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CHRONIC EFFECTS OF CENTRALLY ADMINISTERED ADIPONECTIN ON APPETITE, METABOLISM AND BLOOD PRESSURE REGULATION IN NORMOTENSIVE AND HYPERTENSIVE RATS

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Abstract

Acute studies suggest that adiponectin may reduce sympathetic activity and blood pressure (BP) via actions on the central nervous system (CNS). However, the chronic effects of adiponectin on energy expenditure and cardiovascular function are still poorly understood. We tested if chronic intracerebroventricular (ICV) infusion of adiponectin (1 or 7 $\mu\text{g/day}$) in Sprague-Dawley rats fed a high fat diet (HFD) for 8 weeks and at the high dose (7 $\mu\text{g/day}$) in spontaneously hypertensive rats (SHR), a hypertensive model associated with sympathetic overactivity, evoked chronic reductions in BP and heart rate (HR). We also determined if chronic ICV adiponectin infusion alters appetite, whole body oxygen consumption (VO_2), and insulin and leptin levels. Neither dose of adiponectin infused for 7 days significantly altered BP or HR in the HFD group (115 ± 2 to 112 ± 2 mmHg and 384 ± 6 to 379 ± 6 bpm at 1 $\mu\text{g/day}$; 109 ± 3 to 111 ± 3 mmHg and 366 ± 5 and 367 ± 5 bpm at 7 $\mu\text{g/day}$). The higher dose slightly reduced food intake (14 ± 1 to 11 ± 1 g/day), whereas VO_2 , insulin and leptin levels were not affected by the treatment. In SHRs, ICV adiponectin infusion reduced appetite (22 ± 2 to 12 ± 2 g/day) and insulin levels ($\sim 55\%$), but did not alter BP (162 ± 4 to 164 ± 3 mmHg) or HR (312 ± 5 to 322 ± 8 bpm). These results suggest that adiponectin, acting via its direct actions on the CNS, has a small effect to reduce appetite and insulin levels, but it has no long-term action to reduce BP or HR, or to alter whole body metabolic rate.

Keywords

adiponectin; blood pressure; heart rate; appetite; insulin sensitivity

1. INTRODUCTION

In the past two decades we have witnessed a major change in the field of adipocyte biology in which the traditional view of the adipose tissue as purely an energy storage compartment

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CONFLICT OF INTEREST/DISCLOSURES

None.

has been radically transformed by the fact that the adipose tissue is an important and dynamic endocrine organ producing a variety of bioactive molecules referred to as adipokines [11, 13, 20]. Among these, adiponectin is the most abundant and its regulation appears to contrast with that of other adipokines [20]. For instance, adiponectin levels are reduced under conditions such as obesity, hypertension and insulin resistance which has led to the suggestion of an association between hypoadiponectinemia and metabolic syndrome [1, 4, 6, 14, 19].

Previous acute studies have shown that adiponectin modulates energy balance via activation of AdipoR1 and AdipoR2 receptors present mainly in the arcuate and lateral hypothalamic nuclei [7, 8]. Central nervous system (CNS) single-dose administration of adiponectin in rodents has been shown to reduce body weight by increasing energy expenditure [15] and reducing appetite [2]. However, Kubota et al. (2007) [9] observed increased food consumption and decreased thermogenesis in mice treated with adiponectin. Thus, the acute effects of adiponectin to reduce food intake and to modulate thermogenesis have not been uniform. The chronic CNS effects of adiponectin on food intake have, to our knowledge, not been reported. These observations suggest that the overall impact of adiponectin on energy balance and body weight homeostasis is still not clearly understood.

In addition to its potential effects on energy homeostasis, recent evidence suggests that adiponectin may also modulate blood pressure (BP). When maintained on a high salt diet adiponectin KO mice develop hypertension which can be ameliorated with adiponectin replacement [11]. Also, reconstitution of adiponectin through adenoviral infection in genetically obese KKAy mouse reduces their elevated systolic BP [11]. Moreover, previous studies suggest that the effects of adiponectin to acutely reduce renal sympathetic nervous system (SNS) activity and to lower blood pressure are, at least in part, mediated by adiponectin's action on the CNS [5, 18]. However, whether adiponectin exerts sustained effects in the CNS to promote long-term reductions in the BP is still unclear.

