Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 1, pp. 57–61, 1994
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0091-3057/94 $6.00 + .00

0091-3057(93)E0003-M

Cardiovascular and Analgesic Effects of a Highly Palatable Diet in Spontaneously Hypertensive and Wistar–Kyoto Rats

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Received 25 June 1993

ZHANG, T., K. REID, C. G. ACUFF, C.-B. JIN AND R. W. ROCKHOLD. *Cardiovascular and analgesic effects of a highly palatable diet in spontaneously hypertensive and Wistar–Kyoto rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 57–61, 1994.—Ingestion of highly palatable diets (HPDs), rich in sucrose and fat, has been shown to lead to obesity and alterations in cardiovascular function in animal models. A hypothesis has been advanced which suggests that ingestion of an HPD increases hypothalamic β-endorphin release, an effect which results in an increase in sympathetic nerve outflow during the development of obesity. The hypothesis was tested by chronic (10 weeks) feeding of male spontaneously hypertensive rats (SHRs) and Wistar–Kyoto rats (WKYs) with the HPD or normal rat chow (ND). Cardiovascular function (systolic blood pressure, heart rate) and body weight gain were monitored during the feeding period. Pain sensitivity was tested weekly by measuring tail-flick latency. Body weight gain was greater in WKY rats than in SHRs, but ingestion of the HPD had no effect in either strain. Terminal organ analysis indicated differences between strains of SHRs and WKYs in the heart, the adrenal and pituitary glands, peritesticular fat pad, and testis weights expressed by organ weight/body weight. The heart weight was greater in SHRs on the HPD than in SHRs on the ND. The ingestion of the HPD significantly increased blood pressure only in SHRs, following 10 weeks of dietary intervention. However, tail-flick latency was prolonged in both SHRs and WKYs during ingestion of the HPD. Increases in tail-flick latency suggest that the HPD increases brain opiate levels in both SHRs and WKYs. Exaggerated increases in heart weight and blood pressure were noted in SHRs following feeding with the HPD, indicating enhanced sensitivity of SHRs to HPD-induced hypertension.

Spontaneously hypertensive rat Wistar–Kyoto rat Diet Analgesia Obesity

OBESITY has been linked to the prevalence and severity of arterial hypertension in humans (25,27). The mechanisms which may underlie this association are poorly delineated at present. Indeed, the data obtained from studies examining interactions between blood pressure and the development of dietary obesity in experimental animals are somewhat contradictory. For example, the induction of dietary obesity in Sprague–Dawley rats has been shown variously to elevate (14) or to have no effect (5) on blood pressure. Contreras and King showed that consumption of a diet enriched in sucrose and fat produced mild obesity in spontaneously hypertensive rats (SHRs), while reducing blood pressure (4). Moreover, Wexler has reported that high-fat feeding from weaning caused a reduction in the blood pressure level of SHRs, a response which was accompanied with body weight loss (28). The genetically obese SHR is one example of coexisting obesity and hypertension in a rat model (18,29). However, only the lean heterozygous offspring of the obese SHRs are hypertensive, the corpulent SHRs being normotensive. To further complicate the issue, sucrose feeding has been shown to exacerbate hypertension in the absence of any changes in body weight in the SHR (7,20,21,30,32,33), although similar regimens of sucrose feeding can induce mild obesity in adult Sprague–Dawley rats (12,13). Clearly, alterations in arterial blood pressure and the development of dietary obesity do not always coexist.

Ingestion of a highly palatable diet (HPD), rich in sucrose and fat, has been hypothesized to result in the development of obesity in both the SHR and Wistar–Kyoto rat (WKY) and to exaggerate hypertension in the SHR (21,30). Furthermore, these responses are postulated to be mediated by diet-induced

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release of an opioid peptide, possibly β-endorphin, within the CNS (6,11,22,34), which concurrently generates an increase in sympathetic nerve activity and arterial blood pressure (7, 14,30,32,33). This laboratory has previously demonstrated that intrahypothalamic injection of the opioid peptide β-endorphin elevates blood pressure, heart rate, and plasma glucose concentrations and that these increases are greater in conscious SHRs than in WKYs (11). In addition, a drinking challenge with 10% sucrose solution elevates blood pressure and heart rate and causes a greater decrease in hypothalamic β-endorphin concentrations in SHRs when compared to WKYs (34).

Thus, the purpose of the present experiment was to determine changes of blood pressure and body weight in SHRs and WKYs following feeding of an HPD. Changes in sensitivity to a thermal nociceptive stimulus were used as one indirect index of alterations in opioid peptide activity within the brain.

