Translational value of animal models of obesity-Focus on dogs and cats

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Abstract: A prolonged imbalance between a relative increase in energy intake over a decrease in energy expenditure results in the development of obesity; extended periods of a positive energy balance eventually lead to the accumulation of abnormally high amounts of fat in adipose tissue but also in other organs. Obesity is considered a clinical state of impaired general heath in which the excessive increase in adipose tissue mass may be associated with metabolic disorders such as type 2 diabetes mellitus, hyperlipidemia, hypertension and cardiovascular diseases. This review discusses briefly the use of animal models for the study of obesity and its comorbidities. Generally, most studies are performed with rodents, such as diet induced obesity and genetic models. Here, we focus specifically on two different species, namely dogs and cats. Obese dogs and cats show many features of human obesity. Interestingly, however, dogs and cats differ from each other in certain aspects because even though obese dogs may become insulin resistant, this does not result in the development of diabetes mellitus. In fact, diabetes in dogs is typically not associated with obesity because dogs present a type 1 diabetes-like syndrome. On the other hand, obese cats often develop diabetes mellitus which shares many features with human type 2 diabetes; feline and human diabetes are similar in respect to their pathophysiology, underlying risk factors and treatment strategies. Our review discusses genetic and endocrine factors in obesity, discusses obesity induced changes in lipid metabolism and includes some recent findings on the role of gut microbiota in obesity. Compared to research in rodent models, the array of available techniques and tools is unfortunately still rather limited in dogs and cats. Hence, even though physiological and pathophysiological phenomena are well described in dogs and cats, the underlying mechanisms are often not known and studies investigating causality specifically are scarce.

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Translational Value of Animal Models of Obesity -

Focus on dogs and cats

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Abstract

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Key words:

Obesity; genetics; endocrine components; adipokines; DIO; dyslipidemia; microbiota.

1. Introduction

Obesity results from a prolonged imbalance between a relative increase in energy intake over a decrease in energy expenditure which is often associated with lower physical activity; the prolonged positive energy balance leads to the accumulation of abnormally high amounts of fat. In humans, obesity is defined as a clinical state of impaired general heath in which an excessive increase in adipose tissue mass may be associated with metabolic disorders. Excessive weight gain and obesity have become epidemic in industrialized countries, but the incidence of obesity also increases rapidly in developing countries worldwide. The pathological importance of obesity in humans relates to the increased mortality risk and predisposition to a variety of severe diseases such as type 2 diabetes mellitus, hyperlipidemia, hypertension and cardiovascular diseases (Kopelman, 2000). Obesity and its co-morbidities have become a serious medical concern not only in humans but also in other species with naturally occurring obesity. In the past decades, the incidence of obesity in companion animals in general and in dogs and cats in particular has increased dramatically perhaps even in a more extreme way than in humans, and it has become a serious concern in veterinary medicine (German, 2006).

The genetic predisposition to obesity is considered a key contributing factor for the development of the disease. However, spontaneous single gene mutations (such as leptin deficiency or leptin receptor deficiency) affect only a small number of individuals in the obese population. Considering the rapid rise in the obesity epidemic in recent decades, human obesity is thought to be a polygenic disorder resulting from the integrated activity of many genes; these genes may then contribute to obesity when individuals are exposed to the current obesogenic environment. In other words, only the combined effect of genetic predisposition and of environmental and behavioral factors can explain the marked rise in obesity worldwide (Speakman et al., 2008).

Current therapeutic strategies of obesity include dietary and lifestyle management, behavioral modification, medical and surgical therapy. The former strategies have been rather unsuccessful on a population-wide basis. Many of the therapeutic strategies adopted in humans are also available in companion animals, although with a few exceptions pharmaceutical compounds are not licensed yet; surgical approaches are not yet considered ethically acceptable for weight loss in dogs and cats (German, 2006).

A fundamental contribution to the actual understanding of the etiopathogenesis of obesity has been provided by studies in animal models. Most frequently, rodent models have been widely used to investigate causes and potential treatments for obesity. In these species, obesity can be

induced experimentally by genetic modifications or dietary interventions such as high fat feeding (Lutz and Woods, 2012). Findings based on rodent studies have provided a vast amount of information and have elucidated many aspects of rodent obesity; however, it has to be kept in mind that there is not always a strong correlation to human obesity and its co-morbidities. To name just one example, obesity related effects on lipid and lipoprotein metabolism can often not be directly translated to humans because rodents' lipoprotein and cholesterol metabolism differs from that in humans; this results in a different profile of the major lipoproteins very low-density (VLDL), low-densitiy (LDL) and high-density (HDL) lipoproteins (Breslow, 1993).

Further, the obesogenic pathophysiology in rodents differs from that in humans in many aspects e.g. the dietary composition of human diets is generally much more complex than formulated rodent diets, and there are important strain differences in rodents so that the same strain of rodent from different breeders may show significant phenotypic variability in the metabolism (Lai et al., 2014).

Therefore, the genetic and physiological basis and the environmental factors predisposing to obesity have also been studied in "alternative" animal models, such as nonhuman primates, dogs and cats in which obesity and its co-morbidities occur spontaneously. Hence, the rising epidemic and a continuing need for the development of new therapeutics make imperative to intensify the animal research also in "alternative" animal models in order to accelerate and broaden our understanding of disease mechanisms and of potential differences of human and animal obesity.

Previous reviews have extensively summarized the most important studies performed in rodent models for the understanding of the physiology and genetic basis of obesity (Lutz and Woods, 2012; Speakman et al., 2008). Accordingly, we will only briefly review small rodent work and focus on obesity in cats and dogs. Interestingly, these two species spontaneously develop two of the major metabolic disorders in humans, i.e. a type 2 diabetes-like disease in cats and a type 1 diabetes-like disease in dogs, respectively. We will extensively overview the literature on experimental and epidemiological findings relating to obesity in these two species.

2. Epidemiology and etiology of obesity

In humans, the most widely used measure of body composition is the body mass index (BMI), defined as the weight in kilograms divided by the height in meters squared (kg/m2); despite its limitations (e.g., in people with a very high muscle mass) in a vast part of the population, changes in the BMI reflect changes in fat mass because lean body mass is fairly stable in most

adults. The World Health Organization (WHO) and the National Institutes of Health (NIH) defined overweight as having a BMI between 25.0 and 29.9 kg/m2; and obesity as having a BMI greater than 30.0 kg/m2. The WHO monitors the prevalence of obesity around the world and estimates that it has nearly doubled between 1980 and 2008 in adults and children. In 2008, 35% of adults were overweight and 10% of men and 14% of women were obese, compared with 5% for men and 8% for women in 1980 (Rennie and Jebb, 2005). WHO further projects that, by 2015, approximately 2.3 billion adults will be overweight and that at least 700 million will be obese (http://www.who.int/mediacentre/factsheets/fs311/en/; as of November 2014).

