Coping styles and the pathophysiology of energy metabolism

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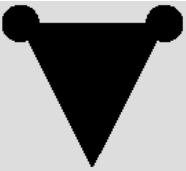
PART 2: Treatment and Personality



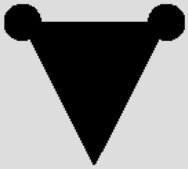
Pharmacological treatment of insulin resistance in rats depends on coping style. European journal of pharmacology (European Journal of Pharmacology DOI 10.1016/j.ejphar.2010.12.017)

Exercise-based control of hyperinsulinemia in rats: role of coping style and compliance. (American Journal of Applied physiology, under review)

Passive personalities adapt physical activity levels to dietary conditions.

Personality types and the success of life style intervention programs: a study in humans.

CHAPTER 5:



Pharmacological treatment of insulin resistance in rats depends on coping style.

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Abstract

Passive and proactive coping styles are associated with marked differences in behavioral and neuroendocrine responses. Previous studies revealed that the passive individuals are more prone to hyperinsulineamia. Likewise, we hypothesize that different coping styles may require different drugs to treat this. We tested this by treating passive and proactive rats (Roman Low Avoidance and Roman High Avoidance rats respectively) with either Rosiglitazone or with RU486. After eight days of treatment we performed and intravenous glucose tolerance test (IVGTT) and we compared the insulin and glucose levels with those measured during the IVGTT at baseline. Rosiglitazone improved insulin levels during an IVGTT in both passive and proactive coping styles. RU486, however, lowered insulin levels only in rats with a passive coping style. This study suggests that insight in the neuroendocrine differences between passive and proactive coping styles may provide an extra impulse to improve treatment of insulin resistance, since it allows the application of drugs targeted at the individual.

Keywords: Rosiglitazone, RU486, glucocorticoids, PPARγ agonist, intravenous glucose tolerance test

1 Introduction:

The significance of personality, stress coping and other psychosocial factors for the development of insulin resistance and type 2 diabetes has become more evident in recent years *(1-4)*. The mechanisms underlying the interaction between psychosocial factors and metabolic pathologies, however, remain to be elucidated. One approach is to study these mechanisms in rodent lines with divergent stress coping and personality profiles. In our previous studies we have shown that rats selected for a passive strategy to cope with stress, the so-called Roman Low avoidance rats (RLA), have a higher sensitivity to develop signs indicative of the metabolic syndrome than proactively coping animals, the Roman High avoidance rats (5). We confirmed these findings in passive and pro-active littermates from an outbred wild-type Groningen (WTG) rat population. These WTG rats display a more moderate dispersion of coping styles and in these rats we again showed that more passive individuals had consistently higher proneness to develop hyperinsulineamia than pro-active individuals (6).

Taken together, these studies indicate that the coping style of an individual plays an important role in the development of metabolic derangements. Likewise one may argue that different coping styles may also respond differently to different treatments for metabolic disorders such as type 2 diabetes and the metabolic syndrome. We should therefore focus on custom made treatments for passive and proactive coping styles for treatment of hyperinsulineamia. To this end, we decided to test the potential beneficial effects of two different drug treatments for hyperinsulineamia, Rosiglitazone and RU486, in both passively and proactively coping rats of the Roman selection lines.

In our first set of experiments focused on the effects of Rosiglitazone, a peroxisome proliferator-activated receptor gamma agonist, known to directly induce translocation of the GLUT4 transporter to the membrane (7;8), and thereby increasing insulin sensitivity of the insulin receptor. This oral anti-diabetic agent is a commonly used treatment strategy for the metabolic syndrome and it has a good succes rate in patients with type 2 diabetes (reviewed in (9)). Since Rosiglitazone directly improves the insulin signaling cascade circumventing possible differences in insulin receptor sensitivity, we assume that treatment with this drug will be equally effective in passive and proactive individuals.

