Introduction

Type 2 Diabetes—An Introduction to the Development and Use of Animal Models

Jay R. Kaplan and Janice D. Wagner

Abstract

Although the epidemiology of type 2 diabetes (T2D) has been well described, there is much about the disease that remains unclear. For example, lifestyle factors—including increased body weight with visceral fat deposition and insufficient physical activity—are thought to be primary contributors to the adverse changes in the metabolism of muscle and fat cells that comprise the first stage of the disease. However, the precise mechanisms underlying these initial alterations are incompletely understood. Other, less obvious questions relate to the presence of sex differences in the development and health consequences of T2D, the etiological role of the central nervous system (“stress”), and the potential evolutionary origins of T2D susceptibility. Some of these issues can be resolved by further study of human populations. However, many questions can be answered only through the kinds of controlled prospective studies that are conducted with appropriate animal models. The use of such models can be an invaluable part of an overall strategy designed to elucidate the mechanisms underlying the development of T2D, understand the natural history of the disease, identify targets for therapy, and evaluate interventions. Current evidence indicates that no single animal model replicates the development of human T2D in all of its details. Nonetheless, the existing models (e.g., naturally occurring and genetically modified rodents, cats, pigs, and nonhuman primates) offer researchers a rich array of opportunities to investigate the myriad complexities of T2D. The individual contributions comprising this issue of ILAR Journal review the research that has been conducted on many of these animals.

Key Words: animal models; insulin resistance; sex differences; “thrifty gene” hypothesis; type 2 diabetes

The collection of articles in this issue is the outgrowth of a previous issue of ILAR Journal that was devoted largely to animal models of type 1 diabetes, an autoimmune disorder often referred to as insulin-dependent diabetes (Barthold and Elliott 2004). Publication of that issue occasioned a demand for a similar review focused on models of type 2 diabetes (T2D), which is sometimes characterized as non-insulin-dependent or adult-onset diabetes. The interest in animal models for this disease is understandable in view of the fact that it accounts for approximately 90 to 95% of all diagnosed cases of diabetes in the United States (CDC 2005). Furthermore, the total prevalence of T2D—both diagnosed and undiagnosed—is approximately 6% of the population, a number that is likely to increase as the population ages and becomes increasingly overweight (Vasudevan and Garber 2005). Magnifying this problem is the fact that there has been a significant national and worldwide increase in the prevalence of childhood obesity, which presages a large increase in the overweight—and thus at-risk—adolescent and adult populations of the future (Deckelbaum and Williams 2001). Finally, the societal impact of T2D is substantial. The disease is currently the sixth leading cause of death in the United States, and it imposes a total annual financial burden estimated to exceed 130 billion dollars in health care and lost productivity (CDC 2005).

The following paragraphs review the need for animal models in the study of T2D and describe the characteristics of the ideal model. Subsequently, there is a brief preview of the major models described in this issue. This introductory article ends by identifying issues in the natural history and pathogenesis of T2D that might be considered nontraditional targets for investigation in animal models. Of particular interest here are questions relating to sex differences in the development and consequences of T2D, the possible role of the central nervous system (CNS) in the etiology of T2D, and evolutionary influences on susceptibility and resistance to the disease. Such investigations extend beyond the usual mechanistic paradigms used in animal models and indeed may involve models that are not generally considered for the study of T2D.

Jay R. Kaplan, Ph.D., is a Professor in the Departments of Pathology (Comparative Medicine) and Anthropology, Wake Forest University School of Medicine (WFUSM), Winston-Salem, North Carolina. Janice D. Wagner, D.V.M., Ph.D., is a Professor in the Department of Pathology and the Deputy Associate Dean for Research at WFUSM.

