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## Overweight and familial hypertension- A comprehensive approach of negative biofeedback in human body

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### Abstract

In a general mode of observation, higher weight is associated with higher blood pressure levels; prospectively, baseline weight and weight gain predict higher blood pressure. The loss of weight is frequently associated with a decrease in blood pressure. These findings suggest that weight gain may pathophysiologically contribute to blood pressure elevation. In this review, we present data to indicate that the reverse is also true; persons of equal weight who had higher initial blood pressures gain more weight in the future. We also propose a plausible hypothesis to explain this reverse relationship. Both the blood pressure elevation and the gain of weight may reflect a primary increase in sympathetic tone. It is well known that in a milieu of increased sympathetic tone, the  $\beta$ -adrenergic responsiveness decreases. Sympathetic over activity and decreased cardiovascular  $\beta$ -adrenergic responsiveness have been described in hypertension.  $\beta$ -Adrenergic receptors mediate increases in energy expenditure. If these metabolic receptors were down regulated in hypertension, the ability of hypertensive patients to dissipate calories would decrease and they would gain more weight. The possible relationship of decreased  $\beta$ -adrenergic responsiveness to weight in hypertension can be experimentally tested. Such research may contribute to an explanation of why patients with hypertension can rarely lose weight. An understanding of this pathophysiological relationship may open new avenues for therapeutic interventions.

**Keywords:** Obesity, Hypertension, Sympathetic Nervous system, Adrenergic receptors.

### Introduction

Although overweight and weight gain are associated with hypertension, <sup>[1, 2]</sup> the reverse is also true; in some subjects destined to become hypertensive, a higher blood pressure (BP) may precede the weight gain <sup>[3]</sup>. We propose a plausible hypothesis to explain this "reverse" relationship. The gain of weight and the BP elevation may be the intermediate phenotypes of an underlying sympathetic overactivity in hypertension. Stimulation of  $\beta$ -adrenergic receptors increases the total body energy expenditure. A chronic increase in sympathetic tone causes downregulation of  $\beta$ -adrenergic receptors. A decreased cardiac, vascular, glucose, and phosphate response to  $\beta$ -agonists has been described in hypertension. If this decrease in  $\beta$ -adrenergic responsiveness were generalized to energy expenditure, the ability of hypertensive patients to dissipate excess calories may be diminished. This would inevitably lead to weight gain.

The pathophysiological relationship between the enhanced sympathetic tone and reduced calorie expenditure may explain why even when patients with hypertension are maximally motivated, they fail to sustain weight loss.

### Relationship between Overweight and Hypertension

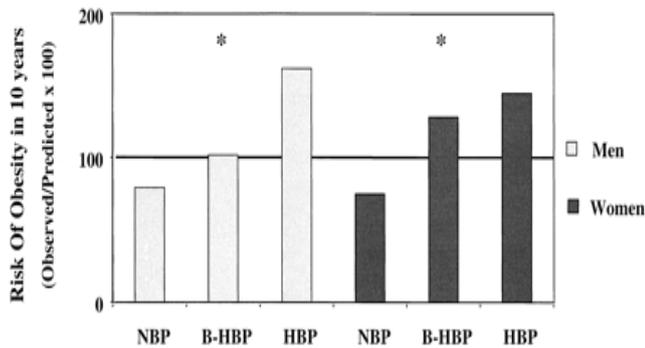
Weight loss reduces BP in hypertensive and normotensive subjects <sup>[4]</sup>, suggesting that excess weight causes higher BP. The mechanisms leading to hypertension in obese persons are not completely known. Landsberg <sup>[5]</sup> emphasized the primacy of eating behavior in the determination of obesity, insulin resistance <sup>[6]</sup>, metabolic abnormalities, and the subsequent increase in BP and suggests that obesity is linked with hypertension through the sympathoadrenal system.

This concept stems from animal studies in which food intake increases sympathetic activity and fasting decreases it [7, 8]. According to this view, the obesity-related increase in insulin in the presence of high glucose levels stimulates central sympathetic outflow [5, 7]. Leptin and its consequent action on central nervous system may also be involved [9]. Salt sensitivity also may contribute to obesity-associated hypertension, either directly or through heightened sympathetic activity [10].

Both theories acknowledge a close association between sympathetic activation and the BP elevation in overweight subjects, and both view the eating behavior as a primary factor in the sequence of events. Within this concept, the sympathetic over activity is an important mechanism that through adaptive thermogenesis [5] permits the dissipation of calories taken in excess.