The second drug, RU486, is specifically targeted at treating the hyperinsulineamic passive coping style (5). RU486 is a glucocorticoid receptor antagonist predominantly used in the treatment of diabetes associated with Cushing syndrome and glucocorticoid secreting tumors (10). This therapeutic agent may be interesting since passively coping rats are characterized by moderate elevated glucocorticoid levels (5;11-14). Elevated glucocorticoid

levels, in turn, are associated with an increase susceptability for insulin resistance. If elevated GR stimulation indeed play a role in the presumed insulin resistance in RLA rats, we expect that blocking the glucocorticoid action with a GR antagonist, RU486, would obliterate differences in glucose homeostasis among RHA and RLA rats. Treatment with RU486 would therefore specifically improve insulin signaling in the RLA rats.

In summary, in the present study we hypothesize that different coping styles may require different drugs for treatment of hyperinsulineamia. To this end, we treated proactive and passive rats with two different drugs and measured glucose and insulin responses to an intravenous glucose tolerance test before and after treatment. We hypothesize that Rosiglitazone will increase insulin sensitivity in both coping styles and that RU486 will only be effective in the passive coping style.

2. Materials and methods

2.1 Animals:

Adult male Roman High (n=16) and Roman Low Avoidance rats (n=16) with body weights between 300-400 grams were used. The rats were obtained from a breeding colony at the Clinical Psychopharmacology Unit (*APSI*), University of Geneva, Switzerland. The Roman High and Low Avoidance rats (RHA and RLA, respectively) were originally selected by Bignami (15)on the basis of their performance in a two-way active avoidance test. Rats with the most extreme coping styles were identified and selectively bred for many generations. This resulted in two sub-strains: Roman Low Avoidance rats with an extremely passive coping style and Roman High Avoidance rats with a proactive coping strategies(16). The passive coping RLA is characterized by low aggression levels, flexible behavioral patterns and a passive stress response, whereas the proactive RHA is characterized by high levels of aggression, rigid behavioral patterns and a proactive strategy towards stressors *(17).*

All rats were housed individually in standard cages (24x24x36 cm), lab chow (*Hope Farms, RMH-B knaagdier korrel, Arie Blok Diervoeding, Woerden, NL*) and water were available ad lib. The room was controlled for temperature and humidity (T=20 ± 2°C, humidity 60%) and was kept at a 12-12 hours light-dark cycle (lights on = CT0). All animal experiments were approved by the local animal care committee.

2.2 Surgery

The rats underwent surgery to place two indwelling jugular vein catheters allowing continuous blood sampling in freely moving animals. Rats were sedated using an isoflurane-O_2/N_2O gas anesthesia. A silicon heart catheter (0.95mm OD, 0.50 mm ID and 0.64 mm OD, 0.28 ID) was inserted into the right jugular vein and kept in place with a ligament. The catheter was pulled under the skin towards the skull where it was connected to a metal bow. This metal bow was fixed to the skull with dental cement and 4 small screws. The same procedure was repeated on the left side. During blood sampling or infusions a piece of tubing could be attached to the metal bow, hereby samples could be taken from conscious rats. In between experiments, the catheter was filled with a PVP/heparin solution preventing blood cloth formation in the catheter (18). The animals were given 0.1 ml Finadine s.c. for analgesia and 0.25 ml penicillin s.c. to prevent infection. After surgery the rats were allowed to recover for at least 7 days

2.3 Intravenous glucose tolerance test

After recovery from surgery, the rats were accustomed to the infusion and blood sampling procedure before the actual onset of the experiments (19). Then, an intravenous glucose tolerance test (IVGTT) was performed to measure the baseline responses in each individual animal. After the baseline IVGTT, the animals were treated with either Rosiglitazone or RU486 for eight days. A second IVGTT was performed at day 8, the last day of treatment. This within subject experimental set-up allowed us to use each individual rat as its own control. During the intravenous glucose tolerance test (IVGTT) an infusion of 15 mg/min glucose was given in 3 ml saline solution over a 30 minutes period. This is a physiological dose that mimics the glucose response after a large meal (20).