METHODS

Subjects

Male SHRs (n = 24) and WKYs (n = 24) were purchased from Taconic Farms, Inc. (Germantown, NY) at 11 weeks of age. The animals were housed in plastic cages (four per cage) under controlled conditions of temperature (22°C), humidity (50–55%), and lighting (12-h light–dark) upon receipt. The SHRs and WKYs were randomly assigned to one of four dietary intervention groups (n = 12 per group). Members of each strain received either free access to Purina pelleted rodent chow (normal diet, ND) or free access to an experimental diet rich in sucrose and vegetable oil (HPD). The HPD (containing 15.8% fat and 3.91 kcal/g) was formulated after that described by Levin et al. (16) and was composed of 47% powdered Purina rat chow mixed with 8% corn oil and 44% sweetened condensed milk (by weight). Deionized water was available ad lib for all rats.

Blood Pressure

All animals were housed in a wooden chamber and warmed at 29 ± 1°C for 20–30 min prior to recording blood pressure. Blood pressure and heart rate were determined by the use of a tail-cuff electrosphygmomanometer (Narco Biosystems, Houston) and a model 7D polygraph (Grass Instrument Co., Quincy, MA) on restrained animals. The rats were handled repeatedly and familiarized with the restraint chamber and tail-cuff measurement procedures. At least five to six similar blood pressure and heart rate measurements were obtained without signs of distress. The average of these readings was taken to provide blood pressure values for each rat.

Myocardial Dimensions

Rats were deeply anesthetized with Nembutal® (50–60 mg/kg, IP) upon completion of the dietary intervention period. The chest was opened and the heart removed and placed immediately into ice-cold saline. Each whole heart was blotted dry, weighed, then fixed by formalin for determinations of myocardial dimensions (19). Left ventricular volume was measured gravimetrically, following filling of the chamber with deionized water. The average of five measurements was taken for each value. The left ventricular vertical and horizontal diameters at the widest point and left ventricular wall thickness (apex, septum, free wall) were measured by using an electronic caliper (Digit-cal, Brown and Sharpe, Inc., North Kingston, RI). The left vertical and horizontal (at the widest point) circumferences were determined by measuring with a piece of 1-0 silk suture.

Tail-Flick Latency

Tail-flick latency was determined weekly in each rat by measuring the time between immersion of the tail in a hot water bath (55°C) and spontaneous tail withdrawal. The tail tip was immersed to a uniform depth of 3 cm. A cutoff time of 10 s was used to ensure that thermal injury to the tail did not occur. Measurements were taken by a single individual (K.R.) at the same time each week, using a manual stopwatch accurate to 0.01 s. Each weekly trial consisted of three separate immersions, at 1-min intervals. The average of these trials was taken as the weekly value for each animal tested. Food was removed from cages prior to delivery of rats for tail-flick latency determination so as to eliminate visual cues as to the dietary condition of animals during testing.

Experimental Protocol

Weekly measurements of individual body weights and tail-flick latencies were obtained in four groups over a 10-week period. Measurements of systolic blood pressure and heart rate were obtained immediately prior to dietary manipulation at week 0, and at the 4th and 10th weeks of dietary manipulation. At the end of this period the rats were sacrificed by anesthetization with Nembutal® (50–60 mg/kg, IP). Peritesticular fat pads, interscapular brown adipose tissue pads, the heart, kidneys, testes, adrenal glands, and the pituitary gland were removed, blotted dry, and weighed to the nearest 0.0001 g using an analytical balance.

Statistical Analysis

A two-way analysis of variance for repeated measurements was performed with strain as the between-group factor and repeated measures after dietary treatment over weeks as the second factor. The Newman-Keuls test was conducted to determine the source of group differences. Mean values ± 1 SEM are reported throughout. Statistical significance was presumed if p values were <0.05.

RESULTS

The body weights of WKYs on both diets (474 ± 3 g, HPD; 470 ± 9 g, ND) were significantly heavier than those of SHRs (349 ± 5, HPD; 352 ± 5, ND) following 10 weeks of feeding, even though the body weights were similar prior to dietary manipulation (WKYs: 302 ± 2 g, HPD and 308 ± 3 g, ND; SHRs: 278 ± 3 g, HPD and 287 ± 4 g, ND). The ingestion of the HPD in SHRs and WKYs produced a weight gain similar to that of control animals fed the normal diet. There were no differences in body weights of SHRs or WKYs between the two different diets during the 10-week period (Fig. 1).