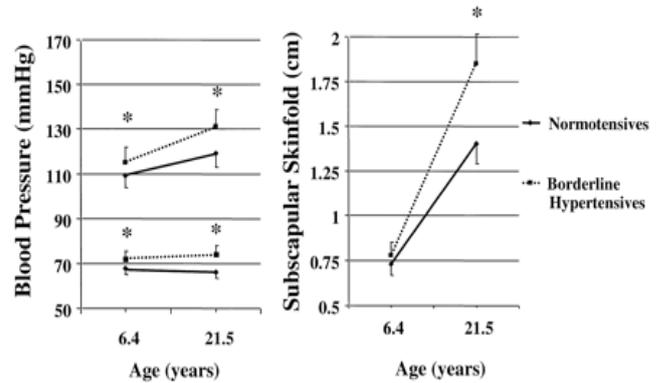
**Hypertension as a Predictor of Overweight**

The Framingham Heart Study investigated, in weight-matched subjects, the risk of the development of obesity according to the entry BP levels in 5127 men and women aged 30 to 62 years followed for >12 years [3] (Figure 1). In men, the standardized relative risk for the development of obesity was 1.62 in the subjects with definite hypertension (BP ≥160 mm Hg systolic, ≥95 mm Hg diastolic, or both), 1.02 in the subjects with borderline hypertension (BP between 140/90 and 164/94 mm Hg), and 0.79 in the subjects with normal BP (<140/90 mm Hg). In the women, relative risks were 1.45, 1.28, and 0.75, respectively.



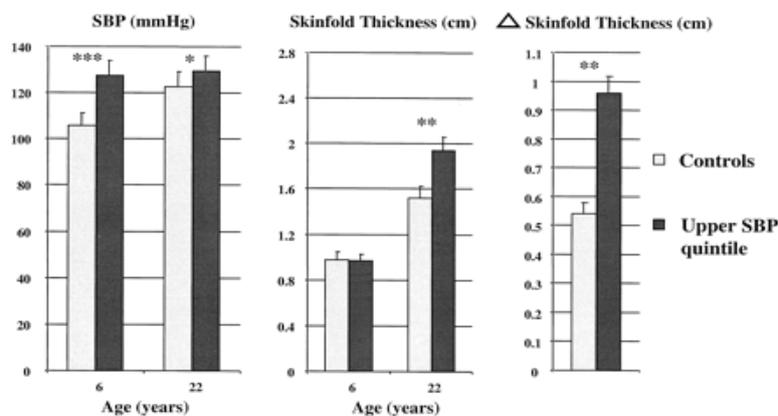
**Fig 1:** Risk of subsequent obesity according to BP status. Subjects were weight matched at baseline and followed for 10 years. NBP indicates normal blood pressure; B-HBP, borderline high blood pressure; HBP, high blood pressure. \*P<0.05 for trend. Adapted from Kannel et al. [3]

In the Tecumseh study, we examined 346 subjects ranging in age from 18 to 38 years who had BP records from previous visits [11]. Subjects who at the average age of 31 years had borderline hypertension (n=123) showed elevated BP values as young children (at age 6), but they were not overweight (Figure 2). Later, as young adults at the age of 20 to 24, their skinfold thickness increased more than in normotensives and their BPs reached marginally hypertensive levels. Finally, at 31 years, they showed hypertension and the other features of the insulin resistance syndrome [11]: increased body weight, increased skinfold thickness, larger waist-to-hip ratio, high insulin levels, and lipid abnormalities. This sequence strongly suggests that in some patients, a high BP precedes the gain of weight.



**Fig 2:** Trends of blood pressure and subscapular skinfold thickness in 563 normotensive and 78 borderline hypertensive subjects participating in the Tecumseh Blood Pressure Study. Subjects were examined and classified at an age of 32 years. Data were then recovered from records of previous Tecumseh examinations when the participants were 6 and 20 years old. Skinfold thickness has been selected as most reliable index of obesity in a population that is still growing. \*P<0.0001. Adapted from Julius et al [11] with permission of the American Medical Association.

In Figure 3 and the Table, 49 children in the highest BP quintile were compared with 49 age-, gender-, and skinfold-matched subjects culled from other quintiles. Figure 3 shows that after 16 years, the subjects in the highest BP quintile had greater skinfold thickness and a larger increase in the skinfold thickness. A similar trend was also observed for the body mass index (Table).