The experiments were performed in the middle of the light phase, between CT4 and CT6. 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. Two baseline blood samples were taken before the start of the infusion (t=-15 and t=-5 minutes). The glucose infusion was given between t=0 and 30 min, during and after infusion blood samples were taken at time points 5, 10, 15 , 20, 25, 30, 35, 40, and 50 minutes. A total volume of 2.8 ml blood was taken and the loss of volume was substituted by saline infusion. 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. The remaining blood was centrifuged for 15 minutes and plasma was stored for insulin determination.

2.4 Rosiglitazone treatment:

Eight RHA and eight RLA rats were treated with a dose of 4 mg/kg/day (21) Rosiglitazone (*AstraZenica, Mölndal, Sweden*) for 8 consecutive days. Rosiglitazone was administered in the drinking water. The water intake of the rats was monitored for a week before the start of the experiment, and the concentration of Rosiglitazone was adjusted accordingly. Since RLA rats drink generally more than the RHA rats (Boersma 2009 and table 1), the actual concentration of Rosiglitazone was calculated on the basis of baseline water intake of each individual rat. On average, the RLA rats received 50 ± 3 mg/L and RHA rats 57 ± 2 mg/L Rosiglitazone solution. During treatment water intake of the rats did not change, which means that that each individual rat received 4 mg/kg/day of Rosiglitazone.

2.5 RU486 treatment:

Eight RHA and eight RLA rats were treated with 20 mg/ kg/day (22) RU486 (*mifepristone, Sigma-Aldrich Chemie, Zwijndrecht*) for 8 consecutive days. RU486 was given

subcutaneously at CT2 and CT14, both injections contained 10 mg/kg RU486 in 0.5 ml saline. Before the start of the treatment the rats were accustomed to the subcutaneous injections procedure; they received a single saline injection (0.5 ml/kg) for 4 consecutive days). The efficiency of the RU486 treatment was assessed by measuring corticosteron levels in the baseline plasma samples prior to the IVGTT.

2.6 Post mortem analysis

The rats were sacrificed after 8 days of treatment, one day after the last IVGTT. Three hours before lights off, blood samples were taken directly from the heart under isoflurane-O_2/N_2O gas anesthesia for determination of blood glucose, plasma insulin and leptin levels. Animals were hereafter sacrificed using an overdose of pentobarbital. Epididymal and retroperitoneal fat pads and the liver were taken out and weighed. The skin with the subcutaneous fat was removed from the carcass. Liver, skin, and carcasses were dried at 80 ℃ for 5 days. Fat content was determined by extracting the fat from tissue using a petroleum based Soxlet fat extractor. After fat extraction the tissue was dried for 5 days again. The relation between dry tissue weight before and after fat extraction provides information on the fat content of the tissue.

2.7 Chemical analyses:

Plasma levels of insulin and leptin were measured using commercial radioimmunoassay (RIA) kits (*Linco Research*). Blood glucose levels were determined using the ferry-cyanide method in a *Technicon* auto analyzer. Plasma corticosteron levels were measured using a commercial radioimmunoassay (RIA) (Biomedics).

2.8 Statistical analysis

Data are expressed as averages with standard error of the mean. Differences in food and water intake, body weight and baseline plasma levels between strains were determined using one-way ANOVA using strain as the between subjects factor. Differences in insulin and glucose levels before, during and after the IVGTT were examined using repeated measures ANOVA, again using strain as the between subjects factor. The area under the curves of both glucose and insulin responses (t= 0 till t = 30 minutes) were calculated and reported as the average area under the curve (AUC) with the standard error of the mean. The differences between the strains were determined using one-way ANOVA. The statistical differences between the strains in corticosteron levels before and after the treatment were assessed using a repeated measures ANOVA, with the strain as the

between subjects factor, and time as the within subjects factor. A confidence interval of 5% was used.