Since obesity is associated with reduced circulating levels of adiponectin and acute studies suggest that adiponectin may reduce BP by suppressing sympathetic activity, we investigated whether chronic intracerebroventricular (ICV) infusion of adiponectin exerts long-term effects on BP and heart rate (HR) in normotensive rats fed a high fat-high fructose diet, and we also tested whether the cardiovascular effects of adiponectin are exacerbated in spontaneously hypertensive rats, a well known model of hypertension associated with high sympathetic activity.

2. METHODS

The experimental procedures and protocols of this study conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center.

2.1 Animals

Male Sprague-Dawley (SD) and spontaneous hypertensive rats (SHR) at 8 weeks of age were purchased from Harlan (Madison, WI) and Taconic Farms (Albany, NY), respectively.

2.1.1 High fat-high fructose diet (HFD)—SD rats were fed high fat diet (Diet No. D12451, Research Diets, New Brunswick, NJ; 4.7 kcal/g) and degassed 7UP (Cadbury Schweppes, Plano, TX; 0.416 kcal/mL) to drink. The rats were maintained on the HFD for 8 weeks before experiments began.

2.2 Surgical Procedures

2.2.1 Telemetry pressure transmitter implantation—SD rats (450 ± 8 g) and SHR (341 ± 1 g) were anesthetized with 50 mg/kg sodium pentobarbital (Nembutal), and atropine sulfate (0.1 mg/kg) was administered to prevent excess airway secretions. Using aseptic techniques, a laparotomy was performed and the catheter of the pressure telemetry transmitter (Model TA11PAC40, Data Sciences International) was inserted into the abdominal aorta, distal to the kidneys according to the manufacturer's instructions. The catheter was fixed in the aorta with a small drop of cyanoacrylate adhesive, and the transmitter was secured to the abdominal wall by sutures. Mean 24-hour BP and HR data were derived from the average BP and HR values measured by bursts of 10 seconds every 10 minutes using the software (Dataquest 4.0) provided by the manufacturer.

2.2.2 Intracerebroventricular cannulation—Immediately after telemetry probe implantation, a stainless steel cannula (26 gauge, 10 mm long) was implanted into the right lateral cerebral ventricle using the coordinates previously described [10]. The steel cannula was secured in place with 2 stainless steel screws, a metal cap, and dental acrylic. A stylet was inserted to seal the cannula until use. During stereotaxic manipulation, anesthesia was maintained with 0.5% isoflurane. After 7 days to recover from surgery, accuracy of the cannula placement was tested by measuring the dipsogenic response (immediate drinking of at least 5 ml of water in 10 minutes) to an intracerebroventricular (ICV) injection of 100 ng of angiotensin II.

Immediately after surgery, rats were housed individually in standard metabolic cages or in an oxygen consumption system (AccuScan system, Harvard Apparatus) for the duration of the study for measurements of oxygen consumption (VO_2), carbon dioxide production (VCO_2) and respiratory quotient (RQ). The rats were allowed to recover for 7 to 10 days before control measurements were initiated. VO_2 , VCO_2 and RQ were determined daily (for 2 minutes every 10-minute interval) and expressed as the average of the last 2 days of control, adiponectin infusion and recovery periods. RQ was calculated by the formula: $\text{VCO}_2 / \text{VO}_2$.

2.3 Experimental Protocols

Mean arterial pressure (MAP), heart rate (HR), food and water intake and oxygen consumption (VO_2) were measured 24-hours/day and average values were recorded daily.

2.3.1 Chronic ICV adiponectin infusion—Eight days after surgeries, adiponectin was infused ICV for 7 days at 2 doses (1 or 7 $\mu\text{g/day}$, 1.0 $\mu\text{l/hr}$ dissolved in saline; $n=6$ and 4, respectively) in SD rats fed HFD using osmotic min-pumps (model 2001, Durect Corp.) implanted subcutaneously in the scapular region as previously described (20). These doses were based on previous acute studies [15]. To test whether the effects of adiponectin on cardiovascular regulation are enhanced in conditions of increased sympathetic activation, we also infused adiponectin at the higher dose (7 $\mu\text{g/day}$, 1 $\mu\text{l/hr}$, $n=4$) for 7 days in SHRs, a model of hypertension associated with high sympathetic activity.