**Fig 3:** Systolic blood pressure (SBP) and skinfold thickness at 6 and 22 years of age in 49 subjects with high blood pressure at age 6 (top quintile) and 49 control subjects matched for age, gender, and skinfold thickness. Increase in skinfold thickness (Δ) from childhood to adulthood in two groups is also shown. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001. Unpublished data from Julius S, Palatini P, Valentini M, Tecumseh Blood Pressure Study.

**Table 1:** Clinical Variables in a Group of 6-Year-Old Children With High Systolic BP (Top Quintile) From the Tecumseh Study and a Group of Children Matched for Age, Gender, and Skinfold Thickness.

### Overweight and Hypertension

Table 1.			
Clinical Variables in a Group of 6-Year-Old Children With High Systolic BP (Top Quintile) From the Tecumseh Study and a Group of Children Matched for Age, Gender, and Skinfold Thickness			
Variable	Control subjects (n=49) (M20/F29)	High Systolic BP (n=49) (M20/F29)	P
Age (6 y)	6.2±2.0	6.3 ±1.8	NS
Age 2 (22 y)	22.2±2.8	22.3 ±2.9	NS
Systolic BP (6 y)	106.0 ±9.0	127.5±7.1	<0.0000
Systolic BP (22 y)	122.9±14.4	129.5±13.6	0.02
Diastolic BP (6 y)	68.4±8.2	74.4 ±10.1	0.002
Diastolic BP (22 y)	66.4 ±12.5	70.9±9.5	0.04
Skinfold thickness (6 y)	0.98 ±0.31	0.97±0.32	NS
Skinfold thickness (22 y)	1.52±0.69	1.94±0.92	0.01
BMI (6 y)	16.5 ±1.9	17.1 ±2.2	NS
BMI (22 y)	23.3 ±3.9	25.3±4.6	0.02

• BP given in mm Hg; BMI, body mass index given in kg/m; skinfold thickness [sum of: (triceps+biceps+subscapular+suprailiac)/4] given in mm.

• All subjects were reevaluated after 16 years of follow-up.

Hyperkinetic circulation is a reliable marker of increased sympathetic tone [12]. Recently [13]. We found that the young offspring of parents with hyperkinetic circulation had greater body mass, skinfold thickness, and waist-to-hip ratio and higher diastolic BP and plasma insulin levels than the offspring of parents with a lower cardiac index.

Overall, these data indicate that high BP may predict a future increase in weight and that this association may be stronger in the subset of the hypertensive population with heightened sympathetic activity.

### Weight Loss in Patients with Hypertension

Numerous trials have shown that weight reduction is effective in lowering the BP [14-16]. However, most of these studies showed that many patients with hypertension cannot lose much weight regardless of how hard they try and that they promptly regain whatever they do lose [14, 15].

In clinical practice, we are daily repeating the experience from the epidemiological trials that weight loss, no matter how vigorously enforced, is mostly a pothole in the road toward further weight gain. Why it is that hypertensive persons cannot lose weight, despite pressure from physicians and the investment of huge amounts of time and energy? The failure to sustain diet-induced weight loss may be secondary to a reduction in adipose stores that activates compensatory responses that restore weight to the previous level [17]. However, another plausible explanation is that there is a physiological connection between higher BP and the tendency to gain weight, a connection that cannot be overcome with dieting. If this is true, our attempts to manage hypertension through weight loss are doomed to failure. It follows that a search for an underlying connection between the hemodynamic condition of hypertension and the metabolic condition of overweight is not only warranted but also, in fact, a clinic imperative. As shown later, we believe that sympathetic overactivity may be the linchpin between hypertension and obesity.

It is noteworthy that normotensive obese subjects are also resistant to weight loss. Inasmuch as adiposity correlates

with sympathetic overactivity in these subjects [18], a similar mechanism, as proposed for hypertension, may also be in part responsible for the failure of obese persons to lose weight with dieting.

### Evidence of Sympathetic Overactivity in Hypertension

In a substantial proportion of patients, the sympathetic nervous system plays a key role in the pathogenesis of the BP elevation. This is particularly characteristic of subjects with mild hypertension who have hyperkinetic circulation [12]. The increased cardiac output in these subjects is neurogenic and can be abolished after blockade with propranolol and atropine [19].