3. Results

3.1 Body weight and food intake:

Table 1 displays body weights and food intake of RLA and RHA rats during the baseline period and after treatment with either Rosiglitazone and RU486. At the start of the experiments, the RLA rats were somewhat but not significantly heavier than the RHA rats ($p = 0.072$). Both Rosiglitazone and RU486 treatment reduced body weights in RLA and RHA rats (for Rosiglitazone RM-ANOVA $F_{3,21} = 7,258$; RLA $p = 0.021$; RHA $p = 0.007$, and for RU486 RM-ANOVA $F_{3,21} = 11,362$ RLA $p = 0.012$; RHA $p = 0.001$). There were no differences in food intake between RLA and RHA rats under baseline conditions. Treatment with RU486 significantly reduced food intake in both strains (RM-ANOVA $F_{1,21} = 12,232$, $p = 0.016$). Treatment with Rosiglitazone had no effect on the food intake. There were no differences between the strains in the effects of either Rosiglitazone or RU486 on both body weight and food intake. At baseline water intake was significantly higher in the RLA rats compared to RHA rats ($F_{3,21} = 9.234$ $p<0.01$). Treatment with either RU486 or Rosiglitazone did not effect water intake.

Table 1: Body weight (BW), food intake (FI) and water intake (WI) of RLA and RHA rats before treatment and after treatment with either Rosiglitazone or RU486. [a] Indicates a significant difference with RLA rats (within treatment) $p<0.05$ [b] Indicates a significant difference with baseline condition (within a strain) $p<0.05$.

	Rosiglitazone		**RU486**	
	RLA	RHA	RLA	RHA
Baseline BW (g)	435.3± 6.7	401.7 ± 9.9	433.3± 7.3	399.8 ± 10.0
Change in BW (g)	43.5 ± 6.3 [b]	47.5 ± 5.4 [b]	40.6 ± 6.9 [b]	53.2 ± 7.3 [b]
Baseline FI (kcal/day))	97.48 ± 3.87	96.45 ± 3.21	96.81 ± 3.51	97.32 ± 4.02
Treatment FI (kcal/day)	98.70 ± 4.44	97.17 ± 2.50	90.10 ± 2.17 [b]	89.73 ± 2.52 [b]
Baseline WI (ml/day)	41.78 ± 2.11	34.80 ± 1.11 [a]	40.62 ± 2.05	34.32 ± 1.86 [a]
Treatment WI (ml/day)	41.28 ± 2.28	35.86 ± 2.31 [a]	40.73 ± 2.62	33.58 ± 4.06 [a]

3.2 Intravenous glucose tolerance test:

Figures 1 and 2 display the glucose and insulin responses to an IVGTT in chow fed RLA and RHA rats at baseline and after treatment with RU486 or Rosiglitazone. Figure 3 provides the areas under the curve (AUC) of the insulin response.

There were no differences in glucose levels between RLA and RHA rats under any of the tested conditions, nor did either treatment affect glucose levels. Baseline plasma insulin levels were significantly higher in RLA rats in comparison to RHA rats ($F_{1,21}$ = 11.095 p = 0.003). Treatment with Rosiglitazone significantly reduced the insulin response to an IVGTT in both RLA and RHA rats (at time points t = 5,10,20, 25 and 30 min, $p<0.05$). Also the AUC for the insulin response was significantly reduced after Rosiglitazone treatment in both strains ($F_{1,21}$ = 5,242 $p<0.05$).

