EFFECTS OF CENTRAL ADMINISTRATION OF RESISTIN ON RENAL SYMPATHETIC NERVE ACTIVITY IN RATS FED A HIGH FAT DIET; A COMPARISON WITH LEPTIN

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ABSTRACT

Resistin acts centrally to increase renal sympathetic nerve activity (RSNA). This is similar to leptin. In high fat fed animals, the sympatho-excitatory effects of leptin are retained, in contrast to the reduced actions of leptin on dietary intake. In the present study we investigated whether the sympatho-excitatory actions of resistin were influenced by a high fat diet. Further, since resistin and leptin combined can induce a greater sympatho-excitatory response than each alone in rats fed a normal chow diet, we investigated whether a high fat diet (22%) could influence this centrally mediated interaction. MAP, HR and RSNA were recorded before and for 3 hours after intracerebroventricular saline (control) (n=5), leptin (7 µg; n=4), resistin (7 µg; n=5) and leptin and resistin combined (n=6). Leptin alone and resistin alone significantly increased RSNA (71±16%, 62±4% respectively). When leptin and resistin were combined there was a significantly greater increase in RSNA (195±41%) compared to either hormone alone. MAP and HR responses were not significantly different between hormones. When the responses in high fat fed rats were compared to normal chow fed rats, there were no significant differences in the maximum RSNA responses. The findings indicate that sympatho-excitatory effects of resistin on RSNA are not altered by high fat feeding, including the greater increase in RSNA observed when resistin and leptin are combined. Our results suggest that diets rich in fat do not induce resistance to the increase in RSNA induced by resistin alone or in combination with leptin.

INTRODUCTION

Resistin is a member of the resistin-like molecule (RELM) hormone family and is so named because of its ability to induce insulin resistance. In obese and diabetic humans and rats resistin levels in plasma are elevated (1-3). Resistin levels correlate with an increased risk of
hypertension and major cardiovascular events like stroke and myocardial infarction (4-7). Resistin acts in the brain, and mRNA for resistin has been detected in several brain nuclei of rodents suggesting there is also endogenous production of resistin in the brain (8, 9).

Resistin acts centrally to increase renal sympathetic nerve activity (RSNA) (10). These effects are similar to those observed with another well-known adipokine, leptin (11, 12). Both leptin and resistin increase RSNA through central mechanisms that involve phosphatidylinositol 3 kinase (PI 3-kinase) (10, 13, 14), and this may explain why the combined administration of leptin and resistin elicits greater increases of RSNA than either alone.

Increased dietary intake of fat leads to increased adipose tissue and increased circulating levels of leptin and resistin (1-3). Cerebrospinal fluid levels of leptin in humans correlate with circulating levels of leptin and adiposity (15). Cerebrospinal fluid levels of resistin also correlate with circulating levels in males but not females and this has been interpreted as an impairment in the uptake process of resistin into the central nervous system in obese women (16). Diets high in fat lead to a reduction in the sensitivity to the anorexigenic actions of leptin (17, 18). However, the sympatho-excitatory action of leptin on renal sympathetic nerve activity is not affected by high fat diets. This has led to the view of a selective resistance to leptin (19-22) and could be a key mechanism contributing to obesity induced hypertension (23, 24).

Since resistin, like leptin, increases renal sympathetic nerve activity, we investigated whether a high fat diet could influence the sympatho-excitatory effects induced by resistin. Furthermore, we also explored whether a high fat diet would influence the increase in RSNA induced by the combination of resistin and leptin, since the combined effect of resistin and leptin in normal chow fed rats results in significantly greater sympatho-excitatory actions on RSNA (25).
METHODS

Ethical approval

All the experimental protocols were performed in accordance with the Prevention of Cruelty to Animals Act 1986 (Australia). The procedures conform to the ‘Guiding Principles for Research Involving Animals and Human Beings’ and the guidelines set out by the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, 2013 (National Health and Medical Research Council of Australia) and were approved by the RMIT University Animal Ethics Committee.

Procedures

General.

