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## Personality, a key factor in personalized medicine?

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### ABSTRACT

The incidence of health problems resulting from obesity is growing and obesity and its related diseases has become one of the main causes in death in industrialized societies. Environmental influences are crucial for the interactions between genetic, neurohormonal and metabolic factors that may be important in understanding individual differences in the development of obesity and metabolic diseases like type 2 diabetes. In particular the interactions between the personality of an individual and the environment play a key role in predicting the chance for successful treatment. Our experimental data clearly point out that the success of interventions designed to prevent or treat metabolic diseases could be considerably improved by adjusting the intervention to the personality of the individual. Furthermore, certain physiological and neuroendocrine characteristics of a personality are strong indicators for pathology development, both in experimental animals and humans. Future research should focus on the identification of easily measurable physiological and neuroendocrine markers indicative of the coping style or personality in humans.

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### 1. Introduction

In this perspective we argue that a deeper insight in the relation between the personality of an individual and the coherent neuroendocrine background may provide an important impulse to the personalized healthcare initiatives that are currently undertaken by the pharmaceutical industry and healthcare systems. Ideally, it will facilitate “tailor made” pharmacological treatment strategies, in which patients are subjected to treatments with optimal efficacy. A key element here is the idea that different populations of patients can suffer from what superficially appears a common disease, but in which the etiology of the disease is, in part, driven by specific traits linked to personality and the neuroendocrine system. Focusing on underpinnings and progression of disease in these specific patient populations – rather than targeting the common disease characteristics displayed by the group as a whole – this may drastically limit the number of patients that are exposed to treatments from which they do not benefit. This will help reducing the burden on health care providers and the ever-increasing costs of our healthcare system, which is becoming a staggering threat to our society. In this perspective, we specifically focus on the role an individual's personality is playing in the success of both pharmacological and life style treatments of insulin resistance, which is a major risk-factor for type 2 diabetes.

### 2. Personality

The number of people developing obesity, and obesity-related disorders is ever increasing (World Health Organisation, 2010). Obesity can be caused by single gene mutations or polymorphisms (Jackson et al., 1997; Montague et al., 1997; Vaisse et al., 1998; Yeo et al., 1998); (Frayling et al., 2007; Hara et al., 2002; Lyssenko et al., 2009; Staiger et al., 2009; van et al., 2008). However, evidence is accumulating that genetic mutations are not the main cause of the dramatic increase in the incidence of obesity and type 2 diabetes in Western societies over the last decades (Chakravarthy and Booth, 2004; Speakman, 2008; Wells, 2006). Generational accumulation of environmental influences appears to add another layer to the interactions between genetic, neurohormonal and metabolic factors that may be a key in understanding individual differences in the development of obesity and metabolic diseases.

The way an individual perceives and interacts with the environment is to a large extent determined by the individual's personality. Personality can be defined as a set of behavioral strategies that are embedded within the individual. These behavioral strategies are deployed throughout life to guide the individual's interaction with the environment (Thurstone, 1987). In most animal species, including humans, two major personality types can be distinguished (reviewed in (Koolhaas et al., 1999)). The proactive (type A) personality is characterized by the so-called “fight/flight” response. Individuals with this personality type display high levels of aggression, impulsivity and often develop routine behaviors (Benus et al., 1991; van Oortmerssen and Bakker, 1981). The passive (type B) personality originates from a “conservation/withdrawal” response (Engel and Schmale, 1972).

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Individuals with this passive personality are characterized by a low aggressive nature, low levels of cue dependency and high levels of behavioral flexibility. The proactive (type A) personality seems to have evolved to assure fitness under stable environmental conditions. This individual is capable to defend a territory against intruders, due to the higher levels of aggression. However, due to its sensitivity to routine formation it will have difficulties to cope with relatively large changes in the environment, which the animal/individual has no influence on. In contrast, the passive (type B) personality is not aggressive and very flexible in its behavior. It will be more successful in an ever changing environment, since it will adapt to the prevailing condition. In nature, for example, type B flexible animals may migrate to avoid psychosocial pressure from conspecifics or predation by others, while type A animals will stick and face the challenge (Koolhaas et al., 1999).

### 3. Personality and development of insulin resistance

In consideration of the apparent relation between treatment efficacy and personality type it is in the first place important to realize that there are potential differences in the susceptibility to develop a disorder and/or differences in the origin of the disorder. The role of personality in the development of type 2 diabetes has been studied in humans as well as in rodents. Data from studies in human are contradictory; i.e., some studies show an increased risk for type 2 diabetes in individuals characterized by high levels of hostility and extraversion, while others show the complete opposite (reviewed in Smith and MacKenzie, 2006). The discrepancy between the studies seems to originate mostly from differences in the methodology used to assess an individual's personality. Studies using a questionnaire to assess personality type generally indicate an increased risk for insulin resistance in type A personalities (Yancura et al., 2006). In contrast, studies focused on the differential physiological characteristics of the personality types find a stronger relation between the type B personality type and metabolic risk (Phillips et al., 2010). Studies in rodent models generally seem to indicate that rats with a passive (type B) personality are more prone to develop insulin resistance than rats with a pro-active (type A) personality.