There were significant differences in the terminal organ measurements (expressed by organ weight/100 g body weight) of adrenals, posterior pituitary, peritesticular fat pads, and testes between SHRs and WKYs on the two diets. Naso-anal lengths also differed ($p < 0.01$). There were no differences in anterior pituitary and interscapular brown adipose tissue weights between WKYs and SHRs on the two diets. The heart weights/100 g body weight of SHRs, on both diets, were heavier than those of the WKYs. The heart weights/100 g body weight of SHRs on the HPD were significantly heavier than

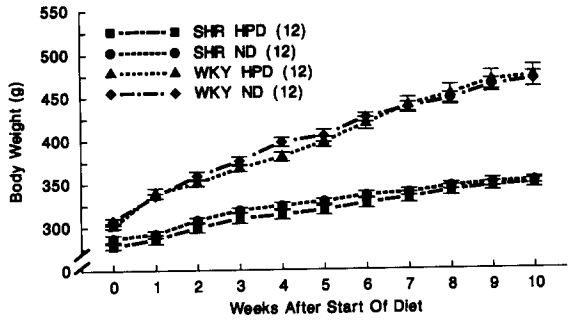

FIG. 1. Effect of dietary intervention on body weight in the four experimental groups. Mean values ± 1 SEM are given. Numbers in parentheses denote the number of animals in each group. SHR = spontaneously hypertensive rat, HPD = highly palatable diet, ND = normal rat chow, WKY = Wistar-Kyoto rat.

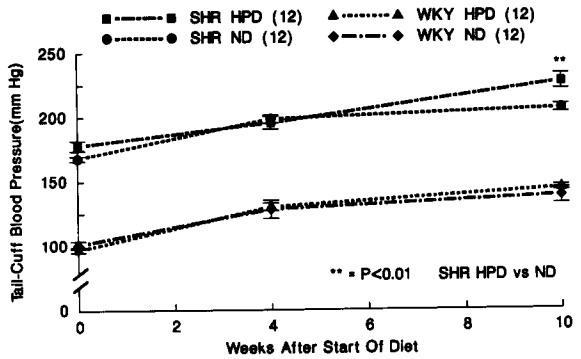

FIG. 2. Systolic (tail-cuff) blood pressure in the four treatment groups. Mean values ± 1 SEM are presented. Numbers in parentheses denote the number of animals in each group. SHR = spontaneously hypertensive rat, HPD = highly palatable diet, WKY = Wistar-Kyoto rat, ND = normal rat chow.

those of SHRs on the ND ($p < 0.01$). There was no significant difference between heart weights of WKYs on the two diets (Table 1). No differences could be found in myocardial dimensions between any of the four groups studied.

The systolic blood pressure of both SHR groups increased gradually, beginning at approximately 170 mmHg on week 0 and increasing to 200–230 mmHg at week 10 ($p < 0.01$, Fig. 2). The blood pressure of SHRs after 10 weeks on the HPD was higher than that of the ND controls (227 ± 6 mmHG vs. 206 ± 3 mmHg, $p < 0.01$). The systolic blood pressure of the two WKY groups also increased from approximately 100 mmHg at week 0 to 130–140 mm Hg at weeks 4 and 10 ($p < 0.01$). There were no differences in blood pressure between the WKY groups on the two diets.

Ingestion of the HPD increased tail-flick latency in SHRs and WKYs, respectively, from 2.99 ± 0.07 s and 2.97 ± 0.20 s at week 0 to 5.13 ± 0.18 s ($p < 0.01$) and 5.04 ± 0.09 s ($p < 0.01$) at week 10. Tail-flick latencies increased from 2.42 ± 0.10 s to 3.64 ± 0.12 s in SHRs ($P<0.01$) and from 2.84 ± 0.18 s to 3.52 ± 0.10 s in WKYs ($p < 0.01$) during ingestion of the ND. Tail-flick latency was lower ($p < 0.01$) at week 0 in the SHRs in the ND group than in all other groups. The absolute increases in tail-flick latency of the two strains during ingestion of the HPD were significantly greater than those of the controls fed the ND. Figure 3 depicts the rate of change in tail-flick latencies, calculated as the change from values obtained at week 0, for each of the four groups. Again, rats fed the HPD demonstrated significantly greater increases in tail-flick latency than did ND groups.

