Coping styles and the pathophysiology of energy metabolism

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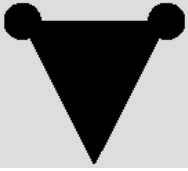
CHAPTER 11: Discussion



Introduction

Differentiation in personality is a wide-spread phenomenon in species across the animal kingdom. It is generally assumed that the development of coping strategies within species is driven by fitness trade-offs that act or have acted over the course of evolution (1). A proactive personality, characterized by high levels of aggression, routine formation and low levels of anxiety, is believed to be well- adapted to a territorial environment that remains stable over a prolonged time. In contrast, a passive personality type, characterized by high levels of behavioral flexibility, is thought to be adapted to a migratory setting. It is reasonable to assume that these adaptations also have repercussion to energy balance and fuel homeostasis characteristics of the individual. Therefore, the overall goal of this thesis was to elucidate the relation between personality and regulation of energy balance and fuel homeostasis and deregulations herein.

Most of the studies in this thesis were performed in rats. We used of rats of breeding lines selected for low avoidance behavior (i.e., passive “Roman” low avoidance: RLA) and high avoidance behavior (i.e., proactive “Roman” high avoidance: RHA) of a psycho-physiological stressor, as well wild type Groningen rats characterized for proactive and passive coping strategies to deal with a psych-physiological stressor. In addition, one study in humans was performed to investigate the face-validity of the results obtained in the rat studies, and to assess personality defined by coping style can be generalized to energy balance regulation in different species. Below, the main results of this thesis are shortly summarized followed by a discussion on how they should be viewed in relation to other types of rodent models, in relation to health and (metabolic) disease, and in relation to adaptiveness and maladaptiveness in terms of evolutionary fitness trade-offs.

Behavior

The first question addressed the characterization of different aspects of energy balance in rat lines selected for divergent coping styles. In the first two chapters of this thesis, it was shown that under standard laboratory conditions only minor differences in body weight or food intake were observed in rats selected for a “proactive” versus a “passive” coping style. More detailed investigation of feeding behavior revealed differences in meal patterning and circadian organization of eating behavior (**chapter 2**). Proactive rats ate fewer meals per 24 hours, but had a higher eating rate and larger meals, and they displayed a stronger day/night rhythm in food intake than passive ones. Additionally, analysis of body fat distribution showed a higher storage of visceral fat in the passive rats than in the proactive rats, without causing a difference in total adiposity. These data show that proactive

and passive rats are equally able to maintain a stable body weight, but they employ different strategies to reach this ability.

Differences in strategy of body weight maintenance became amplified when rats were exposed to an enriched environment where animals could freely access a running wheel, were switched to a highly palatable high fat (HF) diet, or both. When allowed to run in wheels, the proactive rats were initially more physically active than the passive ones. An observation that is consistent with a large body of literature showing higher activity levels in proactive animals in open field, elevated plus maze and other behavioral tests than passive ones (2-4). Interestingly, after a few hours of habituation, passive rats, but not proactive rats, increased their activity level significantly, which finally resulted in higher physical activity levels in passively coping rats than in the proactive ones (**chapter 2; chapter 6**). When sedentary rats were admitted to the HF diet, no major differences in body weight between the passive and proactive animals became apparent (**chapter 4**), despite a more pronounced HF diet induced increase of intake in the passive than in proactive animals. In rats subjected to running wheels, however, the switch from a chow diet to a HF diet markedly increased running wheel activity in passive rats whereas proactive rats did not respond to this switch with alterations in wheel running behavior. It is therefore concluded that under standard laboratory conditions (i.e., chow feeding without enrichment) the coping style of a rat does not profoundly influence regulation of body weight and energy balance. The importance of the coping style, however, becomes apparent under environmentally enriched conditions, where particularly passive rats are relatively more responsive to changes in the environment. The fact that passive rats adapt their food intake and physical activity levels to the prevailing environmental condition is consistent with the literature on the behavioral characterization of coping style, which describes proactive individuals as rigid in their behavioral patterns and passive individuals as behaviorally flexible (5-7).