1Abbreviations used in this article: CNS, central nervous system; HPA, hypothalamic pituitary adrenocortical; SNS, sympathetic nervous system; T2D, type 2 diabetes.
Need for Animal Models in the Study of T2D

Although the epidemiology of T2D has been well described, there is much about the disease that remains unclear. For example, it is generally believed that the first stage of T2D—sometimes referred to as a “prediabetic” state—involves peripheral (e.g., muscle) insulin resistance and a compensatory hyperinsulinemia as the pancreas attempts to re-establish glucose homeostasis (DeFronzo 2004; Reaven 2005). Ultimately, the β-cells of the pancreas begin to fail, resulting in a decline in insulin production and a sustained hyperglycemia. Lifestyle factors, including increasing body weight with visceral fat deposition and insufficient physical activity, are thought to be primary contributors to adverse insulin-related changes in the metabolic activity of muscle and fat cells. However, the precise mechanisms underlying the initial insulin resistance are incompletely understood (DeFronzo 2004). These mechanisms likely include one or more genetic factors inasmuch as every population exhibits naturally occurring variation in insulin resistance that is in part independent of obesity (Reaven 2005). In fact, while most individuals in the upper tertile of insulin resistance are overweight, approximately 30% of individuals in the lower tertile of insulin resistance are also overweight. Other questions and even significant controversies relate to the timing and aggregation of pathophysiological alterations that coincide with insulin resistance and hyperinsulinemia. These factors include visceral fat deposition, dyslipidemia (especially reduced high-density lipoprotein cholesterol and increased triglycerides), elevated blood pressure, and increased concentrations of circulating inflammatory markers, all of which are important elements of what has come to be called the metabolic syndrome (Grundy 2005; IDF 2005). Finally, the factors that affect the transition from insulin resistance and hyperinsulinemia to diabetes remain to be elucidated because many insulin-resistant individuals do not become diabetic. Indeed, there is even one subset of prediabetic individuals with impaired fasting glucose that is not associated with insulin resistance (Reaven, 2005; Unwin et al, 2002).

Although some of the foregoing issues can be resolved by further study of human populations, there are many questions that can be answered only through invasive manipulations or observations that are precluded in humans either for logistical reasons or on ethical grounds. As a result, the use of appropriate animal models comprises an important part of the overall strategy for elucidating the mechanisms that underlie the development of T2D, understanding the natural history of the disease, identifying targets for therapy, and evaluating interventions and treatments. The ideal animal model for such studies would recreate the complete natural history of T2D as it occurs in human populations (CDC 2005; DeFronzo 2004; Reaven 2005; Unwin et al. 2002). Hence, such a model would exhibit natural variability in insulin resistance, which in some individuals would become exacerbated at midlife under conditions of excessive caloric intake and lack of physical activity. A somewhat lower percentage of individuals would exhibit impaired fasting glucose in the absence of marked insulin resistance. However, insulin-resistant individuals would develop a compensatory hyperinsulinemia accompanied by elements of the metabolic syndrome. Furthermore, in the ideal model females would be affected to a similar degree as males, but the health consequences—especially with respect to cardiovascular disease—would be worse for females. In the pancreas, insulin-resistant individuals would develop islet amyloid and experience β-cell apoptosis. Finally, these individuals and those with impaired fasting glucose would be markedly more at risk of becoming hyperglycemic and experiencing the micro- and macrovascular consequences of diabetes (e.g., cardiovascular disease and stroke, blindness, kidney failure, and peripheral limb neuropathy and amputation).

Obviously, no single animal model replicates the development of human T2D in all of its details. Taken together, however, the existing models provide researchers with a rich array of opportunities to investigate the myriad complexities of T2D. The individual contributions in this issue review the research that has been conducted on many of these animals.

Following an overview of the pathophysiology and consequences of diabetes, Cefalu (2006) discusses the characteristics of each of these models. In addition to the various strains of mice and rats that have been found to be resistant or susceptible to T2D, much interest obviously has focused on transgenic preparations that mimic specific aspects of the disorder such as insulin resistance or islet cell amyloid (Matveyenko and Butler 2006; Neubauer and Kulkarni 2006). Extensive use of the foregoing purpose-bred and genetically altered strains of rodents have led to considerable progress in understanding the polygenic nature of T2D as well as the pathogenic mechanisms underlying the progression from obesity and insulin resistance to hyperglycemia. It is also worth noting that desert rodents (Shafrir et al. 2006) offer an important platform for research because these animals spontaneously develop T2D following exposure to a high-fat or high-sucrose diet. Their diabetic susceptibility is hypothesized to reflect a response to an environment discordant with the nutritionally poor conditions under which these animals presumably evolved.