The prevalence of raised BMI varies significantly throughout the world, ranging from low values in South East Asia, where 3% or less of the population are obese, to the Americas and Pacific Islands, where the prevalence of obesity amounts to up to 26% and 80%, respectively. Interestingly, worldwide, markedly more women are obese than men, with roughly twice the obesity prevalence of that in men in regions such as Africa, Eastern Mediterranean and South East Asia. The prevalence of overweight and obesity increases to more than double in high income and upper middle income countries compared to low and lower middle income countries. However, within most of high income countries, there is an inverse correlation between income and education and obesity (http:// www.who.int/nmh/publications/ncd_report_chapter1.pdf; as of November 2014).

Obesity is associated with an increased risk for chronic metabolic diseases and death. Prospective studies estimate that mortality rates increase with increasing degrees of overweight, as measured by body mass index (see: Prospective Studies Collaboration, 2009 doi: 10.1016/S0140-6736(09)60318-4).

Dogs and cats

In Western countries, the obesity in dogs and cats is considered the most common nutritional disorder in companion animals (German, 2006). Similar to the situation in humans, the prevalence of obesity has increased in the pet population. Older reports suggested that 24% of dogs (Edney and Smith, 1986) and 6–12% of cats were overweight while recently published studies reported a prevalence of 29–34% of overweight and of 5–8% of obese dogs and of 19–29% and 6–8% of overweight or obese cats, respectively. In the United States, it is estimated that 55% of dogs and 53% of cats are overweight or obese (German et al., 2010; Lund E.M., 2006; Lund EM, 2005).

There are different systems for evaluating body composition in dogs and cats; the Body Condition Score (BCS) being the most widely accepted because the BCS is easy to use but still

seems to provide reliable information within and between individuals estimating the animals' body condition. Dogs and cats are considered clinically overweight or obese when body weight exceeds ideal body weight for body size by 15 or 30%, respectively (de Godoy and Swanson, 2013). Because the incidence of obesity in pets seems to increase in parallel with the increasing incidence of obesity in humans, the etiology of obesity has been thought to share many similarities.

The causes of obesity in pets, as in humans, are multifactorial; obesity may result from a reduced energy requirement due to decreased levels of exercise, as well as from having *ad libitum* access to food (German, 2006). Although obesity is ultimately related to the energy equation with an imbalance between energy intake and expenditure, social and environmental conditions may play a major role in the development of the disease in companion animals; the latter are a consequence of domestication and increased anthropomorphism (de Godoy and Swanson, 2013; Rand et al., 2004). Most of our pets live indoors and are not obliged to compete for food resources (Rand et al., 2004). Major risk factors for dog obesity are breed predisposition, age, gender, gonadal status and neutering, and hormonal influences. For feline obesity, the recognized factors with significant roles in the development of obesity are inactivity, middle age, male gender, neutering, age at neutering and breed (Scarlett et al., 1994) (Russell et al., 2000). Obesity tends to be more common in younger female dogs, but both males and females have a similar incidence of approximately 40% when they are older than 12 years of age (McGreevy et al., 2005) (Zoran, 2010). Because pets reduce their metabolic rate with age, they may be more prone to developing obesity irrespective of their sex.

Like in humans, obesity has detrimental effects on the animals' health and increases mortality risk in companion animals. Interestingly, recent studies in a group of age-matched, pair-fed Labrador retrievers showed that lean dogs have a significant increase in their median life span of nearly 2.5 years and a significant delay in the onset of signs of chronic diseases compared to obese dogs (Kealy et al., 2002). Overweight and obesity in dogs may predispose to higher incidences of orthopedic disease, cardiorespiratory disease and hypertension, urinary tract and reproductive disorders, some forms of cancer, dermatological disorders and increased risk of anesthetic and surgical complications, hence comorbidities which are very similar to humans (German, 2006). Hyperlipidemia and dyslipidemia are also common findings in obese dogs. In cats, obesity raises the risk of developing endocrine and metabolic diseases such as diabetes mellitus, hepatic lipidosis, urinary tract disease, lameness and dermatopathies (Raffan, 2013).

3. Genetic basis of obesity

The hereditability estimates for human obesity range from approximately 40% to 70% (Day and Loos, 2011). In the vast majority of cases, obesity is not a monogenic disease but polygenic traits with different genetic variations and high hereditability predispose individuals to the development of obesity. Genome-wide studies in humans revealed the presence of numerous susceptibility genes associated with the predisposition to obesity (Day and Loos, 2011). Importantly, such gene variability increases an individual's susceptibility or predisposition to develop a characteristic or a certain disease but the inheritance of such mutation alone is not sufficient to induce the development of the symptoms (Bouchard et al., 1990; Kopelman, 2000). In other words, certain environmental factors are typically necessary to induce obesity in the affected individual. It is worth mentioning that the phenotypic effects of a majority of the identified polymorphisms are small and that monogenic disorders, which often result in marked effects, are rare in humans (1–6% of obese subjects) and are caused mostly by mutations of the FTO and melanocortin-4 receptor (MC4R) genes (Farooqi and O'Rahilly, 2007; Razquin et al., 2011; Santini et al., 2009; Wardle et al., 2008). The MC4R is a transmembrane G-protein–coupled receptor which plays an important role in the control of energy balance and appetite. This receptor is encoded by a single exon and is mainly expressed in the hypothalamus. MC4R gene mutations are the most common single genetic cause of hereditary human obesity accounting for up to 6% of cases (Tao, 2010).

Spontaneous single-gene mutations leading to marked obesity in rodent models have been recognized since the 1950s; i.e. long before the underlying genetic defects were discovered. Greater insight into the underlying mechanisms has been fueled by the identification of the adipocyte-derived hormone leptin and its receptors both of which were first characterized in 1994 in an inbred strain of morbidly obese mice, the leptin deficient ob/ob model (Lee et al., 1996; Zhang et al., 1994) and were further characterized in the leptin receptor defective *db/db* mutant mice (Chen et al., 1996; Hummel et al., 1966; Maffei et al., 1995). Since then, research in the field of genetics of obesity and control of energy metabolism increased dramatically and resulted in the identification of several candidate genes associated with human obesity and to the subsequent use of spontaneous mutants or generation of engineered mutants. Some of the most commonly used rodent models of obesity are the *ob/ob* mouse, the *db/db* mouse, its rat counterparts like the Zucker rat and the MC4R deficient animals (Lutz and Woods, 2012).

<u>Dogs and cats</u>

The dog and the cat are considered good comparative models for human obesity, since clinical signs and the genetic background of obesity are similar in the three species. Because dogs and cats share our same environment, often including the abundance of food, they may be predisposed to similar genetic-based pathophysiologies if the environment favours the expression of certain genetic traits (Lindblad-Toh et al., 2005). Similarly to the findings in humans, it is likely that overweight and obesity in pets are influenced by genetics. Strong breed predispositions to obesity were found in Labrador retrievers, Boxers, Cairn terriers, Scottish terriers, Shetland sheepdogs, Basset hounds, Cavalier King Charles spaniels, Cocker spaniels, Dachshunds, Beagles (Edney and Smith, 1986). In Germany, the breeds with an increased risk of obesity are Boxers, Cocker spaniels, Dachshunds, Poodles and Spitz. Interestingly, some breeds such as greyhounds seem to be resistant to development of obesity (Zoran, 2010).

