as a mixture of cerelose and polycose, and the remaining 15% as milk protein; caloric density was 1.25 kcal/g formula. Water and noncaloric beverages without caffeine were available ad libitum. During weight loss, 800 calories per day of formula were used. In addition, vitamin and mineral supplements, as well as 5 g iodized sodium chloride, were given daily. During weight maintenance, the precise amount of formula required to maintain body weight was given.

Group 3 consisted of 7 obese outpatients (4 male, 3 female) losing weight with the use of an 800 calorie per day commercial diet (Optifast 800, Sandoz Nutrition, St. Louis Park, MN). These patients were studied as outpatients at baseline weight while on their usual diet and during the dynamic phase of weight loss (weight loss on an 800 calorie per day formula diet), at which time their low-salt formula diet was supplemented with 5 g sodium chloride per day. At the point the study was performed, the mean of their weights was 86.0% ± 1.5 of baseline weight.

All subjects were screened to ensure they had no cardiovascular diseases, including hypertension, central nervous system diseases, glaucoma, used no medications, and had no contraindications to the use of atropine or esmolol.

Table 1. *Demographic information*

	Group		
	1 (Lean Weight Gain)	*2* (Lean Weight Loss)	*3* (Obese Weight Loss)
N	7	9	7
Sex	6 M/1 F	6 M/3 F	4 M/3 F
Age, yr	29 ± 6.3	26 ± 6.4	30.9 ± 7.1
$Wt_{initial}$, kg	68 ± 9.5	75 ± 14.3	116.2 ± 26.8
BMI, kg/m^2	21.9 ± 2.9	24.7 ± 2.8	40.1 ± 7.7

Values are means ± SD. M, male; F, female; $Wt_{initial}$, baseline weight; BMI, body mass index [wt in kg/(height in m)^2].

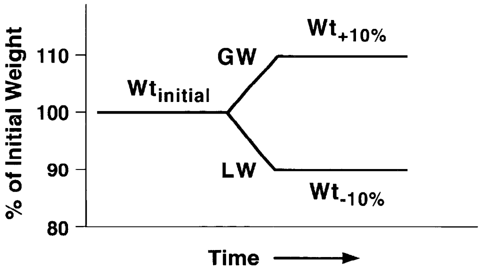

Fig. 1. Schematic representation of weight changes of the subjects. $Wt_{initial}$, baseline weight; $Wt_{+10\%}$, 10% weight gain plateau; $Wt_{-10\%}$, 10% weight loss plateau; GW, dynamic phase of weight gain; LW, weight loss on an 800 calorie per day formula diet.

Procedure. In the case of the inpatient subjects, studies were performed after at least 1 wk of weight stability, except during the dynamic phases of weight change. For the obese outpatients undergoing weight loss, studies were performed at baseline and during the dynamic phase of weight loss. Following an overnight fast, the subjects were studied between 8:30 A.M. and 10:00 A.M. in an air-conditioned room reserved specifically for the purpose. Subjects who were smokers were requested not to smoke on the day of their procedure. With the patient in the recumbent position, lightly clad, and breathing quietly, standard electrocardiogram (ECG) leads were placed on the thorax at approximately the sixth intercostal space. A peripheral IV line was established, delivering 0.9% saline at 1 ml/min. A heart rate monitor (PRM monitor, Novatec, Lancaster, PA) was placed on the subject's right index finger. The ECG was continuously monitored on an oscilloscope screen, and heart rate was monitored with the heart rate monitor. When the patient's minute-to-minute change in heart rate had stabilized, two 256-s samples of the ECG were taken and designated as the baseline recordings. Next, 3 mg of atropine sulfate divided into three 1-mg doses was administered intravenously over 5 min. Heart rate increased, and when a new heart rate plateau was visually observed, the 256-s ECG recording was performed, usually within 3 min of the completion of the infusion. Upon completion of the recording, esmolol (2.5 g diluted with normal saline to a total of 50 ml) was administered at 60 drops/min until a heart rate plateau was visually observed, usually within 3 min, and the 256-s sympathetic recording was performed. Figure 2 shows data from a typical study.

Data acquisition and analysis. ECG signals from the patient were monitored by means of a Healthdyne Infant Monitor (model 16000; Healthdyne, Marietta, GA). The ECG signal was passed through an R-wave detector with an adjustable threshold level (10), which allowed the R-R interval (heart period) for each beat to be determined with 1 ms accuracy. The triggering level of the R-wave was set so that no heart beats were missed. Premature contractions were removed by linear interpolation prior to averaging. In no case was more than 2% of any 256-s sample so corrected. The average heart period for the two predrug samples constituted the baseline against which the average heart period of the postatropine sample and the average heart period of the postatropine and esmolol sample were compared, respectively.