Fasting blood samples (200 μl) were collected from each animal by tail snip on day 5 of the control period, on day 7 of adiponectin infusion, and on day 5 after stopping adiponectin infusion (recovery period). The blood was centrifuged using a refrigerated centrifuge and the plasma used for determination of glucose (glucose oxidase method, Beckman Glucose Analyzer), insulin and leptin concentrations (rat ELISA kits from Crystal Chem and R&D Systems, respectively). The intra and inter-assay sensitivity of these commercially available kits are <10% for intra and inter-assay for the rat insulin ELISA kit and <5% and <7% for intra and inter-assay sensitivity for the rat leptin ELISA kit.

2.4 Statistical Analyses

The results are expressed as mean $\pm$ SEM. The data obtained were analyzed by GraphPad Prism 5 software using 1-way ANOVA with repeated measures followed by Bonferroni's post hoc test for comparisons between control and experimental values within each group when appropriated. Statistical significance was accepted at a level of $P < 0.05$.

3. RESULTS

3.1 Effect of chronic ICV adiponectin treatment on food intake, body weight and metabolic rate

Chronic ICV adiponectin at the dose of 1 μ g/day did not significantly alter caloric intake or body weight in SD fed a HFD for 8 weeks (Table 1). This dose of adiponectin also did not alter carbon dioxide production (VCO_2) or motor activity (Figure 1). Although there was a tendency for a reduction in VO_2 as well as for increased RQ values, these changes did not reach statistical significance (Figure 1). Similar findings were observed when SD rats fed a HFD were infused with a higher dose of adiponectin (7 μ g/day) (Table 1 and Figure 1).

In SHR, however, chronic ICV adiponectin infusion at the higher dose of 7 μ g/day reduced caloric intake and caused a 15 g weight loss (Table 1). Caloric intake increased after cessation of adiponectin treatment, which likely explains the rapid weight gain in the 5-day recovery period where it was no longer reduced compared to control values. We did not evaluate metabolic rate and motor activity in the SHR group.

3.2 Effect of chronic ICV adiponectin treatment on glucose, insulin and leptin levels

Chronic central adiponectin infusion for 7 days at either low or high doses in SD rats fed HFD did not significantly alter fasting plasma glucose, insulin or leptin concentrations (Table 1). However, ICV adiponectin infusion in SHR reduced insulin levels without causing significant changes in plasma glucose or leptin levels (Table 1). It is important to note that baseline fasting insulin levels were about 2 to 3 times higher in SHR compared to SD rats (Table 1). This suggests that central adiponectin infusion may have more pronounced impact on insulin sensitivity in animals with impaired insulin sensitivity. In addition, there was a tendency for increased plasma glucose levels in SHRs after adiponectin infusion was stopped despite the return of insulin levels back to control values (Table 1).

3.3 Effects of chronic ICV adiponectin treatment on MAP and HR

Chronic ICV adiponectin infusion at 1 or 7 μ g/day did not alter MAP or HR in SD rats fed a HFD (Figure 2). Central adiponectin infusion also did not change MAP and HR in SHRs (Figure 3). However, SHRs exhibited a tendency for increased MAP and HR during the first 1 to 3 days of infusion which quickly returned to baseline levels (Figure 3). These results suggest that adiponectin does not appear to play an important role in long-term control of BP and HR by direct activation of its receptors in the CNS.

4. DISCUSSION

In the present study we showed that chronic delivery of adiponectin into the CNS of normotensive as well as hypertensive rats did not significantly alter BP or HR. Except for a small, non-significant, reduction in whole-body oxygen consumption we also found no major alterations in motor activity, food intake, body weight and fasting insulin, glucose and leptin levels in SD rats fed high fat-high fructose diet. However, in the SHR group chronic ICV adiponectin treatment markedly reduced food intake and caused modest weight loss that was accompanied by a significant reduction in fasting insulin levels suggesting an improvement of glucose homeostasis.

