Artery Research (2015) 11, 1–9

Available online at www.sciencedirect.com

ScienceDirect

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

Complex vasoactivity of liraglutide. Contribution of three gasotransmitters

Eszter Sélley [a], Gergő A. Molnár [a], Szilárd Kun [a], István András Szijártó [b], Boglárka Laczy [a], Tibor Kovács [a], Ferenc Fülöp [c], István Wittmann [a,*]

[a] 2nd Department of Medicine and Nephrological Center, University of Pécs, Pécs, Hungary
[b] Medical Clinic for Nephrology and Internal Intensive Care, Charité Campus Virchow Klinikum and Experimental and Clinical Research Center (ECRC), Max Delbrück Center for Molecular Medicine, Berlin, Germany
[c] Institute of Pharmaceutical Chemistry, University of Szeged, Szeged, Hungary

Received 28 January 2015; received in revised form 6 March 2015; accepted 23 April 2015
Available online 9 May 2015

KEYWORDS
Aortic rings;
Central (aortic) vasodilatation;
GLP-1;
Liraglutide

Abstract *Background:* Incretine hormone glucagon-like peptide-1 (GLP-1) causes dose-dependent relaxation of the thoracic aorta of rats and other arteries via nitric oxide (NO), cAMP and ATP-sensitive potassium channels, however, through a mechanism not thoroughly described. Hereby we aimed to determine the mediators involved in the vasoactive effect of liraglutide.
Methods: Isolated rat aortic rings and segments of the femoral artery were mounted in a wire myograph to study the vasoactive effect of liraglutide. Vessels were preincubated either with inhibitors of gasotransmitter-, prostaglandin- or reactive oxygen species-formation, or with inhibitors of protein kinases, potassium channels or the Na^+/Ca^{2+}-exchanger.
Results: According to our findings, liraglutide activates endothelial cells and vascular smooth muscle cells leading to the production of NO, carbon monoxide, hydrogen sulphide, superoxide anion, and hydrogen peroxide. Increased production of such relaxing factors promotes the activation of protein kinase— A and —G, resulting in the activation of potassium channels (ATP-sensitive-, voltage-gated-, large-conductance-calcium activated), which profoundly contributes to the activation of the Na^+/Ca^{2+}-exchanger, thereby leading to calcium efflux and smooth muscle relaxation and vasorelaxation.
Conclusions: We reveal the contribution of all gasotransmitters in the vasorelaxation induced by liraglutide. We provide *ex vivo* evidence that liraglutide is capable of causing vasodilatation in the

* Corresponding author. University of Pécs, Faculty of Medicine, 2nd Department of Medicine and Nephrological Center, 1 Pacsirta St., H-7624 Pécs, Hungary. Tel.: +36 72536050; fax: +36 72536051.
E-mail address: istvan.wittmann@aok.pte.hu (I. Wittmann).

http://dx.doi.org/10.1016/j.artres.2015.04.001
1872-9312/© 2015 Association for Research into Arterial Structure and Physiology. Published by Elsevier B.V. All rights reserved.

central and peripherial vessels, thereby supporting the clinical observation that it lowers blood pressure.
© 2015 Association for Research into Arterial Structure and Physiology. Published by Elsevier B.V. All rights reserved.

Introduction

Liraglutide, a glucagon-like peptide-1 (GLP-1) analogue is a drug used in the therapy of type 2 diabetes.[1] It exerts its effects mainly via the GLP-1 receptor (GLP-1R), although GLP-1R-independent effects have also been described.[1] GLP-1R is expressed, among others, on endothelial cells and vascular smooth muscle cells.[2] A broad expression of GLP-1R mRNA in the thoracic aorta of rats has been identified.[3]

Numerous publications pointed out that native GLP-1 causes concentration-dependent relaxation of different arteries; however, controversial data have been published about the mechanism of the vasodilator effect of GLP-1 and its analogues.[3–7] GLP-1 exerted dose-dependent vasorelaxation in the pulmonary arteries of rats in an endothelium-dependent manner,[4,5] while GLP-1 causing vasodilatation of the rat femoral artery was found to be endothelium-independent.[6] These findings may indicate that GLP-1 evokes vasodilatation via different pathways in the different parts of the arterial system. GLP-1 is known to increase the plasma level of the potent vasodilator nitric oxide (NO).[7] Liraglutide induces NO-production in vascular endothelial cells,[8] however so far there has been no evidence, that any of the GLP-1 analogues would be able to induce the synthesis of other gasotransmitters.