Parasympathetic control (PC), the contribution to the heart period that is blocked by atropine, is defined as the mean RR-interval change after atropine and was calculated as the mean RR-interval before atropine minus the mean RR-interval after atropine. Likewise, sympathetic control (SC) is the contribution to the heart period blocked by esmolol and is defined as the mean RR-interval change after esmolol. It was calculated as the mean RR after esmolol and atropine minus the mean RR after atropine. Intrinsic heart period (I) is the

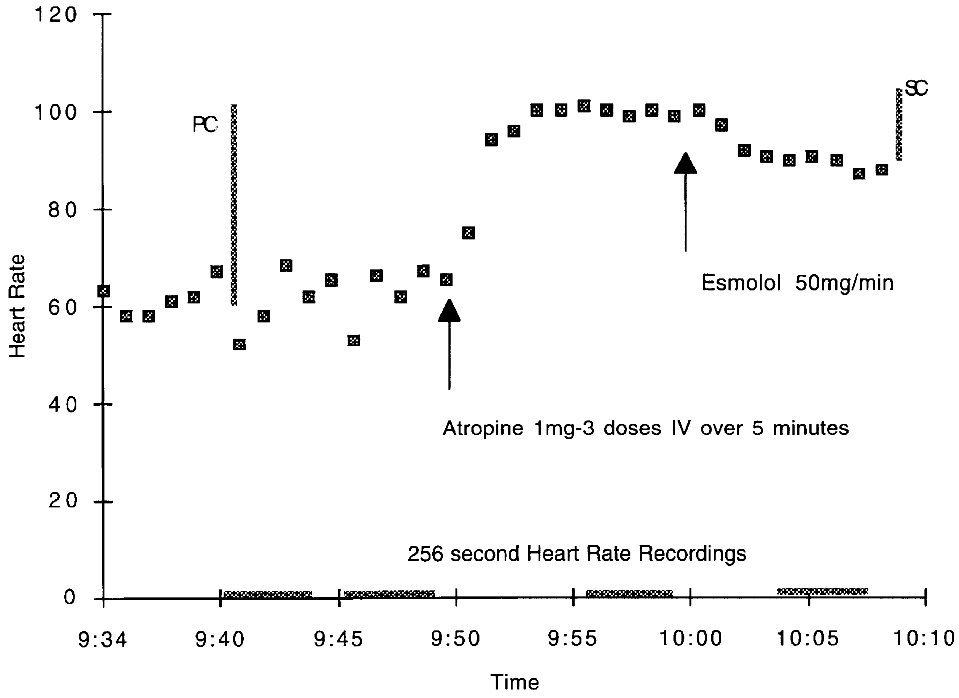

Fig. 2. Sample autonomic system drug study showing baseline heart rate and administration of atropine, resulting in an increase in heart rate to a new plateau. The difference (measured in ms when heart rate is converted to RR-intervals) is defined as parasympathetic control (PC). This is followed by administration of esmolol, which causes a drop in heart rate. The difference, in ms, between the postatropine and postesmolol plateaus is sympathetic control (SC).

mean RR-interval after atropine and esmolol have been administered. The ECG data samples were stored on-line in a dedicated IBM-AT computer. The on-line data storage and subsequent off-line data processing were performed using software written in the ASYST language (Keithly Instruments, Rochester, NY).

For the nonobese groups, statistical analysis was performed by one-way repeated measure analysis of variance followed, when the overall *F*-test was significant, by the Scheffé's post hoc pairwise comparisons. Paired *t*-tests were used for the obese group. All statistical analyses were performed with Statistica/W software (Statsoft, Tulsa, OK).

RESULTS

Figure 3 shows changes in heart period, PC, SC, and intrinsic control for the groups studied. For both the nonobese groups, the analysis of variance tests of the effects of weight status were significant ($P < 0.001$ to $P < 0.0001$) for the variables heart period, PC, and SC. In neither group was variable I significant.

In the nonobese group undergoing weight gain, heart period and PC decreased significantly in both the dynamic phase and at the 10% weight gain plateau, whereas SC increased significantly. Heart period and PC moved in the opposite direction in the nonobese undergoing 10% weight loss, increasing significantly, whereas SC decreased significantly. It is clear in Fig. 3 that the absolute PC changes were much greater than the SC changes for the nonobese subjects. Although there is the suggestion that the ANS changes are greater during the dynamic periods of weight gain and weight loss, none of the dynamic phase versus subsequent maintenance phase mean differences, for any variable, were statistically significant. Just as for the nonobese subjects during dynamic weight loss, the obese outpatients had a significant increase in heart period and PC and a significant decrease in SC during their hypocaloric weight loss.

Even though none of the intrinsic heart period changes for obese or nonobese were statistically significant, it may be noteworthy that the intrinsic heart period of nonobese subjects moved in the same direction as SC.

DISCUSSION

These findings document that changes in cardiac parasympathetic tone detected by spectral analysis during weight loss and weight gain are also found when the pharmacological dissection of heart rate variability is undertaken. Since changes in respiration frequencies that may occur during weight change can also affect heart rate variability (unpublished observations), it is reassuring to note that the changes occurring with drug blockade independently document parasympathetic alterations. In addition,the sympathetic changes that were difficult to detect by spectral analysis because of admixture of parasympathetic signals are more robust when the pharmacological dissection is used. Individuals who gain weight have a significant increase in sympathetic activity. The opposite changes occur with weight loss. These findings on sympathetic activity are consistent with the majority of catecholamine data (6) found in the literature.