Male Sprague–Dawley rats were obtained from ARC animal resources centre (Canning Vale, WA, Australia). Upon arrival rats were acclimatised for one week, before a controlled feeding period began. Rats were divided into two groups, where one group was exposed to normal chow diet (4.8% fat) and the other to a high fat diet (SF14-004 (22% fat), Speciality Feeds, Glen Forrest, WA). Rats were housed in groups of two at 23°C with a 12 h–12 h light–dark cycle and allowed free access to rat chow and water. The feeding period lasted for 8-10 weeks, and body weight, food intake, and caloric intake were monitored weekly. In addition, systolic blood pressure was monitored fortnightly during the feeding period, using a non-invasive tail cuff occlusion method. At the end of the feeding period, the percent whole body fat was determined using an EchoMRI 500 (Houston Texas, USA) in a sample of animals of each dietary treatment.

On the day of the experiment, anaesthesia was induced using isoflurane (2-5% in O₂, followed by femoral artery and vein cannulation as previously described (25). The femoral vein was cannulated so that anaesthesia could be maintained using urethane (1.4–1.6 g/kg; i.v with supplemental doses of 0.05 ml of a 25% solution, if required). The depth of anesthesia was maintained to ensure the absence of corneal and pedal reflexes. The femoral artery was cannulated to monitor mean arterial pressure (MAP) and heart rate (HR) was determined.
from the arterial pressure pulse using LabChart (ADInstruments, NSW, Australia). Rats were kept on a heating pad for the duration of the experiments to maintain body temperature at approximately 37.5 °C. The rats were not fasted prior to the experimental day.

**Renal sympathetic nerve activity**

After a flank incision, the left kidney was exposed retroperitoneally and dissected clear of surrounding tissue, placed onto the hooked, bared-ends of teflon-coated bipolar silver electrodes and insulated from the surrounding tissue by covering them with paraffin oil as previously described (10, 25). RSNA was amplified using a low-noise differential amplifier (models ENG 187B and 133, Baker Institute, Victoria, Australia), filtered (band pass 100–1,000 Hz), rectified, and integrated at 0.5 s intervals. The signals was recorded using a PowerLab data acquisition system (ADInstruments, NSW, Australia) (25). The background electrical noise levels were determined post mortem and subtracted from the nerve activity obtained in the anesthetised rat.

**Microinjections into the lateral brain ventricle.**

Rats were placed prone, with the head mounted in a stereotaxic frame, such that bregma and lambda were positioned on the same horizontal plane. To expose the dorsal surface of the brain, a hole (2 mm diameter), centred 0.7 mm caudal to bregma and 1.4 mm lateral to the mid-line, was drilled into the skull. Unilateral microinjections (5 µl) were made using a fine glass micropipette (50–70µm tip diameter) inserted into the lateral brain ventricle (stereotaxic co-ordinates: 0.7 mm caudal to bregma, 1.4 mm lateral to the mid-line and 3.7–3.9 mm ventral to the surface of the dura). The micropipette was left in place for 1 min, after the microinjection. At the end of the experiment, a small amount of Pontamine Sky Blue was microinjected using the same co-ordinates to confirm microinjection into the lateral ventricle.

**Experimental protocols**

The MAP, HR and RSNA were measured before and for 180 min after administration of saline vehicle (n = 5; 5µl), leptin (7 µg in 5µl; n = 4), resistin (7 µg in 5µl; n = 5) and the
combination of both resistin and leptin (n = 6; leptin was administered 15 min after resistin). The doses of each hormone were chosen on the basis of previous studies (25-27). At the end of the experiment, the epididymal fat was removed and weighed.

**Statistical analysis**

**Within high fat diet**

The average resting levels of MAP, HR and integrated RSNA prior to hormone administration were compared between groups using one-way ANOVA. The integrated RSNA, averaged over 1-2 minutes, was calculated at 15 minute intervals over the period of 180 min, and expressed as a percentage of the resting level before the intracerebral injections. Changes in MAP, HR and RSNA over time following hormone/saline administration were compared between groups by using two-way ANOVA. When an overall significant difference between groups was detected, comparisons were made between individual groups, using Holm-Sidak’s test for multiple comparisons. The maximum responses in each variable were calculated by averaging the last 30 min of the observation period in each rat.