Advanced knowledge of the canine and feline genome was completed between 2004 and 2007 (Lindblad-Toh et al., 2005; Pontius et al., 2007). This together with the availability of powerful molecular tools facilitated studies for the identification of genes that are responsible for monogenic hereditary diseases and also for polymorphisms similar to human obesity. Extended studies in humans indicated that polymorphisms of genes encoding adipokines and their receptors are associated with obesity. In dogs, although the knowledge of the endocrine function of the adipose tissue and the study of adipokines is advanced, only few preliminary studies have been reported on the polymorphism of adipokines genes (Radin et al., 2009) (Ricci and Bevilacqua, 2012).

MC4R, MC3R, FTO and PPARgamma gene polymorphisms were identified in the dog but unfortunately, the functional relevance of these gene polymorphisms for the pathogenesis of obesity was not studied (Switonski and Mankowska, 2013). Recently, some single nucleotide polymorphisms (SNPs) in the canine MC4R gene were identified in different cohorts of dogs. However, no significant associations were found between these SNPs and an increased risk of obesity (Skorczyk et al., 2007; van den Berg et al., 2010). Nevertheless, in Beagle dogs, two SNPs were shown to affect the function of the MC4R gene relative to body weight control and were proposed as a genetic marker for selecting different size dogs (Zeng et al., 2014).

In cats, the sequence of feline MC4Rs was confirmed and SNPs in its coding region were associated with diabetes mellitus in overweight domestic shorthair cats (Forcada et al., 2014). It remains, however, to be established whether this is simply an association or whether a causal relationship may be involved. Generally, studies for the identification of genetic markers associated with the predisposition to obesity are rare in cats. However, a genetic study describing the mode of inheritance of the overweight phenotype in an experimental cat population was recently published. Complex segregation analysis revealed that a genetic as yet

unidentified component might be responsible for the development of overweight in cats (Haring et al., 2012).

4. Endocrine component

Obesity is one of the major risk factors for the development of several endocrine conditions and is associated with important metabolic and hormonal changes. The list of recognized metabolic, hormonal and inflammatory conditions associated with obesity increases. However, the development of obesity may also be secondary to endocrine disorders. Dogs and cats are susceptible to similar hormonal diseases and share many of the detrimental effects that are associated with human obesity.

4.1 Adipose tissue and adipokines

The anatomical distribution of body fat, especially the intra-abdominal visceral deposition of adipose tissue, plays an important role in the development of co-morbidities of obesity in humans. Excess of adipose tissue in the upper body has been termed android, central, or abdominal obesity and usually correlates better with increased mortality and the risk for type 2 diabetes, hypertension, dyslipidemia and cardiovascular disease than the subcutaneous fat (Kissebah et al., 1982). This type of fat distribution is more frequently found in men, while women, at least before menopause, usually show greater adipose mass in the lower parts of the body in subcutaneous depots, which seems to have less metabolic consequences. Irrespective of these gender differences, women with upper body obesity are significantly more glucose intolerant than women with lower body obesity and are at increased risk for the occurrence of metabolic and cardiovascular complications (Carey et al., 1997).
White adipose tissue is the major storage depot of excess dietary energy. It is important to note that the deposition of excess fat in white adipose tissue should also be considered protective for the rest of the body. In other words, ectopic deposition of fat e.g. in skeletal muscle or liver is per se associated with an increased metabolic risk (Shimabukuro et al., 2013). This is best exemplified in patients suffering from lipodystrophy who are unable to store fat in white adipose tissue. These patients who are leptin deficient suffer from massive metabolic disturbances some of which can actually be treated by the administration of leptin (Weber et al., 2014).

White adipose tissue produces and secretes “adipokines” which either directly or indirectly modulate many metabolic processes. Primary adipokines (such as leptin and adiponectin) are produced primarily or exclusively, respectively, by adipocytes. In the face of a nutritional

overload, the excessive accumulation of fat in adipocytes appears to cause a condition of cellular stress and dysfunction, which may lead to the development of inflammatory responses of the adipose tissue (Pickup and Crook, 1998). Specifically, hypertrophied adipocytes are suggested to initiate an inflammatory response in adipose tissue via an increased secretion of adipokines and cytokines. Paracrine, autocrine, endocrine signals as well as adipocyte hyperplasia and hypertrophy are also involved in the recruitment of macrophages. Hence, the number of macrophages within the adipose tissue dramatically increases with increasing fat accumulation and correlates with adipocyte size in obesity (Weisberg et al., 2003). The inflammatory signals are eventually potentiated by the cross-talk between macrophages and adipocytes which together contribute to the overall increase in the inflammatory state in adipose tissue and to the development of the “low-grade” chronic inflammation associated with obesity. The inflammation in obesity is also characterized by an increased release of proinflammatory cytokines and chemokines into the general circulation and higher plasma levels of acute phase proteins like C-reactive protein and serum amyloid A (Hotamisligil, 2006).

Leptin was the first adipocyte hormone identified in 1994 (Zhang et al., 1994). It is a cytokine-like hormone encoded by the *ob* gene that influences food intake and energy expenditure at least in part through a direct effect in the hypothalamus. The plasma leptin concentration correlates with body fat mass (Considine et al., 1996) and increases and decreases in response to weight gain or weight loss, respectively, but leptin also increases more acutely in response to food intake (Romon et al., 1999; Weigle et al., 1997). Leptin stimulates fatty acid β-oxidation and inhibits lipogenesis in peripheral tissues; hence leptin functions to decrease triglyceride content in these tissues and to decrease fatty acid levels in the circulation. In obesity, responses to leptin are diminished in the hypothalamus (de Lartigue et al., 2011), and leptin-target cells become resistant to its actions. The resistance to leptin’s effects in the hypothalamus and the concurrent lowering of the body's energy metabolism may contribute to further weight gain in obese subjects because the brain is unable to adequately “measure” the body’s adipose tissue stores. Resistance to leptin action is associated with severe insulin resistance as the result of increased ectopic fat accumulation and lipotoxic effects in insulin-sensitive tissues.

Because leptin is well suited to inform the brain about the availability of energy stores in adipose tissue, leptin is also involved in the control of many other functions in the body; to name just two examples, leptin modulates normal reproductive function and immune function, and it also modulates insulin sensitivity with opposite effects to adiponectin (see below) (Loffreda et al., 1998).

Adiponectin is produced exclusively by mature adipocytes and circulates in plasma in multimeric form, with the high molecular weight form being the most biologically active. Its secretion is stimulated by insulin and by dietary constituents such as amino acids. Adiponectin levels inversely correlate with fat mass, hepatic lipid content and dyslipidemia, but positively with insulin sensitivity. Adiponectin influences glucose metabolism also by increasing glycolysis and fatty acid oxidation, it has anti-inflammatory properties and it is thought to play a role in the inhibition of the development of atherosclerosis (Kadowaki et al., 2006). Plasma levels of adiponectin are lower in subjects with obesity, type 2 diabetes mellitus, cardiovascular disease, hypertension, and metabolic syndrome compared to healthy patients (Ziemke and Mantzoros, 2010).

