Trends in Food Science & Technology 54 (2016) 1–16

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: http://www.journals.elsevier.com/trends-in-food-science-and-technology

Food-derived dipeptidyl-peptidase IV inhibitors as a potential approach for glycemic regulation – Current knowledge and future research considerations

Isabelle M.E. Lacroix, Eunice C.Y. Li-Chan*

The University of British Columbia, Faculty of Land & Food Systems, Food Nutrition & Health Program, 2205 East Mall, Vancouver, BC, Canada V6T 1Z4

ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form
9 May 2016
Accepted 12 May 2016
Available online 18 May 2016

Keywords:
Dietary constituent
Dipeptidyl-peptidase IV inhibitor
Phenolic compound
Peptide
Protein hydrolysate
Type 2 diabetes

ABSTRACT

Background: Diabetes, which currently affects 1 in 11 adults, is considered one of the biggest worldwide health crises of the 21st century. Over the last decade, synthetic inhibitors of the enzyme dipeptidyl-peptidase IV (DPP-IV) have emerged as an effective pharmaceutical approach for the management of type 2 diabetes. These molecules exert their beneficial effect by preventing the inactivation of gut-derived hormones that play a pivotal role in glycemic regulation. More recently, food components have been suggested as sources of DPP-IV inhibitors with the potential to help manage blood glucose levels.

Scope and approach: This review examines the sources, production, molecular characteristics and modes of action of food-derived DPP-IV inhibitors. Insights into the needs for future research to validate their efficacy and to establish their application in the management of type 2 diabetes are also discussed.

Key findings and conclusions: To date, hydrolysates of protein from a variety of food commodities, including both plant and animal sources, have been shown to be able to inhibit the activity of the DPP-IV enzyme. Moreover, a number of peptides, either isolated from these hydrolysates or synthetically produced, as well as non-protein-derived compounds such as polyphenols, have also been identified as DPP-IV inhibitors. These food-derived constituents present different degrees of potency and modes of action on the DPP-IV enzyme. While their effectiveness in humans is currently unknown, findings from *in vitro* and animal studies conducted to date warrant further research to evaluate their potential as functional food ingredients for glycemic regulation.

1. Introduction

Diabetes and its complications are major causes of mortality, accounting for 14.5% of global all-cause mortality among adults aged 20–79 years old (International Diabetes Federation, 2015). In spite of the increasing awareness of the social and economic impacts of diabetes and the development of new treatments, the incidence and prevalence of this multifactorial disorder have been unrelentingly rising. The International Diabetes Federation estimates that 415 million people (1 in 11 adults) are currently living with diabetes and predicts that, if the present demographic growth continues, 642 million (1 in 10 adults) will be affected with this metabolic disorder by 2040.

Characterized by hyperglycemia resulting primarily from defects in insulin secretion and insulin action (DeFronzo, 2009), type 2 diabetes is the most prevalent form of diabetes, accounting for about 90% of cases diagnosed (International Diabetes Federation, 2015). While the exact causes leading to the development of type 2 diabetes are still unknown, a number of risk factors, including physical inactivity, excess body weight, and unhealthy diet, have been identified (International Diabetes Federation, 2015). Inadequate glycemic control can lead to an array of serious and debilitating microvascular (e.g. retinopathy, nephropathy, neuropathy) and macrovascular (e.g. cardiovascular diseases such as stroke and heart attack) complications (Fowler, 2008). Therefore, developing effective strategies to restore and maintain blood glucose homeostasis is of primary importance.

Type 2 diabetic patients have access to a number of pharmacologic therapies that are based primarily upon increasing insulin availability, either by direct administration of insulin or via agents

* Corresponding author.
E-mail address: Eunice.Li-Chan@ubc.ca (E.C.Y. Li-Chan).

http://dx.doi.org/10.1016/j.tifs.2016.05.008
0924-2244/

promoting insulin secretion, improving insulin sensitivity, delaying gastrointestinal absorption of carbohydrates and/or increasing glucose excretion (DeFronzo, Triplitt, Abdul-Ghani, & Cersosimo, 2014). Of the twelve classes of glucose-lowering drugs currently available for the management of diabetes, inhibitors of the enzyme dipeptidyl-peptidase IV (DPP-IV) are among the newest agents to have been introduced to the type 2 diabetes pharmacopeia. These synthetic inhibitors, which can be used either as monotherapy or in combination with other anti-diabetic drugs (Craddy, Palin, & Johnson, 2014), exert their glucose-lowering effect by preventing the degradation of gut-derived hormones that play a pivotal role in glycemic regulation (Filippatos, Athyros, & Elisaf, 2014).

Diet is well recognized to play an important role in the prevention and management of diabetes. Over the past few decades, numerous studies have reported putative associations between the consumption of certain foods, or their constituents, and the incidence of diabetes (Lacroix & Li-Chan, 2014a). Moreover, compelling findings from *in vitro* as well as animal and clinical studies have shown that some dietary factors, such as peptides and phenolic compounds, can help regulate blood glucose levels (Lacroix & Li-Chan, 2014a). Recent research has suggested that one of the plausible mechanisms of action underlying the anti-diabetic effect of various food commodities could reside in the ability of their constituents to inhibit the DPP-IV enzyme. In particular, several food proteins, such as those found in milk, egg and fish, were shown by *in silico* analysis to contain within their sequences peptides able to inhibit the activity of the DPP-IV enzyme (Lacroix & Li-Chan, 2012a). The discovery that dietary factors may be sources of natural DPP-IV inhibitors that could potentially complement pharmacotherapy in the regulation of blood glucose levels has truly captured the attention of the scientific community. As a result, there has been an emergence of literature from research groups around the world describing the production and identification of DPP-IV inhibitors from a variety of food commodities.

