Biochimie 152 (2018) 149–154

Contents lists available at ScienceDirect

Biochimie

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

Mini-review

Glucagon-Like peptide-1: A new therapeutic target to treat abdominal aortic aneurysm?

Juliette Raffort [a, b, *], Giulia Chinetti [a, b], Fabien Lareyre [b, c]

[a] Clinical Chemistry Laboratory, University Hospital of Nice, France
[b] Université Côte d'Azur, CHU, Inserm, C3M, Nice, France
[c] Department of Vascular Surgery, University Hospital of Nice, France

ARTICLE INFO

Article history:
Received 7 May 2018
Accepted 29 June 2018
Available online 3 July 2018

Keywords:
Abdominal aortic aneurysm
Glucagon-like peptide-1
GLP-1
Dipeptidyl peptidase-4 inhibitors
DPP-IV inhibitors
Proglucagon-derived hormones

ABSTRACT

Recent antidiabetic drugs including GLP-1 receptor agonists and DPP-IV inhibitors have demonstrated protective effects in several cardiovascular diseases but their effect in abdominal aortic aneurysm (AAA) is far less known. AAA can be associated with extremely high rates of mortality and pharmacological treatments are still lacking underlining the real need to identify new therapeutic targets. The aim of this review was to summarize current knowledge on the role of GLP-1 pathway in AAA. A systematic literature review was performed and 6 relevant studies (2 clinical and 4 experimental) were included. Experimental studies demonstrated a protective effect of both GLP-1 receptor agonists and DPP-IV inhibitors through targeting the main pathophysiological mechanisms underlying AAA formation. The effects of these drugs in human AAA are still poorly known. In the limelight of clinical and experimental studies, we discuss current limits and future directions.

1. Introduction

Proglucagon-derived hormones correspond to a family of peptides whose various biological functions in glucose metabolism, energy homeostasis, control of appetite, gastrointestinal motility and trophicity have revolutionized the understanding of metabolic diseases and led to the development of innovative therapeutic targets [1–4]. Among them, Glucagon-Like peptide-1 (GLP-1), a peptide mainly produced in the entero-endocrine L-intestinal cells, is a major incretin hormone that stimulates insulin secretion after nutrient ingestion [5,6]. Its involvement in pancreatic beta-cells proliferation and survival, regulation of glucagon secretion, control of food intake as well as regulation of gastric and intestinal motility has led to the development of efficient pharmacological treatment for diabetes and obesity [5,6]. Several GLP-1 receptor agonists (i.e., liraglutide, exenatide, lixisenatide) with distinct structure and pharmacokinetics properties are currently used for the treatment of type 2 diabetes [7,8]. As GLP-1 has a short half-life in the blood and is rapidly hydrolyzed by the Dipeptidyl peptidase-4 (DPP-IV) enzyme [9], DPP-IV inhibitors (i.e. alogliptin, sitagliptin) have also been developed and are used as antidiabetic drugs [7,8]. Interestingly, epidemiological studies demonstrated that patients treated with antidiabetic drugs targeting GLP-1 pathways had significantly reduced risk of major cardiovascular complications [5,10,11]. These drugs exhibited protective effects on several cardiovascular diseases including myocardial infarction, ischemia/reperfusion injury or heart failure [5,10,11]. The protective effect on vascular system is complex and plurifactorial involving actions on cardiomyocyte, endothelial and vascular smooth muscle cell functions as well as modulation of glucose and lipid metabolism [5,10,11]. While the role of GLP-1 has been widely explored in the context of ischemic cardiac disease, its potential involvement in abdominal aortic aneurysm (AAA) is far less known. AAA represents a major health concern associated with extremely high rates of mortality in case of aortic rupture [12]. The main features of the disease include inflammatory cell infiltration in the aortic wall, extracellular matrix (ECM) remodeling, impairment of vascular smooth muscle cells (VSMCs) homeostasis as well as intraluminal thrombus formation [13]. The only curative treatment relies on surgical repair and drug-based therapy are still lacking, underlining an unmet need in clinical practice [14]. A better understanding of pathophysiological mechanisms underlying the disease could lead to develop new therapeutic drugs. The aim of this review is to summarize current knowledge on the role of GLP-1 pathway in AAA and discuss potential applications for clinical practice.

* Corresponding author. Clinical Chemistry Laboratory, University Hospital of Nice, 30 Avenue de la Voie Romaine CS 51069, 06002 Nice Cedex 1, France.
E-mail address: raffort.j@chu-nice.fr (J. Raffort).

https://doi.org/10.1016/j.biochi.2018.06.026
0300-9084/

2. Methods

Two authors (FL, JR) independently performed a literature search to identify studies investigating the effect of GLP-1 signaling pathway in aortic aneurysm. Electronic health database Medline was searched using the PubMed database on January 2018. The search strategy was unrestricted and used exploded MeSH (medical subject heading) terms “aneurysm”, “aortic aneurysm”, “Glucagon Like peptide”, “dipeptidyl peptidase”, “proglucagon”. A review protocol guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was established following inclusion criteria for article selection: publications had to be written in English language and included experimental and clinical studies that investigated the potential relationship between GLP-1 signaling pathway and aortic aneurysm. Relevant titles were independently identified and full texts were retrieved. Original articles were selected. Case reports and reviews were excluded. All suitable references were included. The methodology and study design of the selected articles were analyzed to evaluate the heterogeneity of the studies. In total, 6 studies fulfilled the inclusion criteria including 2 clinical and 4 experimental studies.

