Coping styles and the pathophysiology of energy metabolism
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Personality determines physical activity levels dependent on dietary conditions.

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Running wheel activity was shown to attenuate the development of hyperinsulineamia in the extremely passive coping RLA rats (1). In the current study, we studied the effects of voluntary activity on body weight, glucose homeostasis and insulin sensitivity in animals with more moderate passive and proactive personalities on either a standard chow or an obesity promoting high fat diet. Passive and proactive rats from the Roman (extreme) and the WTG (moderate), were given voluntary access to treadmills for three weeks. Glucose and insulin profiles were assessed during an intravenous glucose tolerance test (IVGTT) before and after wheel running. In a second experiment all groups of rats initially had treadmill access on control diet, but after 20 days were switched to the high fat diet. This study revealed that 1) voluntary running in beneficial for extreme and moderate passive rat characterized by hyperinsulineamia, and 2) that passive coping rats increase voluntary running activity in response to a switch in diet, whereas proactive rats do not. The results of this study indicate that passive rats are vulnerable for the development of hyperinsulineamia under sedentary conditions, but that these rats adapt their physical activity level to changes in dietary conditions and are thus benefit from availability of physical activity opportunities. Proactive rats, on the other hand are less susceptible to develop hyperinsulineamia, however, these rats do not display alterations in physical activity levels in response to overeating and may therefore benefit less from physical activity when hyperinsulineamia does occur.
Introduction:

Obesity is one of the most important risk factors for cardiovascular disease and metabolic disorders such as type 2 diabetes. In western societies, obesity is mainly caused by a combination of increased availability of palatable energy rich food and a sedentary lifestyle. Treatment of obesity is predominantly focused on lifestyle intervention, focusing on diet and physical exercise (2;3). Generally, exercise-based intervention programs are relatively successful in decreasing the risk for diabetes and cardiovascular diseases (4;5). There are, however, large individual differences in the success rate of most lifestyle interventions programs (6). Several factors have been identified that play a role. The type of exercise, intensity, duration and frequency will influence the success of an exercise program (7;8). The degree of supervision is a factor too; highly supervised subjects do better than less supervised individuals (8). Psychosocial factors and the personality of an individual, seem to play an important role as well: less successful participants in a lifestyle intervention program are characterized by higher amounts of body dissatisfaction, higher perceived impact of weight on work and lower self motivation (6;9;10).

The personality of the individual may serve as a risk factor for metabolic diseases such as obesity and type 2 diabetes. In humans, it was found that a type B personality, characterized by introversion and a passive response to stress, has an increased risk to develop the metabolic syndrome (11;12). This is supported by our own studies in experimental rats in which we found that individuals with a passive personality (or coping style), characterized by a high behavioral flexibility, would overeat and become insulin resistant on a highly palatable high fat diet. Proactive personalities, characterized by rigid behavioral patterns were remarkable resistant to the aversive effects of the high fat diet (13). Based on these data, we concluded that a passive (or re-active) personality may serve as a significant risk factor for weight gain and development of hyperinsulinaemia, especially in an environment rich in dietary fat (13;14).

Based on these observations, one could hypothesize that the personality of the individual could also serve as a crucial factor determining the success of lifestyle interventions, in particular exercise, in the treatment or the prevention of metabolic diseases such as obesity, type 2 diabetes and the metabolic syndrome. Evidence for this in human literature is conflicting. Some argue that individuals with proactive personality traits would be more successful since they are more competitive, have a lower perception of exertion and endure higher amounts of exercise than individuals with passive personality traits (15). However, others claim that passive personalities might perform better in a lifestyle...
Chapter 7

intervention program since they are the first to improve their performance when externally motivated, whereas proactive personalities are not susceptible to external motivation (16).

We therefore decided to test the hypothesis that personality determines the success of lifestyle intervention on metabolic parameters in a series of studies in experimental animals with different coping styles. The experiments were performed with passive and proactive individuals from two different rat strains: the Roman Low and High Avoidance rat strain and the Wild Type Groningen (WTG) rat strain. Roman High and Low avoidance rats (RHA and RLA, respectively) are selection lines, originally selected for their performance in a two-way active avoidance test, and a breeding colony of these rats is maintained for more than 30 generations (17). RHA rats are characterized by high levels of aggression, rigid behavioral patterns and a proactive approach towards stressors, RLA rats are characterized by low aggression levels, flexible behavioral patterns and a passive stress responses (18). Passive and proactive Wild type Groningen (WTGp, and WTGa, resp.) show the same behavioral characteristics as the Romans, but are both derived from the same population that is characterized by a large intra-strain variation in coping behavior (19). Since the passive and proactive WTGs are selected from the same litters, the difference between individuals is less pronounced when compared with the Roman strains.

