Nature and nurture effects of voluntary activity and nutrition on energy balance and nutrition

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CHAPTER 1

GENERAL INTRODUCTION

Most animal species can move across the environment. This is usually brought about by muscular activity at the expense of metabolic fuels, and is general referred to as "physical activity". The level of physical activity can vary tremendously between animal species and even between animals belonging to the same species. This may, for example, depend on the environmental challenges which animals sometimes face, or the goals that animals have set out to achieve (e.g. for certain needs or rewards). Besides the level of planned or goal-oriented physical activity, the level of unplanned or "voluntary" activity can also differ largely between individuals. In human beings, for example, this may be related to the degree of fidgeting, non-specific ambulation, or other spontaneous every-day-life behavior (Levine et al. 2005; Ravussin 2005). Within individuals, levels of planned and unplanned behavior can be inversely related over some time, for example, when periodical heavy exercise is interspaced by increased resting and recovery. Besides this interdependency, it is clear that some individuals are more active than others under any condition. Evidence exists that the display of increased physical activity is a complex trait composed of several subordinate traits (John G. Swallow and Theodore Garland Jr 2005). These subordinate traits may be represented by several aspects of neurobiology, physiology, morphology, and performance, and is probably regulated by numerous genes (Garland, Jr. and Kelly 2006; Lightfoot et al. 2008; Simonen et al. 2003; Benjamin et al. 2002). In nature, the array of subordinate traits may have evolved because the cumulated trait of increased physical activity had advantageous effects on animal fitness under certain environmental conditions (Garland, Jr. and Kelly 2006). A major aim of the current thesis is to investigate differences in the subordinate traits in mice which display high and normal physical activity. A second major aim was to investigate whether and how mice with these presumed differences in subordinate traits are resistant to metabolic derangements when provided with "Western-type" unhealthy diets. This issue is extremely relevant in light of the consensus that obesity and associated metabolic derangements are the result of ingesting an unhealthy diet consisting of too much saturated fat and unrefined sugars combined with a sedentary life-style (Phelan 2009; Manfredini et al. 2009; Blair and Morris 2009).

1. Complex diseases

According to evolutionary biologists, the human genome was inherited from the paleolithic time when human life was programmed for daily physical activity and ingestion of a high-fibered diet (Eaton and Eaton, III 2000). Since then, our genome changed little, but environmental factors transformed to a large extent into the one that we are living today (i.e., lower physical activity, changes in dietary patterns but also other factors like psychosocial stress, smoking, alcohol consumption and hazardous environmental compounds). At the basis of this theory is the thrifty genotype hypothesis which explains that genetic factors only predispose individuals to diseases but environmental factors determine phenotypic expression whether the disease becomes manifest (Neel 1999). Perhaps one of the most important factors is the increase in sedentary lifestyle, mostly caused by prolonged sitting (Rosenberg et al. 2008) Levine and colleagues found that this is associated with a reduction in non-exercise activity thermogenesis (NEAT), and might propel weight gain in a situation of overfeeding (Levine et al. 2005; Ravussin 2005). This global trend is likely to continue, given the increasing availability of personal computers, TV and transportation trends (Robinson et al. 2003; Sturm 2004). One of its detrimental effects is the loss of activity of large skeletal muscles which are known to utilize a large amount of bodily fuels (Hamilton, Hamilton, and Zderic 2007). Moreover, changes in the world food economy increased consumption of energy-dense diets high in saturated fat and high in refined carbohydrates and together with a sedentary lifestyle this obviously favors weight gain. Particularly, visceral obesity is a strong risk factor in attracting cardiometabolic disturbances such as hypertension, hypertrigliceridemia, arteriosclerosis, hyperglycemia and hyperinsulinemia (collectively called "the metabolic syndrome") that all predispose to the development of type 2 diabetes and cardiovascular diseases (Despres et al. 2008). It has been suggested that an insufficient increase in the storage capacity of white adipose tissue leading to overflow of fats in metabolic tissues and organs is responsible for the occurrence of above-mentioned diseases (Frayn 2005). Consuming a diet rich in saturated fat and/or refined sugars calls forth an excess in body fat. This further leads to elevated insulin and leptin levels, and usually is accompanied by insulin- and leptin resistance (two of the hallmark in obesity, type-2 diabetes and metabolic syndrome) in the periphery and the central nervous system. A protective factor that is down-regulated in the state of progression towards cardiometabolic disease is adiponectin (Arita et al. 1999), an adipose tissue secreted product, and its low levels are correlated with visceral obesity (Okamoto et al. 2006) and insulin resistance (Weyer et al. 2001).

