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## Forced and voluntary exercise counteract insulin resistance in rats: The role of coping style

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### ABSTRACT

There are large individual differences in the success rates of exercise intervention programs aimed at the prevention and treatment of obesity-related disorders. In the present study, we tested the hypothesis that differences in coping style may impact the success rates of these intervention programs. We tested insulin responses before and after voluntary wheel running in both passive (insulin resistant) Roman Low Avoidance (RLA) and proactive (insulin sensitive) Roman High Avoidance (RHA) rats using intravenous glucose tolerance tests (IVGTTs). To control for a potential difference between voluntary and forced exercise, we also included RLA and RHA rats that were subjected to forced running. We found the following: 1) when given the opportunity to run voluntarily in a running wheel, passive RLA rats run more than proactively than RHA rats; 2) voluntary exercise leads to a normalization of insulin responses during an IVGTTs in RLA rats; and 3) there were no behavioral and physiological differences in efficacy between voluntary and forced running. We conclude that exercise, both forced and voluntary, is a successful lifestyle intervention for the treatment of hyperinsulinemia, especially in individuals with a passive coping style.

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### Introduction

Successful lifestyle interventions may halt the ever-increasing prevalence of metabolic disorders such as obesity, metabolic syndrome and type 2 diabetes (Dunstan et al., 1997). Exercise-based intervention programs are particularly successful (Torjesen et al., 1997); for a recent review, see McCall and Raj, 2009. Exercise reduces body adiposity, improves glucose tolerance and increases insulin sensitivity (Afonso and Eikelboom, 2003; Alessio et al., 2005; DeFronzo et al., 1987; Ebeling et al., 1993; Hughes et al., 1993; Mayer-Davis et al., 1998). There are, however, large individual differences in the success rates of exercise intervention programs (Teixeira et al., 2004), partly due to large individual differences in susceptibility to these metabolic disorders (recently reviewed in Andreassi, 2009). Our working hypothesis is that differences in coping style may explain the large individual variation in success rates of exercise intervention programs for metabolic disorders such as type 2 diabetes and metabolic syndrome.

Differences in coping style are a widespread phenomenon in the animal kingdom (Careau et al., 2010; Wolf et al., 2008). In general, there are two distinct coping styles: a proactive coping style and a passive coping style. Evolutionarily, these coping styles are thought

to be adaptive in different environmental settings; the proactive coping style has a higher fitness in a territorial setting, but the passive coping style has a higher fitness in a migratory setting. These different behavioral strategies may also have led to different metabolic profiles in passive or proactive coping individuals. This is, however, largely ignored in animal studies modeling the development of type 2 diabetes, insulin resistance or metabolic syndrome. In recent studies, we have addressed this issue using the Roman High (RHA) and Low Avoidance (RLA) rat selection lines (Boersma et al., 2009, 2010, 2011b). Rats from these selection lines differ in several neuroendocrine, cardiovascular and metabolic parameters (Boersma et al., 2009; Corda et al., 1997; Giorgi et al., 2003), as well as in emotional reactivity and coping style. RLA rats are highly emotional and have a passive coping style; RHA rats have an active coping style and low emotional reactivity. We recently demonstrated that the passive animals already at normal weight display several characteristics of metabolic syndrome, such as insulin resistance, visceral adiposity and hypertension (Boersma et al., 2009, 2010, 2011a, 2011b). We have extended and confirmed these findings in both passive and proactive outbred, wild-type Groningen rats. In these rats, coping style appeared to predict changes in metabolic profiles that were analogous to those observed in RHA and RLA rats (Boersma et al., 2010, 2011b).

In the present study, we focused on how differences in coping style affect the potential benefits of exercise on insulin resistance and visceral adiposity. Using both passively coping (insulin resistant) RLA and proactively coping (insulin sensitive) RHA rats, we performed a

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series of experiments where the insulin response of each rat was measured using an intravenous glucose tolerance test (IVGTT) under sedentary conditions and after 18 days of exercise in a running wheel.

