Pharmacology & Therapeutics xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: B. Teicher

Cancer risks from diabetes therapies: Evaluating the evidence

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ARTICLE INFO

Keywords:
Diabetes
Cancer
Insulin
Anti-diabetics
Cannabinoid
Obesity

ABSTRACT

Epidemiological studies have identified positive associations between diabetes, obesity and cancer. Insulin, metformin and thiazolidinediones (TDZs) are among the major diabetes therapies that improve glycaemic control by acting via molecular targets including the insulin receptor and insulin-like growth factor pathways, adenosine monophosphate-activated kinase and peroxisome proliferator-activated receptor γ. It is well-established that clinical application of insulin and TDZs is associated with weight gain, but the potential of these therapies to promote tumourigenesis is less well-studied. In addition, although anti-tumour properties of metformin have been proposed, recently published data do not support a protective effect of metformin against cancer in diabetic patients.

Given that diabetes and cancer each account for 8% and 13% of global deaths and there is a substantial financial burden incurred by both disorders, developing diabetes therapies that are safe, efficacious and cost-effective has never been more desirable. This timely review examines recent progress in delineating the molecular mechanisms responsible for the anti-diabetic actions of insulin, metformin and TZDs and considers evidence implicating these therapies in cell transformation and tumourigenesis. In addition, since the endocannabinoid signalling system (ECS) is now considered a therapeutic target and biomarker candidate for hyperglycaemia, obesity and cell growth, a brief section covering recent scientific advances regarding the ECS, particularly its functions in regulating glucose metabolism and cell survival, is also included in this review.

Contents

Abbreviations: 2-AG, 2-arachidonoyl glycerol; ACC, acetyl-CoA carboxylase; AMPK, adenosine monophosphate-activated protein kinase; CB_1R, cannabinoid 1 receptor; CB_2R, cannabinoid 2 receptor; CPT-1, carnitine palmitoyltransferase-1; ECS, endocannabinoid system; Gluc-6-P, glucose-6-phosphatase; FAS, fatty acid synthase; FFAs, free fatty acids; GLUT4, glucose transporter 4; GPR55, G-protein receptor 55; IGF, insulin growth factor; IGFBP, insulin growth factor binding protein; IR, insulin receptor; IRS, insulin receptor substrate; IP_3, inositol 1,4,5-triphosphate; IP_3R, inositol 1,4,5-triphosphate receptor; MAPK, mitogen-activated protein kinase; MCD, malonyl-CoA decarboxylase; MGL, monoacylglycerol lipase; mTOR, mammalian target of rapamycine; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, PPARγ coactivator-1α; PIP_2, phosphatidyl bisphosphate; PPAR, peroxisome proliferator-activated receptor; PPREs, PPAR response elements; RXR, retinoid X receptor; T2D, type 2 diabetes; TZDs, thiazolidinediones.

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http://dx.doi.org/10.1016/j.pharmthera.2014.05.006
0163-7258/

Please cite this article as: Li, C., & Kong, D., Cancer risks from diabetes therapies: Evaluating the evidence, *Pharmacology & Therapeutics* (2014), http://dx.doi.org/10.1016/j.pharmthera.2014.05.006

1. Introduction

Diabetes and cancer are among the most common forms of chronic disorders, each account for 8% and 13% of global all-cause deaths. Type 2 diabetes (T2D) accounts for 90–95% of all cases of diabetes and is largely due to the worsening of glycaemic control, primarily caused by insufficient insulin secretion to counteract impaired peripheral tissue insulin sensitivity. Deterioration of β-cell function and onset of insulin resistance are central features of T2D, often characterised by hyperglycaemia, hyperinsulinaemia and dyslipidaemia, all of which have been implicated in cell transformation.

Indeed, it has been shown that high levels of fasting and postprandial plasma glucose are strongly correlated with increased cancer mortality (Zhou et al., 2010). Elevated plasma insulin and C-peptide levels are also positively associated with increased risks of prostate (Ma et al., 2008) and colon cancer (Piatkiewicz et al., 2012), implicating a detrimental impact of hyperglycaemia and hyperinsulinaemia in cancer control. Ample epidemiological analyses further reported positive association between elevated cancer risk and diabetes, classified diabetes as an independent risk factor of numerous malignancies (Aljada & Mousa, 2012). Thus, increased risks of 24 types of malignant cancers were reported in participants with T2D, with endometrial, cervical, ovarian, stomach, lung and kidney cancers having the highest frequencies; while pancreas and hepatocellular cancers were moderately correlated with T2D (Hemminki et al., 2010). A separate study also observed increased occurrence of leukaemia, melanoma, liver, pancreas, bile ducts, rectum and kidney cancers in diabetic individuals (Atchison et al., 2011). Moreover, patients with pre-existing diabetes showed an increased risk of cancer-related death, exhibiting 40% higher mortality than non-diabetic subjects with cancer (Landman et al., 2008, 2010).