Dogs and cats**:**

Similar to humans, the secretion of adipokines from adipose tissue seems to be dysregulated in obese pets (Radin et al., 2009). Visceral obesity correlates with greater insulin resistance, hyperinsulinemia and alterations in plasma lipoprotein and lipid levels than subcutaneous obesity in humans; the underlying mechanisms are still unclear but may be related to different levels of estrogen receptor expression in the different fat depots (Davis et al., 2013).

In dogs and cats, the metabolic differences between excessive intra-abdominal and peripheral subcutaneous fat depots have not been demonstrated yet. Nonetheless, increasing fat mass positively correlates with serum leptin concentrations (Appleton et al., 2000) (Sagawa et al., 2002) while weight loss results in a decrease in circulating leptin (Hoenig et al., 2007). Fat rich or high-energy meals increase leptin concentrations in both species (Ishioka et al., 2005) but at least in cats, higher circulating levels of leptin also positively correlate with insulin resistance regardless of the cats' body condition score and fat mass (Appleton et al., 2002). Similar to experimental rodents, there is evidence that the leptin transport through the blood-brain barrier is defective in obese dogs (Nishii et al., 2006).

Interestingly, the *ob* gene seems to be expressed exclusively by pre-adipocytes and mature adipocytes from white adipose tissue of dogs but no expression in any other tissue (e.g., in the stomach where it is found in rodents) was observed (Eisele et al., 2005). In dogs, breed, glucocorticosteroid therapy and the feeding status may influence circulating leptin concentrations (Ishioka et al., 2005; Nishii et al., 2006). The association between increased leptin levels and neutering in both female and male cats is most probably related to the increase in fat mass gained post-neutering (Martin et al., 2006). However, a causal inter-relationship between leptin, insulin resistance and diabetes has not been demonstrated in cats (Appleton et al., 2002).

Similar to other species, adiponectin is produced and secreted exclusively by mature adipocytes in both dogs and cats, and it shows a strong homology to adiponectin in other species (Brunson et al., 2007) (Ishioka et al., 2006). Plasma adiponectin concentrations negatively correlate with increased fat mass, and most studies report that circulating levels of adiponectin are significantly lower in obese than in normal-weight dogs and cats (Hoenig et al., 2007) (Ishioka et al., 2009) (Grant et al., 2011; Muranaka et al., 2010).

In cats, adiponectin gene expression is significantly higher in visceral than other adipose depots (Ishioka et al., 2009; Zini et al., 2009a). Recent reports showed that the high molecular weight (HMW) multimers of adiponectin account for about 80% of total adiponectin in cats while they only account for 30% of total adiponectin in humans (Kaser et al., 2008) (Lusby et al., 2009). Dogs also appear to have a greater HMW adiponectin concentration than humans (Verkest et al., 2011b). HMW multimers are more active and are more closely associated with insulin sensitivity and body fat mass than total adiponectin (Lusby et al., 2009). In contrast to humans, dog obesity does not seem to be associated with selectively reduced HMW adiponectin. Thus, adiponectin may be a less important biomarker of canine obesity-associated insulin resistance. Further, one study reported that total adiponectin levels are lower in obese neutered male than in female cats; this difference was not related to larger total body size and fat mass in male cats (Bjornvad et al., 2014). This gender difference may also not be directly attributable to sex hormones, since the levels of testosterone which is known to directly decrease adiponectin levels in humans and rodents (Combs et al., 2003; Nishizawa et al., 2002), are expected to be minimal in neutered male cats (Bjornvad et al., 2014). However, in other feline studies, adipokines levels were reported to be similar between male and female cats (Hoenig et al., 2007; Muranaka et al., 2010). The role of adiponectin as anti-inflammatory adipokine has not been investigated in cats.

There are only few studies in dogs and cats that directly addressed the role of proinflammatory cytokines in the pathogenesis of obesity. It has been shown that almost 50% of dogs with naturally occurring obesity had increased concentrations of circulating TNF-α, C-reactive protein and haptoglobin; all three parameters decreased significantly after weight loss (German et al., 2009). In an another study, 30 weeks of overfeeding caused insulin resistance in dogs which was associated with increased plasma TNF-α, insulin-like growth factor, and non-esterified fatty acid concentrations (Gayet et al., 2004). In contrast to human studies, C-reactive protein concentrations were decreased significantly in insulin resistant obese dogs (Veiga et al., 2008).

Several studies in cats have shown that TNF-α expression in adipose tissue and in skeletal muscle is increased in obese cats (Hoenig et al., 2006; Miller et al., 1998). Further, obesity was

associated with increased adipocyte cell size and increased gene expression of pro-inflammatory cytokines and chemokines; surprisingly, the latter was more pronounced in subcutaneous than in visceral adipose tissue. Further the number of T-lymphocytes but not of B-lymphocytes or macrophages was increased in the adipose tissue of obese cats (Van de Velde et al., 2013). However, the role of inflammation in the development of obesity-induced insulin resistance has been discussed controversially in cats. Some studies, in fact, reported no changes in anti-oxidant enzymes' activity or inflammatory cytokines in obese cats (Hoenig et al., 2013; Jaso-Friedmann et al., 2008). Moreover, assays for the quantification of feline circulating cytokines and chemokines are currently not available or have not been validated appropriately.

4.2 Insulin resistance and diabetes

Insulin resistance is a state of reduced responsiveness of insulin-target tissues to normal circulating levels of insulin (Lozinski and Frohlich, 1942). Insulin resistance results from genetic or acquired factors; however, the most common type of insulin resistance is associated with overweight and obesity in a condition which, at least in humans and cats, often progresses to type 2 diabetes mellitus. The combination of genetic and environmental factors in peripheral insulin resistance generates deficits in the insulin signal transduction. Early studies suggested that circulating free fatty acids are elevated in many insulin-resistant states and that they compete with glucose for substrate oxidation in diabetes and obesity (Randle et al., 1963). Increased free fatty acids levels counteract the effects of insulin by inhibiting glucose uptake, glycogen synthesis and glucose oxidation, and by increasing hepatic gluconeogenesis which contributes to increased blood glucose levels. Quantitatively, skeletal muscle has long been considered the primary site for insulin-stimulated glucose uptake, with adipose tissue contributing less to whole-body glucose disposal in the insulin stimulated state and following the consumption of mixed meals. In insulin resistant states, pancreatic β-cells initially increase insulin secretion to adequately compensate for the diminished insulin sensitivity and the resultant increase in plasma glucose levels (Hull et al., 2004). Concurrent with the effects of hyperinsulinemia, abnormalities in amylin secretion, and in particular abnormalities in the processing of amylin and its deposition as amyloid in the islets may be responsible for the progressive loss of β-cells in human type 2 diabetes mellitus. Studies in several animal species with naturally occurring amylin derived-amyloid (such as cats and primates, but not rodents) and in transgenic rats and mice expressing the human amyloidogenic form of amylin demonstrated that islet amyloid formation plays a key role in β-cell apoptosis and dysfunction (Ma et al., 2000; Westermark et al., 2000). Amylin oligomers which are formed in the early stages of fibril