In most animal studies, exercise consists of voluntary running in a wheel. Voluntary running in rats is used to mimic exercise programs in humans. However, these programs are perceived, at least by some of the participants, as unpleasant, stressful or aversive. Therefore, there is a discrepancy between voluntary exercise in the rat model and exercise in humans. To control for a potential difference between stressful and stress-free exercise, we also included two groups of RHA and RLA rats that were subjected to 18 days of forced running in a motorized running wheel. The forced running was designed to mimic the voluntary running patterns of proactively coping rats. This set-up ensured that we did not overexert the animals and that their normal circadian patterns were not disturbed.

## Materials and methods

### Animals

The experiments were approved by the local animal experimental welfare and care committee (DEC, Groningen, the Netherlands). Male RHA and male RLA rats obtained from a breeding colony at the Clinical Psychopharmacology Unit (APSI) at the University of Geneva were 10 weeks of age at the start of the experiment and were housed in a room controlled for temperature and humidity ( $20 \pm 2$  °C; 60%). The room was kept on a light–dark cycle of 12–12 h (lights on = CT 0 at 01:00 h, lights off = CT 12 at 13:00 h). The rats were fed a standard lab chow diet (*Hope Farms, RMH-B knaagdier korrel, Arie Block Diervoeding, Woerden, NL*; 3.7 kcal/g, 14% fat, 28% protein, 58% carbohydrates). Food and water were available ad libitum.

### Experimental design

In experiment 1, both RHA and RLA rats underwent an intravenous glucose tolerance test (IVGTT) at baseline and after 18 days of voluntary wheel running. In experiment 2, both RHA and RLA rats underwent IVGTTs at baseline and after 18 days of forced wheel running. For both studies, the rats underwent surgery to place two indwelling jugular vein catheters for use in infusion and blood sampling (Steffens, 1967). The rats were accustomed to the infusion and blood sample procedures before the onset of the experiments (Steffens, 1969). The experiments began 2 weeks after surgery, and throughout the experiments, body weights and food intake were measured daily (Table 1). The experimental design is summarized in Fig. 1.

### Experiment 1

Twelve rats (6 RHA and 6 RLA) were housed in standard cages ( $24 \times 24 \times 32$  cm). Two weeks after surgery, at day  $-14$ , a baseline IVGTT was performed. At day  $-10$ , the rats were transferred to standard running wheel cages (Nalgene polycarbonate running wheel cages [50–27–36 cm]) where they had free access to a running wheel (diameter 27 cm, Mini Mitter, Oregon, USA). The rats were

**Table 1**

Body weights of RLA and RHA rats during forced and voluntary running. Weights are presented in grams. Baseline = last day of baseline measurements, Habituation = last day of habituation to running, and intervention = last day of intervention period.

Group	Time	RLA	RHA
Voluntary	Baseline	410 ± 13	386 ± 8
Forced	Baseline	485 ± 11	446 ± 19
Voluntary	Habituation	417 ± 16	403 ± 10
Forced	Habituation	446 ± 14	419 ± 11
Voluntary	Intervention	431 ± 10	412 ± 10
Forced	Intervention	431 ± 12	406 ± 10

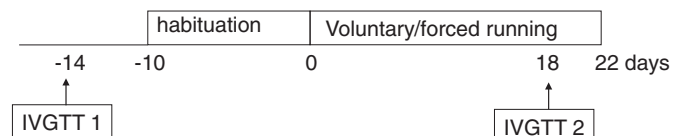
habituated to wheel running for 10 days. During this habituation period, running activity typically increases then subsequently stabilizes (Afonso and Eikelboom, 2003). After the habituation period, rats were allowed to run voluntarily for 18 days (intervention period: day 0 until day 18). A second IVGTT was performed on day 18. Four days later, the rats were sacrificed for carcass analysis.