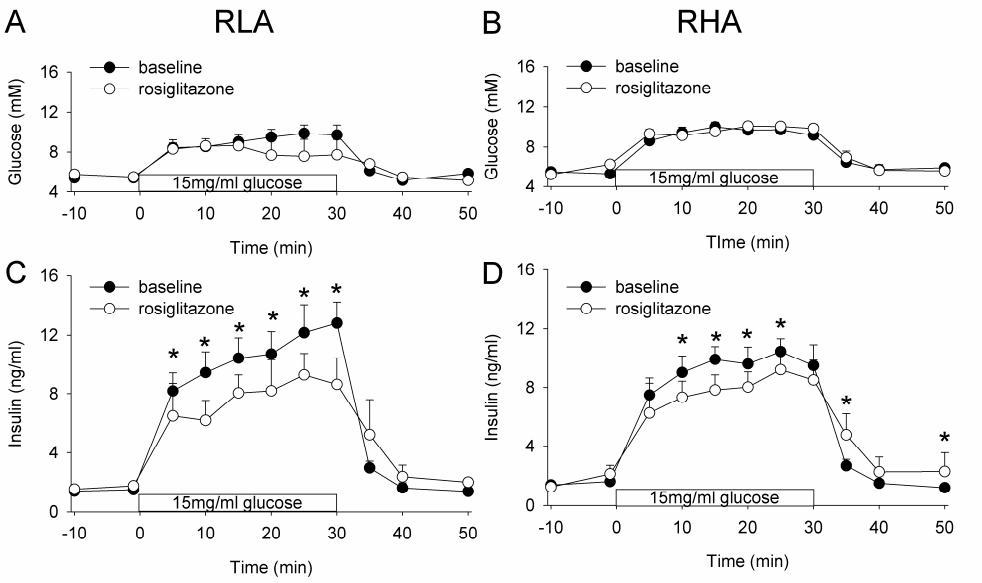

Figure 1: Glucose and insulin levels before, during and after an intravenous glucose tolerance test in RLA and RHA rats under baseline conditions and after treatment with Rosiglitazone. **A:** Glucose response in RLA rats. **B:** Glucose response in RHA rats. **C:** Insulin response in RLA rats. **D:** Insulin response in RHA rats. Black symbols represent baseline samples, white symbols represent samples after Rosiglitazone treatment. * Indicates a significant difference ($p<0.05$).

Treatment with RU486 significantly lowered the insulin response to an IVGTT in the RLAs but not in the RHAs. The reduction in the RLAs was significant at time points t = 5,10,20, 25 and 30 min (fig 2c)(ANOVA $F_{1,5} = 8.210$ $p<0.05$). Also the AUC for insulin was significantly lower in RLA rats after treatment with RU486 ($F_{1,21} = 4,356$ $p<0.05$).

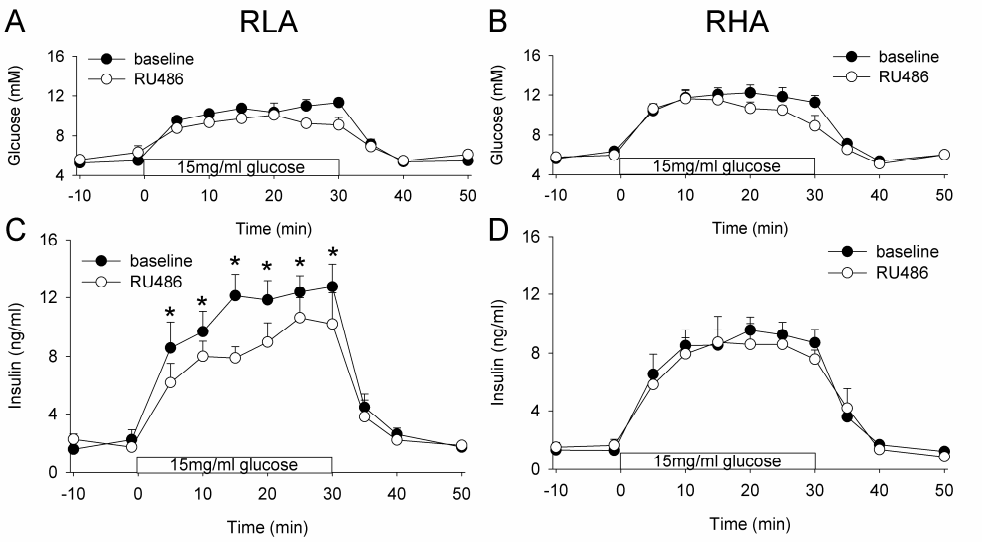

Figure 2: Glucose and insulin levels before, during and after an intravenous glucose tolerance test in RLA and RHA rats under baseline conditions and after treatment with RU486. **A:** Glucose response in RLA rats. **B:** Glucose response in RHA rats. **C:** Insulin response in RLA rats. **D:** Insulin response in RHA rats. Black symbols represent baseline samples, White symbols represent samples after RU486 treatment. * indicates a significant difference ($p<0.05$).