aggregation seem to be the principle toxic entity responsible for amylin-mediated β-cell cytotoxicity and death. The toxicity of amyloid or oligomers deposition relies on different mechanisms that act together intra- and extracellulary (Lorenzo et al., 1994). Aggregated amylin has been recently suggested to have inflammatory properties. Soluble oligomers of amylin may activate the inflammasome, a multiprotein oligomer expressed in myeloid cells and components of the innate immune system, to produce proinflammatory cytokines which are toxic to β-cells (Donath and Shoelson, 2011; Masters et al., 2010). The worsening of insulin resistance together with abnormalities in compensatory insulin secretion may eventually lead to the development of type 2 diabetes mellitus (Hull et al., 2004).

Dogs and cats

Obesity-induced insulin resistance and hyperinsulinemia have been observed in dogs (Gayet et al., 2004). The degree of insulin resistance associated with diet-induced obesity appears to be dependent on age, with older dogs being more insulin resistant than young dogs (Serisier et al., 2008). Weight loss leads to a recovery of insulin sensitivity and decreased insulin concentrations (Diez et al., 2004) (Yamka et al., 2006). Contrary to obese humans and cats, insulin resistance in obese dogs does not spontaneously progress to type 2 diabetes mellitus (Verkest et al., 2011a; Verkest et al., 2012) ENREF 74.

Dogs might be protected from the development of type 2 diabetes by either compensating adequately for obesity-induced insulin resistance or by additional factors. Obese dogs appear to compensate for years of insulin resistance by maintaining high fasting insulin concentrations and an increased first-phase insulin secretion during glucose tolerance tests (Verkest et al., 2012). Other factors may also protect dogs from obesity-induced diabetes, i.e. factors that are involved in the pathophysiology of β-cell failure in humans and cats but not in dogs. The most important of these factors may be the lack of amylin derived islet amyloid in canine diabetes. Contrary to humans and cats, canine amylin does not aggregate and form pancreatic islet amyloid in diabetes. Therefore, because islet amyloid is absent in obese and diabetic dogs, this species may be protected from the development of diabetes mellitus in obesity. Nonetheless, amylin-derived amyloid deposits have been observed in dogs with insulinomas which supports the concept that in addition to an amyloidogenic property of the amylin molecule and high local amylin concentrations, a defect in amylin processing may predispose to its aggregation into amyloid fibrils (Jordan et al., 1990; O'Brien et al., 1990).

In obese cats, insulin sensitivity is typically decreased by more than 50% compared to healthy lean animals (Appleton et al., 2001; Hoenig et al., 2007). Each kilogram of weight gain leads to a loss of about 30% in insulin sensitivity and glucose effectiveness in cats (Hoenig et al., 2007). Cats with naturally low insulin sensitivity are at increased risk of becoming glucose intolerant with weight gain. Interestingly, obese male cats have lower innate insulin sensitivity and higher basal insulin concentrations and therefore are probably more prone to diabetes than obese females which is consistent with epidemiological data (Appleton et al., 2001). This also reflects the situation in humans where males are at higher risk of developing type 2 diabetes than females, at least up to the age of menopause. Obesity induced insulin resistance is reversible because weight loss improved insulin sensitivity and reduced hyperinsulinemia in overweight cats (Biourge et al., 1997; Tvarijonaviciute et al., 2012).

As a strict carnivore, cats have a reduced ability to metabolize large carbohydrate loads, most likely due to the limited activity of liver glucokinase. To maintain euglycemia, cats rely on higher activity of enzymes related to energy metabolism such as hexokinases. It is however still controversial whether cats may regulate gluconeogenesis and endogenous glucose production in response to diet changes (Hoenig et al., 2007; Rogers et al., 1977; Russell et al., 2002; Zoran, 2002). Obese cats have high insulin levels in both the fasted and postprandial state and are insulin resistant in most insulin-sensitive tissues. Despite that, fasting normoglycemia is often maintained, and endogenous glucose production is decreased compared to lean cats. Although these findings are in contrast to humans, they might suggest that hepatic insulin sensitivity is still somewhat preserved in obese cats (Hoenig, 2014; Hoenig et al., 2011).

Even though inter-species differences in enzyme activities have to be interpreted with caution, it seems that cats may be less insulin sensitive than dogs because the expression of genes involved in glucose and lipid metabolism is lower in insulin-sensitive tissues in cats than in dogs (Mori et al., 2009a; Mori et al., 2009b). Nonetheless, and similar to dogs, obese cats have an increased expression of lipid and carbohydrate metabolism-related genes compared to their lean counterparts (Brennan et al., 2004; Mori et al., 2009b).

Although most obese cats seem to compensate for their peripheral insulin resistance and maintain normal fasting and post prandial glucose levels for extended periods (Hoenig et al., 2012), obesity in cats is a major risk factor for the development of diabetes. In fact, obese cats have an almost 4 times increased risk of developing diabetes mellitus compared to cats with an optimal body weight (Scarlett and Donoghue, 1998). The high incidence of diabetes and in particular of type 2 diabetes like features in cats is probably related to β-cell dysfunction and the resulting impairment of glucose tolerance. One important mechanism involved in β-cell

dysfunction is the presence of amyloid deposition. Like in humans and non-human primates, feline amylin contains an amyloidogenic-promoting region which predisposes feline amylin to aggregate and to form pancreatic islet amyloid fibrils. Amylin levels are elevated in obese cats (Henson et al., 2011; Lutz and Rand, 1996) and amyloid deposition is a common finding in diabetic cats (Herndon et al., 2014; Lutz et al., 1994). However, amylin-derived amyloid is also present in nondiabetic age, gender and body weight matched cats, and it has been recently demonstrated that 56% of diabetic cats versus 42% of control cats had similar amount of amyloid deposition (Zini E, 2012). Further, because not all diabetic cats develop amylin derived amyloid, the exact contribution of amylin oligomers as a cause of β-cell dysfunction and death need to be further clarified in this species.

Another important pathogenic factor of β-cell dysfunction is hyperglycemia. Increased glucose concentrations have been shown to be detrimental and toxic for β-cells in humans and in experimental animals. In cats, insulin therapy may be able to reverse some of the toxic effects of hyperglycemia by improving glycemic control (Nelson et al., 1999). However, if sustained hyperglycemia is induced by 10 days of glucose infusion, early and severe β-cell dysfunction is provoked even in healthy cats. Hyperglycemia promoted also an inflammatory response increasing circulating levels of inflammatory markers in healthy experimental cats (Zini et al., 2009b).

