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Animal models for assessing the impact of natural products on the aetiology and metabolic pathophysiology of Type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus is a complex and heterogeneous disorder which in its most common manifestation arises from insulin resistance and later insulin insufficiency. Type 2 diabetes is characterised by impaired insulin sensitivity and diagnosed as hyperglycaemia. Because of its cardiovascular consequences, Type 2 diabetes represents one of the world's leading causes of mortality and morbidity. Drug discovery and development are required to produce better ways to prevent, treat and manage diabetes and its complications. Diabetes is a human, not an animal disease, so animals do not get Type 2 diabetes. However there are animal models which are variously suitable for the investigation of new agents for the treatment of Type 2 diabetes. In this Review we have examined the various models that are available for the study of natural products with a focus on models (genetic, nutritional and spontaneous) for the metabolic abnormities of diabetes. These models are also relevant to the investigation of Western medicines for the treatment of diabetes. A suitable experimental model plays an important role in drug discovery for translational studies leading to increased understanding of the molecular basis and management of diabetes.

Contents

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1. Introduction

There has been an enormous increase in the number of people in the world with Type 2 diabetes in the last two decades [1]. In Asia, the number of people with Type 2 diabetes has risen to be well over 100 million people. This rise has mostly been driven by the rapid increase in community affluence with levels of obesity rising in breadth and extent – more individuals with higher body mass indices (BMI). Although Type 2 diabetes can occur in thin people, most patients with Type 2 diabetes have the form which is driven by insulin-resistance as a corollary to obesity [2–4]. Changes in community behaviour and especially increasing economic status has led to increased energy intake, changing employment characteristics have led to decreasing physical activity at work and life style factors related to technology have increased sedentary time and all of these components are independent predictors of diabetes [5,6]. Diabetes is diagnosed by hyperglycaemia although the full metabolic pathophysiological profile is much more extensive. Hyperglycaemia has devastating effects on the cardiovascular system precipitating both microvascular and macrovascular disease [7,8]. From a pathophysiological perspective, diabetes is a cardiovascular disease although the pathophysiological consequences extend well beyond the cardiovascular system. Atherosclerosis is the major underlying pathology of most cardiovascular disease and it is accelerated by the metabolic milieu of diabetes but the pathological mechanism(s) of atherosclerosis and of the mechanism(s) of the accelerating effect of diabetes remain largely unknown [9–13]. Drugs for treating hyperglycaemia/diabetes aim to prevent or reduce the impact of atherosclerosis by addressing various molecular mechanisms of disease [11,14–17]. Diabetes *per se* represents an independent risk factor for cardiovascular disease [18]. Cardiovascular disease is the largest single cause of mortality in the community and with the superimposition of diabetes, cardiovascular disease becomes the majority cause of death in people with diabetes [18]. Rising diabetes and CVD is having a major impact on human health and also on the fiscal position of the budget of many countries.

For many decades the treatment of diabetes, essentially the treatment of hyperglycaemia, relied on insulin and several oral agents, mostly sulfonylureas and metformin. These drugs addressed some conditions but did not reduce mortality and were generally considered to have a low safety profile with insulin linked to hypoglycaemic episodes, sulfonylureas also associated with hypoglycaemia and metformin with lactic acidosis. With the biggest rise in the number of people with Type 2 diabetes being in Asia, which is the home of natural product medicines such as Traditional Chinese Medicines (TCM), there has been an increase in interest in the historical and future use of natural medicines for the treatment of Type 2 diabetes. Interest in TCM extends to the identification and development of new Western drugs from natural products. There is also a perception, not necessarily strongly founded, that natural medicines are safer than Western medicines. So in its best outcome, natural product derived medicines might be both efficacious and safe.

In all areas of therapeutic discovery the most important aspect is the availability of animal models which reproduce the human disease condition with high fidelity. For Type 2 diabetes the three leading parameters of these aetiologies are insulin resistance, pancreatic beta cell failure and dysfunction of the incretin system all of which lead to hyperglycaemia [19–21]. For the cardiovascular disease of diabetes the major pathology is atherosclerosis which is markedly accelerated by the diabetic milieu; this is a very important point but will not be directly addressed in this review whilst noting that essentially different models are required to study atherosclerosis from those which are suitable for the study of the aetiology and pathology of diabetes [22,23]. The biggest experimental issue is that the metabolic abnormalities of diabetes and their consequential effects on the cardiovascular system have not been able to be reproduced with animal models that meet the required level of fidelity. Similarly, there are issues with *in vitro* cell models of hyperglycaemia and diabetes [22]. Various animal models have been used to evaluate natural products and Western derived mechanistic medicines but in most cases the results have not been translatable to the clinic because the models are not adequate and the utility and extrapolation of the results have been over estimated

In this Review we have examined the various models that are available for the study of natural products with a focus on models for the metabolic abnormities of diabetes; these models are also relevant to the investigation of Western medicines for the