In a previous study, running wheel activity was shown to attenuate the development of hyperinsulineamia in the extremely passive coping RLA rats (1). The first set of experiments was set up to confirm the effects of voluntary activity on body weight, glucose homeostasis and insulin sensitivity in animals with more moderate passive and proactive personalities. To this end, passive and proactive personalities from the Roman (extreme coping style ) and the WTG (moderate coping style) strains, were given voluntary access to treadmills for three weeks. Food intake and body weight were measured continuously and glucose and insulin profiles were assessed during an intravenous glucose tolerance test (IVGTT) before and after exercise. In the second set of experiments, we added a risk factor for metabolic diseases, dietary fat, to the experimental design. Rats were fed a highly palatable high fat diet for several weeks before allowing them access to the treadmills. Again, food intake and body weight were measured continuously and glucose and insulin profiles were assessed during an intravenous glucose tolerance test (IVGTT) before and after three weeks of physical activity. Finally, we performed a third study in which all groups of rats initially had treadmill access on control diet, but were switched to the highly palatable high fat diet after 20 days. Food intake, body weight and running activity was daily measured.
Materials and methods:

Animals:

Studies were performed with male rats from two different rat strains, the Roman High and Low Avoidance strain and the Wild Type Groningen (WTG) strain. Roman rats (n=32) were obtained from a breeding colony at the Clinical Psychopharmacology Unit (APSI), University of Geneva, Switzerland. Wild type Groningen rats (n=32) were derived from our own breeding colony at the University of Groningen, the Netherlands. The rats were housed in a room controlled for temperature and humidity (20 ± 2 °C; 60%) and the room was kept at a 12-12 hours light-dark cycle (Light on = CT0, lights off = CT12). The rats were fed either a standard lab chow diet (Hope Farms, RMH-B knaagdier korrel, Arie Block Diervoeding, Woerden, NL; 3.7 kcal/g, 14 % fat), or a high fat diet (Hope Farms, RMH-B knaagdier korrel, Arie Block Diervoeding, Woerden, NL; 4.8 kcal/g, 45 % fat). Food and water was available ad libitum. In the initial phase of the study, all animals were individually housed in standard cages (24x24x36 cm) with a food hopper on the side. When submitted to exercise, the rats were housed in Nalgene polycarbonate running wheel cages (50-27-36) with free access to the running wheel (diameter 27cm, mini mitter, Oregon, USA). The experiments were approved by the local animal welfare committee (DEC, Groningen, the Netherlands).

Defensive bury test:

We performed a defensive bury test to characterize the coping style of the WTG rats. During this test, the animals were housed in specialized cages (standard rat cages of 24x24x36 cm with a hole of approximately 1 cm diameter). Through the hole, an electric prod could be inserted. After a habituation period of at least a week the animals were tested. The rats were tested in the middle of the light phase. The electric prod was inserted into their cage and when the rats touched the prod they received a mild shock (200 µA). After the first shock was given, the behavior of the rat was monitored for 10 minutes (Eline software program). The following behaviors were scored: immobility, exploration of the prod, exploration of the cage and burying of the prod. The percentage time spent burying the prod was the main criterion for the coping style: animals burying 10 or less percent of the time were characterized as passive, rats burying 20 or more percent of the time were characterized as proactive. Rats that were between the cut-off criteria (10-20% burying) were not included in the study. Previous studies from our lab have shown that rats from the Roman strain display a more extreme coping style than the rats derived from the WTG population (13).
**Experimental set-up:**

*Experiments 1 and 2:*

In the current study, we studied whether coping style and physical activity interact in the susceptibility to hyperinsulinaemia. To this end, we used rats with an extreme coping style, the Roman High/Low avoidance rats and rats with an intermediate coping style, the proactive and passive WTG rats. We subjected the extreme copers from the Roman strain to an IVGTT with a relatively high dose (15%, a of glucose that still remained within the physiological range, (20)) under baseline and running conditions. The more moderate WTG rats were subjected to a lower dose IVGTT (10 %). These doses were chosen based on previous studies with the two strains in our lab (Boersma 2010). The rats were equipped with two indwelling jugular vein catheters, to allow for stress-free blood sampling and glucose infusion. The rats were given 2 weeks to recover from surgery. Baseline measurement of food intake and water intake were made for 1 week, hereafter a baseline intravenous glucose tolerance test (IVGTT) was performed in all animals (day 0).