4.3 Dyslipidemia

The most important aspects of dyslipidemia in human obesity and in the metabolic syndrome are the presence of small, dense low density lipoprotein particles (sdLDL), low levels of high density lipoprotein-cholesterol (HDL-C), and high plasma triglycerides (Grundy, 1998). A predominance of sd-LDL particles is strongly associated with an increased risk of coronary artery disease and the development of atherosclerosis in nondiabetic patients (Austin et al., 1990), and the sdLDL phenotype is also a consistent feature in insulin resistant subjects. sd-LDLs are thought to be highly atherogenic because they penetrate the arterial wall more rapidly, have a higher binding affinity to proteoglycans of the arterial wall, and have lower resistance to oxidative stress than LDLs of normal size (Chapman et al., 1998). Further, low concentrations of HDL-C are also associated with a higher risk of atherosclerosis and increased severity of cardiovascular disease in humans. In insulin resistant and hypertriglyceridemic states, the exchange of VLDL triglyceride for HDL-C is increased. The resultant HDL particles are enriched with TG and depleted of cholesterol (Rashid et al., 2003). Further, hyperglycaemic states are associated with increased glycation of HDL particles resulting in a reduced capacity of HDL to prevent LDL

oxidation (Parthasarathy et al., 1990). The hepatic overproduction of VLDLs is one of the hallmarks of dyslipidemia in insulin resistance and associated with compensatory hyperinsulinemia (Adiels et al., 2008). The inability of insulin to inhibit VLDL secretion and to suppress hepatic glucose production, and the increased flux of free fatty acids and glucose to the liver increase the production and secretion of VLDLs. VLDLs are mainly degraded from the circulation by lipoprotein lipase (LPL). Because insulin stimulates LPL activity, and because the regulation of LPL activity is impaired in insulin resistant states, VLDL clearance is decreased (Panarotto et al., 2002). Fasting triglyceride concentration is a major predictor of postprandial lipemia (Kolovou et al., 2005), and both parameters are associated with cardiovascular disease and abnormalities in lipid metabolism. Prolonged postprandial hypertriglyceridemia is thought to create metabolic perturbations such as an increase in oxidative stress and ectopic fat deposition which may promote atherosclerosis through peroxidation of LDLs (Heine et al., 2004).

Dogs and cats

Only few studies on changes in serum lipids exist in dogs and cats with naturally occurring obesity. In obese dogs, published data suggest that significant changes in lipid and lipoprotein metabolism occur and may be important for the development of other obesity-associated comorbidities. Obese dogs have been reported to have higher serum triglycerides and total cholesterol than lean dogs (Pena et al., 2008) (Jeusette et al., 2005). Both alterations seem to be reversed by weight loss (Diez et al., 2004; Jeusette et al., 2005). Lipoprotein concentrations, plasma nonesterified fatty acids and triglyceride concentrations increased in laboratory dogs fed energy-dense diets (Bailhache et al., 2003). Although such changes were associated with insulin resistance and hypertension (Truett et al., 1998), the prevalence of cardiovascular problems and atherosclerosis in obese dogs is very low. Alterations in lipid particle size in dogs may not have the same consequences on coronary artery disease as in humans; it is also possible that the shorter life span of dogs may be associated with less marked changes and subsequently a lower clinical relevance. Nonetheless, hypertriglyceridemia observed during obesity has been associated with an increased risk for pancreatitis in dogs (Chikamune et al., 1995) (Rogers et al., 1975). However, further studies are warranted to assess cause and effect relationships.

Generally, dyslipidemia in obese cats appears to be similar to that observed in obese and diabetic humans including increases in NEFAs and triglycerides, decreases in HDL, and increases in VLDL and total cholesterol (Jordan et al., 2008). It has been shown that lipoprotein metabolism varies in cats as a result of age and sex and that the effects of neutering on plasma

lipid and lipoprotein concentrations are greater in adult compared to adolescent cats (Butterwick et al., 2001).

High sdLDL and low HDL-C levels are major risk factors for atherosclerosis in obese humans; it is important to note that not only the total concentration of HDL determines HDL's vasoprotective effects, but that their antioxidative, anti-inflammatory and cholesterol scavenging properties may be affected without changes in measured total HDL-C (Ansell et al., 2005); we are not aware of any such test having been done in cats.

Atherogenesis and coronary artery disease are usually not observed in obese or diabetic cats or in fact in cats in general; we are only aware of a single study where the susceptibility to diet-induced atherosclerosis was shown in this species (Ginzinger et al., 1997). In humans, plasma HDL-C concentrations are regulated by plasma cholesteryl ester transfer protein (CETP), the protein responsible for the transfer of cholesteryl esters from HDL to LDL and VLDL (Bauer, 2004). In human hypercholesterolemic states, the excess of cholesterol esters-enriched VLDLs or LDLs overwhelms the clearing capacity of the liver and results in the accumulation of atherogenic apo B-containing particles enriched with cholesterol esters. Dogs, and possibly also cats, present with lower activity of CETP compared to other species (Tsutsumi et al., 2001). This peculiarity in the CETP activity may prevent the excessive transfer of cholesterol esters to VLDLs or LDLs and the subsequent formation of atherogenic modified LDLs in cats.

In humans, LPL activity varies according to the different phases of obesity, being higher in the early phase and lower in more established obesity. In cats that were obese for at least one year, LPL tissue activity and tissue-specific expression were decreased in adipose tissue and increased in muscle compared to lean cats. These changes in LPL activity were considered as an adaptive response of the lipoprotein metabolism and lipid deposition and indicative of a redistribution of fatty acids from fat to muscle tissue during obesity (Hoenig et al., 2006).

When hyperlipidemia was induced by a 10-day lipid infusion in healthy experimental cats, hepatic steatosis and systemic inflammation developed. However, the sustained increase in plasma triglyceride concentrations and the resulting increase in inflammatory processes were not sufficient to affect plasma insulin or glucose concentrations or whole-body insulin sensitivity, or result in β-cell apoptosis (Zini et al., 2009b; Zini et al., 2010). Acute inflammation in humans is associated with transient insulin resistance and dyslipidemia. Chronic low-grade inflammation is a pathogenic component of insulin resistance and adipose tissue dysfunction in obesity-induced type 2 diabetes. Prolonged lipopolysaccharide (LPS) infusion that was sufficient to induce a subacute state of inflammation in cats caused acute insulin resistance, followed by long-lasting

tissue-specific dysfunctions of lipid-, glucose-, and insulin metabolism-related targets; this ultimately resulted in dyslipidemia but not whole-body insulin resistance (Osto et al., 2011).

All together these studies indicate that in cats as in humans, changes in lipid and lipoprotein metabolism and inflammation are mutually linked. However, whether hyperlipidemia or inflammation are sufficient key initiating events in the development of insulin resistance and β-cell dysfunction in the absence of obesity remains to be determined in cats.