To compare the effect of the treatments between the strains we calculated the differences in the area under the curve before and after treatment (day 0 versus day 8) for each individual rat. The differences between the RLAs and the RHA with respect to the effect of RU486 was significant (reduction in the AUC for insulin in RLAs: -41.6 ± 16.6, in RHAs: -3.9 ± 8.3 ng/ml insulin* 30 min, ANOVA $F_{1,11} = 5.654$ $p<0.05$). There were no significant differences between the strains with respect to the effect of Rosiglitazone (reduction in the AUC for insulin for RHAs: -33.6 ± 15.6 and for RLAs: -51.4 ± 21.3 ng/ml insulin* 30 min) (ANOVA $F_{1,11} = 2.238$ $p = 0.089$).

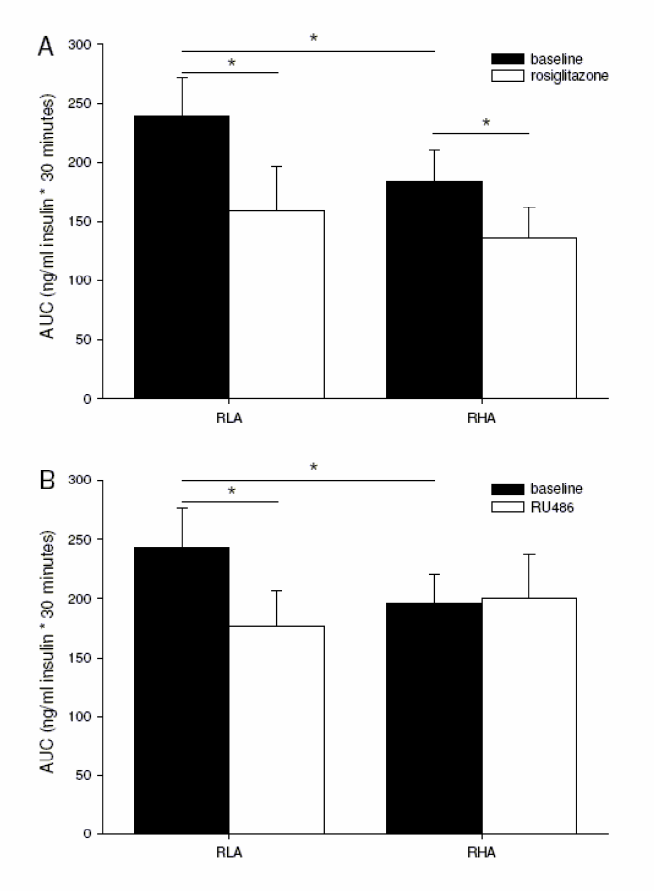

Figure 3: The area under the curve of the insulin responses (t =0 until t=30) during a 30 minute infusion of glucose (15 mg/min) under baseline and treated conditions. RLA and RHA rats **A:** The response in rats under baseline and Rosiglitazone treated conditions. **B:** The response in rats under baseline and RU486 treated conditions. Black bars represent baseline conditions, White bars represent treated conditions. * indicates a significant difference ($p<0.05$).

3.3 Corticosterone levels :

Figure 4 displays the plasma corticosteron levels at baseline and after treatment with RU486 or Rosiglitazone. Baseline corticosteron was significantly elevated in the RLA rats when compared to the RHA rats ($F_{3,21} = 5,242$ $p<0.01$). Treatment with RU486 significantly lowered plasma corticosteron levels in both RLA and RHA rats ($F_{3,21} = 3,842$ $p<0.01$). The reduction in corticosteron levels after treatment was significantly larger in the RLA rats compared to the RHA rats (ANOVA $F_{1,11} = 6.342$ $p<0.05$). After treatment with

RU486 there were no differences between the strains in corticosteron levels. Rosiglitazone treatment did not change corticosteron levels in either strain.