**Experiment 1: Chow diet**

The rats in this study had ad lib access to a standard chow diet. After the baseline IVGTT, the rats were given access to the running wheel. During the first 10 days the rats were left to adapt to the running wheel, hereafter food intake, body weights and running activity were monitored for 20 days. After having access to a running wheel for 30 days, a second IVGTT was performed (day 31). The rats were given one week to recover (running wheel remained accessible), where after they were sacrificed to allow post-mortem analysis (day 38).

**Experiment 2: High fat diet**

The rats in this study had ad lib access to a highly palatable high fat diet. The rats were habituated to this diet for 21 days before the first IVGTT. After this baseline IVGTT, the rats were given access to the running wheel. During the first 10 days the rats were left to adapt to the running wheel, hereafter food intake, body weights and running activity were monitored for 20 days. After having access to a running wheel for 30 days, a second IVGTT was performed (day 31). The rats were given one week to recover (running wheel remained accessible), where after they were sacrificed to allow post-mortem analysis (day 38).
Experiment 3: Switch in diets

In the third experiment we investigated the response in voluntary running activity to a change in the diet. In this study both the Roman High/Low avoidance and the WTG strain were used. First, all rats had ad lib access to standard chow and access to the running wheel. The rats were habituated to the running wheel for 10 days. 10 days later, the rats were switched from chow to the high fat diet (ad lib). Their running wheel activity was monitored for the entire period, allowing a detailed analysis of running behavior. Food intake and body weights were measured daily.

IVGTT:

Rats were accustomed to the infusion and blood sample procedure before the onset of the experiments (21). On the experimental day the rats were denied access to their food from the beginning of the light phase until the end of the IVGTT; food was removed at CT0. Experiments were performed in the middle of the light phase, between CT4 and CT6. The blood samples were kept on ice and stored in files with 10 µl EDTA (0.09g/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 (22) in a Technicon auto analyzer. The remaining blood was centrifuged for 15 minutes and plasma was stored for insulin determination. Plasma levels of insulin were measured using commercial radioimmunoassay (RIA) kits (Linco Research).

For the Roman rats the IVGTT consisted of a 30 minutes infusion of 15 mg in 0.1 ml saline per minute (total 450 mg in 3 ml). Before the onset of the infusion, two baseline samples (0.2 ml) were taken at time points t = -11 and 1 minutes. The infusion of glucose was started at t = 0 minutes. Additional blood samples (0.2 ml) were taken at time points t = 5, 10, 15, 20, 25, 30, 35, 40, and 50 minutes. A total blood volume of 2.2 ml was taken and blood loss was substituted with saline.

For the WTG rats the IVGTT consisted of a 20 minutes intravenous infusion of 10 mg glucose in 0.1 ml saline per minute (total 200 mg glucose in 2 ml saline). Before the onset of the infusion, two baseline samples (0.2 ml) were taken at time points t = -11 and 1 minutes. The infusion of glucose was started at t = 0 minutes. During the 10 mg/min glucose IVGTT blood samples (0.2 ml) were taken at time points t = 3, 5, 7, 10, 15, 20, 25, 30, and 40 minutes. A total blood volume of 2.2 ml was taken and blood loss was substituted with saline.
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Post mortem analysis:

After the IVGTT, the rats had one week to recover before they were sacrificed (day 38). Animals were sedated using isoflurane anesthesia. 5 ml blood was removed through heart puncture (left ventricle), hereafter the rats were sacrificed with an overdose Pentobarbital (1 ml pentobarbital-sodium 6%). Epididymal fat pads, retroperitoneal fat pads, and the liver were removed weight. In the plasma, leptin levels were measured using commercial radioimmunoassay (RIA) kits (Linco Research).

Data Analysis:

All data are displayed as an average of the strain with the standard error of the mean. Differences in food intake, body weight, running activity and body fat distribution between the different experimental groups were determined with a one-way ANOVA with the dietary conditions as the within subjects factor, and the strain as the between subject factor. With this test an interaction between diet and strain could also be determined. A tukey post-hoc test was performed to analyze the different diet-strain interactions. Differences between the strains, the diets and the different coping styles in the insulin and glucose responses were assessed with a repeated measures ANOVA with the diet as the within subjects factor and the strain as the between subjects factor. With this test interactions between diet and strain were assessed as well. Post hoc analysis (Tukey) was performed to assess diet-strain interactions. In all statistical tests a confidence interval of 5% was used.