Several other lines of research have confirmed those findings. Plasma norepinephrine and epinephrine levels [20], as well as norepinephrine turnover [21] and platelet norepinephrine content [22], are elevated in hypertensive subjects. An increased release of norepinephrine from regions that regulate the BP in the brain was described by Esler *et al.* [23] in essential hypertension. Excessive sympathetic activity in hypertensives has been demonstrated through spectral analysis of heart rate variability [24] and microneurographic assessment of sympathetic nerve traffic to skeletal muscle circulation. With this technique, Anderson *et al.* [25] and Grassi *et al.* [26] found a marked increase in muscle sympathetic nervous activity in subjects with borderline and established hypertension.

The earlier an abnormality appears, the more likely is that it has a primary role and that it is not a mere consequence of some other aberration. Sympathetic overactivity is a common feature among young individuals, and it may precede the development of hypertension. In a recent analysis of the Tecumseh population, we found that 29% of the women and 19% of the men had tachycardia according to mixture analysis [27]. Although they were still normotensive, subjects with a fast heart rate exhibited a higher BP than those with normal heart rate and they had some features of the insulin resistance syndrome. Among the Tecumseh subjects with borderline hypertension (mean age 32 years), 37% showed a hyperdynamic circulation and other signs of sympathetic overactivity [11, 12]. As 7-year-olds, these subjects had elevated heart rates but their BPs were not elevated. At the age of 20, hyperkinetic borderline hypertensives maintained elevated heart rates, and their BPs became significantly elevated.

These findings are apparently in contrast with the results from other investigators who demonstrated that sympathetic activation can be secondary to insulin resistance state [5, 6]. In fact, insulin resistance can reciprocate sympathetic stimulation and sympathetic stimulation can cause insulin resistance [28]. This could evolve into a vicious cycle in which the components reinforce each other.

In conclusion, sympathetic overactivity is present in a large portion of the hypertensive population, it starts early in life, and it precedes the development of hypertension.

### Role of the Sympathetic Nervous System in Energy and Substrate Metabolism

#### Energy Metabolism

The major determinants of 24-hour energy expenditure in adult humans include the resting metabolic rate, which accounts for 50% to 70%. The other determinants are the thermic effect of food and the caloric cost of physical activity and thermoregulation [29, 30].

The sympathetic nervous system plays a crucial role in energy metabolism through its involvement in the regulation of the resting metabolic rate (obligatory thermogenesis) [31]. Resting metabolic rate increases after exogenous catecholamine infusion [32, 33] and decreases with  $\beta$ -adrenoceptor blockade [34]. A strong relation between resting metabolic rate and the activity of the sympathetic nervous system has been identified with direct intraneural recording [18], norepinephrine turnover studies [35], and power spectral analysis of heart rate variability [36].

Ingestion of food and its processing promote an additional increase in energy expenditure (facultative thermogenesis) [37] that is also mediated by the sympathoadrenal system [38, 39].

The sympathetic nervous system exerts its thermogenic effect through the stimulation of all  $\beta$ -adrenoceptor subtypes [40]. Nonselective  $\beta$ -adrenergic blockade fully abolishes the facultative thermic effect of either glucose or insulin infusion [41, 42]. In humans,  $\approx 30\%$  of isoproterenol-induced [43] and  $\approx 40\%$  of ephedrine-induced thermogenesis [44] could be ascribed to  $\beta_3$ -adrenoceptor activation, although this could not be reproduced in another study [45].

The skeletal muscle,  $\approx 40\%$  of body weight in nonobese subjects, is both the major site of catecholamine-induced ( $\beta_2$ -adrenoceptor-mediated) thermogenesis and a major determinant (up to 30%) of resting metabolic rate in adult humans.<sup>46</sup> An estimated 40% of epinephrine-induced [39, 47] and  $\approx 50\%$  of ephedrine-induced [48] thermogenesis take place in the skeletal muscle. The white adipose tissue could account for 5% of the sympathetic thermogenesis, [47, 49] whereas the brown adipose tissue, the primary site of  $\beta_3$ -receptor-mediated thermogenesis in adult rats and mice [31] seems to play a negligible role in adult humans [48].

### Sympathetic Nervous System and Dietary Intake

As mentioned earlier, the activity of the sympathetic nervous system consistently decreases after energy restriction in both experimental animals<sup>6</sup> and humans [50, 51]. Conversely, overfeeding in humans activates the sympathetic nervous system [37, 50, 51].

### Evidence for Downregulation of $\beta$ -Adrenergic-Mediated Responses in Hypertension

Central to our hypothesis is the assumption that in a milieu of increased sympathetic tone, the  $\beta$ -adrenergic receptors tend to downregulate their responsiveness. Desensitization of a number of  $\beta$ -adrenergic-mediated effects has been demonstrated both in vitro and in vivo as a consequence of the prolonged  $\beta$ -adrenergic stimulation [52, 53], although the  $\beta_3$ -adrenoceptor subtype somewhat resists acute  $\beta$ -agonist exposure in vitro [54].