Energy balance

The second goal of this thesis was to elucidate whether the differences in energy balance responses to environmental challenges in passive versus proactive rats have implications for sustainable metabolic health. In **chapters 3** and **4** we described an increased susceptibility of passive rats to the development of hyperinsulineamia during an intravenous glucose tolerance test (IVGTT), which is one of the hallmarks of the insulin resistance syndrome. In fact, extremely passive rats displayed hyperinsulineamic responsiveness during an IVGTT already under standard chow feeding conditions (**chapter 3**). Moderately passive rats displayed a relative low insulineamic response to an IVGTT on

the chow diet, but also displayed hyperinsulineamia during an IVGTT when fed a HF diet (**chapter 4**). Proactive rats, both extreme and moderate, appeared resistant to the deleterious effects of the HF diet on insulineamia. To investigate whether passive rats were generally more prone to disturbances in energy balance, we investigated the behavior and physiology of passive and proactive rats when subjected to activity based anorexia (ABA). ABA is an animal model mimicking several aspects of Anorexia Nervosa in humans. We observed that passive RLA rats were more prone to weight loss when subjected to ABA than proactive rats (**Chapter 10**). Overall we can conclude that relative to proactive rats, passively coping rats have increased susceptibility for disregulation of energy balance and fuel homeostasis when subjected to environmental challenges.

Treatment

The third aim of this thesis was to investigate efficacy of a number of treatments of insulin resistance in proactive and passive rats. Because passive rats have been characterized by increased HPA-axis activity relative to the proactive ones, and because glucocorticoids are known to impair insulin signaling in target tissues (8-11), we first studied the effect of treatment with the glucocorticoid antagonist, RU486, on IVGTT-induced hyperinsulineamia in passive and proactive rats. The effects of RU486 treatment were compared to the standard antidiabetic drug Rosiglitazone, which is known to increase insulin sensitivity by means of PPARgamma activation (12;13). We showed that treatment with Rosiglitazone lowered insulin responses in rats of both coping styles. Treatment with RU486, selectively lowered the insulin response in the passively coping rats (**chapter 5**). This indicates that there might be a causal relationship between the elevated HPA-axis activity and the hyperinsulineamia in the passive rats.

Based on the differences in behavioral responses between rats of the two coping styles, we investigated - next to pharmacological treatments - the effects of physical activity as a “life style” treatment of hyperinsulineamia. First we studied the efficacy of voluntary wheel running. Free access to a running wheel attenuated the hyperinsulineamic response during an IVGTT in both chow fed and HF diet fed passive rats. Interestingly, passive rats increased their voluntary running wheel activity when switched from chow to a HF diet, whereas proactive rats did not (**chapter 7**). When subjected to a forced running protocol, the increased physical activity again lead to normalization of the insulin response to an IVGTT in the passive coping rats (**chapter 6**). This suggests that an increase in physical activity has beneficial effects independent of the nature of running (i.e., voluntary or forced). Although insulin levels were lowered in both passive and proactive rats, the difference in physical

activity levels on the high fat diet may suggest that passive individuals are more receptive to behavioral interventions than proactive rats.

In summary, the data suggest that rats of both coping style are able to maintain energy balance, but that rats with a passive personality type employ other strategies than those with a proactive personality style. Additionally, these studies emphasize the importance of the interaction between the coping strategy and the environmental conditions. Thus, relative to proactive rats, passive rats respond stronger to changes in external factors that influence energy balance (e.g. HF diet and physical activity). The enhanced responsiveness in passive rats results in the development of derangements in stable energy rich environments. This behavioral profile, however, seems beneficial in environmental settings that require compensatory behaviors.