Potassium channels and protein kinases might be targets of gasotransmitters and other mediators of vasorelaxation.[9] GLP-1 and other related peptides were found to cause vasodilatation of the rat thoracic aorta with the contribution of ATP-sensitive potassium channels (K_{ATP}) and they are also known to influence the activity of the voltage-dependent potassium channels (K_v).[3,10,11]

In an $ApoE^{-/-}$ deficient mouse model, liraglutide was shown to have non-PKA, GLP-1R dependent effects in the regulation of eNOS (endothelial nitric oxide synthase) enzyme expression and attenuated intracellular adhesion molecule-I (ICAM-1) expression in aortic endothelial cells, referring to the role of liraglutide in the inhibition of endothelial cell dysfunction.[13]

Moreover, an increased cAMP production was found in aortic tissue incubated with GLP-1.[3]

A number of studies demonstrated that both native GLP-1 and its mimetics induce vasodilation, furthermore, some studies focused on their effect in the thoracic aorta, however, the precise mechanism of vasodilatation still remains unclear.[3,18]

A previous study, which demonstrated the GLP-1R dependent, NO-independent systolic blood pressure lowering effect of liraglutide, also reported that the anti-hypertensive effect of liraglutide evoked due to the increased secretion of the atrial natriuretic peptide (ANP).[12]

Central (aortic) blood pressure, the pressure measured in the aorta, is a major determinant of cardiovascular outcomes,[14] therefore, the possible effects of liraglutide to lower the pressure in the aorta as well as in other arteries could be beneficial in clinical practice.

Considering the wide diversity of the data mentioned above, we concluded that the precise mechanism of vasodilatation caused by GLP-1 analogue liraglutide is not thoroughly described, thereby in our study we aimed to determine whether liraglutide relaxes the rat thoracic aorta and identify mediators and second messengers involved in the vasodilator effect of liraglutide. Therefore, we studied the effect of liraglutide on gasotransmitters and ion channels.

Materials and methods

Chemicals

Liraglutide (Victoza® injection) was purchased from Novo Nordisk Hungary (Budapest, Hungary). Exenatide (Byetta® injection) was purchased from Bristol-Myers Squibb—AstraZeneca (Budapest, Hungary). Acetylcholine, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), N_ω-Nitro-L-arginine methyl ester hydrochloride (L-NAME), N[2-(p-Bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide dihydrochloride (H89), tetraethylammonium chloride (TEA), glibenclamide, superoxide dismutase (SOD), catalase, DL-Propargylglycine (PPG), indomethacin and Mg_2SO_4 were purchased from Sigma—Aldrich (St. Louis, MO, USA). Tin-protoporphyrin IX dichloride was purchased from Santa Cruz Biotechnology (Dallas, Texas, USA). XE991 was purchased from Ascent Scientific Ltd. (Avonmouth, Bristol, UK) Epinephrine was purchased from Richter-Gedeon Hungary (Budapest, Hungary). SEA0400 was synthesized in the Institute of Pharmaceutical Chemistry, University of Szeged, Szeged, Hungary by Professor Ferenc Fülöp. NaCl, KCl, KH_2PO_4, $NaHCO_3$, glucose and $CaCl_2$*$2H_2O$ were purchased from Merck (Merck KGaA, Darmstadt, Germany).

Animals

All experiments were approved by the Hungarian Local Animal Experiment Committee, in accordance with the 'Principles of laboratory animal care' (NIH publication no. 85—23, revised 1985). Animals were originally purchased from Charles River Laboratories GmbH (Sulzfeld, Germany). Adult, 10—12 week old male Sprague-Dawly rats weighing between 280 and 340 g were kept on a standard diet. On

Download English Version:

https://daneshyari.com/en/article/2891374

Download Persian Version:

https://daneshyari.com/article/2891374

Daneshyari.com