Results:

Experiment 1: chow diet

Sedentary conditions:

Body weights and food intake of the rats are displayed in table 1. There were no differences in body weight between proactive and passive individual of the WTG (WTGa and WTGp, resp.) strain on either diet. The rats of the WTG strain weighed significantly more than rats of the Roman strain (F(1, 63) = 4.516 p<0.05). Figure 1 displays the glucose and insulin response of WTG rats during an IVGTT. On chow there were no differences between the WTGa and WTGp rats in the insulin levels during the IVGTT.
Coping style and physical activity

Table 1: Body weight and food intake of RLA, RHA, WTG passive (WTGp) and WTG proactive (WTGa) rats under sedentary and voluntary running conditions fed either chow or high fat diet. Food intake is expressed as average daily intake in kcal. Body weights were measured after 21 days exposure to the diet. * indicates a significant difference with sedentary rats of the same strain (p<0.05). a indicates a difference from chow fed rat of the same strain and under the same environmental conditions.

<table>
<thead>
<tr>
<th></th>
<th>RLA</th>
<th>RHA</th>
<th>WTG p</th>
<th>WTGa</th>
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<tr>
<td><strong>Body weight (g)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline chow</td>
<td>415 ± 14</td>
<td>390 ± 9</td>
<td>405 ± 9</td>
<td>386 ± 14</td>
</tr>
<tr>
<td>Running chow</td>
<td>409 ± 13</td>
<td>386 ± 8</td>
<td>399 ± 19</td>
<td>375 ± 18</td>
</tr>
<tr>
<td>Running high fat</td>
<td>436 ± 15</td>
<td>412 ± 9 a</td>
<td>487 ± 15 a</td>
<td>458 ± 22 a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Food intake (kcal/day)</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Baseline chow</td>
<td>91.2 ± 3.6</td>
<td>92.7 ± 3.9</td>
<td>88.2 ± 4.8</td>
<td>90.6 ± 3.6</td>
</tr>
<tr>
<td>Running chow</td>
<td>107.4 ± 2.5*</td>
<td>104.2 ± 2.6*</td>
<td>94.4 ± 3.4</td>
<td>92.2 ± 2.9</td>
</tr>
<tr>
<td>Running high fat</td>
<td>118.4 ± 4.3 a</td>
<td>108.2 ± 3.3 a</td>
<td>115.8 ± 3.9 a</td>
<td>116.4 ± 4.2 a</td>
</tr>
</tbody>
</table>

Under baseline conditions there were no significant differences between RLA and RHA rats. Rats, of either coping style, weighed significantly more when fed a high fat diet in comparison with chow fed rats (F(1,28) = 6.888 p<0.05). There were no significant differences between the coping styles under baseline, chow fed conditions. Figure 2 displays the insulin and glucose responses to an IVGTT in proactive and passive rats of the Roman rat strain. There were no differences in the glucose response between the experimental groups. Under sedentary, chow fed conditions the insulin response of sedentary RLA rats was significantly higher than the response in the RHA rats (F (3,20) = 5.168, p<0.01).
Figure 1: Glucose and insulin responses to an intravenous glucose tolerance test (IVGTT, 20 minutes glucose infusion at 10mg/ml) in sedentary and running Wild Type Groningen rats on chow. A: glucose levels in WTGp rats. B: glucose levels in WTGa rats. C: insulin levels in WTGp rats. D: insulin levels in WTGa rats. E: area under the insulin response curve (AUC) in WTGp rats. F: area under the insulin response curve (AUC) in WTGa rats. Black symbols represent baseline sedentary conditions, white symbols represent voluntary running conditions. * indicates a significant difference p<0.05.
Figure 2: Glucose and insulin responses to an intravenous glucose tolerance test (IVGTT, 30 minutes glucose infusion at 15mg/ml) in sedentary and running rats of the Roman strain on chow. A: glucose levels in RLA rats. B: glucose levels in RHA rats. C: insulin levels in RLA rats. D: insulin levels in RHA rats. E: area under the insulin response curve (AUC) in RLA rats. F: area under the insulin response curve (AUC) in RHA rats. Black symbols represent baseline sedentary conditions, white symbols represent voluntary running conditions. * indicates a significant difference p<0.05.
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After running:

When a running wheel was available, there were no significant differences in body weight or food intake between WTGa and WTGp rats. During access to a running wheel, food intake increased significantly in chow fed rats independent of their coping style ($F(1,15) = 5.456 \ p<0.05$). On chow there were no differences in the distance ran between WTGa and WTGp rats. Figure 1 displays the glucose and insulin levels during the IVGTT. Under running conditions there were no differences between WTGa and WTGp rats in glucose levels during the IVGTT. The insulin responses of rats with access to a running wheel and fed the chow diet were not significantly different from their responses during baseline in either coping style. The daily running activity of the WTG rats is displayed in figure 3A. There were no differences between passive and proactive WTG rats in running activity on a chow diet.

Access to the running did not induce a difference in body weight or food intake between the RLA and RHA rats. When chow fed rats were given access to a running wheel their food intake increased significantly, this effect was not determined by the coping style of the rats ($F(3,28) = 5.456 \ p<0.05$). Figure 3B displays the distance ran daily in the running wheel by proactive and passive rats of the Roman strains. The RLA ran significantly more than the RHA rats (Chow: $F(1,15) = 9.332$). Figure 2 displays the glucose and insulin levels during the IVGTT. Under running conditions there were no differences between RLA and RHA rats in glucose levels during the IVGTT. When a running wheel was available, passive coping chow fed rats significantly lowered their insulin response to an IVGTT in comparison to sedentary rats ($p<0.01$).

**Figure 3:** Daily running activity of the rats on chow. **A:** running activity of rats of the Roman rat strain. White bars = RLA, black bars = RHA. **B:** running activity of rats of the WTG rat strain; white bars = WTG passive, black bars = WTG proactive. * indicates a significant difference ($p<0.01$).
**Experiment 2: High fat diet**

*Sedentary conditions:*

Under sedentary conditions all WTG rats ate and weighed significantly more when fed a high fat diet when compared to chow fed WTG rats ($F(1,31) = 4.587 \ p<0.05$ and $F(1,31) = 5.678 \ p<0.05$, respectively). Figure 4 displays the glucose and insulin response of WTG rats on the high fat diet during an IVGTT. Neither diet nor coping style influenced the glucose response to an IVGTT. The insulin levels of the passive WTG rats on a high fat diet were significantly increased as compared to chow fed passive WTG rats and proactive WTG rats on either diet ($F(3,28) = 5.176 \ p<0.05$). On the high fat diet, the passive WTG rats displayed increased insulin levels compared to proactive rats (WTGa) ($F(1, 15) = 3.465, \ p<0.05$).

Under baseline conditions there were no significant differences between RLA and RHA rats. Rats, of either coping style, weighed significantly more when fed a high fat diet as compared to chow fed rats ($F_{1,28} = 6.888 \ p<0.05$). Figure 5 displays the insulin and glucose responses to an intravenous glucose tolerance test in proactive and passive rats of the Roman strain on the high fat diet. There were no differences in the glucose response between the experimental groups. The diet did not alter the glucose response to an IVGTT. Passive RLA rats on the high fat diet displayed higher insulin levels as compared to RHA rats and chow fed RLA rats ($F(3, 20) = 3.425 \ p<0.05$).

*After running:*

Figure 4 displays the glucose and insulin levels during the IVGTT. Under running conditions there were no differences between passive and proactive WTG rats in glucose levels during the IVGTT. On the high fat diet, availability of a running wheel resulted in a significantly lower insulin response to an IVGTT in the passive rats ($F(1,15) = 5.341 \ p<0.05$). In the proactive rats, no differences in the insulin response were observed between baseline and running conditions. On the high fat diet, the passive WTG rats ran significantly more than the proactive WTGa rats ($F(1,15) = 8.529 \ p<0.01$). Passive WTG rats on a high fat diet ran significantly more compared to chow fed passive WTG rats ($F(1,15) = 8.529 \ p<0.01$). High fat diet fed and chow fed proactive WTG rats showed similar running activity.
Figure 4: Glucose and insulin responses to an intravenous glucose tolerance test (IVGTT, 20 minutes glucose infusion at 10mg/ml) in sedentary and running Wild Type Groningen rats on the high fat diet. A: glucose levels in WTGp rats. B: glucose levels in WTGa rats. C: insulin levels in WTGp rats. D: insulin levels in WTGa rats. E: area under the insulin response curve (AUC) in WTGp rats. F: area under the insulin response curve (AUC) in WTGa rats. Black symbols represent baseline sedentary conditions, white symbols represent voluntary running conditions. * indicates a significant difference p<0.05.
Coping style and physical activity