**Comparisons between high fat and normal chow diets**

The changes in RSNA, MAP and HR over time following leptin alone, resistin alone and the combination of leptin and resistin were compared between high fat and normal chow diets using two-way ANOVA. Data for the normal chow fed rats used for this comparison has been reported previously (25). The calculated maximum responses were compared between the dietary groups using Student’s unpaired t-test.

The body weight, average food intake, average caloric intake, and systolic blood pressure during the feeding period were compared between dietary groups using two-way ANOVA. Systolic blood pressure was measured via indirect tail cuff plethysmography. Due to a technical issue, systolic blood pressure was recorded before and for 6 weeks after the start of feeding. The percentage of whole body fat and the epididymal fat were compared between the dietary groups using Student’s unpaired t-test.

All results are expressed as means ± SEM. A value of P<0.05 was considered to be statistically significant. PRISM software was used (GraphPad San Diego, California, USA).
RESULTS

Rats fed a high fat diet

Effect on RSNA

The intracerebroventricular (ICV) injection of resistin alone and leptin alone increased RSNA significantly compared with the saline control (P<0.0001, figure 1). Resistin alone increased RSNA, which followed a similar time course to that of leptin and reached a maximum of 62±4%. Leptin alone increased RSNA, to a maximum of 71±16%. When resistin and leptin were combined, there was a significantly greater increase in RSNA (maximum change of 195±41%) than that observed following resistin or leptin alone (P<0.0001)(figure 1).

Effect on MAP and HR

There were no significant differences in the changes in MAP between the groups over the duration of observation (figure 2).

There was a significant difference between the groups in the HR responses over time (P<0.0001). However, by the end of the observation period, neither resistin nor leptin alone or both in combination induced a statistically significant change in HR compared to saline (figure 2).

The resting levels of both MAP and HR prior to hormone administration did not show any significant differences between groups (see figure 6).

Comparison of responses to leptin and resistin in rats fed high fat vs normal chow diets

RSNA
There was no statistically significant difference overall in the RSNA response elicited by resistin over time or in the maximum response in rats fed a high fat diet compared to the response in rats fed a normal chow diet (figure 3). Similarly, the RSNA response to leptin was not significantly different between rats fed the different diets (figure 3).

When resistin and leptin were combined, the increase in RSNA appeared to be slower in onset in the high fat fed rats and there was an overall statistically significant difference between groups (P<0.005 two-way ANOVA) (figure 3), but comparisons between individual time points failed to show a significant difference at any time point. Despite the apparent slower start, the maximum increase in RSNA was not significantly different by the end of the observation period from the response seen in rats fed normal chow (figure 3).

**MAP and HR**

There was a statistically significant difference detected in the change in MAP induced by resistin alone over time between rats fed the high fat and normal chow diets (P<0.05) (figure 4). The maximum change in MAP in the rats fed a high fat diet was significantly less than that seen in the normal chow fed rats (P<0.005) (figure 4). However, there were no significant differences in the changes on MAP over time or in the maximum responses in rats fed the high fat diet compared to the normal chow diet when leptin was administered alone or when leptin and resistin were combined (figure 4).

The HR response over time and the maximum change in HR induced by resistin alone in the high fat fed rats were significantly smaller than that observed in the rats fed a normal chow diet (figure 5). The HR response over time induced by leptin alone was also significantly smaller in the high fat fed rats (P<0.05), however, the maximum change in HR was not significantly different between the rats fed the different diets (figure 5). When leptin and resistin were combined there were no significant differences in the HR responses over time, or in the maximum HR changes observed in rats fed the two different diets (figure 5).
Basal MAP and HR prior to hormone administration in rats fed a high fat diet were not significantly different from those observed in rats fed a normal chow diet (figure 6).

**Comparison of systolic BP and metabolic parameters in rats fed high fat vs normal chow diets**

**Systolic blood pressure changes during the feeding period**

Systolic blood pressure in the high fat fed rats rose over time but this was not sustained and was not statistically different from that observed in rats fed the normal chow diet (figure 7).