The central actions of atropine sulfate can cause symptoms that are distressing to some subjects and are a potential source of bias because the distress itself can lead to alterations in autonomic outflow. Random administration of esmolol or atropine would have dealt with this bias. In our study, however, atropine was always administered first and esmolol second. This order was chosen rather than random administration of drugs because of the bradycardia that accompanies weight loss. Administering a β-blocker to a subject with a sinus bradycardia was not considered to be safe, and so a consistent, rather than random, method of administration was adopted.

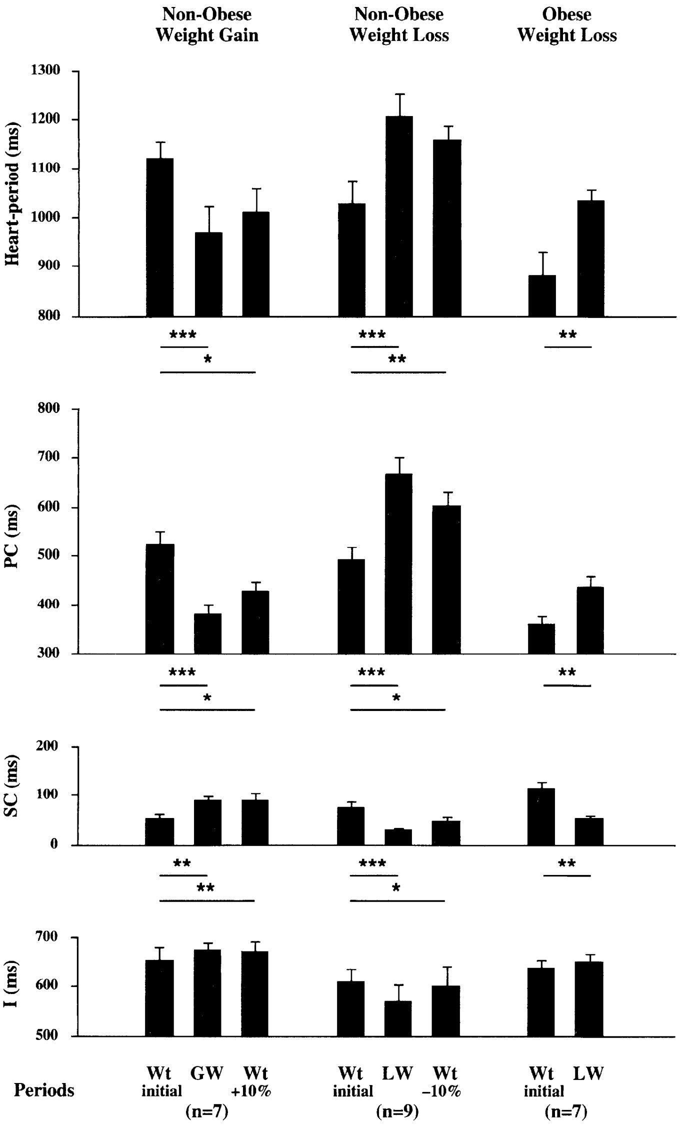

Fig. 3. Effect of changes in weight and caloric intake on heart period, PC, sympathetic control (SC), and intrinsic heart period (I). Results of post hoc statistical analyses for the nonobese subjects and paired *t*-tests for the obese subjects while undergoing dietary manipulations are as described in text. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Intrinsic heart rate changes are small and do not achieve statistical significance with alterations in weight; heart period rises with weight gain and declines with weight loss. This may reflect a response to chronic "overactivation" during weight gain and the reverse during weight loss.

The two normal groups differed in their beginning heart period and autonomic activity. This variation among groups may be the explanation for the differences found in the obese; however, the data on heart period and autonomic activity in the obese at usual body weight seem so different from the other groups that there is the suggestion that the obese may have initially had higher sympathetic and lower parasympathetic tone and consequently a shorter heart period than the nonobese. More definitive work with larger groups of obese versus nonobese will need to be done to document this finding. The dose of atropine was the same for both obese and nonobese subjects. The obese, who have higher lean body mass than the nonobese, may require larger doses of atropine and esmolol for complete pharmacological blockade of the relevant receptors. No studies of the effect of dose on a per unit of body weight or per unit of lean body mass were undertaken.

These changes in cardiac autonomic activity as a function of body weight could be important in the regulation of body weight. A coordinated change in autonomic activity with a decline in parasympathetic and an increase in sympathetic activity setting heart rate at a higher level with weight increase and the contrary changes setting heart rate at a lower level with weight decline could reflect autonomic participation in energy storage regulation as with body temperature and blood pressure. Furthermore, prolonged setting of the autonomic nervous system at a higher level in the case of weight gain may be a factor in some of the comorbidities of obesity, such as hypertension and cardiac arrhythmias. Further study is needed to define the exact status of the autonomic nervous system in obese versus normal subjects.

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