Personality and insulin resistance

To gain a deeper understanding in the relation between coping style and development of hyperinsulineamia, we performed a meta-analysis on the collective data set gathered in this thesis, complemented with some additional data from pilot studies performed in preparation of this thesis. The database contains the characteristics of a total of 379 rats (see table 1) with area-under-the curve (AUC) of the insulin response during the IVGTT in rats with or without access to running wheel as dependent variables, and any other parameter linked to energy balance and personality as independent variables. In all animals, coping style was assessed by scoring the percentage time spent burying an electrified shock prod inserted in the home cage of a rat (i.e., defined as defensive burying, with proactive rats burying the prod, and passive rats showing excessive freezing behavior without showing any burying behavior). Linear backward regression analyses on the complete data set was performed to assess relation of (any of) the different measured parameters on the insulin response during an IVGTT. The significance of the model constructed based on this analysis was calculated by means of a multiple linear regression model. Under standard laboratory conditions, the insulin response during an IVGTT had the strongest relation with the defensive burying behavior interacting with the amount of epididymal fat ($F(1,36) = 12,896$ $p<0.001$). When access to a running wheel was given, the insulin response during an IVGTT had the strongest relation with the percentage time spent burying, interaction with the average number of revolutions ran in a running wheel, and with the amount of epididymal fat ($F(1,36) = 11,759$ $p<0.001$). Overall, this analysis showed that risk factors associated with body weight gain, like increased total body fat and increased retroperitoneal fat depots, are

not highly related to the development of hyperinsulineamia in the passive rats. This suggests that the passive rats develop hyperinsulineamia independent of body weight gain.

Table 1: P-values of a linear backward regression analysis in either sedentary or voluntary running rats. The dependent factor in this model was the area under the insulin response to an IVGTT. The independent factors in the model were: Defensive bury score, body weight, fat mass, fat free mass, Epididymal fat mass, retroperitoneal fat mass, leptin levels, diet (chow or high fat) and running activity. epi = epididymal fat mass, retro = retroperitoneal fat mass, BW = body weight. – indicates no statistical relevant correlation, * indicates a statically significant correlation.

Factors in regression	Sedentary (IVGTT)	Running (IVGTT)
Defensive bury score	0.021 *	0.020 *
Body weight	0.077	-
Fat mass	-	-
Fat free mass	-	-
Epididymal fat	0.069	0.071
Retroperitoneal fat	-	-
Running activity	not analyzed	0.032
leptin	-	-
diet	-	0.098
bury score x epi x retro	0.005 *	not analyzed
bury score x epi	0.000 *	not analyzed
bury score x epi x retro	not analyzed	0.000 *
bury score x epi x running	not analyzed	0.000 *

Although not assessed in the above-shown meta-analysis, probably the most prominent mechanism explaining hyperinsulineamia, but also visceral obesity and potentially hypertension (which are all hallmarks of the insulin resistance syndrome) in “passive” coping individuals might be the elevated HPA-axis activity in passive individuals relative to proactive ones. As mentioned in the introduction of this thesis, “passive” individuals are characterized by a higher responsiveness of the HPA-axis to mild stressors and we have indeed shown in the extremely passive RLA rats chronically elevated corticosterone levels (**chapter 3**). Animals with chronically elevated glucocorticoid levels, homologous to patients with Cushing syndrome, are known to be prone to develop hyperinsulineamia, insulin resistance and visceral obesity (11). Consistent with this, we showed in **chapter 5** that the development of hyperinsulineamia and visceral adiposity was attenuated by treating the RLA rats with a glucocorticoïd antagonist, suggestive of a role for the elevated HPA-axis activity in the development of the obesity related metabolic derangements. Additionally, we found that the RHA rats had an increased sympathetic outflow expressed by significantly higher plasma noradrenalin levels than their RLA counterparts. Similar observations were made in WTG rats (14). Since elevated sympathetic outflow may stimulate thermogenesis (15), this might

account for higher heat production in RHA rats (data not shown), potentially contributing to their resistance for metabolic derangements. Another effect of higher sympathetic outflow is that it directly lowers insulin release from pancreatic B-cells (16), causing a reduction in storage of nutrients (including fat in the visceral depots). Apparently, mass discharge of sympathetic outflow in the visceral depots (17) of RHA and subsequent exposure of the liver to lipids did not occur to the extent that it caused metabolic derangements since levels of liver triglycerides and liver cholesterol were lower in RHA rats than in RLA rats (**chapter 3**). A difference in the autonomic balance between "passive" and "proactive" individuals including HPA axis differences may be the basis of the differential susceptibility for development of metabolic derangements. This hypothesis is strengthened by the results described in **chapters 5, 6** and **7**. Lowering of HPA-axis activity by means of glucocorticoïd receptor antagonist treatment (**chapter 5**) as well as elevating sympathetic activity by means of exercise (**chapters 6 and 7**) both proved to attenuate hyperinsulineamia.