### Experiment 2

Sixteen rats (8 RLA and 8 RHA) were housed in standard cages ( $24 \times 24 \times 32$  cm). A baseline IVGTT was performed at day  $-14$ . At day  $-10$ , the rats were transferred to forced activity cages (TSE, Bad Homburg, Germany). These cages consist of polycarbonate running wheels, with a diameter of 25 cm and a width 15 cm, which are motor operated and force the animal to run. The cages were equipped with food hoppers and water bottles, giving the animal ad libitum access to food and water. The rats were housed in these cages during the forced running period. Both running speed and running time are controlled. All animals were forced to run on a schedule that mimicked the voluntary running activity patterns of the proactive RHA rats that participated in experiment 1 (see Fig. 3B). Because we observed that rats run in cycles of approximately 5 min, we decided to force the animals to run on a schedule of 5 min of running and 5 min of rest. The speed (max 20 m/min) was adjusted so that the total distance per hour was similar to that of the RHA rats. The rats were habituated to forced running for 10 days (day  $-10$  until day 0). Intensity and duration were slowly increased according to the increase in running during the habituation period of the voluntary running animals in experiment 1. Although we cannot exclude possible stress responses to forced running during the training period. Running occurred only during the dark phase, and running patterns mimicked the average hourly running activity of the voluntary running RHA rats. Similar to the voluntary running rats, the forced running rats had ample time to eat, sleep and drink, and the effects of altering their circadian rhythms were minimized. During the forced activity intervention period, day 0 until day 18, the rats were forced to run 5000 m/day. A second IVGTT was performed on day 18. Four days later, the rats were sacrificed for carcass analysis.

### Intravenous glucose tolerance test

On the day of an IVGTT, food was removed at the beginning of the light phase at CT 0. The IVGTTs were performed during the light phase between CT 4 and CT 6. An IVGTT consisted of an infusion of 15 mg glucose in 0.1 ml saline per minute for 30 min, resulting in a total infusion of 450 mg glucose in 3 ml saline. Before the infusion, two baseline samples (0.2 ml) were taken at  $t = -11$  and  $-1$  min, and the infusion of glucose was started at  $t = 0$  min. Additional blood samples were taken at time points  $t = 5, 10, 15, 20, 25, 30, 35, 40,$  and 50 min; a total blood volume of 2.2 ml was taken. Blood samples were kept on ice and stored using 10 µl EDTA (0.09 g/ml). For glucose determination, 50 µl of full blood with 450 µl heparin solution (2%) was stored at  $-20$  °C until analysis. Blood glucose levels were determined using the ferry-cyanide method with a *Technicon AutoAnalyzer*. The remaining blood was centrifuged for 15 min, and plasma was stored for the determination of insulin and corticosterone concentrations. Plasma levels of insulin and corticosterones were measured with commercial radioimmunoassay (RIA) kits (Linco Research and M P Biomedicals). Intra- and inter-assay coefficients of variation for



**Fig. 1.** The experimental design for experiment 1 and experiment 2.

reference plasma were analyzed in duplicate, and the coefficients for the insulin and corticosterone assays were between 6.5–11.3% and 10.3–16.8%, respectively.

### Carcass analysis

An extensive carcass analysis was performed 4 days after the final IVGTT. Rats were sacrificed using an overdose of pentobarbital. Epididymal and retroperitoneal fat pads and the liver were removed and weighed, the skin and subcutaneous fat were removed from the carcass, and the liver, skin, and carcasses were dried at 80 °C for 5 days. The fat content was measured by extracting fat from the tissue using a petroleum-based Soxhlet fat extractor. After fat extraction, the tissue was dried for 5 days again. The difference between dry tissue weight before and after fat extraction was used to determine the fat content of the tissue.

### Data analysis

Food intake and body weight data are presented as daily averages with the standard error of the mean (SEM). Average running wheel activity for each individual animal was calculated as an average from day 0 until day 18. Glucose and insulin levels of each group are presented as an average with the standard error of the mean. Significant differences between groups were determined using repeated measures ANOVA followed by Tukey's post-hoc test where coping style and type of intervention were the between-subject factors and time of measurement was the within-subject factor. The area under the curve (AUC) of insulin responses was calculated and averaged in Microsoft Excel using the Lebesgue approach. The percentage of fat mass was calculated by dividing the total dry fat mass by the total dry, lean body mass and multiplying by 100%. Fat mass and weight of the different fat pads are presented as group averages with the standard error of the mean. Differences in the area under the insulin response curve and body composition were statistically tested with one-way ANOVA followed by Tukey's post-hoc analysis where coping style and type of intervention were the between-subject factors. All statistical analyses used a 5% confidence interval.