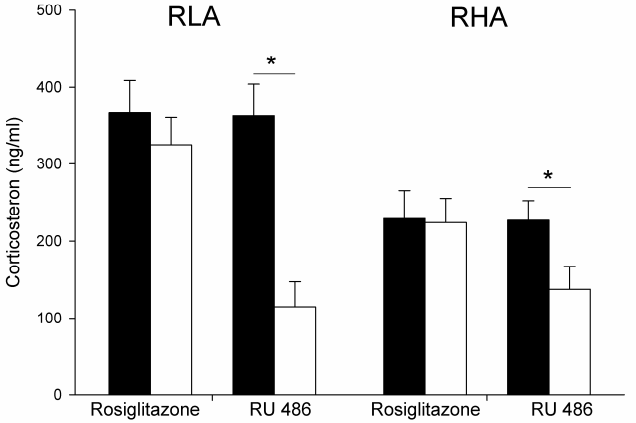

Figure 4: Corticosteron levels in RLA and RHA before and after treatment with either Rosiglitazone or RU486. Black bars represent untreated baseline conditions, white bars represent treatment conditions. * Indicates a significant difference ($p<0.05$)

3.4 Body composition:

Body composition was determined at the last day of treatment; the results of the analysis are summarized in table 2.The body weights of the RLA rats were significantly higher compared to the RHA rats in both treatment groups ($F_{3,25} = 2.925$ p ,0.05). Total fat mass of RLA rats was higher that the fat mass of RHA after both treatments ($F_{3,25} = 3.052$ p =0.032). RU486-treated RLA rats had more adipose tissue distributed in their epididymal compartment when compared to RU486 treated RHA rats ($F_{3,25} = 4.851$ p =0.009). There was no difference in the amount of retroperitoneal fat mass between RLA and RHA rats treated with RU486. After treatment with Rosiglitazone the RLA rats had more fat distributed in their epididymal compartment than RHA rats ($F_{3,25} = 3.899$ p= 0.018). The amount of retroperitoneal adipose tissue after Rosiglitazone treatment was not different between RLA and RHA rats. Within each strain, there were no differences in the body composition of rats treated with Rosiglitazone compared to those treated with RU486.

Table 2: Body fat distribution of RLA and RHA rats treated with either Rosiglitazone or RU486.* Indicates a significant difference with RLAs (within treatment) $p<0.05$.

	Rosiglitazone		**RU486**	
	RLA	RHA	RLA	RHA
Body weight (g)	391 ± 8.9	354 ± 9.6*	392 ± 8.2	344 ± 9.7*
Lean body mass (g)	186 ± 4.1	177 ± 6.3	187 ± 3.6	171 ± 4.0
Total body fat (%)	11.7 ± 1.77	9.5 ± 0.76*	11.1 ± 0.77	9.5 ± 0.77*
Epidydimal fat (g)	5.1 ± 0.62	3.3 ± 0.16*	4.5 ± 0.23	3.3 ± 0.24*
Retroperitoneal fat (g)	6.7 ± 1.16	6.3 ± 0.67	6.6 ± 0.57	6.2 ± 0.57
Subcutaneous fat (g)	25.4 ± 4.9	18.3 ± 4.2	23.7 ± 2.3	19.6 ± 2.25
Liver weight (g)	17.6 ± 1.3	16.9 ± 1.5	18.4 ± 1.6	16.5 ±1.8
Leptin (ng/ml)	4.0 ± 0.42	3.5 ± 0.58	3.9 ± 0.45	3.8 ±0.66

4. Discussion

The present study investigated the effectiveness of two different drugs for treating hyperinsulineamia in rat strains that were selected for either a passive or a proactive coping style. It was found that RU486 was only effective in reducing plasma insulin levels in passively coping rats whereas the effect of Rosiglitazone on insulin was similar in both rat strains.