Face validity and translation to humans

An important issue regarding the findings obtained in the animal studies is whether they have relevance for the human population. To what extent can the differential susceptibility for development of metabolic derangements found in proactive and passive rats be translated to humans with a proactive or passive personality? This is highly relevant since personality type has been found to influence the course and development of several physical illnesses, like cancer, immune disease and cardiovascular disease (18-22). Based on the animal studies we hypothesized that humans characterized as having a passive coping style would be more prone to develop metabolic derangements under standard conditions. In humans, however, data on the interaction between the personality and the risk to develop metabolic derangements is contradictory. Studies using questionnaires to assess personality generally report an increased risk to symptoms of the metabolic syndrome and diabetes development in proactive personalities *(23-25)*, but others report an increased risk in the passive individuals (26;27). However, results from studies assessing personality related a passive coping style to several of physiological and behavioral characteristics, including increased HPA-axis activity and anxiety (28;29). Since the latter are viewed as risk factors for the development of the metabolic syndrome, it might be justified to point out that individuals characterized by a passive personality are at least more at risk for the development of hyperinsulineamia and related co-morbidities (28-31). For future studies investigating the interaction in humans it may thus be suggested to combine personality questionnaires with more scrutinized analysis of physiological/neuroendocrine parameters.

A major conclusion based on the rodent studies in this thesis was that enrichment of the environment is a major factor in the relation between coping style and energy balance regulation and derangements. Such interdependency between environment, personality, and energy balance probably exists in the human condition as well. Because in most human studies the environmental conditions of the test subjects was not strictly controlled due to the outpatient set-up, this causes interpretational problems in many human studies. In part, this may explain why several studies investigating the role of personality in the success of treatments for weight loss displayed conflicting results (32-34). In our rodent model, we showed that the passive coping type increased voluntary physical activity in response to HF diet feeding whereas the proactive coping type did not (35). Based on these data, we hypothesized that the personality of the individual may be a prospective marker for weight loss during an intervention. Several studies in humans have shown differences between the so-called type A and type B personality types during exercise interventions. Type A and Type B subjects differ in perceived exertion ratings during ergo-meter cycling (36). Furthermore, type A personalities were shown to have a stronger internal motivation to perform the exercise protocol, however, type B persons appear to respond better to instructions and may therefore do better during exercise interventions (37).

To further investigate above-mentioned predictions, we performed a study in which we investigated in humans interactions between personality type (proactive or passive) and compliance to, and efficacy of, a life style intervention program (including “training” activity in a gym, and voluntary activity assessment) in the aim to lose body weight. In both personalities, the weight loss program resulted in a successful reduction in body weight and weight circumference. Interestingly, there were differences in the activity levels during the intervention between the passive and proactive individual. The passive individuals were show to be more active on training days. However, on the days in between training the passive individuals lowered their activity levels considerably, whereas the proactive individuals displayed similar activity levels on resting days during the intervention and during baseline measurements (**chapter 8**). These data suggest that passive individuals are more responsive to instructions given during the intervention, but also compensate for the increased activity on the days they are not exercising. We therefore concluded that informing the individuals with passive personality about the risk of compensatory behavior on the resting days may improve their results during an exercise-based intervention. Finally, the increased levels of physical activity in humans with a passive coping style (chapter 8) as well as in the rodents with a passive coping style (chapter 7) suggest biologically common pathways in humans and rodents linking aspects of energy balance regulation,

derangements and treatment to type of personality. For this reason, a model for coping style in rodents may have a high face-validity for the study of metabolic health and disease in humans.