**Metabolic Parameters**

The percent whole body fat mass was approximately 40% greater in the rats fed the high fat diet compared to the rats fed a normal chow diet (P<0.05) (figure 8). Similarly, epididymal fat was significantly greater, by approximately 50%, in the high fat compared to the normal chow fed group (P<0.005) (figure 8).

**Body weight, food and caloric intake**

Over time, body weight increased in both the high fat and normal chow fed groups of rats, with a small but significantly greater increase seen in the high fat fed group (P<0.005) (figure 9). This occurred despite the significantly lower average daily food intake in the high fat fed rats (P<0.0001) (figure 9). However, the average daily caloric intake was significantly greater in rats fed the high fat diet (P<0.0001) (figure 9).

**DISCUSSION**

The key findings of the present work are that in the high fat fed rats, resistin and leptin (alone and in combination) act in the brain to induce significant increases in RSNA and that combining resistin and leptin elicited significantly greater effects than either hormone alone.
Further, MAP and HR responses induced by resistin, leptin and both combined were not significantly different from the control group. Comparing the responses induced by the hormones in the high fat fed rats to those observed in the rats fed normal chow showed that the high fat diet had no effect on the maximum increases in RSNA. The results suggest that with high fat feeding, the increase in RSNA induced by resistin is not reduced.

The increase in RSNA induced by centrally administered resistin in the high fat fed rats was significantly greater than in the control group, and was similar to that observed in rats fed a normal chow diet. Thus, the sensitivity to the sympatho-excitatory effects on RSNA induced by resistin was not affected by high fat feeding. This was similar to our observations with leptin. Our findings with leptin are in agreement with studies in the rodent that show high fat feeding does not reduce the sympatho-excitatory RSNA responses to leptin (14, 20, 28). In the rabbit, however, the RSNA response to leptin was greater following high fat feeding (23).

Since the effects of leptin on sympathetic outputs like lumbar and brown adipose tissue are reduced by high fat diets, as is the effect on dietary intake (14, 20), the evidence indicates that the RSNA response elicited by leptin may be selectively resistant to the actions of high fat feeding (19, 21, 22, 29). Our present findings suggest that the excitatory effects on RSNA are not influenced by high fat diets and this could be interpreted to mean that resistin’s actions on RSNA are also resistant to the desensitising effects of high fat diets. The influence of high fat diets on responses in lumbar- and brown adipose tissue sympathetic nerve activity elicited by resistin have not been investigated to date. In rats fed normal chow resistin increases lumbar sympathetic nerve activity which also occurs with leptin (11, 27). In contrast, resistin reduces sympathetic nerve activity to brown adipose tissue, and hence thermogenesis, which is opposite to leptin (27, 30). This could contribute for the conclusion that resistin induced resistance to leptin’s thermogenic effects (31).

In the high fat fed rats, the combined administration of leptin and resistin produced a greater response in RSNA compared to each hormone alone. A similar effect was observed in normal chow fed rats (25). The magnitude of the enhancement was similar by the end of the
observation period irrespective of the dietary regime. This also suggests that the sensitivity of the RSNA response elicited by resistin and leptin is not markedly affected by high fat diets.

There did appear to be a slower onset in the RSNA response elicited by the combination of resistin and leptin in the high fat fed rats compared to normal chow fed rats. This suggests there may be some influence of diet on the development of the sympatho-excitatory RSNA response, though not on the magnitude of the response. The influence of the high fat diet, on the development of the RSNA response, however, was not observed when either hormone was administered alone. The renal sympatho-excitatory effects of resistin and leptin involves phosphatidylinositol-3-kinases (10, 13). Thus the present findings suggest that this mechanism is not influenced by high fat feeding. This contrasts to the anorexigenic effect of leptin where the evidence suggests that intracellular transduction pathways involving SOCs3, PTP1B and PKA mediate the decreased sensitivity to leptin receptor activation seen with high fat diets (32-34).

It has been argued that changes in receptor densities with different diets could also influence sensitivity to leptin and resistin. The receptor for resistin has not been identified, hence, there are no studies investigating receptor distribution for resistin. Leptin receptors have been investigated and the receptor density in the brain does not appear to change markedly with high fat feeding (35). However, the receptor protein levels were reduced with high fat feeding suggesting this could contribute to the decreased sensitivity observed to some of the actions of leptin (35). The increased circulating levels of leptin and resistin that are associated high fat feeding and increased adiposity would therefore be less effective if the receptor protein levels are reduced. However, the present study suggests this does not appear to influence the RSNA response elicited by centrally administered leptin or resistin.