4.4 Other endocrine disorders

The prevalence of obesity increases significantly in women after menopause (Flegal et al., 2012). In rodents, gonadectomy in females leads to an increase in body weight associated with an initial increase in eating. The lack of estradiol seems to be the critical obesity-triggering factor (Clegg, 2012) since gonadal steroids and in particular estradiol reduce food intake via a variety of peripheral feedback controls of eating including cholecystokinin, glucagon, hepatic fatty acid oxidation, insulin and leptin (Asarian and Geary, 2006) (Asarian and Geary, 2013).

Neutering has been shown to induce changes in basal metabolism and to be one of the major risk factors for canine and feline obesity. Interestingly, the incidence of obesity is higher in spayed female dogs than in neutered males (Edney and Smith, 1986; Mao et al., 2013), and d_ENREF_7aily food intake is higher in neutered compared to ovariohysterectomised dogs (Houpt et al., 1979). Another study found that female dogs have a significant decrease in daily energy expenditure after ovariectomy which may also contribute to the neutering induced obesity risk (Jeusette et al., 2004).

In cats, gonadectomy is also associated with an increased body weight gain and elevated risk for obesity (Kanchuk et al., 2003) (Nguyen et al., 2004). This may result from increased food intake, since neutered cats eat more as early as 3 days after surgery compared to intact cats (Kanchuk et al., 2003). The contribution of lower energy expenditure to the increase in body weight is not yet clear because energy expenditure was reported not to decrease after gonadectomy in neutered cats fed ad libitum in a number of studies (Kanchuk et al., 2003) (Martin et al., 2006).

In female rats and mice, it has been demonstrated that gonadectomy removes the estrogenic inhibition of eating (Asarian and Geary, 2002, 2006) and that these changes are reversed by physiological estradiol treatment (Geary et al., 1994). Withdrawal of estradiol following ovariectomy or menopause is sensed centrally and influences brain centers that control food

intake and energy metabolism, resulting in increased energy intake, body weight and fat accumulation (Kanchuk et al., 2003; Martin et al., 2006)_ENREF_50. In principle, consistent with these reports, daily pharmacological administration of estradiol prevented the increase in food intake and body weight following gonadectomy in both male and female overweight cats (Cave et al., 2007b). However, data from studies with a physiological pattern of estradiol replacement or data regarding the relationship between the release of sex hormones after gonadectomy and the development of obesity in dogs and cats are scarce.

The role of changes in thyroid hormones for the development of obesity is considered controversial in dogs. In one study, obese dogs had normal thyroid function with only slightly increased total T4 and T3 concentrations (Daminet et al., 2003). On the contrary, a more recent study showed that 42% of obese dogs had increased TSH and decreased free T4 concentrations, i.e. biochemical evidence indicative of subclinical hypothyroidism. The prevalence of hypothyroidism is however very low in dogs (Daminet et al., 2003) and it is unlikely to be considered a major reason for general obesity.
In obese cats, free serum T4 concentrations are increased significantly but total T4 and TSH concentrations are normal (Ferguson et al., 2007). However, whether there is a cause-effect relationship between obesity and thyroid dysfunction is still not clear. Hence, the situation is similar to humans.

4.5 Diet-induced obesity and body-weight loss

Rodent models of diet-induced obesity are broadly used to study polygenic causes of obesity. The diet-induced obesity paradigm seems to better reproduce the state of common obesity in humans than most of the genetically modified models, including the control of food intake when individuals are exposed to high fat food (Lutz and Woods, 2012).
Feeding rats with a varied and palatable diet which mimic the “cafeteria”, “western type” diet often result in the development of obesity and hyperphagia (Perez et al., 1999). In non–human primates and rodents, it has been observed that the development of obesity in response to high fat or high-fat-sucrose diets is species- and strain-dependent (Speakman et al., 2008). Most interestingly, even within the same strain, some animals seem to be resistant to weight gain when fed with high-fat diets and are therefore called diet resistant.
The rodent models of diet-induced obesity (DIO) share several physiological and genetic mechanisms with human obesity. Importantly, DIO in rodents and humans is an inherited polygenic trait whose phenotypic expression is exacerbated by exposure to high energy diets

(Levin et al., 1997). DIO individuals and rodents develop the metabolic syndrome with insulin and leptin resistance, hyperlipidemia, and hypertension when the caloric density and fat content of the diet are increased (Levin and Dunn-Meynell, 2000; Levin et al., 1997; Levin and Routh, 1996). Studies on the effects of high fat diet feeding in rodent models of obesity have been previously extensively reviewed (Lutz and Woods, 2012; Speakman et al., 2008).

Obviously, physical activity and food intake are the two most important factors involved in body weight control. Body weight loss and maintenance of this body condition in humans is achieved mostly by restriction of dietary carbohydrate and fat intake both during and after weight loss. An important concern with energy restricted diet, however, is the increase in hedonic hunger and decreases in the feeling of fullness, both factors which increase the risk for body weight regain (Martinez et al., 2014). In addition, fat loss during weight loss programs should be accomplished while maintaining energy expenditure and lean body mass. Among the variety of dietary interventions which have been designed to reduce energy intake, the use of moderately high-protein diets (<35% of total calories) and low-carbohydrate and fibre-rich foods has been shown to be more effective in inducing satiety and reducing weight gain (Abete et al., 2008; Halton and Hu, 2004; Martens and Westerterp-Plantenga, 2014). However, the long-term effects on weight control of low-carbohydrate diets is often not sufficient to reduce marked obesity and needs to be further investigated.

Dogs and cats

When exposed to ad libitum high-fat feeding, dogs often develop an increase in body fat (Backus et al., 2007) (Nguyen et al., 2004). However not all studies in dogs and cats showed that *ad libitum* exposure to food resulted in obesity, perhaps similar to the situation in diet resistant rodents. It seems however, that more frequent feeding might increase the risk of developing body weight gain and obesity in cats (Colliard et al., 2006; Courcier et al., 2010). Most studies suggest that the higher the dietary fat content, the greater body fat accumulation in companion animals will be.

Like in humans, the primary care strategy to treat obesity in companion animals is by applying an energy restriction diet. An important concern with energy restricted diets, however, is that the amount of calories needed to induce weight loss and for the long-term maintenance of energy balance can greatly differ among individual animals (Laflamme, 1997) (Butterwick and Hawthorne, 1998). Too dramatic reductions in total food supply may result in a deficiency of essential nutrients; therefore, it is important that the appropriate diet for body weight loss covers

all these requirements and that the adjustment in calorie allowance is made on a regular basis in order to preserve the fat free mass (Laflamme, 2012).

The consumption of low-calorie diets with increased protein content during weight loss programs has been shown to increase fat loss while maintaining lean body mass in both cats and dogs (Laflamme, 2006). Because of its stronger effect on diet induced thermogenesis, protein intake may induce an increase in energy expenditure which results in a minor but significant increase in total daily energy expenditure in subjects fed high-protein diets (Mikkelsen et al., 2000; Wei et al., 2011). The consumption of high-protein diets has also been demonstrated to limit the decrease in resting energy expenditure which is a typical metabolic adaptation observed during caloric restriction (Rosenbaum et al., 2008; Schwartz et al., 2003). Hence, higher protein diets may help to maintain body weight loss and prevent weight regain. In cats, high-protein diets during weight loss also help to reduce oxidative stress and chronic inflammation associated with obesity (Laflamme, 2012).