Figure 5: Glucose and insulin responses to an intravenous glucose tolerance test (IVGTT, 30 minutes glucose infusion at 15mg/ml) in sedentary and running rats of the Roman strain on a high fat diet. A: The glucose levels in RLA rats. B: glucose levels in RHA rats C: insulin levels in RLA rats. D: insulin levels in RHA rats. E: area under the insulin response curve (AUC) in RLA rats. F: area under the insulin response curve (AUC) in RHA rats. Black symbols represent baseline sedentary conditions, white symbols represent voluntary running conditions. * indicates a significant difference p<0.05.

No significant differences in body weight or food intake between RLA and RHA rats on either diet were observed in the period that the animals had access to the running wheel. Figure 5 displays the glucose and insulin levels during the IVGTT. Under running conditions there were no differences between RLA and RHA rats in glucose levels during the IVGTT. When a running wheel was available, passive coping high fat fed rats significantly lowered their insulin response to an IVGTT compared to baseline conditions (F_{1,28} = 5.435 p<0.05).
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Figure 6B displays daily running activity. The passive RLA ran significantly more than the RHA rats \(F(1,15) = 9.941 \ p<0.01\). RLAs showed significantly higher activity when fed a high fat diet as compared to chow fed condition \(F(1,15) = 10.919 \ p<0.01\). High fat diet fed RHAs and chow fed RHAs were not different in running activity.

![Figure 6](image)

**Figure 6**: Daily running activity of the rats on a high fat diet. A: running activity of rats of the Roman rat strain. White bars = RLA, black bars = RHA. B: running activity of rats of the WTG rat strain white bars = WTG passive, Black grey bars = WTG proactive. * indicates a significant difference \(p<0.01\).

**Experiment 3: dietary switch**

In figure 7, daily food intake on both chow and the high fat diet is displayed. All rats increased food intake when they were switched to the medium fat diet (RM-ANOVA; diet \(F(3, 30) = 5.289 \ p<0.05\). The increase was significantly higher in the passive animals when compared to the proactive counterparts \(p<0.05\). Figure 8 displays the body weight gain during the experimental period. There were no significant differences in body weight gain between the experimental groups.

Figure 9A displays the running activity of the WTG rats. Under chow fed conditions, there were no difference between the proactive and passive rats of this strain in running activity. When switched to the high fat diet, passive individual significantly increased running activity, while the running activity of the proactive rats remained unchanged (RM-ANOVA; \(F(3, 29) = 4.659 \ p<0.01\)).

Figure 9B displays the running wheel activity of rats of the Roman rats before and after the switch in diets. Already on the chow diet, the RLA ran significantly more the RHA rats \(F(1,15) = 9.332 \ p<0.01\). When switched to the high fat diet, the RLA rats further increased their running activity (RM-ANOVA; diet*coping \(F(3, 30) = 3.459 \ p<0.05\)). The RHA rats did not change their running activity when they changed to the high fat diet.
Figure 7: Body weight in percentage of baseline at day -14 of rats that switch from chow to a high fat diet at day 7. **A:** body weight gain in RLA and RHA rats. White symbols = RLA, black symbols = RHA. **B:** body weight gain in WTG passive and proactive rats. White symbols = WTG passive, black symbols = WTG proactive rats.
Figure 8: Daily food intake in kcal/day when of rats that switch from chow to a high fat diet at day 7. A: Food intake of RLA and RHA rats. White symbols = RLA, black symbols = RHA. B: Food intake of WTG passive and WTG proactive rats. White symbols = WTG passive, black symbols = WTG proactive. * indicates a significant difference (p<0.01).
Figure 9: Daily running activity in wheel revolution/day of rats that switch from chow to a high fat diet at day 7. A: Running activity of RLA and RHA rats. White symbols = RLA, black symbols = RHA. B: Running activity of WTG passive and WTG proactive rats. White symbols = WTG passive, black symbols = WTG proactive. * indicates a significant difference (p<0.01).
Table 2: Body fat distribution RLA, RHA, WTG passive and WTG proactive rats under voluntary running conditions fed either chow or high fat diet. * indicates a significant difference between chow fed and high fat diet fed rats within a strain.