## Results

Fig. 2 displays body weight gain and food intake of the different groups during the intervention period from days 0 to 18. There were no differences in food intake or body weight gain among any of the groups. In all groups, food intake was higher during the intervention period compared to intake during the baseline period (baseline:  $101 \pm 4.8$  kcal/day; intervention:  $120 \pm 5.6$  kcal/day;  $F(1, 27) = 4.562$   $p < 0.05$ ). Fig. 3A displays the circadian pattern of running activity for all groups on the last day of habituation. The total daily activity

remained constant in all experimental groups after habituation (RM-ANOVA, TIME: no significant difference). In experiment 1, RLA rats ran significantly more than RHA rats (RM-ANOVA, Time\*group  $F(17, 151) = 9.332$   $p < 0.01$ ; Group  $F(1, 27) = 14.236$   $p < 0.01$ ).

Blood glucose and plasma insulin levels are presented in Fig. 4. There were no significant differences in blood glucose levels among the groups. Insulin responses were significantly different ( $F(5, 39) = 6.294$ ,  $p < 0.01$ ) in the following ways: 1) at baseline, RLA rats have a much higher insulin responses than RHA rats ( $p < 0.01$ ); 2) insulin responses in RLA rats were much higher at baseline than after 18 days of both voluntary and forced exercise (voluntary running  $p < 0.01$ ; forced running  $p < 0.01$ ); and 3) insulin responses in RHA rats were higher at baseline than after 18 days of voluntary but not forced exercise (voluntary running  $p < 0.05$ ; forced running  $p = 0.103$ ). There were no differences in plasma insulin responses between voluntary runners and forced runners, both under baseline conditions and after 18 days of exercise.

Corticosterone levels at the end of the light phase were not different between the forced and voluntary running rats under any circumstances (RLA baseline:  $250 \pm 35.3$  ng/ml; RHA baseline:  $225 \pm 29.3$  ng/ml; RLA voluntary running:  $242 \pm 29.7$  ng/ml; RHA voluntary running:  $226 \pm 25.3$  ng/ml; RLA forced running:  $263 \pm 29.7$  ng/ml; RHA forced running:  $233 \pm 25.26$  ng/ml). Baseline levels of corticosterones at the circadian peak tended to be higher in the passive RLA rats compared to the proactive RHA rats, but this difference did not reach statistical relevance.

Carcass analysis showed that there were no differences in the percentages of body fat at the end of the study (RLA voluntary running:  $35.9 \pm 0.47\%$ ; RHA voluntary running:  $34.9 \pm 0.54\%$ ; RLA forced running:  $33.3 \pm 0.56\%$ ; RHA forced running:  $33.1 \pm 0.62\%$ ). The distribution of body fat was, however, different between the groups; the passive RLA rats have relatively more fat in the epididymal depot compared to the proactive RHA rats (RLA voluntary running:  $4.42 \pm 0.24$  g; RHA voluntary running:  $3.91 \pm 0.21$  g; RLA forced running:  $5.8 \pm 0.49$  g; RHA forced running:  $3.6 \pm 0.26$  g; ( $F(3, 25) = 6.426$   $p < 0.05$ )). There was no difference between RLA rats and RHA rats in the amount of fat distributed in the retroperitoneal fat depot (RLA voluntary running:  $7.7 \pm 0.77$  g; RHA voluntary running:  $7.1 \pm 0.69$  g; RLA forced running:  $8.1 \pm 0.76$  g; RHA forced running:  $7.6 \pm 0.84$  g).

## Discussion

The aim of the current study was to investigate the interaction between coping style and exercise and its effects on the treatment of hyperinsulinemia. The major findings of this study were as follows: 1) when given the opportunity to run voluntarily in a running wheel, passively coping RLA rats run more than proactively coping RHA rats; 2) voluntary exercise by the passively coping RLA rats leads to the normalization of their insulin responses during IVGTTs;