Alternative models linking personality and metabolic health and disease.

An alternative approach to investigate a potential cause-effect relation between the coping style of an individual and the risk development of metabolic derangements is to study the behavioral profiles of well known models for hyperinsulineamia, insulin resistance and obesity. From the data gathered in this thesis it appears that in particular the proactive coping rats are resistant to the metabolically derangements induced by feeding a HF diet. Diet-induced obesity is a frequently used paradigm to study obesity in rodents; with this model rodents are fed a calorically dense diet and as a consequence about half the number of rats becomes obese on this diet (DIO rats), whilst the other half does not develop obesity and are thus diet-resistant (DR) (38). Diet-induced obesity is often accompanied by insulin an leptin resistance, hyperlipidemia and hypertension. Interestingly, DIO rats were characterized by higher sympathetic output, as measured by increased noradrenalin levels (39). Furthermore, DIO rats subjected to a HF diet have higher increases in glucocorticoids, and have higher levels of anxiety than DR rats (40). This suggest that the DIO rats in those studies have a mixture of the proactive and passive phenotypes. In the DIO/DR model, the DIO rats have significantly higher energy intake that the DR rats (38), a difference that was not observe between the RLA and RHA rats in our studies. Furthermore, another major difference characterizing DIO and DR rats is their difference in body weight gain on a HF diet. Although the RLA rats have higher adiposity that the RHA rats, we did not observe major difference in body weight gain. We may therefore state that the RHA are not necessarily diet resistant with respect to body mass increase, but that these proactive coping rats may be resistant to the maladaptive (pathological) consequences of DIO.

Studies in rat models selected on the basis of a genetic defect are consistent with the view that a passive coping style is only uni-directionally related to visceral adiposity and insulin resistance. The spontaneously diabetic fa/fa rat, for example, is characterized by a genetic defect in the leptin receptor leading to obesity, hyperlipidemia, insulin resistance and hyperglycemia (41). These rats were investigated in several different behavioral paradigm, like the open field, elevated plus maze and the black/white box tests, however, no behavioral differences were found between the diabetic fa/fa rats and their heterozygous non-diabetic counterparts (42). This suggest that insulin resistance, leptin resistance or obesity do not per se alter the behavioral profile. We can thus state that insulin resistance

associated with hyperinsulineamia would not lead to a more passive behavioral profile, which suggests that the coping style of a passive individuals is not the consequence of an altered metabolic profile. Instead, the passive coping style of an individual triggers a maladaptive responses to abundance of energy, which than in turn leads to a higher susceptibility to develop metabolic derangements.

To investigate whether other specific aspects of coping style, such as HPA-axis activity, plays a role in the development of the metabolic profile characteristic for the different coping styles, it can be useful to study animal models displaying either the behavior or the physiological characteristics of a coping style, but not both. A potential rat model of interest in this respect is the Fischer 344 / Lewis inbred rat strains. The Fischer 344 rat is characterized by increased HPA-axis activity, whereas the Lewis rats have blunted glucocorticoïd responses to stress and generally have lower diurnal glucocorticoïd levels (43). The Fischer and Lewis rats display some similarities to, respectively, the “passive” and “proactive” coping rats. Several other, but not all related behavioral characteristics of “active/proactive” have homology to those found in the “Fisher/Lewis” strains. For example, the Lewis rats are more explorative in a novel environment than the Fisher rats (44). However, in contrast to the RHA/RLA strains, the Lewis and Fischer strains do not display differences in anxiety or aggression. These rats thus seem to display the physiological parameters typical for the coping styles, but not all of the behavioral characteristics. Moreover, both the Lewis and Fischer rats are prone to develop obesity. It is not known to what extent this may be a consequence of inbreeding rather than a strain specific effect since inbred rats are known to develop obesity easily (45). The point here is that the more HPA-axis reactive Fischer rats were shown to be less insulin sensitive than Lewis rats (46). In young Fischer rats, the decreased insulin sensitivity does not lead to insulin resistance and glucose intolerance, however, a considerable percentage of Fischer rats develop insulin resistance at a later age (47). It thus seems that a hyperactive HPA-axis, induced through increased stressor sensitivity or a differential genetic profile, is a risk factor for the development of insulin resistance in these animals; an effect that might be independent of the behavioral expression of a passive coping style. Unfortunately, the eating patterns, nor physical activity patterns of these rats have been investigated leaving it impossible to conclude whether the increased HPA-axis activity also plays a crucial role in the other differences in energy regulation observed in the passively and proactively coping rat strains we studied.

