Journal of Surgical Research **168,** 179–187 (2011)
doi:10.1016/j.jss.2010.02.013

Glucose-Induced Intestinal Vasodilation *Via* Adenosine A1 Receptors Requires Nitric Oxide but Not K^+_{ATP} Channels

Paul J. Matheson, Ph.D.,*[,1] Na Li, M.D.,† Patrick D. Harris, Ph.D.,† El Rasheid Zakaria, M.D., Ph.D.,† and R. Neal Garrison, M.D.*,†,‡

**Department of Surgery; †Department of Physiology and Biophysics, University of Louisville, Louisville, Kentucky; and ‡Louisville Veterans Affairs Medical Center, Louisville, Kentucky*

Submitted for publication June 8, 2009

Background. **Both nitric oxide (NO) and adenosine A1 receptor activation mediate microvascular vasodilation during intestinal glucose absorption. Our overall hypothesis is that adenosine triphosphate (ATP) utilization during glucose absorption would increase adenosine metabolite release, which acts on adenosine A1 receptors to alter endothelial production of NO and/or activate ATP-dependent potassium channels (K^+_{ATP}) to dilate intestinal microvessels.**

Methods. **Intravital videomicroscopy of the rat jejunum was used to record the vascular responses of inflow (termed 1A) arterioles, proximal (p3A), and distal (d3A) premucosal arterioles during exposure to isotonic glucose or mannitol solutions alone or in the presence of the selective nitric oxide synthase (NOS) inhibitor (L-NMMA), an adenosine A1 receptor antagonist (8-cyclopentyl-1,3-dipropylxanthine (DPCPX)), or a K^+_{ATP} channel inhibitor (glibenclamide).**

Results. **As expected, glucose exposure caused rapid dilation of both p3A and d3A arterioles, while mannitol exposure had no effect on microvascular diameters. Adenosine A1 receptor blockade completely prevented glucose-induced dilation of the premucosal arterioles. NOS inhibition significantly blunted the glucose-induced vasodilation of the premucosal arterioles, but had little effect in the mannitol group. Simultaneous application of both the NOS inhibitor and the adenosine A1 receptor antagonist gave the same reduction in glucose-induced dilation of the premucosal arterioles as the adenosine A1 receptor antagonist alone. Blockade of K^+_{ATP} channels with glibenclamide did not attenuate glucose-induced vasodilation of the premucosal arterioles.**

Conclusion. **These data suggest that glucose-induced vasodilation of premucosal jejunal arterioles is mediated through adenosine A1 receptors, and NO at least partially mediates the adenosine A1 receptor-induced vasodilation. In addition, K^+_{ATP} channels are not involved in premucosal arteriolar vasodilation during intestinal glucose exposure.** © 2011 Elsevier Inc. All rights reserved.

Key Words: **glucose-induced intestinal hyperemia; adenosine A1 receptor; nitric oxide; ATP-dependent potassium channel; intravital videomicroscopy.**

INTRODUCTION

Postprandial intestinal hyperemia, or increased blood flow during absorption of ingested nutrients in the gastrointestinal tract, depends on vasodilation of the gastrointestinal microvasculature and microvessel recruitment to open previously unperfused premucosal arterioles and capillaries. Glucose and many L-amino acids are absorbed by sodium-linked, secondary active transport from the intestinal lumen into the mucosal epithelial cells, which requires adenosine triphosphate (ATP) utilization by the epithelial cells. As an ATP degradation product, adenosine participates in many regulatory processes, including vascular reactivity *via* adenosine receptor activation [1], and studies have shown that adenosine-related mechanisms are involved in absorptive hyperemia [2, 3, 4]. Adenosine, an endogenous purine nucleoside, mediates many physiologic actions through four known purinergic (P1) receptors, designated A1, A2a, A2b, and A3 [5]. The actions of adenosine are well described and include

[1] To whom correspondence and reprint requests should be addressed at Department of Surgery, University of Louisville, ACB 2nd Floor, Louisville, KY 40292. E-mail: paul.matheson@louisville.edu.

0022-4804/$36.00
© 2011 Elsevier Inc. All rights reserved.

decreased heart rate (A1), coronary artery vasodilation (A2a), and bronchospasm (A2b). Adenosine receptors are thought to be ubiquitous, but the receptor subtypes most commonly implicated in vascular physiology are the A1 and A2a receptors and, to a lesser extent, A2b receptors [5–7]. Adenosine A1 receptors mediate vasoconstriction in many vascular beds, while A2a receptors mediate vasodilation. The activity of each adenosine receptor subtype involves second messenger systems, either stimulatory (A2) or inhibitory (A1, A3) G-proteins and subsequent increase or decrease in cyclic AMP. A recent intravital videomicroscopy study in rat intestine suggested that glucose-induced vasodilation of the intestinal microvessels is primarily mediated by the A1 and A2b adenosine receptors [8].