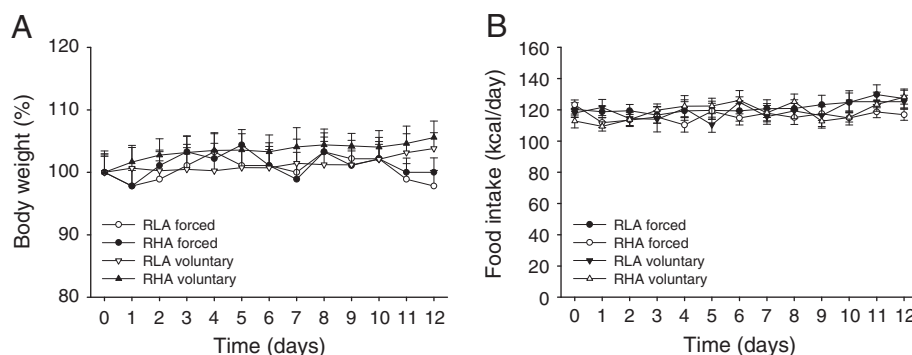
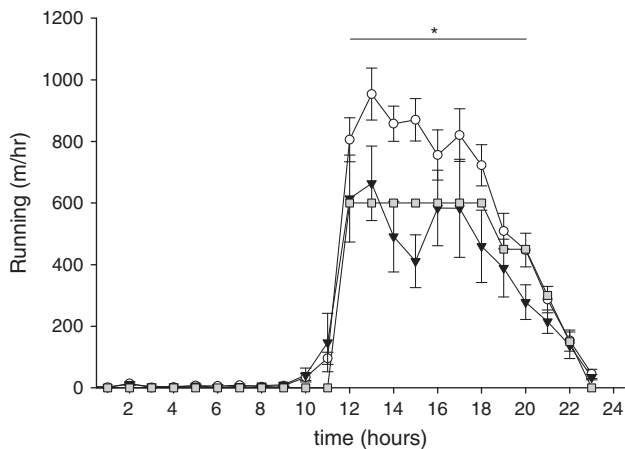


Fig. 2. Body weight gain and food intake during voluntary or forced exercise in passive and proactive rats. Black circles = proactive forced runners ( $n = 8$ ), white circles = passive forced runners ( $n = 8$ ), black triangles = proactive voluntary runners ( $n = 6$ ), white triangles = passive forced runners ( $n = 6$ ).





**Fig. 3.** Average running activity the last day of habituation during experiments 1 and 2. White symbols = voluntary running RLA rats, black symbols = voluntary running RHA rats, gray symbols = forced running rats of both strains. \* indicates a significant difference between voluntary running RLA and RHA rats.

and 3) there are no behavioral and physiological differences between voluntary and forced running.

Consistent with our previous studies, passive RLA rats displayed a much higher insulin response to an intravenous glucose tolerance test under baseline conditions compared to proactively coping RHA rats (Boersma et al., 2009). Although no hyperglycemia was observed and the hyperinsulinemia in these animals may not reflect a pathological state, the increased insulin response to an IVGTT suggests that these passively coping RLA rats may be more prone to insulin resistance and possibly type 2 diabetes. Exercise completely normalized this elevated insulin response to control levels, indicating that our relatively short-term exercise intervention was successful in the treatment of hyperinsulinemia, particularly in rats with a passive coping style.