Dietary fibers provide less dietary energy due to their lower digestibility than fat or carbohydrates. Cats fed with combinations of diets high in fiber and water decreased their caloric intake which may also contribute to weight loss (Morris et al., 2006); hence, the enhanced satiety provided by dietary fiber may help to reduce caloric intake and be useful in the prevention and treatment of both obesity and diabetes mellitus (de Godoy et al., 2013).

Among the many compounds which have been evaluated for the use in weight management in companion animals, soy isoflavones have been shown to increase lean body mass in cats (Cave et al., 2007b) (Cave et al., 2007a) and to reduce the post-neutering weight gain in dogs (Laflamme, 2012). In humans, dietary isoflavone supplementation also reduced the risk of developing metabolic disorders such as cardiovascular diseases, diabetes, and obesity (Bhathena and Velasquez, 2002) and seemed to improve fasting insulin levels and insulin resistance in postmenopausal diabetic women (Jayagopal et al., 2002). Further, diacylglycerols and carnitine have also been proposed to improve rates of weight loss and to be of help in body weight management in both dogs and cats (Laflamme, 2012; Mitsuhashi et al., 2012). Similarly to humans and rodents (Hibi et al., 2008) (Murase et al., 2001), the mechanism of action of diacylglycerols was suggested to be linked to an increase in fat oxidation and to a lowering of serum triacylglycerol levels postprandially which may result in increased satiety (Rudkowska et al., 2005).

4.6 Gut microbiota

Studies in humans and mice have shown that alterations of the gastrointestinal microbiota are associated with the development of fat mass, insulin resistance and low-grade inflammation in conjunction with obesity (Backhed et al., 2004; Ley et al., 2005). By modulating the capacity to harvest energy from indigestible dietary polysaccharides or other nutrients, gut microflora may affect the host metabolism and the host's control of body weight and energy homeostasis (Turnbaugh et al., 2006). Numerous experiments indicate that changes in microbiota may actually be causally related to the development of obesity, and not be a mere consequence (see below).

Further, the fat content of food has been shown to change the composition of intestinal microbiota and to modulate the metabolic concentrations of plasma LPS in mice. It appears, in fact, that changes in the fat content of the diet may alter the mechanisms of LPS absorption from intestinal microbiota through the intestinal epithelium and to increase the transfer of intestinal LPS into lymph (Cani et al., 2007a). In accordance with this hypothesis, it has been demonstrated that the specific modulation of the gut microbiota by means of antibiotic treatment and prebiotic nutrients decreased the effect of high-fat diet-induced metabolic endotoxemia and subsequently reduced inflammatory disorders in high-fat fed mice (Cani et al., 2008; Cani et al., 2007b). Further, weight loss achieved by dieting (Duncan et al., 2008) or surgically through gastric bypass reverses the obesity or high fat feeding induced changes in the gut microflora (Cani et al., 2012; Liou et al., 2013; Osto et al., 2013).

A causal relationship between alterations in intestinal microbiota and the control of body weight has been demonstrated in rodent models. Transplanting intestinal microbiota from obese mice to lean recipients increased the adiposity of the recipients; further, recipient germ free mice that received gut microbiota from obese versus lean donors differed markedly in their adiposity. Changes in intestinal microbial populations have also been shown to improve the metabolic phenotype of human patients with metabolic syndrome. In fact, transplantation of the gut microbiota from lean donors to patients with metabolic syndrome resulted in improved insulin sensitivity (Qin et al., 2012; Vrieze et al., 2012). The mechanisms involved are not defined but may involve direct modulations of the immune system (Cani et al., 2007a; Everard et al., 2014). Consistent with the important role of gut microbiota in a number of metabolic diseases, gut microbial gene profiling has been shown to help distinguishing type 2 diabetic subjects from control subjects with a predictive power far better than that of the body mass index (Karlsson et al., 2013).

<u>Dogs and cats</u>

In dogs and cats, the overall composition of the intestinal bacteria is generally similar to that found in other mammals. Further, canine and feline gut microbiota can be modulated by dietary intervention and antimicrobial therapy but also depend on the host's age (Barry et al., 2012; Garcia-Mazcorro et al., 2011). Data characterizing the intestinal microbiota in diseased states are currently poorly available in companion animals. Clinical studies suggest the presence of a dysbiosis in inflammatory bowel disease (Inness et al., 2007). However, only one study has been published on the composition of the faecal microbiota of lean versus obese pet dogs. The study population of research dogs was small, and the inter-individual variation was high (Handl et al., 2013). No such studies have been published in cats yet, though it has been shown recently that surprisingly, the faecal microbiota composition of insulin-treated, diabetic cats did not differ from that of non-diabetic cats. Furthermore, no associations were found between changes in faecal microbiota composition and cat breed or gender, dietary protein, carbohydrate or fat content, or dietary formulation (Bell et al., 2014). Further studies are required to increase our understanding of the role of gut microbiota in diseases such obesity and diabetes in companion animals.

5. Summary

Obesity is not a "simple accumulation" of fat but it leads to impaired general heath which may be associated with metabolic disorders such as type 2 diabetes mellitus, hyperlipidemia, hypertension and cardiovascular diseases. Animal models provide invaluable tools to study the underlying mechanisms of obesity, of its comorbidities and potential therapeutic options. Most research has traditionally been done in rodents but other species, including dogs and cats, may offer additional benefit because they may spontaneously develop obesity induced changes which typically do not occur in common rodent models of obesity. To name just one example, cats are a much better model for human type 2 diabetes than most rodents because they develop the full pathophysiology, including pancreatic islet amyloid deposition. Unfortunately, the array of available techniques and tools is still restricted in dogs and cats compared to rodents; this refers to classical laboratory techniques, but in particular also to techniques of genetic manipulation. Hence, even though physiological and pathophysiological phenomena are well described in dogs and cats, the underlying mechanisms are often not known and studies investigating causality are scarce.

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European Journal of Pharmacology
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Zurich, 24 December 2014

Submission of paper to the European Journal of Pharmacology

Dear colleagues,

We want to thank you again for giving us the opportunity to contribute to the Special Issue of the European Journal of Pharmacology. Please find our paper entitled "**Translational Value of Animal Models of Obesity - Focus on dogs and cats**" for consideration. As you will see, we decided to focus more specifically on these two species when describing their benefits and potential shortcomings as animal models of obesity. For that reason, you may consider our contribution for the "species-specific" section of the Special Issue. We hope that yourself and the reviewers of our contribution will evaluate our manuscript positively and we are looking forward to hearing from you soon.

Merry Christmas and best wishes

Thomas Lutz and Melania Osto