### Cardiovascular Responses in Hypertension

Although in hypertensives the heart rate response to isoproterenol infusion was occasionally reported as increased [55] or not different [56] from that of normotensives, in a number of investigations the response to isoproterenol was attenuated [22, 57-61]. Thus, McAllister *et al.* [57], Bertel *et al.* [58], Jennings *et al.* [59], Volpe *et al.* [60], and Trimarco *et al.* [61] are all in agreement that regardless of age, patients with hypertension show decreased chronotropic responses to  $\beta$ -adrenergic agonists.

In our laboratory, borderline hypertensives with normal [62] or elevated [63] cardiac output exhibited a lower increase in

both heart rate and cardiac output in response to graded infusion of isoproterenol compared with normotensive subjects. Decreased  $\beta$ -adrenergic responsiveness in hypertensive patients has also been described in the dorsal vein [64] and after infusion of isoproterenol into the brachial artery [65]. In general, when concomitantly evaluated, indexes of sympathetic nervous system activity were inversely proportional to indexes of  $\beta$ -adrenergic responsiveness [58]: the more active the sympathetic nervous system, the lower the chronotropic responsiveness to isoproterenol.

### Other $\beta$ -Adrenergic Responses in Hypertension

When the lymphocyte  $\beta$ -adrenoceptor has been used as a model of the human  $\beta$ -adrenoceptor complex [66],  $\beta$ -adrenoceptor responsiveness (adenylate cyclase activity in the presence of isoproterenol) was reduced in hypertensives. The presence of hypertension in obese patients was associated with a greater decrease in both basal lipolytic rate and lipolytic response to epinephrine [67].

In an investigation performed in our laboratory [22], hypertensives who display enhanced sympathetic nervous system activity proved to have, in addition to an attenuated heart rate ( $\beta_1$  mediated), decreased glucose and phosphate (metabolic  $\beta_2$  mediated) responses to epinephrine infusion.

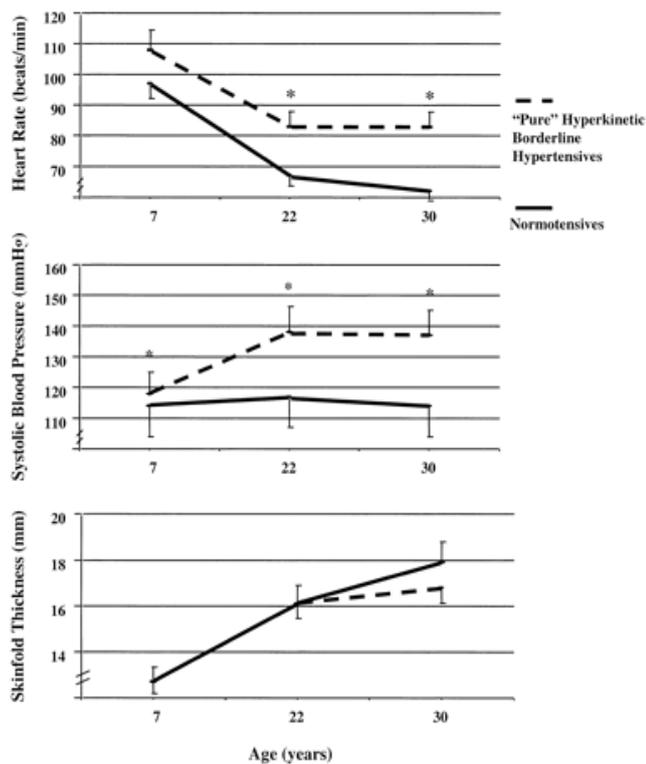
### Data That Support the Hypothesis

Our hypothesis that decreased  $\beta$ -adrenergic responsiveness leads to overweight draws support from studies of  $\beta$ -adrenergic blockade in the treatment of hypertension. An increase in body weight has been shown to occur during either short-term [67] or long-term [68]  $\beta$ -blocker therapy. In the Heart Attack Primary Prevention in Hypertension Trial Research Group (HAPPHY) [69], body weight significantly increased in the  $\beta$ -blocker-treated patients during a 37-month period, whereas it remained unchanged in the patients treated with diuretics. Similar results were found after 3 years of therapy in a retrospective analysis of the  $\beta$ -Blocker Heart Attack Trial [70].