The objectives of this review are to describe the role of DPP-IV in blood glucose regulation and to investigate the potential of dietary constituents to serve as natural inhibitors of this enzyme. The sources, production, molecular characteristics and modes of action of these food-derived inhibitors will be discussed and the needs for further research to validate their efficacy and potential commercialization for application in the management of type 2 diabetes will be examined.

2. DPP-IV, the incretin hormones and their roles in blood glucose regulation

First described in 1966 (Hopsu-Havu & Glenner, 1966), dipeptidyl-peptidase IV (DPP-IV; EC 3.4.14.5), also originally known as lymphocyte cell surface marker CD26 or as the adenosine deaminase (ADA)-binding protein, is a 110 kDa glycoprotein existing primarily as a membrane-anchored cell-surface enzyme (Filippatos et al., 2014). DPP-IV belongs to the prolyl oligopeptidase family, a group of structurally related enzymes that preferentially remove N-terminal dipeptides from substrates (Thoma et al., 2003), and is known to take part in a number of biological processes as both a regulatory protease and a binding protein (Zhong, Rao, & Rajagopalan, 2013). While *in vivo* the enzyme is responsible for cleaving the amide bond that releases a dipeptide from the amino terminal end of a number of molecules such as neuropeptides, chemokines and regulatory peptides (Zhong et al., 2013), DPP-IV is more widely known for its catalytic activity against the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GIP is a 42 amino acid long peptide derived from the proGIP gene, while GLP-1 is produced from processing of the proglucagon gene to yield primarily two active forms, glycine-extended GLP-1_{7-37} and GLP-1_{7-36} amide, the latter being the most abundant in human plasma (Tasyurek, Altunbas, Balci, & Sanlioglu, 2014).

Secreted from the neuroendocrine L and enteroendocrine K cells respectively in response to intake of nutrients (Fig. 1), GLP-1 and GIP exert glucose lowering effects by engagement of G-protein-coupled receptors (GLP-1R and GIP-R) that are expressed on pancreatic β- and α-cells as well as peripheral tissues (Tasyurek et al., 2014). By way of its action on the pancreatic β-cells, GLP-1 promotes insulin secretion as well as insulin gene transcription and biosynthesis. This incretin hormone has also been suggested to have trophic effects on pancreatic β-cells and has been reported to inhibit glucagon release, suppress appetite and food intake, as well as retard gastric emptying (Phillips & Prins, 2011; Tasyurek et al., 2014). Like GLP-1, GIP stimulates insulin secretion in a glucose-dependent manner. Besides its insulinotropic effect, the GIP hormone also elicits glucagon release and is involved in fat metabolism (Tasyurek et al., 2014).

Being responsible for approximately 50–70% of the total insulin secreted following glucose intake, the incretin hormones are important mediators of glycemic homeostasis (Baggio & Drucker, 2007). However, once secreted, GLP-1 and GIP are rapidly hydrolyzed by the DPP-IV enzyme into shorter and inactive molecules (Fig. 1). The discovery that DPP-IV is responsible for the inactivation of more than 95% of the secreted GLP-1 has drawn considerable attention to this enzyme as a target for the management of type 2 diabetes (Thoma et al., 2003). Consequently, extensive efforts have been put towards the development of small molecules able to inhibit the activity of DPP-IV and therefore prolong the activity of the incretins. This growing body of research has led to the discovery of a number of DPP-IV inhibitors that were designed based on molecular modeling and knowledge from X-ray crystallographic data of the amino acid residues forming the enzyme's active site, including the catalytic triad (Havale & Pal, 2009). Since the launch in 2006 of the first DPP-IV inhibitor, sitagliptin, at least 10 other synthetic inhibitors have been approved for the management of type 2 diabetes (Deacon & Lebovitz, 2016). While these molecules, often referred to as 'gliptins', all competitively and reversibly bind to the active site of DPP-IV, they differ greatly in their pharmacodynamic as well as their pharmacokinetic properties. Nevertheless, meta-analyses have shown no major differences between them in terms of their ability to improve blood glucose regulation (Craddy et al., 2014).

3. Dietary proteins as precursors of DPP-IV inhibitory peptides

Over the past few years, proteins from a variety of food commodities have been studied for their potential to serve as sources of inhibitors against the DPP-IV enzyme. Complementary to empirical methods, computer-assisted techniques have also been employed to predict the potential of dietary proteins as precursors of DPP-IV inhibitors and therefore assist in the selection of the best proteins to produce these bioactive peptides (Lacroix & Li-Chan, 2012a; Nongonierma & FitzGerald, 2014a; Udenigwe, Gong, & Wu, 2013). These *in silico* investigations, which are based on the occurrence within the food protein molecule of peptide sequences reported to possess DPP-IV inhibitory activity, have revealed the presence of potential DPP-IV inhibitors within the sequences of a variety of proteins from both plant and animal sources. Among the proteins investigated, those from milk (Lacroix & Li-Chan, 2012a; Nongonierma & FitzGerald, 2014a; Udenigwe et al., 2013), collagen (Lacroix & Li-Chan, 2012a), as well as canola, chicken egg, oat and wheat (Nongonierma & FitzGerald, 2014a) were suggested to be particularly promising sources of DPP-IV inhibitory peptides.