In addition, emerging evidence also established strong association between obesity and malignancy (Renehan et al., 2008; Key et al., 2010). Incidents of oesophageal, colorectal, endometrial, kidney, pancreas and post-menopausal breast cancers are positively correlated with body mass index (BMI). Cancer-related mortality is also higher in obese individuals as indicated in an early study reporting 14% of cancer deaths directly caused by obesity in men and 20% in women. These figures raise to 52% (male) and 62% (female) in cancer patients with BMI over 40 kg/m^2 (Calle et al., 2003). The aggravation of malignant neoplasms observed in obese cancer patients is primarily caused by intra-abdominal obesity. Over-expression of leptin, adiponectin and other pro-inflammatory cytokines due to excessive abdominal fat has been shown to promote neoplastic development in vitro (Bluher, 2012). Since abdominal obesity is a major determinant of insulin resistance and that the majority of T2D individuals are obese or overweight, targeting adiposity is also important to improve cancer control in T2D. It is of particular relevance as weight gain is one of the adverse side effects of multiple glucose-lowering agents. Furthermore, several anti-diabetics have also been reported to impact tumour development. Given the growing concerns over current anti-glycaemia treatments and their impact on weight management and tumourigenesis, this review focuses on the molecular mechanisms underlying some major anti-diabetic agents and their effects on tumour progression.

2. Insulin and the insulin growth factor system

Insulin replacement is the most commonly used therapy in the management of type 1 diabetes (T1D) and certain cases of T2D (Fig. 1). The delivered insulin compensates for the loss of β-cell response to food intake, suppresses peripheral glucose production, enhances glucose utilisation and decreases postprandial blood glucose levels. Cellular actions of insulin include regulation of glucose transport, glycogen synthesis, hepatic glucose output and fat deposition in insulin sensitive tissues, which are responsible for maintaining glucose homeostasis. It binds to the insulin receptors (IRs) and promotes energy storage via the insulin signalling pathways (Fig. 2). The IR consists of two α and two β-subunits, forming a heterotetrameric complex that is linked by disulphide bonds. Insulin binding to the extracellular α-subunits activates tyrosine kinase activity of the intracellular β-subunits, resulting in β-subunit autophosphorylation, which further phosphorylates intracellular substrates, such as the insulin receptor substrate (IRS) proteins. Following phosphorylation, IRS proteins then recruit downstream effectors such as the phosphatidylinositol 3 kinases (PI3Ks), a family of lipid kinases (classes I, II and III), which indirectly activate the phosphoinositide-dependent kinases (PDKs), a serine/threonine kinase Akt/PKB and protein kinase C (PKC) λ/ι and ζ, which in turn stimulate intracellular activities of target cells (Copps & White, 2012). Four members of the IRS protein family have been identified, of which IRS-1 and 2 are considered the primary mediator of hepatic insulin action and glucose metabolism in skeletal muscles. IRS-1/2 also directly regulates insulin secretion and β-cell development in the islets of Langerhans (Long et al., 2011).

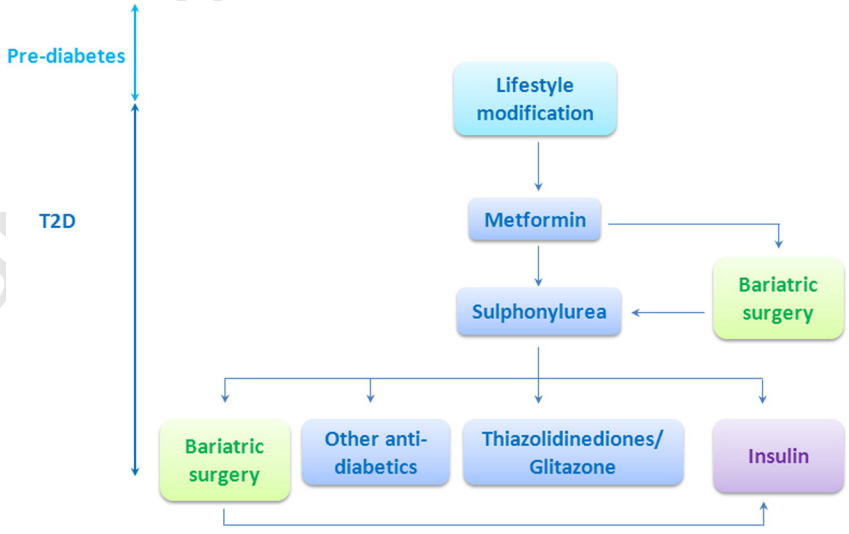

Fig. 1. IDF proposed model for T2D management. This schematic illustrates the main steps to achieve glycaemic management in T2D. Lifestyle modification including dietary restriction combined with increased exercise is recommended after initial diagnosis. Pharmacologic therapies should only be considered in the presence of severe hyperglycaemia, and if hyperglycaemia persists after reinforced lifestyle modification. The bariatric surgery has been recognised as an appropriate treatment for diabetic patients with obesity and poor glycaemic management. Surgery may be considered if patients have T2D and a BMI >35 kg/m^2, with other major co-morbidities. Diabetic patients who fail to achieve therapy target with front-line anti-diabetics are also eligible for surgery with BMI >30 kg/m^2.

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