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Coping styles and the pathophysiology of energy metabolism

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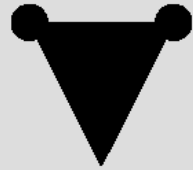
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CHAPTER 1: General Introduction



Introduction:

The incidence of health problems resulting from an imbalance between energy intake and expenditure - like obesity and anorexia nervosa - is growing and has become one of the main causes of death in industrialized societies (1). To enable effective treatment of these disorders, a better understanding is required of how these imbalances may develop. The concept of energy balance was initially introduced in the 1950s by Kennedy (2) who recognized that the amount of energy consumed over time almost precisely matched the amount of energy utilized, and that a factor related to the amount of fat stored in the body interacting with central neuronal networks may be key in this regulation (2).

Energy balance was thought to be controlled by two brain regions. Experiments in mid twentieth century already had shown that electrolytic lesioning of the ventromedial hypothalamus augmented food intake and this brain area was therefore considered to be the satiety center in the brain. In contrast, lesioning of the lateral hypothalamus induced anorexia, and this brain region was considered to be the brain's hunger center (3). Over the next decades, the number of pathways found to be involved in the regulation of energy balance expanded dramatically (i.e., due to the advent of molecular biological techniques), and has led to the notion of complex neuronal networks spanning hypothalamic, brainstem, limbic, and cortical circuitry interacting with peripheral neuro-hormonal and metabolic signals that regulate body weight, fuel fluxes, and energy balance (4;5).

Although many people are still able to maintain their body weight (and thus energy balance) within a range that is considered to be healthy (1), the number of individuals developing obesity and the severity hereof is ever increasing (1). The cause of the obesity epidemic probably originates from the abundance of palatable high energy foods combined with a sedentary way of life, but not every individual is equally susceptible for weight gain under these conditions. The origins of the differences in susceptibility for obesity probably resides in genetic factors predisposing an individual to weight gain. For those who are predisposed to weight gain, the internal "settling-point" of body weight might be higher than those resistant to weight gain, making it more difficult for the obesity-prone individuals to avoid weight gain in the face of the environment of plenty.

In fact, eating less may have repercussions for energy expenditure that opposes weight loss. This is very-well illustrated by a case study of an obese woman who followed a strict diet for 15 weeks limiting her caloric intake by 35%. However, after finishing the 15 weeks of diet intervention, her body weight was higher than it was before starting dieting. It turned out that a reduction in her resting metabolic rate from 1479 kcal/24h at baseline to

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927 kcal/24h at the end of the intervention had entirely compensated the reduction in caloric intake (6).

The most extreme forms of obesity are usually caused by single gene mutations (7-10). In addition, several polymorphisms were identified that may explain more moderate versions of this condition (11-15). However, evidence is accumulating that genetic mutations are not the main cause of the rapid and dramatic increase in the incidence in obesity and type 2 diabetes in Western society in the last decades (16-18). Generational accumulation of environmental influences appear to add another layer to the interactions between genetic, neuronal/hormonal and metabolic factors that may be key in understanding individual differences in the development of obesity and metabolic disease.

The way humans perceive and interact with the environment is, for a large part, determined by personality. The personality can be defined as a set of behavioral responses that are imbedded (by nature and/or nurture) within an individual. These behavioral strategies are employed throughout life to guide the individual's interaction with the environment. The most well known methodology to assess one's personality is by using the big five model (19;20). This model describes five traits, (i.e., neuroticism, extraversion, conscientiousness, agreeableness and openness to experience), each of which individuals may express differently relative to the population average (20). Although there is some debate on the details of each of these five personality traits, there is consensus that this five factor model describes ones personality optimally (*reviewed by 21*). Already in 1934, *Thurstone (22)* identified that these aforementioned traits could account for the variation found in personality ratings in 1300 test subjects using 60 personality adjectives. The five identified personality traits remain relatively stable throughout development from infancy to adulthood and are not affected by major live events (20).

This classification of the personality has been used to asses risk factors for several psycho-social disorders, like depression, anxiety disorder and addiction (23;24). Additionally, one's personality has been found to influence the course and development of several physical illnesses, like cancer, immune disease and cardiovascular disease (25-29). Another, perhaps more objective characterization of personality in humans may be found in the so-called Type A and Type B personalities. This distinction in personality types was predominantly based on the physiological responses to changes in the environment (30). The Type A personality is characterized by high catecholamine responses to environmental stressor and, additionally, these personalities are more aggressive, impatient and

competitive (31-34). Type B personalities, on the other hand, are characterized by elevated cortisol release during stress, and display a more passive behavioral strategy when faced with stressors (35).