2. Possible mechanism through which physical activity can help in the treatment of complex diseases

Evidence over the past decades, including epidemiological, prospective- and intervention studies has documented that physical activity, combined activity and diet interventions can relieve progression of chronic diseases or even reverse existing diseases (Donnelly et al. 2009). The degree of physical activity is positively related to improvement of cardiometabolic functions (training effect), while physical inactivity causes degeneration in many bodily functions. In the cardiovascular system, physical activity causes an increase in oxygen consumption and blood flow to meet the increased energy demands of muscular work. On the long term, physical activity increases cardiac volume, decreases heart rate and blood pressure through the mechanism of influencing the flexibility and elasticity of blood vessels. In contrast, when these functions start to decline, cardiovascular diseases could take place, which mostly track the degree of obesity (Richardson et al. 2000). Furthermore, the increased oxygen consumption may cause a shift in substrate utilization from carbohydrates to fat oxidation, which has been highlighted to give protection against obesity and diabetes type 2 (Metz et al. 2005; Wasserman and Vranic 1986). In the same time, changes occur in the musculoskeletal system shifting muscle fiber type from fast to slow twitches which has also been shown to provide protection against obesity and type 2 diabetes (Tanner et al. 2002). Moreover, the increased aerobic metabolism, increasing plasma clearance of glucose, free fatty acids, triglycerides and sensitivity to insulin and leptin provides protection against obesity (Goodpaster and Kelley 2002). The nervous system is also stimulated since physical activity increases the numbers and intensities of connections between neurons increasing memory and learning (Dishman et al. 2006; Rhodes et al. 2003) which all provide protection against neurological disorders that has also been associated with the development of diabetes type 2 and obesity (Ristow 2004).

3. Animal studies

Numerous animal studies have focused on energy balance regulation under conditions of feeding diets differing in fat/sugar content, but much less attention has been paid to the role of physical activity. Although one can study individual difference in the display of physical activity in animals of outbred populations or in inbred strains which display large variations in it, we took the advantage of mouse lines that were selectively bred for high and normal running wheel behavior. Selective breeding uses a largely heterogeneous animal population from which lines of animals are then selectively inbred for a given character or trait of interest. Each generation of inbreeding increases the probability of attaining homozygosity at specific genetic loci resulting in a clear divergence in the phenotypic expression of the given trait (Britton and Koch 2001). Through this technique, Garland and colleagues have made selection lines of mice for high running wheel activity in four replicate lines, and four control bred lines which were not selected, in order to ascertain that observed differences are attributed to the effects of selection rather than random genetic drift (Swallow, Carter, and Garland, Jr. 1998b; T.Garland 2003). Animals selectively bred for the trait of high voluntary wheel running activity ran 2.7 times more than mice from the randomly bred control lines already in generation 16, and this difference was sustained throughout the following generations (T.Garland 2003). In addition, they ran with higher velocities (Swallow, Carter, and Garland, Jr. 1998a) and more intermittently in shorter bouts (Girard et al. 2001). The running-wheel selected mice were also more active in their homecages when deprived from wheels (Rhodes et al. 2001) relative to controls. In this thesis, I used two of the replicate lines selectively bred for high wheel running activity (lab designated line 7 and line 8) that showed the most phenotypic characteristics and one of their randomly bred control lines (line 2). Animals were obtained from generation 31 in chapter 3, generation 49 in chapter 2,5,6,7 and generation 52 in chapter 4.

Artificial selection is thus a tool to investigate in the laboratory line differences in a specific characteristic which originated from certain individuals in the population (Landgraf and Wigger 2002). As expected, differences in the trait of running wheel activity results in alterations of subordinate traits, as has mentioned in previous studies revealing several specific differences in physiology and morphology between selected and control lines differing in the level of wheel running activity. Active lines have smaller body masses, lower body fat percentage, increased food intake, low plasma levels of leptin and elevated plasma levels of adiponectin (Vaanholt et al. 2008; Vaanholt et al. 2007) relative to control lines, and the differences become particularly striking when they are subjected to a high fat diet (Vaanholt et al. 2008). Furthermore, their hind limb muscles have reduced mass, have an increase in oxidative fibers, in mitochondrial enzyme activity, in mass-specific capillarization, in glycogen storage and in muscle glucose transporter (GLUT-4) number (Gomes et al. 2009; Wong et al. 2009; Guderley et al. 2008). These physiological/morphological changes may be viewed as "adaptive" to sustain high physical activity levels.

