PART- A

Studies of Novel Dipeptidyl peptidase-IV inhibitors On Glucose Homeostasis

β-Cell Functions Genes And Protein Expression In Diabetic Rats
Introduction
1. Introduction

Type 2 diabetes is a chronic metabolic disorder characterized by hyperglycemia as a result of diminished insulin secretion and insulin resistance of peripheral tissues including liver, skeletal muscle and adipose tissue (DeFronzo., 1997). Diabetes mellitus is recognized by the World Health Organization (WHO) as a growing worldwide epidemic with more than 171 million people worldwide (2.8%) afflicted in 2000 and it is conservatively estimated that the number will more than double to 366 million (4.4%) by 2030 (Wild et al., 2004). The WHO predicts that diabetes mellitus will become one of the world's leading causes of death and disability within the next quarter century (World Health Organization Fact Sheet N° 236., 2006). In 2005, it was estimated that between 1.1-2.9 million people died from diabetes and its complications, making it the fifth leading cause of death in the world (Roglic et al., 2005).

Type 2 diabetes accounts for 90-95% of all cases of diabetes and is largely associated with obesity and physical inactivity, which have been shown to lead to insulin resistance. In fact, obesity is the greatest risk factor and it is estimated that 80% of diabetics are overweight (Triplitt et al., 2006). The increase in this global phenomenon has been largely attributed to the spread of the "western lifestyle", which refers to the combined detrimental effects of decreased exercise and bad diet. In terms of the total number of people afflicted, the top three countries are India, China and the United States (US) (Wild et al., 2004). In India, 31.7 million people had diabetes in 2000 but this number is expected to skyrocket to 79.4 million by 2030. In China, 20.8 million had diabetes in 2000 increasing to 42.3 million by 2030. 17.7 million people had diabetes in the US in 2000 and it is predicted to rise to 30.3 million by 2030.

Type 2 diabetes is part of the "metabolic syndrome", also referred to as syndrome X, which includes a set of disorders characterized by obesity, insulin resistance, hypertension and dyslipidemia. It is a chronic metabolic disorder that even with current therapies progressively worsens with time and some of its complications include retinopathy, nephropathy, neuropathy and atherosclerotic cardiovascular disease (i.e. stroke, heart attack and foot ulcers).

Insulin resistance and β-cell failure underlie the disease. In the initial stages of insulin resistance, glucose homeostasis can be maintained through hyperinsulin secretion by β-
cells. Overt diabetes only occurs when β-cells can no longer compensate for insulin resistance. It is reported that newly diagnosed patients with type 2 diabetes mellitus have approximately 50% β-cell function (UK Prospective Diabetes Study Group., 1995), due in part to a 30% reduction in β-cell mass.

There is no cure for diabetes, but the progression of the disease may be slowed down considerably through proper diet and regular physical activity. Present treatment is aimed at maintaining strict glycemic control and while some patients may be managed by diet and exercise, more typically, one or a combination of oral hypoglycemic agents are required for effective glycemic control. However, even with current pharmacological treatment the disease progressively worsens with time. For these reasons, the development of new drugs is actively being pursued.

The United Nations (UN) has recognized the diabetes epidemic as a threat to the entire world and in an effort to raise public awareness has declared November 14 (beginning in 2007) as World Diabetes Day (United Nations: General Assembly., 2007). Aside from the human pain and suffering, the financial burden that this disease places on economic development throughout the world is enormous. The total cost in 1997 in the US alone has been estimated at $98 billion (World Health Organization Fact Sheet N° 236., 2006). This includes $44 billion in direct healthcare costs and another $54 billion in indirect loss of productivity. In 2002, the cost increased to $132 billion and is estimated to rise to $192 billion in 2020 (American Diabetes Association., 2003). Health-care costs for nations range from 2.5-15% of annual health care budgets (World Health Organization Fact Sheet N° 236., 2006). Because of the enormous scale of the disease, cost-effective therapies will be required to treat people, especially those from poorer developing parts of the world that cannot afford expensive medications. The solution to this problem is certainly complex and will require a novel and concerted global effort that combines modern "western" medicine with alternative traditional systems used throughout many parts of the world.