Evolutionary consideration of personality and energy balance.

It was mentioned in the beginning of this chapter that differentiation in personality is a wide-spread phenomenon in species across the animal kingdom, and that the development of coping strategies within species is driven by fitness trade-offs that act or have acted over the course of evolution (1). In this section, a number of theories are outlined which focus on the nature of these trade-offs.

Thrifty gene hypothesis.

The most well known theory addressing the evolution of energy balance is the Thrifty genotype theory. This hypothesis states that the so-called thrifty genotype, a genotype designed to collect and store energy during periods of food abundance to prepare for times of food scarcity, was advantageous in the time of the hunter-gatherers (48). Loosely translated this suggest that the thrifty phenotype is designed to deal with flexible environmental conditions. This implies that this phenotype would be advantageous for the more passive coping individual. Building on this assumption, one would expect an increased number of passively coping individuals in the human population. Epidemiological studies indeed suggest a higher prevalence of the Type B personality - the passive personality -, in human populations (49). Whether and how this increased incidence of a passive personality also explains the obesity prone phenotype of most humans remains to be elucidated.

Thrifty genes prepare for famine that is not common anymore in the Western-industrialized society, and the increased incidence of obesity and type two diabetes in recent years are a direct result of this thrifty trait interacting with the abundance of nutritional supply (48). Although still widely accepted the thrifty genotype has received critique because it may not explain the exponential increase in obesity and diabetes in the last 20 years. Several other theories have been postulated that might be able to explain the current developments. *Watve & Yajnik (50),* for example, hypothesized that insulin resistance is an adaptation in the transition of muscle dependent to more brain dependent individuals. The so-called muscle dependent individual is characterized by relatively high levels of aggression, active responses to environmental threats and challenges, and high sympathetic reactivity. There is a clear resemblance between the muscle-dependent type and the proactive personality type. The brain-dependent type relies on the brain to respond to threats and challenges, is more passive and low in physical aggression, resembling the passive coping style. This theory hypothesizes that in the current society a brain-dependent individual will be more successful and that for the brain dependent strategy glucose transport to the brain should be favored over transport to peripheral areas. In that situation peripheral insulin resistance

could be adaptive as it leads to increased insulin hitting the brain (i.e., provided that neuronal and/or neuron-supporting tissue do not become insulin resistant) and thereby increasing glucose levels centrally. A critical remark to this theory is that a decrease in peripheral glucose uptake does not necessarily lead to an increased glucose transport to the brain. Peripheral insulin resistance generally leads to peripheral intracellular hypoglycemia without changes in central glucose levels (*reviewed in (51)*). Recently Belsare and colleagues (52) proposed an interesting variation on the theory of Watve & Yajnik *(50)*. In their revision, the suppression of the phenotypic expression of a proactive strategy, like suppression of aggression, was suggested to be causal to the increase in insulin resistance incidence in passive individuals. Although it is difficult to tease apart cause and effect relations in this theory, suppression of aggression does induce increased serotonergic signaling (53) which in turn is shown to induce insulin resistance (54;55). In light of this theory it would be interesting to investigate whether proactive individuals limited in their coping response display a more passive metabolic profile.

Predation-release hypothesis.