The final three articles in this issue are related to nonrodent models. Among these models are domestic cats, which comprise one of the few outbred models characterized by insulin resistance, defective insulin secretion, islet amyloid formation, and β-cell loss (Henson and O’Brien 2006). As among humans, the disorder appears to be polygenic and is associated with midlife obesity. The penultimate article deals with the wide variety of swine models that are appropriate for the study of T2D (Bellinger et al. 2006). It is perhaps not surprising that swine, long considered an excellent model for the study of cardiovascular disease (e.g., Ratcliffe and Lugnibuhl 1971), are also useful in the investigation of diabetes. They are particularly applicable for
testing pharmacological interventions and for evaluating the inflammatory and vascular changes associated with insulin resistance or hyperglycemia. The final article in this issue (Wagner et al. 2006) deals with nonhuman primates, particularly the Old World monkeys. Animals of these species, which include the macaques and baboons, naturally develop T2D with clinical changes and pancreatic pathology similar to that observed in their human counterparts. As reviewed in this article and in the overview by Cefalu (2006), the nonhuman primates offer enormous potential to illuminate T2D pathogenesis and effectively test experimental treatments. It must be said, however, that such studies are costly and can be conducted at only a limited number of facilities.

Assessment of Existing Models

It will become clear from a careful reading of the ensuing chapters that any particular animal model is characterized by both strengths and weaknesses. Nevertheless, by focusing on the strengths of the numerous existing models, investigators have the opportunity to employ a wide variety of approaches to study T2D and indeed to address a large number of unanswered questions. One of the prominent uses of animal models includes a search to identify the polygenic basis of the disorder, as implied by the results of studies in numerous human populations (e.g., Hansen and Pedersen 2005). Successes in these studies will not only increase our understanding of factors that underlie disease vulnerability but will also lead to identification of new therapeutic targets. Another prominent area of investigation involves determining how inflammation is involved in the etiology of T2D. Related to this area are the studies directed toward understanding the relative roles of obesity and insulin resistance in the progression to T2D and, in particular, identifying the cellular signals among muscle cells, adipocytes, and the liver that presage and accompany the development of the disorder.

Novel Questions That Can Be Addressed with Animal Models

Among the questions that have received less attention are those relating to sex differences in the development and consequences of T2D. For example, although the prevalence of diabetes is approximately equivalent in men and women (CDC 2005), the health consequences—especially with respect to cardiovascular disease—are much worse for women. It is estimated that the hazard ratio for fatal heart disease is at least 50% greater for diabetic women than men, a figure that escalates even more when nonfatal events are included (Huxley et al. 2006; Juutilainen et al. 2004). Although some of this disparity is associated with differences in risk factors such as insulin resistance and elements of the metabolic syndrome (Bruns and Kemnitz 2004), there remains considerable unexplained variance in this phenomenon. The results of recent clinical trials suggest that estrogen deficiency, as occurs at menopause, may contribute to the elevated risk for women. In both the Women’s Health Initiative and the Heart and Estrogen Replacement study, the use of hormone therapy reduced the incidence of diabetes, possibly through reduction in insulin resistance (Kanaya et al. 2003; Margolis et al., 2004). Clearly there is a need to study hormonal effects on development of T2D. Such studies could utilize newly emerging animal models of the menopausal transition (e.g., Lohff et al. 2005; S. Appt et al. manuscript in preparation). However, the premenopausal period is likely also important for the development of T2D because the association among polycystic ovarian syndrome (a common reproductive disorder characterized by hyperandrogenism), obesity, and insulin resistance is not yet fully understood (De Leo et al. 2003).