The occurrence of trait-differences may appear not only in physiology and morphology, but may also be expressed in emotionality/personality (Heinrichs and Domes 2008; Wolf et al. 2007). In general, animals can cope actively in psychological stressful situations with low emotional reactivity characterized by impulsiveness, or they cope passively with high emotional reactivity characterized by anxiety. These two emotional and behavioral characteristics have been shown to be associated with specific neuroendocrine and physiological profiles (Steimer, la Fleur, and Schulz 1997). The inter-individual differences in these profiles and emotional behaviors in any animal and human population could be critical in regard of adaptive responses and capacity to challenging situations and also in resistance or susceptibility to certain stress-related pathologies (McEwen and Stellar 1993). Furthermore, this could depend on the type of diet which is eaten. For example, a palatable high fat/high sugar diet is known to have "psychological stress"-relieving properties compared to the situation when a healthy, but less palatable diet is eaten (la Fleur et al. 2007; van Dijk and Buwalda 2008). In turn, the expression of these psychological stress relieving actions of certain diets might depend on the subordinate traits for emotionality/personality which animals occupy. In the present thesis, differences in these emotionality/personality styles were studied in addition to the physiological/metabolic profiles in order to better understand and characterize mice with high activity levels versus those with normal activity levels.

4. Early life experience

Not only adult life-style factors, but nutritional factors during the perinatal stage could predispose an individual towards obesity and other associated diseases such as type 2 diabetes, metabolic syndrome (Levin 2006; Parente, Aguila, and Mandarim-de-Lacerda 2008). This could particularly occur when the availability of energy dense foods are high during perinatal stage, resulting a programming effect on neuroendocrine system and hypothalamic feeding circuits later in life. These are stated in the theory of "Developmental Origins of Adult Disease" or "developmental programming" and in the "thrifty phenotype" hypothesis (Hales and Barker 2001; Barker 2004). This can be studied in laboratory animals either by changing the quantity of energy availability to offspring with altering litter size or by changing the quality of maternal diet through supplying pregnant and lactating mothers with a high energy dense diet, rich in saturated fats and sugars (Plagemann 2005; Plagemann 2005; Armitage, Taylor, and Poston 2005). In both ways, susceptibility to metabolic diseases can be affected in adult offspring due to early programming.

Since the perinatal environment is a strong determining factor in the development of offspring energy balance and behavior later in life, a third major aim of the current thesis was to investigate the influence of the perinatal environment on development of the trait of high physical activity. For this reason, pregnant mice from control and selection lines were submitted to a healthy fibered low-fat diet, or to a "western type" high fat diet. Furthermore, the relevance of the post-natal period was investigated by cross-fostered pups between mothers from control and active lines to follow up their energy homeostasis and behavior later in life. The procedure of "cross-fostering" needs to be performed right after birth when the biological offspring is removed from their mother and placed with a surrogate mother (McGowan, Meaney, and Szyf 2008). In general, cross-fostering is used to study the impact of the postnatal environment on gene expression as well as on behavioral patterns. When cross-fostered offspring show similar traits as their biological parents but different than their foster parents, the trait is considered to have a mixed genetic and prenatal basis. Contrary, when the offspring develops a trait different than their biological parents and similar to their foster parents, the environmental factors are considered to be dominant. However, in most of the cases, there is a blend of the two, which shows both genetic and environmental influences at play.

5. Aim and outline of this thesis

Since selective breeding for a complex trait causes several associated physiological, morphological and psychological changes, it may also be regarded as an appropriate tool to study complex diseases. With respect to obesity and the associated metabolic syndrome, the trait of high physical activity clearly causes resistance to these phenomena. The use of mice selectively bred for increased physical activity can therefore facilitate a better understanding of aetiology and prevention of obesity and associated metabolic derangements at adulthood, as well as during perinatal development.

Chapter 2 is aimed at studying behavioral consequences of selective breeding for high voluntary wheel running activity for anxiety, exploration and learning. Circadian patterns of energy balance-related factors such as food intake, carbohydrate-, fat oxidation, energy expenditure and also running wheel activity were studied in relation to food preference in presence of normal or 60% high fat diet feeding in **chapter 3**. **Chapter 4** is aimed to study effects of high fat-high sugar diet feeding on energy balance, stress related behavior and corticosterone levels. **Chapter 5** focuses more on perinatal implications, where perinatal effects of high fat-high sugar diet feeding is described on maternal energy regulation and litter characteristics in relation litter size at pre-weaning stage. **Chapter 6** presents the consequences of the perinatal high-fat-high sugar diet feeding on the offspring energy balance later in life. The last experimental chapter (**chapter 7**) is aimed to study effects of litter size equalization to 10 pups/litter and effects of cross-fostering on maternal energy regulation and offspring energy balance at pre- and post-weaning periods. Finally, general conclusions and implications of the results presented in this thesis are discussed in **chapter 8**.

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