A recent evolutionary theory with regards to the interaction between the coping style and the energy balance is the predation release hypothesis, introduced by *Speakman (56)*. The predation release hypothesis is based on the concept of a set-range rather than a set-point for the maintenance of energy balance. The theory hypothesizes that the lower boundaries of this set-range are determined by evolutionary selection pressures related to the risk of starvation, analogous to the thrifty gene hypothesis. The higher boundary of the set-range in this hypothesis is determined by selection pressure related to the risk of predation. Since especially this higher boundary would be important in an evolutionary basis for the obesity epidemic, the constraints for predation become important. When there is a high risk of predation, the body weight should not be to high since a high weight decreases escape possibility. When however the predation risk is low, like in the current society, the upper boundary for maximal body mass could be set at a higher level. This theory becomes interesting with respect to the research discussed in this paper if proactive and passive individual prove to be differentially affected by predation risk. Hints that a differential predation risk is indeed observed in proactive and passive coping individuals is found in populations of sticklebacks. Sticklebacks from high predation populations tend to show increased aggressive and bold behaviors compared to fish from low predation populations (57). This suggests that a proactive coping style is preferred in environments with a high predation risk, whereas a passive coping style is more successful in low risk environments.

Combining this with the predation release hypothesis (56) that in a low predation environment the upper limit of the energy balance set-point is placed higher with the increased passivity traits in stickleback in low predation environment, this leads to the hypothesis that in the current low predation environment co-selection of a passive personality with a lose upper boundary of the energy balance might have caused the increased risk to obesity development in passive coping individuals. Overall we may conclude that it is plausible that evolutionary drift may have induced co-selection of traits for a passive behavioral strategy and obesogenic traits. The mechanisms responsible for this evolutionary drift, however, remain to be elucidated.

Although this hypothesis may be thought provoking, the question remains how this would explain the recent explosion in obesity prevalence, as genetic drift is an inherently slow process. One potential mechanism that may speed-up this process is through epigenetic modification. Epigenetic modifications alter the existing genome in ways that affect gene expression. These occur during normal development allowing for differentiation of specific organ tissues. The epigenetic modifications responsible for this process include DNA methylation and histone modifications. Epigenetic modifications can also arise in response to varying environmental conditions, especially during (fetal and post-natal) development. Epigenetic alterations occur much faster than genetic changes because epigenetics allow for alterations in the genome and the phenotype without changes in the DNA sequence itself (58). The importance of epigenetic alterations in the development of obesity and insulin resistance was shown in studies in which both maternal obesity as well as maternal under nutrition were associated with the development of the metabolic syndrome (59;60). Likewise, neonatal environmental enrichment, diet, and maternal care were shown to influence the development of metabolic disorders (reviewed in 61). Thus it is tenable that epigenetic in addition to genetic factors might be involved in the current epidemic of metabolic diseases such as obesity and type 2 diabetes. Epigenetics factors seem also to have an influence on the personality of the individual. This was indirectly shown by Fernandez-Teruel (62) who found that neonatal environmental enrichment induces a “passive” individual to display a more “proactive” behavioral strategy in adulthood. This implies that epigenetic factors may also determine how an individual will respond to changes in its environment later in life. Based on this we hypothesize that excessive weight gain and insulin resistance might be the maladaptive consequences of a personality that is well adapted to its neonatal environment, but is in mismatch with the environmental conditions at adulthood. Future studies should therefore investigate the interaction between

epigenetics, personality and the possible pathological consequences.

Epilogue

Overall the studies presented in this thesis indicate that the interactions between personality and environment are key in understanding individual differences in the development of obesity and metabolic disease as well as development of activity based anorexia. The data in this thesis clearly point out that the success of life style interventions designed to prevent or treat metabolic diseases could be considerably improved by adjusting the intervention to the personality or coping style of the individual. Furthermore, certain physiological/neuroendocrine characteristics of a coping style are strong indicators for pathology development. Since assessed personality type are not always correlated to these physiological/neuroendocrine parameters in humans (due to variations in environment), future research should focus on the identification of easily measurable physiological/neuroendocrine biomarkers indicative of the coping style in humans. These biomarkers and tailored interventions may help to halt or even turn around the current epidemic in metabolic diseases. Finally, improved understanding of the evolutionary basis and epigenetic mechanism underlying the link between personality and energy balance and fuel homeostasis may prove to be an important angle to understand development of metabolic derangements.

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