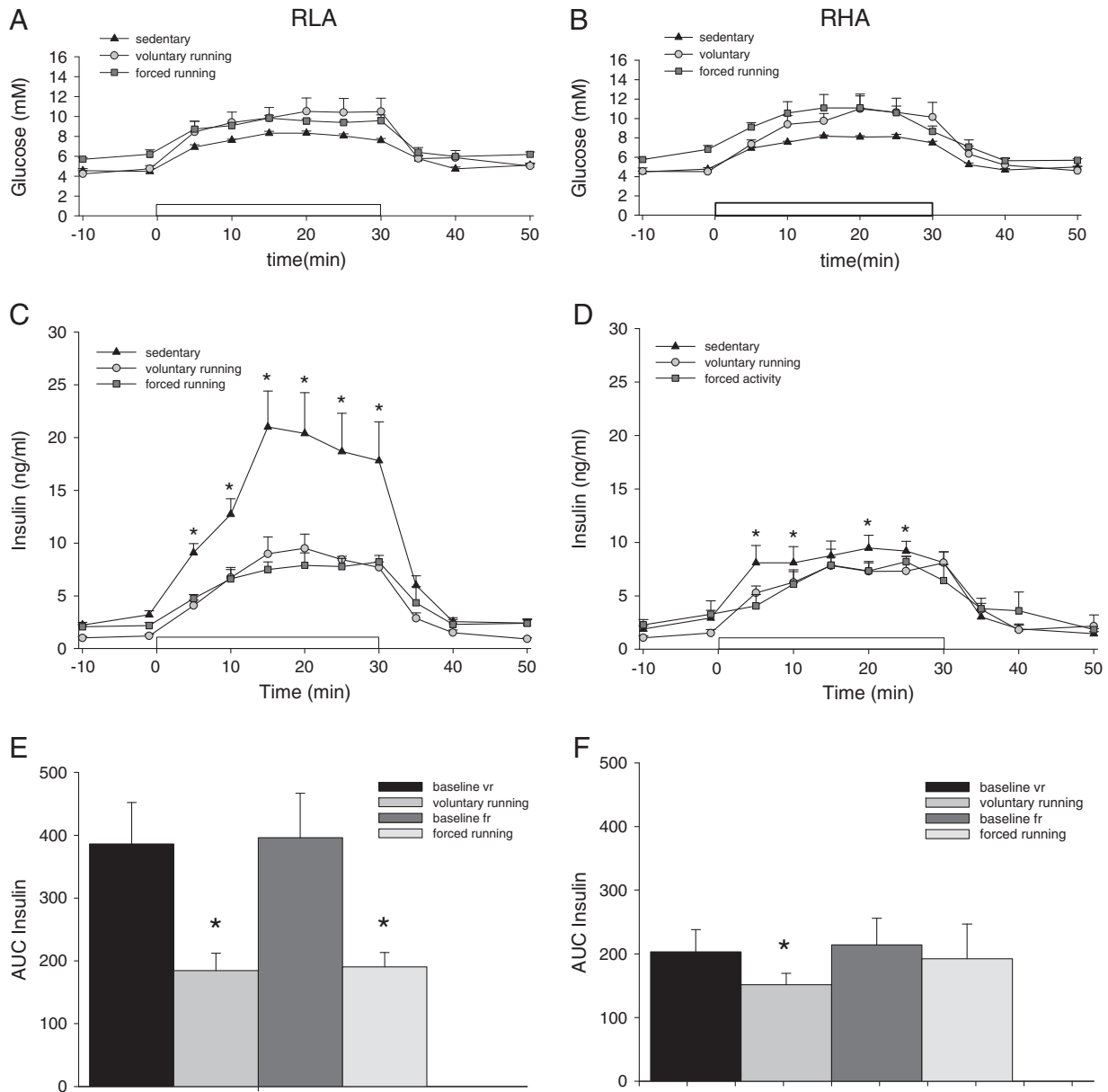
Interestingly, passively coping RLA rats showed increased running activity when they were allowed to run voluntarily. This is remarkable because these 'passive' rats are generally characterized as having lower activity levels during behavioral tests. This typical passive behavior has been observed in several different experiments such as the open field test, the Porsolt forced swim procedure and the elevated plus maze test (Ferre et al., 1995; Smith and MacKenzie, 2006; Steimer and Driscoll, 2005). However, these tests all record short-term responses to unfamiliar conditions, whereas in our study, we monitored internal motivation for activity in a familiar environment. This difference in activity levels under novel versus habituated conditions became apparent when the rats were first housed in running wheel cages. For the first 3 h, running wheel activity was higher in the proactively coping RHA rats; however, after 4 h, the running activity of passively coping RLA rats exceeded that of their proactively coping RHA counterparts (data not shown).

Increased running by the passively coping RLA rats resulted in a normalization of the insulin response during an IVGTT, which is a strong indicator of improved insulin sensitivity. Increased spontaneous wheel running in metabolically deranged rodents has been reported before in overweight animal models such as the OLETF rat (Bi et al., 2005) and the MC4 knockout mouse (Haskell-Luevano et al., 2009), among others. Both the OLETF and the MC4 knockouts have an obese and insulin-resistant phenotype under sedentary conditions, but these animals compensate for this phenotype by increased activity when voluntarily running in wheels, leading to a normalization of their body weight. In the present study, we observe that presumably insulin-resistant rats increase running activity to normalize their insulin sensitivity.