Previous studies have shown that acute adiponectin injection into the CNS may alter food intake and energy expenditure [9, 15]. Our results, however, suggest that chronic activation of adiponectin receptors in the CNS does not appear to play a major role in regulating body weight homeostasis either by altering appetite or energy expenditure in a HFD rodent model. Of note, chronic adiponectin reduced food intake in SHR. The mechanisms by which adiponectin reduces food intake in SHR but not in SD rats are still unclear. One possible explanation is that despite the high fat-high fructose feeding SD rats remain sensitive to the endogenous circulating levels of adiponectin and further increases in adiponectin by exogenous infusion into the CNS exert little additional effect. However, SHR exhibit impaired adiponectin signaling [16], and increasing brain adiponectin levels beyond the endogenous levels by direct ICV infusion may have resulted in more pronounced effect in these animals.

ICV adiponectin treatment also improved insulin sensitivity in SHR and had a tendency to reduce fasting plasma insulin levels in HFD SD rats. It is important to note that despite being fed standard chow and weighing less than HFD rats, SHR exhibited 2-fold greater fasting insulin levels at baseline which corroborates previous studies that showed insulin resistance in SHR [16]. Therefore, one may speculate that adiponectin treatment may exert its beneficial effects on metabolic parameters such as insulin sensitivity in states of established insulin-resistance, while these effects are not as evident under normal circumstances. Another factor that may help explain the lack of a major impact of adiponectin treatment on energy balance and metabolic profile in HFD rats is that we delivered adiponectin directly into the CNS. It is possible that most of the effects of adiponectin are mediated by its peripheral actions rather than being mediated via activation of its receptors in the brain. Our study, however, was designed to investigate only the brain effects of adiponectin on energy balance and metabolic function and additional studies are needed to test this hypothesis.

A unique aspect of our study is that we evaluated the chronic effects of central adiponectin delivery on long-term control of BP and HR in both normotensive and hypertensive rats using state-of-the-art telemetry technique to measure BP and HR 24-hours a day. Contrary to our original hypothesis, we observed no significant impact of chronic increases in CNS adiponectin levels on BP and HR. Previous studies have shown that adiponectin deficiency predisposes to salt-sensitive hypertension, whereas acute adiponectin injection in the CNS reduces renal SNS activity and lowers BP [18]. One potential explanation for lack of a chronic brain-mediated effect of adiponectin on cardiovascular regulation may be that long-term activation of adiponectin receptors in the CNS leads to compensatory changes that offset adiponectin's ability to lower SNS activity. Adiponectin may also exert opposing effects on BP regulation by acting in different areas of the brain. For example, injections of adiponectin into the area postrema in anesthetized rats depolarizes neuronal cells causing a significant increase in blood pressure [3], while microinjection of adiponectin in the medial nucleus of the tractus solitarius decreases BP [5]. Thus, acute ICV injection of adiponectin may exert a rapid effect to reduce SNS activity and BP by acting in certain areas of the brain but when more homogenous activation of adiponectin receptors occurs with prolonged delivery of adiponectin, as in the case of the present study, then no sustained effect of adiponectin on SNS activity and BP is observed. Since adiponectin is produced by adipocytes and reaches the brain via diffusion from the blood into the cerebral spinal fluid, it is likely that many areas of the brain involved in the regulation of cardiovascular function are exposed to adiponectin. Therefore, our observations using chronic intracerebroventricular delivery of adiponectin may better represent the long-term physiologic effects of adiponectin on BP and HR regulation.

It is also possible that adiponectin may exert a more prolonged effect on cardiovascular function by its peripheral actions including improved endothelial function. For instance,

adiponectin KO mice develop larger infarcts associated with myocardial cell apoptosis and TNF- α production that can be reversed by adenovirus-mediated delivery of adiponectin in these mice [17]. Adiponectin KO mice also exhibit reduced mRNA levels of endothelial nitric oxide synthase in aorta and kidneys, suggesting impaired nitric oxide (NO) production, and adiponectin treatment increased NO production in vascular endothelial cells [12]. Taken together, adiponectin may exert rapid beneficial effects on BP regulation via a brain-mediated mechanism leading to acute reduction in SNS activity, while its long-term effects on cardiovascular function are mediated by a more slow progressive improvement on endothelial function. Our studies suggest, however, that direct CNS actions of adiponectin do not play a major role in long-term blood pressure regulation.