DISCUSSION

Under the conditions of our experiment, the blood pressure of SHRs on a highly palatable, sucrose-rich diet increased to a greater degree than did that of SHRs on an ND. Moreover, the heart weights of SHRs ingesting the HPD were heavier than those of SHRs on an ND. These results are consistent with a report which demonstrated an increased blood pressure in SHRs, but not in WKYs, after feeding for three months with a high sucrose diet which had a caloric composition similar to the HPD in the present study (33). There is also a report showing a mild increase in blood pressure in WKYs after two months of feeding with a high sucrose diet (7). It should be

TABLE 1

NASO-ANAL (N-A) LENGTH AND ORGAN WEIGHTS AT THE TIME OF SACRIFICE, FOLLOWING 10 WEEKS OF DIETARY INTERVENTION

Groups	N-A Length	Terminal Organ Weights (g/100 g body weight)						
		Heart	Adrenals	Post-P*	Ante-P*	IBFP	PTFP	Testes
SHR HPD	225.3† ± 1.6	0.440†‡ ± 0.007	0.0131† ± 0.0006	0.632† ± 0.023	2.47 ± 0.076	0.229 ± 0.035	1.454† ± 0.081	0.842† ± 0.023
SHR ND	225.7† ± 1.6	0.390† ± 0.013	0.0118† ± 0.0004	0.607† ± 0.040	2.45 ± 0.059	0.212 ± 0.025	1.369† ± 0.042	0.843† ± 0.044
WKY HPD	246.3 ± 2.4	0.334 ± 0.006	0.0100 ± 0.0008	0.442 ± 0.020	2.22 ± 0.090	0.219 ± 0.039	2.454‡ ± 0.189	0.635 ± 0.034
WKY ND	248.1 ± 2.1	0.306 ± 0.015	0.0097 ± 0.0004	0.435 ± 0.021	2.07 ± 0.194	0.198 ± 0.033	1.909 ± 0.162	0.609 ± 0.029

Mean values ± 1 SEM are given. Organ weights expressed as g/100 g terminal body weight (*mg/100 g terminal body weight). Values are obtained from eight animals in each group. Post-P = posterior pituitary, Ante-P = anterior pituitary, IBFP = interscapular brown fat pads, PTFP = peritesticular fat pads, SHR = spontaneously hypertensive rat, HPD = highly palatable diet, ND = normal rat chow, WKY = Wistar-Kyoto rat. †$p < 0.01$, SHR vs. WKY. ‡$p < 0.01$, HPD vs. ND within strain of WKY or SHR.

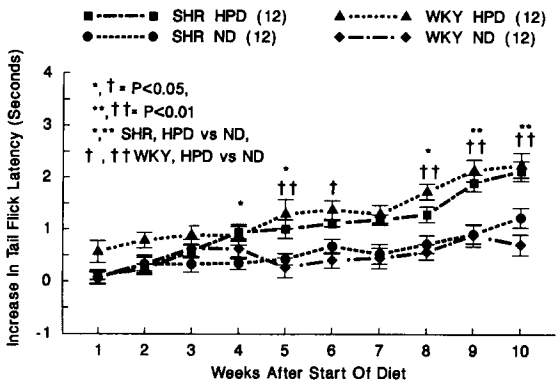

FIG. 3. Changes in tail-flick latency induced by dietary intervention in the four treatment groups. Mean values ± 1 SEM are given. Values were calculated as change from tail-flick latencies recorded at week 0 in each animal. Mean values (± 1 SEM) for absolute tail-flick latencies at week 0 were 2.42 (±0.10) s, 2.84 (±0.18) s, 2.99 (±0.02) s, and 2.97 (±0.20) s in the spontaneously hypertensive rat eating normal rat chow (SHR ND), Wistar-Kyoto rat (WKY) ND, SHR with a highly palatable diet (HPD), and WKY HPD, respectively. Numbers in parentheses denote the number of animals in each group.

noted that longer term periods of ingestion of high caloric diets have been shown to elevate blood pressure in both SHR and WKY strains (33). The increases in blood pressure induced by the ingestion of diets rich in sucrose and other carbohydrates have been attributed, at least in part, to increased activity of the autonomic nervous system (i.e., increased catecholamine production and/or release) (3,7,20,21,30,32). For example, SHRs showed higher urinary catecholamine output and myocardial norepinephrine turnover rates compared to normotensive controls after sucrose ingestion (7,15,21). The results of studies documenting the production or exaggeration of hypertension by dietary manipulation must be contrasted with those in which diet-induced hypotensive effects were noted (4,28). However, the results may not be readily comparable, since there were differences in experimental settings employed by different investigators. Key variables—for example, the introduction of dietary manipulation at an early age (at four to six weeks of age), different compositions of saturated and unsaturated fatty acids, and/or the different blood pressure measurement conditions (i.e., measurement under anesthesia by ether or urethane)—may be responsible for the apparent hypotension in these studies. In at least one instance, the reduction of blood pressure noted in SHRs following feeding with a high fat diet (without excess sucrose or carbohydrates) was accompanied by a loss of body weight, caused presumably by anorexia (28).