A possible explanation for the observed difference in running activity between the passively coping RLA and proactively coping RHA rats may be the different metabolic states of these animals under sedentary conditions. The passively coping RLA rats are hyperinsulinemic and may have impaired insulin signaling. With exercise, muscular contractile activity causes glucose transporter type 4 (GLUT4) translocation and increases glucose uptake (Ploug and Ralston, 1998); hence, exercise may benefit the insulin resistant passively coping RLA rats in particular. Along these lines, it may be speculated that exercise has a larger impact on glucose availability to neuronal circuitry (Bequet et al., 2000) in passively coping RLA rats than in proactively coping RHA rats. This effect might be a mechanism by which passively coping RLA rats sustain a higher level of running wheel activity than proactively coping RHA rats. Additionally, because the proactive coping style seems to have a higher fitness under territorial stable conditions whereas the passive coping style seems better suited to migratory setting, there may be differences in evolutionary drive towards high activity in familiar conditions in passive and proactive coping rats. This hypothesis, however, needs further investigation. Another implication of these results is that the sedentary state, at least in rodents, should not be considered as the proper control condition because physical activity and health are inevitably linked (Booth et al., 2006). This point is illustrated by the healthy insulin profiles in the voluntary running passively coping RLA rats.

We argued in the Introduction that the translational value of results derived from voluntarily exercising animals might be limited because humans subjected to exercise-based interventions may perceive these interventions as a stressful workload. Our second study, therefore, investigated differences in the efficacy of forced and voluntary exercise in passively coping RLA rats. We showed that both forced and voluntary running resulted in normalized insulin responses to an IVGTT in the passively coping RLA rats. This result suggests that the exercise itself rather than the voluntary or forced nature of running determines the beneficial effects of running on insulin sensitivity. In the current study, the amount of forced running was based on the average voluntary running activity of the proactively coping RHA rats. Proactive rats were shown to voluntarily run less than passive rats. Because this forced running improved insulin signaling in the passively coping RLA rats, the amount of running might not be crucial for the attenuation of hyperinsulinemia in the RLA rats. Although it seems that the higher level of activity observed in passive coping rats does not influence their plasma insulin levels, the hyperactivity observed in the passive coping individual may have a beneficial effect on the metabolic parameters of these animals. Further research is needed to elucidate possible functional properties of hyperactivity in the passively coping rat.

The current set-up was chosen to minimize the stress of the forced running paradigm, especially because it might be perceived differently in passively coping RLA and proactively coping RHA rats. A correlation between the circadian corticosterone levels and hyperinsulinemia in the passively coping RLA rats was previously reported in sedentary RLA and RHA rats (Boersma et al., 2009), and a more recent study using a glucocorticoid receptor antagonist confirmed the hypothesis that glucocorticoid signaling plays a major role in the development of hyperinsulinemia in the sedentary RLA rat (Boersma et al., 2011a). However, in the current study, no correlations between hyperinsulinemia and corticosterone levels at the circadian peak were observed in exercising animals. Because exercise may alter the circadian rhythmicity of corticosterone release in both RLA and RHA rats, more thorough studies of circadian corticosterone levels in exercising RLA and RHA rats are needed to fully understand the relationship between glucocorticoids and hyperinsulinemia in exercising rats. Furthermore, a difference in perceived workload might also be important when studying exercise-based lifestyle interventions. In humans individuals with proactive personality traits arguably have a lower perception of exertion and endure higher amounts of exercise than individuals with passive personality traits (Hassmen et al., 1993). Nevertheless, observing no behavioral and



**Fig. 4.** Blood glucose (A and B) and plasma insulin (C and D) levels before, during and after an IVGTT at baseline and after 18 days of voluntary or forced running in both RLA (A and C) and RHA rats (B and D). Black triangles = baseline, light gray circles = voluntary runners, dark gray squares = forced runners. Figs. 4E and F present the area under the insulin curve at baseline and after 18 days of voluntary and forced running in RLA (E) and RHA (F) rats. Black bars = baseline voluntary runners, medium gray bars = 18 days voluntary running, dark gray bars = baseline forced runners, light gray bars = 18 days forced running. vr = voluntary running, fr = forced running. \* indicates a significant difference between baseline conditions and both voluntary running and forced running conditions.

physiological differences between voluntary and forced running animals strengthens the validity of the voluntary rat model for translation to human studies. Finally, we conclude that exercise, either forced or voluntary, may serve as a successful lifestyle intervention for the treatment of hyperinsulinemia, especially in rats with a passive coping style.

#### Disclosure

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