The role of the CNS in diabetes also remains poorly understood. Numerous lines of evidence suggest that psychosocial stress—a CNS-mediated feature of modern life—contributes to insulin resistance and thus risk of T2D (Björntorp 1999; Rosmond 2003). The hypothalamic pituitary adrenocortical (HPA1) system and the sympathetic nervous system (SNS1) comprise the two major axes associated with the stress response (Kaplan et al. 1996). Activation of the HPA is accompanied by release of cortisol, which promotes visceral fat deposition and promotes the release of free fatty acids. Not surprisingly, individuals that are hypercortisolemic are often insulin resistant (Chrousos 2000; Rosmond 2003). Epidemiologically, depression, which is often associated with hypercortisolism, is accompanied by an increased prevalence of the metabolic syndrome and insulin resistance, especially among women (Kinder et al. 2004). Individuals showing excessive SNS activation also exhibit an increased prevalence of the metabolic syndrome and insulin resistance (Brunner et al. 2002). In addition, it has been observed in a community sample that reduced central serotonergic neurotransmission, a factor associated with increased impulsivity and excess cardiovascular risk, is also associated with increased insulin resistance (Muldoon et al. 2006). The direction of causality in the foregoing observational studies remains unclear, suggesting the utility of mechanistic explorations in appropriate animal models. It should be noted also that nonhuman primates often have been used to study stress-related phenomena, although generally not in association with diabetes (e.g., Kaplan and Manuck 2004). A model not reviewed in this issue, the Watanabe heritable hyperlipidemic rabbit, may prove especially useful in such manipulations because these animals become insulin resistant when stressed (Gonzales et al. 2005).

Finally, animal models can provide insights into the evolutionary origins of T2D. Probably the best known evolutionary hypothesis concerning T2D involves the suggestion that humans have developed a series of “thrifty genes” that were selected during the ice ages to accomplish the following two functions: (1) to provide for rapid uptake and storage of energy in the form of fat during periods of plenty.
to ensure survival during periodic famines; and (2) to spare sufficient glucose for critical CNS and splanchnic activities by allowing for peripheral insulin resistance in the context of a low-carbohydrate high-protein diet (e.g., Colaguir and Miller 2002; Neel 1999; Zimmet and Thomas 2003). Presumably, the discordance between this genetic heritage and the calorically rich environment that characterizes many modern human populations results in an exaggerated and sustained insulin resistance and visceral fat deposition and, ultimately, the development of T2D (Cordain et al. 2005; Zimmet and Thomas 2003). Partially supporting this idea is the observation that the human brain is dependent on glucose, which exerts an energetic load that accounts for more than 20% of the resting metabolic rate compared with 3% in rodents (Leonard et al. 2003; Zimmet and Thomas 2003). It seems reasonable that there would be an adaptive advantage for a glucose-sparing mechanism in a large-brained mammal exposed to a harsh energetic environment. However, such adaptations are not necessarily limited to humans. A homologous set of responses apparently extends to other anthropoid primates including the macaque monkeys and baboons described in this issue (Wagner et al. 2006). These animals also have relatively large brains, accounting for approximately 10% of the resting metabolic rate. Other mammals such as desert rodents (e.g., the desert gerbil [Psammomys obesus]) do not have large brains but have adapted to relatively harsh environments. These animals are also able to conserve glucose but through a mechanism that does not involve peripheral insulin resistance. Continued study of the foregoing models is likely to help hasten resolution of the “thrifty gene” puzzle. Future investigations will complement current knowledge about living populations of hunter gatherers, various groups of Native Americans and South Sea Islanders, and the archæological record.

Closing Remarks

Animal models have a vital role to play in extending our understanding of T2D. The data generated by studies conducted on appropriate models can help elucidate the mechanisms underlying the development of T2D, identify targets for intervention, evaluate therapies, and shed light on the genetic and evolutionary bases of the disease.

References