The increase in body weight caused by  $\beta$ -blocking agents could be attributed to their negative effect on thermogenesis. Heat production rate has been shown to be significantly reduced in human skeletal muscle with propranolol administration ( $-25\%$ ). According to Lithell *et al.* [68], the increase in body weight for subjects with  $\beta$ -blockers is greater in subjects with less capillary density in skeletal muscles, who are known to have fewer  $\beta$ -receptors in the skeletal muscle and the heart. Overall, these data reinforce the concept that sympathetic activity is crucial in the promotion of calorie dissipation and that this action is mediated through  $\beta$ -receptors. However, it must be noted that the weight increase seen in subjects on  $\beta$ -blockers is of a lesser degree than the weight gain seen in hypertensives. Very likely, other factors (eg, appetite, leptin responsiveness) are also involved in the weight gain of hypertensive subjects. Furthermore, the gain of weight while on  $\beta$ -blockers may be due to decreased physical activity.

Findings from a previously published Tecumseh study [71] strongly support the present hypothesis. In that report, we investigated subjects who at age 32 exhibited hyperkinetic hypertension consisting of a fast heart rate and an elevated cardiac output. Characteristically, such patients have increased sympathetic tone. Figure 4↓ shows that these subjects had an elevated heart rate as children and that they

remained tachycardic as young adults. We interpreted the fact that these subjects had tachycardia before they developed BP elevation as evidence that sympathetic overactivity may precede hypertension. At that time, almost as an aside, we reported that these subjects never gained weight. The observation in Figure 4 that hyperkinetic subjects had consistent tachycardia during a period of 26 years suggests that despite enhanced sympathetic stimulation, their  $\beta$ -adrenergic responses did not downregulate. From the vantage point of our hypothesis, it is reassuring that those hypertensives, who preserved their  $\beta$ -adrenergic responsiveness, never gained weight. Furthermore, normotensive subjects in Figure 4 had a larger age-related decrease in heart rate, which validates the notion that hyperkinetic hypertensive subjects have not downregulated in a normal fashion.



**Fig 4:** Heart rate, systolic BP, and triceps skinfold thickness in 787 normotensive and 24 "pure" borderline hypertensive subjects. Lines of skinfold thickness for both groups overlap from age 7 to 22 years. \* $P < 0.0001$ . Adapted from Julius S, et al. [71]

### Conclusions

We present sufficient evidence that in some patients with hypertension, an increase in BP precedes the gain of weight. We also propose the hypothesis that enhanced sympathetic tone not only may increase the BP in hypertension but also could, via the ensuing down regulation of the  $\beta$ -adrenergic responsiveness, be responsible for the weight gain in these patients.

Our hypothesis can be experimentally tested. Among patients with hypertension, the degree of overweight should negatively relate to  $\beta$ -adrenergic cardiovascular and metabolic responsiveness. The  $\beta$ -adrenergic responsiveness should be negatively correlated to various indexes of sympathetic tone. In prospective studies, the degree of metabolic  $\beta$ -adrenergic responsiveness should be a predictor of weight gain.

Although we intend to test some of these postulates, even if they were proved, we could not claim that this is the only mechanism via which hypertension and overweight are associated. Insulin resistance and the ensuing increased sympathetic tone very likely play a role in the development of subsequent hypertension. A defect in the regulation of appetite may be a primary factor in such cases. However, sympathetic activity is postulated in most proposed hypotheses that link hypertension and overweight [5, 6] From that viewpoint, it is not crucial to search for factors that initiate the cycle of overweight, high BP, and sympathetic over activity. Regardless of where the process starts, the down regulation of metabolic  $\beta$ -adrenergic responses may further accentuate the vicious cycle of ever-increasing weight in hypertension.

An elucidation of the connection between decreased  $\beta$ -adrenergic responsiveness and weight gain may open new avenues of research. Molecular methods may reveal differences in the sensitivity or resistance to  $\beta$ -adrenergic down regulation. This in turn could contribute to resolution of why, despite honest efforts, most patients with hypertension are unable to lose weight. Eventually, new treatments for effective prevention of obesity in hypertension may be developed.

### Author's contribution

All of the authors achieved extreme guidance favoring the in depth cultivation with a positive output from Dr. Amitabha Kar, Associate Professor, Department of Human Physiology, Women's College, Govt. of Tripura, Agartala India. Dr. Amitabha Kar contributed a pioneer role to the design of the study, data analysis, and revision of the manuscript.

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