<table>
<thead>
<tr>
<th></th>
<th>RLA</th>
<th>RHA</th>
<th>WTGp</th>
<th>WTGa</th>
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<tr>
<td><strong>Epididymal fat (g)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Chow (run)</td>
<td>4.07 ± 0.21</td>
<td>4.53 ± 0.24</td>
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<tr>
<td>High fat (run)</td>
<td>5.24 ± 0.59*</td>
<td>4.12 ± 0.24</td>
<td>5.10 ± 1.40</td>
<td>5.31 ± 0.92</td>
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<td><strong>Retroperitoneal fat (g)</strong></td>
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<tr>
<td>Chow (run)</td>
<td>7.65 ± 0.8</td>
<td>7.22 ± 0.7</td>
<td>7.58 ± 0.43</td>
<td>10.58 ± 1.39</td>
</tr>
<tr>
<td>High fat (run)</td>
<td>7.66 ± 0.80</td>
<td>7.23 ± 0.70</td>
<td>9.12 ± 1.42</td>
<td>10.23 ± 1.33</td>
</tr>
<tr>
<td><strong>Subcutaneous fat (g)</strong></td>
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<td></td>
</tr>
<tr>
<td>Chow (run)</td>
<td>33.50 ± 1.19</td>
<td>32.99 ± 1.34</td>
<td>29.13 ± 4.13</td>
<td>27.37 ± 2.45</td>
</tr>
<tr>
<td>High fat (run)</td>
<td>37.52 ± 0.91</td>
<td>33.79 ± 1.42</td>
<td>33.27 ± 3.27</td>
<td>31.24 ± 4.12</td>
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<tr>
<td><strong>Fat mass (%)</strong></td>
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<td></td>
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</tr>
<tr>
<td>Chow (run)</td>
<td>14.28 ± 0.30</td>
<td>13.93 ± 0.37</td>
<td>11.38 ± 1.77</td>
<td>11.72 ± 0.93</td>
</tr>
<tr>
<td>High fat (run)</td>
<td>14.31 ± 0.16</td>
<td>13.55 ± 0.41</td>
<td>10.51 ± 1.33</td>
<td>10.28 ± 1.76</td>
</tr>
<tr>
<td><strong>Fat free mass (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chow (run)</td>
<td>86.49 ± 4.03</td>
<td>86.07 ± 3.93</td>
<td>88.62 ± 3.66</td>
<td>88.28 ± 4.62</td>
</tr>
<tr>
<td>High fat (run)</td>
<td>85.69 ± 4.03</td>
<td>86.45 ± 3.93</td>
<td>89.49 ± 4.65</td>
<td>89.72 ± 4.56</td>
</tr>
</tbody>
</table>

Table 3: Leptin levels of RLA, RHA, WTG passive and WTG proactive rats under sedentary and voluntary running conditions on either a chow or a high fat diet. * indicates a significant difference with sedentary rats of the same strain (p<0.05).

<table>
<thead>
<tr>
<th></th>
<th>RLA</th>
<th>RHA</th>
<th>WTGp</th>
<th>WTGa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow baseline leptin (ng/ml)</td>
<td>8.09 ± 1.76</td>
<td>3.80 ± 0.76</td>
<td>10.51 ± 4.69</td>
<td>5.25 ± 2.53</td>
</tr>
<tr>
<td>Chow running leptin (ng/ml)</td>
<td>4.95 ± 0.95*</td>
<td>3.86 ± 0.75*</td>
<td>6.09 ± 0.82</td>
<td>4.86 ± 0.75</td>
</tr>
<tr>
<td>High fat baseline leptin (ng/ml)</td>
<td>9.32 ± 2.31</td>
<td>6.53 ± 1.42</td>
<td>8.67 ± 3.64</td>
<td>7.25 ± 3.25</td>
</tr>
<tr>
<td>High fat running leptin (ng/ml)</td>
<td>5.63 ± 1.34*</td>
<td>4.23 ± 0.89*</td>
<td>5.89 ± 1.45</td>
<td>5.83 ± 2.46</td>
</tr>
</tbody>
</table>
Discussion:

The current study investigated the potential beneficial effect of voluntary physical activity on hyperinsulineamia in rats characterized by a passive or proactive coping style. In the present study, voluntary wheel running indeed resulted in increased insulin sensitivity. This occurred in all experimental groups on all diets, although the effects of wheel running were significantly more pronounced in the passive individuals of both strains.