The MAP responses to resistin alone, leptin alone and both combined were not significantly different compared to control in the high fat fed rats. Compared to the responses seen in the rats fed a normal chow diet, the maximum changes in MAP induced by leptin alone, or leptin combined with resistin were not significantly different to those in the high fat fed rats.
Interestingly, the maximum change in MAP elicited by resistin alone was lower in the high fat fed group compared to the normal chow fed group.

Previous studies with leptin in high fat fed rodents have shown that the acute effect of leptin on MAP was not influenced by the diet (20). In rabbits fed a high fat diet, however, acute ICV administration of leptin resulted in an increased MAP and this response was similar to that seen in rabbits fed a normal diet (23, 36). In longer term studies, the MAP response induced by a chronic infusion of leptin was not increased by a high fat diet in rodents (20).

To date there are no reports of the effects of chronic longterm infusion of resistin on blood pressure. Thus, it remains to be determined whether chronic infusion of resistin can increase blood pressure and whether the response can be influenced by a high fat diet.

In the high fat fed rats the HR responses to each hormone alone or in combination were not significantly different compared to control. The comparisons of the maximum changes in HR seen in the rats fed a normal chow or a high fat diet showed there were no significant differences following leptin alone or in combination with resistin. However, the maximum change in HR with resistin alone was lower in the high fat fed group, as was seen with MAP. The physiological relevance of the differences in the HR and MAP responses between the diets following resistin alone are difficult to interpret. We suspect the differences are probably a statistical anomaly since the changes in MAP and HR elicited by resistin alone within the high fat diet group was not significantly different from the saline control.

In the present study, systolic BP over the duration of the dietary feeding regime was not significantly elevated by the high fat diet compared to normal chow feeding. This is similar to previous studies using wistar rats fed a high fat diet for 10-20 weeks which did not show an elevation in blood pressure (37). Sprague-Dawley rats may segregate into obese prone and obese resistant rats but only those prone to obesity are reported to have increased blood pressure following 8-10 weeks of a high fat diet (38) or 13 weeks of a high fat diet (39). In the present study we used Sprague Dawley rats fed for up to 10 weeks and we suspect the difference may be that we did not see any evidence of segregation. We did see a small but
significantly greater increase in body weight over time in the high fat fed rats though this was smaller than that observed in the obese prone rats previously reported (38, 39). By contrast we have observed that Long-Evans rats fed a western diet (60% fat) had a small but significant increase in blood pressure compared to normal chow fed rats (40). In mice it has been found that when they are fed a high fat diet for 10 weeks they become obese with an elevated blood pressure when measured directly using radiotelemetric probes (20). In the present study we measured blood pressure via tail cuff plethysmography which will not detect small differences accurately. In rabbits, high fat feeding for only 4 weeks appears sufficient to induce hypertension (23). Thus, elevations in blood pressure in rodents fed high fat diets seems to be variable and may depend on various factors including the strain, amount of fat in the diet and the duration of feeding, whereas rabbits appear to be particularly susceptible to obesity-induced hypertension.

There was a small increase in body weight over time with the HFD. This was due to the increased intake of calories by rats on the high fat diet, even though the rats reduced their average daily intake of the high fat diet. We did not observe any segregation of rats into obese-sensitive or obese-resistant groupings in this study, although this has been reported (39). Nonetheless, there was a clear redistribution of body fat in rats fed the high fat diet such that there was a 40% increase in percent body fat and a larger increase in the amount of epididymal fat present. Thus, although we did not observe an overt obesity in the high fat fed rats, a clear redistribution of body fat was seen.