3. GLP-1 and GLP-1 receptor agonists in aortic aneurysm

Among the past few years, several experimental models of aortic aneurysm have been developed [15]. Dissecting AAA models mainly include continuous angiotensin II perfusion in *ApoE−/−* mice. This model is characterized by intramural blood infiltration and inflammatory cell infiltration, ECM degradation and atherosclerotic lesion formation thus leading to aortic dilatation usually located in the suprarenal region [15]. Chemically induced non-dissecting AAA models mainly include application of elastase or calcium chloride, which provoke disruption of ECM, induction of inflammatory responses and AAA formation in the infrarenal aortic region [15]. To address the role of GLP-1 in AAA formation, investigators used GLP-1 receptor (GLP-1R) agonists (i.e., liraglutide, lixisenatide) (Table 1). In both angiotensin II and elastase/calcium chloride AAA model, administration of GLP-1R agonists reduced AAA development, suggesting its protective effect [16,17]. The drug administration increased the concentration of plasma active GLP-1 without affecting other metabolic parameters such as body weight, blood glucose and mean arterial pressure [17]. This was associated with a decreased inflammation in the aortic wall and a reduced macrophage infiltration and TNFα mRNA expression [16,17]. Given the role of macrophages in AAA pathogenesis through their effects on ECM remodeling, inflammation and intramural haemorrhage [18], their decreased infiltration in the aortic wall may account for the protective effect on AAA formation. Elevated circulating levels of TNFα have been reported in patients with AAA [19]. Besides, experimental studies in a murine AAA model revealed that both mRNA and protein levels of TNFα were increased in aneurysm tissue compared with normal aortic tissues [20]. In this model, genetic and pharmacological inhibition of TNFα inhibited AAA formation [20]. Hence, decreased TNFα expression induced by GLP-1R agonists may limit AAA development. Treatment with GLP-1R agonists (liraglutide and lixisenatide) also led to a better preservation of ECM [16,17]. ECM remodeling results from a balance between the synthesis of its components (such as elastin and collagen) and their degradation by several enzymes such as metalloproteinases (MMPs). GLP-1R agonists administration induced a decrease of MMP-2 and MMP-9 mRNA and protein expression in the aorta [16,17], which may have contributed to ECM preservation and prevention of AAA development, given the known pathogenic effects of these proteases [21]. Mice treated with GLP-1R agonists (lixisenatide) exhibited less presence of reactive oxygen species (ROS) in the aortic wall [16]. As the enhanced production of ROS in the aorta is associated with inflammatory responses and tissue damages [22–24], the protective effect of GLP-1R agonists may be, at least partly, attributed to their anti-oxidant properties [16]. Moreover, in vitro experiments further revealed that treatment with liraglutide reduced angiotensin II-induced ROS production by U937 human monocytic cell line confirming its anti-oxidative action [17]. Finally, GLP-1R agonist administration was associated with a decreased phospho-Extracellular Signal-Related Kinase (ERK) protein expression in the aortic tissue [16]. Given the important role of ERK pathway in the modulation of MMP expression during AAA formation [25], this may also contribute to the protective effect of GLP-1R agonists on AAA formation.

The results of these studies suggest potential applications of GLP-1R agonists as therapeutic agents in AAA. To investigate the relevance of these findings in human disease, some authors characterized GLP-1 plasma concentrations in patients with aortic valve and ascending aorta disease [26]. Interestingly, they found that patients with tricuspid or bicuspid aortic valve associated with aortic dilatation had a higher total plasma GLP-1 concentration compared to those without aortic dilatation. Given the known role of GLP-1 in experimental mouse models, the authors suggest that increased GLP-1 concentration observed may serve as a compensatory mechanism upregulated during the processes contributing to aortic dilation [26]. To the best of our knowledge, no clinical study has reported yet the association between the use of GLP-1R agonists and AAA prevalence, incidence or progression. Given the current use of GLP-1R agonists as anti-diabetic drugs, it would be worth to perform epidemiological studies in this field, which could serve as a basis to develop further clinical trials.

4. DPP-IV inhibitors in aortic aneurysm

GLP-1 has a very short half-life in blood an is rapidly hydrolyzed by DPP-IV within 1.5–5 min [9,27]. Consequently, DPP-IV inhibitors (i.e alogliptin, sitagliptin) have been developed and are currently used as anti-diabetic drugs [7]. As expected, administration of DPP-IV inhibitors in rodent models decreased plasma DPP-IV activity and increased plasma concentration of active GLP-1 [17,28,29]. No difference in metabolic parameters including body weight, food intake, lipid profile and glucose concentration was observed between treated mice and controls [17,28]. However, treatment with sitagliptin significantly decreased mean arterial pressure in angiotensin II-infused mice [17]. Experimental studies unraveled a protective effect of DPP-IV inhibitors on AAA development and progression in angiotensin II/*ApoE−/−* as well as in elastase and calcium chloride-induced AAA models. Indeed, the treatment reduced AAA dilatation and aortic wall thickness, preserved ECM, and decreased apoptosis in the aortic tissue [17,28]. A significant decrease in ROS expression was observed in the AAA wall in a dose dependent manner [29]. While all these studies revealed a protective effect of DPP-IV inhibitors on ECM, the molecular mechanisms are not completely elucidated. Several investigators demonstrated a decrease of MMP-2, MMP-9 protein, gene expression as well as enzymatic activity following the treatment [17,29]. However, Kohashi et al. only found a tendency of a decreased MMP-9 gene expression, with no change in MMP-2 expression [28]. They also reported an increase of Tissue Inhibitor Metalloproteinase-2 (TIMP-2) gene expression [28] whereas no difference was observed by Lu et al. [17]. The discrepancy between these studies may be explained by the differences of the experimental protocols used including AAA model, age of mice, diet and aortic tissue sample preparation. Nevertheless, taken together, the studies revealed a protective effect of DPP-IV inhibitors through ECM preservation via modulation of the expression and activity of MMPs and/or their inhibitors.