For the general anti-diabetic agent, Rosiglitazone, we expected a comparable effect in passive and proactive individuals. Our study confirmed this: treatment with Rosiglitazone reduced the insulin response to an IVGTT in both RLAs and RHAs. As mentioned before, passive individuals are characterized by a hyperinsulineamic response to an IVGTT(5). Therefore, the effect of Rosiglitazone on plasma insulin seemed somewhat larger in the passive RLA rats. Treatment with Rosiglitazone was very effective in reducing the insulin response in the RLA rats to a level that was similar to that of the RHA rats. Treatment with Rosiglitazone was very effective in reducing the insulin response in the RLA rats to a level that was similar to that of the RHAs. It was not surprising that Rosiglitazone improved insulin responses in both the passive and proactive individuals in the present study. Thiazolidinediones, like Rosiglitazone, are thought to increase insulin sensitivity by activation of PPAR gamma, which in turn leads to an increased translocation of the glucose transporter 4 (GLUT4). This increased availability of GLUT 4 then facilitates glucose transport into the cell. Several studies have shown the beneficial effects of Rosiglitazone (23) although the exact mechanism by which the drug may increase GLUT4 translocation in skeletal muscle cell remains to be elucidated. It seems that Rosiglitazone affects the insulin receptor cascade directly and may circumvent most of the differences in origin of hyperinsulineamia.

The second drug that was tested in the present study is RU486, commonly used for treating insulin resistance in patients in which type 2 diabetes is secondary to chronically increased glucocorticoid levels, such as Cushing syndrome (10). Evidence in literature suggests that there are moderate differences between passive and proactive individuals in HPA-axis activity and baseline glucocorticoid levels (14). Therefore, we hypothesized that treatment with RU496 might be particularly effective in lowering plasma insulin levels in the passively coping RLA rats. The data obtained in the present study supported this hypothesis. Treatment with RU486 significantly lowered the insulin response to an IVGTT in the passively coping RLA rats and had no effect in proactive RHAs.

Since RU486 was effective in attenuating hyperinsulineamia in the passively coping rat one may assume that the effect was secondary to the effect of RU486 on circulating glucocorticoid levels. Indeed, the data of the present study revealed that: 1) corticosterone

levels are increased in untreated RLA's and 2) that treatment of RLAs with RU486 normalized corticosterone (and insulin) to a level comparable to the proactive RHAs. The data also suggest that moderately increased corticosterone levels may serve as an useful treatment strategy for hyperinsulineamia in passive coping individuals. The underlying mechanisms are not well understood. Glucocorticoids are thought to induce insulin resistance through several pathways. First, glucocorticoids decrease the sensitivity of muscle glucose uptake to insulin by decreasing translocation of GLUT4 transporters to the membrane. Second, glucocorticoids can inhibit the rate of glucose phosphorylation (24). Finally, glucocorticoids affect insulin sensitivity indirectly by stimulation of distribution of adipose tissue in the visceral compartment (*reviewed in (25)*).

Even though, the average body weight of the rats from the two strains did not differ in a statistically significant manner, RLA were heavier, and this is consistent with previous observations (6;26). Treatment with both RU486 and Rosiglitazone significantly lowered body weight in both the RHA and RLA rats but the difference between the strains remained unchanged throughout the experimental period. The decrease in body weight after RU486 can, in part, be explained by the concomitant decrease in food intake during treatment (27). In contrast, Rosiglitazone treatment did not affect daily food intake suggesting that the reduction in body weight is secondary to increased energy expenditure rather than being caused by reduced energy intake.

Total and epidydimal fat mass were significantly different between RHA and RLA rats after both treatment with RU486 and Rosiglitazone. Due to the within-subject design of the present study, we have no data on the body composition in untreated animals. However, in a previous study with (untreated) RLAs and RHAs of similar age (5;6), we already observed that total and epidydimal fat mass are significantly higher in RLAs in comparison with RHAs. This means that the observed differences in body fat distribution in the present study are presumably not caused by direct effects of either RU486 or Rosiglitazone.

In conclusion, the data of the present study reveal that Rosiglitazone improves the insulin response to an IVGTT independent of the coping style of the individual. In contrast, RU486, improves hyperinsulineamia solely in the passive coping style, by targeting the specific hormonal characteristics of this coping style. We conclude that insight in the neuroendocrine differences between different personalities may provide an extra and important impulse to improve treatment of insulin resistance.

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