Although there is some discrepancy in the human studies, data from both human and rodent studies indicate that individuals with elevated HPA-axis responses – typically found in the passive personality types – are more prone to develop insulin resistance than those with a low HPA axis responsiveness (Boersma et al., 2011a; Marissal-Arvy et al., 2007; Phillips et al., 2010). In our laboratory, we observed these specificities in different animal models including the outbred Wild Type Groningen rat characterized by a passive coping style, and the passive Roman Low Avoidance inbred rat strain (Boersma et al., 2011b), both displaying HPA axis hyperactivity and disturbances in insulin action (evidenced by a hyperinsulinemic response to an intravenous glucose tolerance test under sedentary conditions) (Boersma et al., 2010). Likewise, several studies by others have shown that Fischer rats, characterized by elevated Hypothalamus–Pituitary–Adrenal-axis (HPA-axis) reactivity, develop insulin resistance at a later age (Fink et al., 1980; Marissal-Arvy et al., 2007). We may thus conclude that at least some of the physiological characteristics that are typical for the passive personality type may serve as risk factors for the development of insulin resistance.

### 4. Personality and treatment of insulin resistance

One may argue that an individual's personality may also play a role in the treatment efficacy. Treatment of type 2 diabetes and insulin resistance can generally be dissociated in two different approaches. The first approach aims at reducing symptoms by directly interfering with the glucose and insulin signaling pathways. These, mostly pharmacological, interventions generally circumvent the origin of the

problem and the efficacy of these kinds of interventions are therefore independent of the environment of the individual. A second approach is more aimed at eliminating the origin of the obesity and thereby decreasing symptoms. Life style interventions are good examples of the latter. In the following paragraphs we will focus on the role of personality on both of these treatment strategies.

First, we focus on the pharmacological interventions aimed at reduction of insulin resistance. Metformin and Thiazolidinediones are the most frequently employed pharmacological treatments for insulin resistance. Both drug types aim at increasing glucose transport and decreasing circulating glucose levels (Saltiel and Olefsky, 1996; Spiegelman, 1998). On average, treatment with either Metformin or Thiazolidinediones results in a reduction of the HbA1c concentration with approximately 8% after a year of treatment. However, results for different individuals vary between 6 and 12% reduction (Scherthaner et al., 2004). To our knowledge there are no studies in humans that have investigated differences in efficacy of these agents in the different personality types. In a rat study we, however, have shown that treatment with the Thiazolidinedione, Rosiglitazone, lowered the insulin response during an intravenous glucose tolerance test in both passive and proactive (Boersma et al., 2011a). For these drugs it thus seems that the personality does not play a major role in the treatment efficacy.

Recently, another class of drugs has been developed aiming at lowering glucocorticoid levels and thereby reducing the insensitivity of the insulin receptor. Originally, these drugs were administered to patients with chronically elevated glucocorticoid levels such as patients with Cushing syndrome (Johanssen and Allolio, 2007). However, currently these drugs also proved to be beneficial for the average diabetes patient (Combettes and Kargar, 2007). This third class of therapeutic agents may be of interest since passive personalities are characterized by moderately elevated glucocorticoid levels (Aubry et al., 1995; Boersma et al., 2009; Fernandez-Teruel et al., 1997; Gentsch et al., 1982). Unfortunately, up till now there are no studies available in the literature that focus on the efficacy of these drugs in humans characterized on the basis of their personality. Studies in rats are nevertheless promising. In a recent article published in European Journal of Pharmacology, we showed that RU486, a glucocorticoid receptor antagonist, improved hyperinsulinemia solely in rats with the passive personality, by targeting the specific hormonal characteristics of this coping style (Boersma et al., 2011a).

One should note that personality may affect the treatment of insulin resistance through two different pathways. Knowledge on the personality may help to match the pharmacological treatment of the patient with his/her neuroendocrine characteristics. But knowledge on the personality type of the patient may also prove to be important to predict the compliance of these patients to non-pharmacological treatments such as dieting and increased physical activity. Generally, these life style interventions are effective in lowering both body weight and improving insulin signaling (Torjesen et al., 1997). However, there are indications that the efficacy of– and/or compliance to– these life style intervention programs are directly associated to the personality of the individual (Hassmen et al., 1993; Ryden et al., 2001). The proactive personality type was shown to have stronger internal motivation to perform an exercise protocol, while the passive personality type appears to respond better to instructions and may therefore perform better during life style interventions (Hassmen et al., 1993). In our studies we have found that when experimental rats were offered access to a running wheel in which the animals can voluntarily exercise, rats with a passive personality tend to run more, particularly when they were fed on a palatable, high-fat diet. And even more striking, rats with a passive personality seem to adapt the level of physical activity to their energy intake, whereas proactive rats do not (Boersma et al., 2011b). We concluded from this that the passive personality type might be more receptive to life style

intervention (if at least properly coached). A pilot study in humans seems to support this view since we found recently that obese individuals with a passive personality showed stronger increases in physical activity and more profoundly improved dietary habits during a lifestyle intervention, when compared to their proactive counterparts. A more detailed investigation of their activity pattern, however, leads us to believe that passive individuals also have compensatory responses on the days they do not have to perform guided exercise (Boersma, 2011). This latter observation indeed confirms our hypothesis that the individuals with a more passive personality are more susceptible to environmental cues.

## 5. Conclusions

Progressive knowledge indicates that the interactions between the personality of an individual and the environment are crucial in understanding individual differences in both the development and the treatment of metabolic diseases such as obesity and insulin resistance. Data clearly point out that the success of both pharmacological and life style interventions for prevention and/or treatment of metabolic diseases could be considerably improved by adjusting the intervention to the personality of the individual. Furthermore, experiments in laboratory rodents clearly reveal that certain physiological and/neuroendocrine characteristics related to personality are strong indicators for pathology development. In humans the relation between the assessed personality types and these physiological and neuro-endocrine parameters are less clear. Future research should therefore focus on the identification of easily assessable physiological/neuro-endocrine biomarkers of coping style in humans. These biomarkers and tailored interventions may help to halt or even arrest 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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