In the present study, we confirmed our previous observation that the extremely passive RLA rats are hyperinsulineamic, even when fed a standard chow diet (14). Voluntary wheel running completely normalized insulin responses of the RLABs. A similar phenomenon was observed in the moderately passive WTG rat on a high fat diet: their elevated insulin levels under sedentary conditions returned to normal when a running wheel was accessible.

But the most striking finding was the spontaneous increase in wheel running behavior that occurred in all passive, but none of the active individuals when the diet changed from chow to high fat. This increase in running paralleled the increased energy intake on the high fat diet which was, again, significantly higher in the passive individuals. In fact, the data of the present study suggest that passive animals may spontaneously increase their voluntary physical activity to compensate for an increased metabolic risk, in particular on the high fat diet. The following lines of evidence support this assumption: 1) on chow, sedentary RLABs are hyperinsulineamic (14), but when a running wheel is available they run more than their proactive counterparts and insulin levels turn back to normal, 2) on a high fat diet, sedentary RLABs are even more hyperinsulineamic than on chow (13), when a running wheel is available they run even more than on chow, 3) both passive and proactive sedentary WTGs are normo-insulinemic on chow (13), when allowed to run there is no difference in wheel running behavior, 4) passive WTGs are hyperinsulineamic on a high fat diet (13), when allowed to run they suddenly run much more than the proactive WTGs on a high fat diet, 5) both passive RLA and WTG rats immediately increase their spontaneous wheel running behavior when their diet is switched from chow to high fat and 6) sedentary proactive RHA and WTGa rats are insulin sensitive both on chow and on a high fat diet (so they are not metabolically at risk) and they do not change their spontaneous wheel running behavior when the diet is changed.

We may speculate that differences in behavioral flexibility may lay at the origin of the observed difference in running activity in response to the dietary switch. Passive individuals seem more sensitive to environmental cues (19), which may translate to the adaptive increase in voluntary running when energy intake is increased. In future studies,
this hypothesis should be tested by exposing individuals clearly differing in the level of behavioral flexibility to shifting dietary conditions, in which their behavioral responses to compensate for dietary intake are challenged more through roughly. This study shows that the passive coping individual, evolutionary primed for varying environmental conditions, are insulin sensitive under running conditions. These individuals only seem to have a problem when their environmental conditions do not match the migratory conditions they are evolutionary prime for. It thus seems that we may be studying a mismatch phenomenon, instead of the mechanism of the disorder.

Most of the studies in literature that focus on the regulation of the energy balance use standard laboratory rats housed under sedentary conditions. This in itself is not a problem, since that might exactly mimic the present obesogenic environment of the overweight human in the Western world. As previously argued by Booth et al (23), the standard control group in human experimentation has switched from a lean physically active individual to a sedentary, moderately overweight person over the course of years, without a change in the interpretation of these ‘control’ data. This may lead to misinterpretation of experimental data in human studies. Likewise, the results from the present study emphasize that we should be aware of the environmental conditions of our experimental animals and adapt our line of reasoning accordingly.

The differences in spontaneous running activity between proactive and passive rats under high fat diet conditions is very intriguing. It suggest that running should be considered as a behavioral adaptation to poor metabolic control. This finding is not completely new: rats have been known to adapt their activity levels to match the nutritional levels; rats fed a high energy diet may increase activity levels (24). Likewise, there are reports in literature that experimental animals that are characterized by an obese phenotype under sedentary conditions such as Olef rats and MC4 knockout mice will (almost) return to normal body weight when they are allowed to exercise, they indeed show increased levels of wheel running in comparison to the lean controls (25;26). However, we are not aware of studies in normal weight animals and a direct relationship between insulin profiles and the amount of voluntary physical activity.

In summary, we showed in the present study that 1) voluntary running is beneficial for improving insulin sensitivity, in particular in extreme and moderate passive rats that are characterized by hyperinsulineamia, and 2) that passive coping rats spontaneously increase their running activity when their diet is switched from chow to palatable high fat whereas proactive rats do not. We conclude that passive individuals are vulnerable for the development of diet-induced hyperinsulineamia under sedentary conditions, but that these
individuals may adapt their spontaneous physical activity level when in the dietary conditions change. In contrast, proactive individuals are less susceptible to develop hyperinsulineamia, however, these individuals do not display alterations in physical activity levels in response to overeating. One might speculate that these proactive may therefore benefit less from an opportunity to become physically active, so they might be at risk when hyperinsulineamia does occur.
Chapter 7

Reference List