5. CONCLUSIONS

Overall, our results suggest that adiponectin, acting via its direct actions on the CNS, has a small effect to reduce appetite and insulin levels in insulin-resistant spontaneously hypertensive rats, but it has no long-term action to reduce BP or HR in normotensive or hypertensive models, or to alter whole body metabolic rate.

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GLOSSARY

BP	blood pressure
HR	heart rate
VO2	oxygen consumption
VCO2	carbon dioxide production
RQ	respiratory quotient
SNS	sympathetic nerve activity
ICV	intracerebroventricular
CNS	central nervous system
HFD	high fat-high fructose diet
SD	Sprague-Dawley
SHR	spontaneously hypertensive rat

HIGHLIGHTS

- ✓ Chronic CNS adiponectin infusion does not alter appetite or energy expenditure in Sprague-Dawley rats.
- ✓ Chronic CNS adiponectin infusion reduces appetite and improves insulin sensitivity in SHR.
- ✓ Chronic CNS adiponectin treatment does not exert major chronic effects on BP and HR.

Figure 1.

(A) respiratory coefficient (RQ), (B) oxygen consumption (VO_2), (C) carbon dioxide production (VCO_2) and (D) motor activity in Sprague-Dawley rats fed high fat-high fructose diet during chronic ICV adiponectin infusion at 1 µg/day (black bar, n=4) or 7 µg/day (gray bar, n=4). Data expressed as mean $\pm$ S.E.M.

Figure 2. (A) mean arterial pressure and (B) heart rate of Sprague-Dawley rats fed high fat-high fructose diet during chronic ICV adiponectin infusion at 1 µg/day (black squares, n = 6) or 7 µg/day (gray squares, n = 4). Data expressed as mean ± S.E.M.

Figure 3. Mean arterial pressure (A) and heart rate (B) of spontaneous hypertensive rats (SHR) during chronic ICV infusion of adiponectin (7 $\mu\text{g/day}$). Data expressed as mean $\pm$ S.E.M.

Table 1

Responses to chronic ICV adiponectin infusion on body weight, food intake and plasma hormones in Sprague-Dawley (SD) rats fed a high fat-high sucrose diet and in spontaneously hypertensive rats (SHR) fed standard chow.

Experimental Groups	Body Weight (g)	Caloric Intake (kcal)	Leptin (ng/mL)	Glucose (mg/dL)	Insulin (μ L/mL)
<u>SD (n=6)</u>					
Control	455 $\pm$ 12	81 $\pm$ 4	1.4 $\pm$ 0.2	132 $\pm$ 2	14 $\pm$ 8
ADP (1 μ g/day)	445 $\pm$ 10	75 $\pm$ 3	1.6 $\pm$ 0.4	145 $\pm$ 12	8 $\pm$ 2
Recovery	466 $\pm$ 11	73 $\pm$ 5	1.5 $\pm$ 0.2	128 $\pm$ 15	10 $\pm$ 2
<u>SD (n=4)</u>					
Control	448 $\pm$ 6	79 $\pm$ 7	1.5 $\pm$ 0.2	120 $\pm$ 8	10 $\pm$ 2
ADP (7 μ g/day)	449 $\pm$ 6	68 $\pm$ 4	1.5 $\pm$ 0.2	112 $\pm$ 3	11 $\pm$ 1
Recovery	456 $\pm$ 8	77 $\pm$ 5	1.6 $\pm$ 0.3	121 $\pm$ 2	14 $\pm$ 7
<u>SHR (n=4)</u>					
Control	341 $\pm$ 11	95 $\pm$ 10	1.4 $\pm$ 0.3	146 $\pm$ 11	30 $\pm$ 3
ADP (7 μ g/day)	326 $\pm$ 10	52 $\pm$ 7 *	1.6 $\pm$ 0.5	155 $\pm$ 14	13 $\pm$ 2 *
Recovery	341 $\pm$ 10	75 $\pm$ 7 *	1.3 $\pm$ 0.2	183 $\pm$ 10	28 $\pm$ 4

Values represent Mean $\pm$ SEM.

* indicates $p < 0.05$ vs. control period within group.