Little is understood about the interaction between the personality and regulation of energy balance and fuel homeostasis, and disorders thereof. Data from human studies investigating the relationship between personality and metabolic disorders are contradictory (36). Most studies investigating personality differences use a self-rated personality scale, such as "the big five". Conclusions from those studies are probably confounded, because the personality itself may influence the rating process. In studying interactions between the neurobiology of personality and regulation of energy balance and fuel homeostasis (and their dysregulations), the use of the Type A and Type B personalities may be more useful. Moreover, in rodents (but also in many other species) two distinct personality types can be identified which are highly homologous to the human Type A and Type B personalities; the proactive coping style and the passive coping style, respectively. The proactive coping style is based on the so-called fight/flight response (37). Rodents with a proactive coping style are characterized by a proactive response to stressors, higher levels of aggression, impulsivity, and they are more prone to develop routines (38;39). The passive (or reactive) coping style originates from a conservation/withdrawal response. Individuals with a passive coping style are characterized by passive responses to stressors, a low aggressive nature, low levels of cue dependency and high levels of behavioral flexibility (38-40).

This thesis aims to study the relations between personality and the neurobiology of energy balance and fuel homeostasis. The thesis focuses on those behavioral and physiological parameters that impact body weight, energy balance, and fuel homeostasis and associated derangements that lead to pathologies relevant to human disease. The following questions will be addressed:

- 1) Are proactive and passive individuals different with respect to regulation of energy balance and fuel homeostasis?
- 2) If so, do these metabolic differences between the coping styles pertain to differences in susceptibility to develop related pathologies, such as insulin resistance and or Anorexia Nervosa?
- 3) Do differences between coping styles in rats have a) implications for the success of treatment of metabolic disorders and b) face-validity for human disease and treatment?

Part one of this thesis describes the (patho)physiological and behavioral characterization of energy balance in rats that differ in coping style. In **Chapter 2**, a characterization of behavioral and physiological strategies of energy balance regulation is described for the Roman and the Wild Type Groningen rat. Energy balance in these passive and proactive individuals is described in terms of differences in body weight, body composition, food intake patterns, energy expenditure, cardiovascular functioning and plasma hormone levels. In **Chapter 3** the potential susceptibility for developing hyperinsulinemia and visceral obesity (which are hallmarks of the insulin resistance syndrome) and the underlying mechanisms are investigated in passive Roman Low Avoidance (RLA) and proactive Roman High Avoidance (RHA) rats. **Chapter 4** continues on this theme and describes the interaction between diet and coping style in relation to the risk for the development of metabolic disorders.

Part two of this thesis is focused on the treatment of metabolic risk factors, in particular insulin resistance. In this section we aim at elucidating possible differences in treatment success between proactive and passive individuals. In **Chapter 5** we mainly concentrate on pharmacological interventions by treating proactive and passive individuals with the PPAR γ -agonist Rosiglitazone and the glucocorticoid receptor antagonist RU486. The following chapters focus on physical activity as treatment for insulin resistance and visceral obesity. In **Chapter 6**, the potential beneficial effects of voluntary wheel running behavior are investigated in proactive and passive rats with particular emphasis on the potential differences between voluntary and forced wheel running behavior. This topic is continued in **Chapter 7**, that focuses on voluntary wheel running activity in relation to diet interventions and the effects on glucose and insulin homeostasis. In **Chapter 8**, the face validity of the animal studies is tested in humans, in a study in which the success of an exercise-based and a diet-and-activity-based life style intervention program is studied in passive and proactive overweight human volunteers.

The final part of the thesis focuses on the potential importance of personality in the development of hyperactivity in Anorexia Nervosa. **Chapter 9** provides a theoretical framework for the role of the dopaminergic reward system in development of anorexia nervosa, supported by data from an animal model. **Chapter 10** further elaborates on this and shows that passive individuals are particularly sensitive for the development of anorexia nervosa.

Finally, the data presented in this thesis will be summarized and discussed in **Chapter 11**.

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