**Perspective Views**

In high fat fed rats ICV administration of resistin or leptin alone increased RSNA. The combination of both hormones resulted in a greater increase in RSNA compared to each hormone alone. The responses were similar in magnitude to those observed in rats fed a normal chow diet, suggesting that feeding a high fat diet sufficient to markedly alter visceral fat distribution, but elicit only a small, but statistically significant, increase in body weight, does not diminish the greater increase in RSNA. Thus, we find no evidence of a reduced sensitivity of the RSNA response elicited by centrally administered resistin.
Furthermore, our study suggests that in conditions in which both resistin and leptin are elevated, such as in obesity and diabetes, there may be greater sympatho-excitatory actions on RSNA, compared to that elicited by each hormone alone. This may contribute to the long term cardiovascular complications associated with those conditions, however, this requires further investigation.

Legends

Figure 1. Percent change in renal sympathetic nerve activity (RSNA) from baseline levels over time in rats fed a high fat diet after intracerebroventricular injection of leptin (n=4) (7μg/5μl), resistin (n=5) (7μg/5μl), control (saline, n=5) (5μl) and the combination of leptin and resistin (n=6).

(*P<0.0001 leptin alone, resistin alone and the combination of both hormones compared to saline; #P<0.0001 combination of leptin and resistin compared to leptin alone or resistin alone)

Figure 2. Change in mean arterial pressure (MAP) and heart rate (HR) over time in rats fed a high fat diet induced by the intracerebroventricular administration of leptin (n=4) (7μg/5μl), resistin (n=5) (7μg/5μl), control (saline, n=5) (5μl) and the combination of leptin and resistin (n=6).

Figure 3. Renal sympathetic nerve activity (RSNA) responses between rats fed a normal chow (ND) and a high fat diet, elicited by intracerebroventricularly administered resistin (n=4 ND, n=5 HFD) (7 μg/5 μl), leptin (n=5 ND, n=4 HFD) (7μg/5μl), the combination of leptin and resistin (n=6 ND and HFD) and saline (n=5 ND, n=5 HFD) (5μl). Left panels show changes in RSNA over time; Right panels show the average maximum change in RSNA. *P < 0.005 compared to ND.

Figure 4. Comparison of the mean arterial pressure (MAP) responses between rats fed a normal chow (ND) and a high fat diet, elicited by intracerebroventricularly administered resistin (n=4 ND, n=5 HFD) (7 μg/5 μl), leptin (n=5 ND, n=4 HFD) (7μg/5μl), the combination of leptin and resistin (n=6 ND and HFD) and saline (n=5 ND, n=5 HFD) (5μl). Left panels show changes in MAP over time; Right panels show the average maximum change in MAP. *P < 0.005 compared to ND.
Figure 5. Comparison of the heart rate (HR) responses between rats fed a normal chow (ND) and a high fat diet, elicited by intracerebroventricularly administered resistin (n=4 ND, n=5 HFD) (7 μg/5 μl), leptin (n=5 ND, n=4 HFD) (7μg/5μl), the combination of leptin and resistin (n=6 ND and HFD) and saline (n=5 ND, n=5 HFD) (5μl). Left panels show changes in HR over time; Right panels show the average maximum change in HR. *P < 0.05 compared to ND; #P < 0.0001 compared to ND.

Figure 6. Basal levels of integrative renal sympathetic nerve activity (RSNA), mean arterial pressure (MAP) and heart rate (HR) in rats fed normal chow diet (ND; open bar) (n=15) and high fat diet (HFD; black bar) (n=15) before intracerebroventricular administration of resistin (7 μg/5 μl), leptin (7μg/5μl) and the combination of both hormones.

Figure 7. Systolic blood pressure over time in rats fed a normal chow diet (ND) (n=11) and high fat diet (HFD) (n=11).

Figure 8. Upper panel: Effect of high fat diet (HFD (n=13) on the whole body fat mass compared to rats fed a normal chow diet (ND) (n=12). *P < 0.05. Lower panel: Effect of high fat diet (HFD (n=16) on the epididymal fat mass compared to rats fed a normal chow diet (ND) (n=15). #P< 0.005 between groups.

Figure 9. Effect of high fat diet (HFD; n=17-19) on the body weight, food intake per day and average calorie intake per day over time compared to rats fed a normal chow diet (ND) (n=13). #P < 0.005, *P< 0.0001 between groups.

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