Although the HPD used in the present study was identical to that which has been shown to induce a 50–70% incidence of obesity in Sprague–Dawley rats by Levin and his coworkers [(16); a result reproduced in our laboratory], feeding with such a diet for 10 weeks failed to produce any increases in body weight in either SHRs or WKYs, compared to the control diet of regular chow. These results are quite similar to those of Rattigan and coworkers (23), which demonstrated a complete resistance of stroke-prone SHRs to development of obesity following maintenance on a high fat, high sucrose diet. It was suggested that hypertensive rats (SHR), in contrast to other laboratory rats which develop dietary obesity, may possess a gene or genes for leanness. This gene (or genes) can be expressed as an increased capacity to utilize energy, resulting, at least in part, from an increased activity of the sympathetic nervous system (23). Our results concur with this line of reasoning. The argument is supported further by evidence that those Sprague–Dawley rats which became obese following three months feeding with an HPD had decreased tissue norepinephrine levels and turnover rates (even though the Sprague–Dawley rats had increased tissue norepinephrine levels and turnover rates after 1-week feeding of same diet). In addition, studies have shown that SHRs demonstrate an increased production and/or release of norepinephrine following both short and long period feeding with sucrose-rich diets without becoming obese (7,16,32). In two other studies, only mild obesity appeared after chronic feeding (14 weeks) of a high fat and high sucrose diet to SHRs (4,5). In the present study, while WKYs on the HPD did not increase their body weight significantly, they did show increases in white fat pad weight compared to the ND controls, which is also partially consistent with the observation made by Rattigan et al. (23). Approximately 50% of the DNA fingerprint band of the WKY is identical to that of the SHR (26). As such, it is conceivable that the responses of WKYs to diet-induced body weight increases might parallel to a moderate degree those of SHRs. Although the age-matched WKYs had heavier body weights than SHRs, the organ weights (expressed as a percentage of the body weight) of SHR were generally heavier than those of WKYs, with the exception of peritesticular fat pads. Thus, it may be possible that the SHRs increased organ weights by decreasing carcass fat tissue, at the expense of body weight increase, compared to WKYs.

A salient aspect of the results of this investigation is that significant and progressive increases in tail-flick latency were noted in both SHRs and WKYs fed the HPD. A body of evidence exists in support of interactions among sucrose or sucrose-rich diets, pain sensitivity, and central opioid systems in normal and genetically hypertensive rats (2,24,31). Specifically, data have been reported which indicate that ingestion of sucrose or an HPD can activate hypothalamic release of β-endorphin (6) and decrease the pain sensitivity (2). In addition, the intraventricular administration of β-endorphin has been shown to cause increases in feeding behavior (8) and hyperglycemia (11,22) and to produce analgesia (17). Since the endogenous opiates play an important role in pain perception and analgesia (9,17), the increased tail-flick latency noted following ingestion of the HPD may be due to the effect of endogenous opiates, possibly of increased turnover of hypothalamic β-endorphin. We have recently shown that ingestion of 10% sucrose in drinking water causes an acute reduction in the levels of immunoreactive β-endorphin in the dorsal but not the ventral hypothalamus of the SHR (34). Such data suggest that acute sucrose ingestion increases hypothalamic β-endorphin release. However, the present data show roughly equivalent increases in tail-flick latency in both SHRs and WKYs given the HPD. The relationship between that finding and hypothalamic β-endorphin levels remains to be examined.

The tail-flick latencies reported here showed a lack of difference between SHRs and WKYs. This result does not agree with the reports (24,31) which showed that SHRs exhibit an increased basal tail-flick latency compared to normotensive controls. Methodologically speaking, tail-flick latency is influenced by tail skin temperature and drug- or stress-induced vasoconstriction and vasodilation (1). All measurements in the present study were performed by a single individual under standardized conditions of temperature and handling. Factors which might have contributed to the discrepant results include

a different experimental setting and the probable interference exerted by genetic difference, since the SHRs used in the different experiments were obtained from several sources. It is well known that SHRs from different breeders (or even from the same breeder) exhibit heterogeneity in many respects (10,28).

In conclusion, SHRs and WKYs show resistance to the development of obesity during feeding with a high fat, high sucrose diet. The resistance of SHRs and WKYs to dietary obesity may relate to alterations in central opioid systems.

ACKNOWLEDGEMENTS

This work was supported by HL39387 and the AHA-Mississippi Affiliate.

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