The mechanisms of adenosine-induced vasodilation have been widely explored in *ex vivo* studies [4, 9, 10] and vary with tissue. Some have proposed that adenosine A2x receptors are the major subtypes involved in adenosine-related vasodilation [9–11], while activation of the adenosine A1 receptor (ADO A1R) produces vasoconstriction. However, adenosine A1 receptor-mediated vasodilation has been reported in some *in vivo* studies [5–7]. Perhaps due to the diversity of effectors coupled with adenosine receptors, the adenosine A1 receptor appears to produce either constriction or dilation in a tissue-dependent and adenosine concentration-dependent manner. Coupling of nitric oxide (NO), ATP-dependent potassium channels (K^{+}_{ATP}) and/or prostaglandins to the activation of adenosine A1 receptors has been reported in some tissues, which also might explain the diversity of possible effects during adenosine A1 receptor activity [7]. Also, an unusual low-affinity type of the adenosine A1 receptor has been proposed that might explain adenosine A1 receptor-induced vasodilation [5], which fits with the observation that high concentration of an adenosine A1 receptor agonist caused vasodilation in some vascular beds, while low concentration of the agonist did not [4]. The mechanisms of adenosine A1 receptor-induced vasodilation have not been reported in the intestinal microvasculature.

Nitric oxide (NO), a potent local vasodilator, has been shown to mediate intestinal hyperemia during nutrient absorption [12–14], and synergy between NO and adenosine has been suggested in different tissue and vascular beds [15–18]. We have previously shown that adenosine A1 receptors are involved in glucose-induced intestinal vasodilation [8], but the hypothesized predominant role of the adenosine A1 receptor subtype in mediating adenosine-related vasodilation during glucose absorption in the intestine has not been demonstrated. The focus of the present study was to examine the mechanisms of adenosine A1 receptor-mediated vasodilation during intestinal glucose absorption. We hypothesized that adenosine A1 receptor-mediated vasodilation of intestinal microvessels during glucose absorption involve NO release or K^{+}_{ATP} channel activation. To test this hypothesis, we performed intravital videomicroscopy in the rat jejunum during intestinal glucose exposure alone or in the presence of an adenosine A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), the selective NO synthase inhibitor, L-NMMA, or the K^{+}_{ATP} channel inhibitor, glibenclamide.

MATERIALS AND METHODS

Chemicals and Solutions

All chemicals were purchased from Sigma Chemical Co. (St. Louis, MO). The baseline physiologic salt solution (PSS) for the exposed intestinal segment was a modified glucose-free Krebs solution, which consisted (in mM) of 25.5 $NaHCO_3$, 112.9 NaCl, 4.7 KCl, and 2.55 $CaCl_2 \cdot 2H_2O$. This solution was used to bathe the intestinal tissue during both surgical preparation and the baseline period of the microcirculation protocol. To initiate glucose-mediated vasodilation, a modified salt solution with Tris pH buffering was used that contained (in mM) 36.29 Tris-HCl, 13.71 Tris-base, 11.1 D-glucose, 88.98 NaCl, 5.87 KCl, and 2.55 $CaCl_2 \cdot 2H_2O$ [19]. An isotonic mannitol solution was used as an osmotic control for the glucose solution and had the same components with the exception that mannitol was substituted for glucose (11.1 mM). Selective NOS inhibitor (L-NMMA) and ATP-dependent potassium channel inhibitor (glibenclamide) were applied topically to the jejunum segment in the tissue bath at the final concentrations of 100 μM and 10 μM, respectively. We have previously utilized these inhibitors in other studies of the intestinal microcirculation and the doses used in the present study were based on EC50 levels determined from dose-response curves generated in previous animals. The doses used in this study are 100-fold greater than the previously observed EC50 doses for each inhibitor.

Animal and Tissue Preparation

Animals were maintained in a facility approved by the American Association for the Accreditation of Laboratory Animal Care in temperature- and humidity-controlled rooms with a 12-h light/dark cycle. The research protocol was approved by the Institutional Animal Care and Use Committee, the Biohazard Safety Committee, and the Research and Development Committee at the Louisville VA Medical Center. Fifty-six [56] male Sprague-Dawley rats (190–210 g body weight) were acclimated for 2 wk and received standard rat chow (20 g/d) and water *ad libitum* prior to experimental use. Food, but not water, was withheld 16 h prior to experimental use to minimize the presence of digestive products in the intestinal lumen. Rats were anesthetized *via* intra-peritoneal administration of pentobarbital (60 mg/kg). A surgical plane of anesthesia was maintained by regular administration of supplemental pentobarbital (2.5 mg/kg) as needed. Core body temperature was maintained at 37.0 ± 0.5°C using a servo-controlled feedback controller, rectal thermistor, and heating pad. Tracheotomy was performed to maintain airway patency. The right carotid artery was cannulated to monitor mean arterial blood pressure and heart rate, and the left femoral vein was cannulated to infuse saline (1 mL/h) to maintain body fluid homeostasis.

A right paramedian abdominal laparotomy was performed and a segment of the upper jejunum was selected 5–6 cm from the attachment of the jejunum and transverse mesocolon. A jejunal segment (1.5-2 cm) supplied by a single mesenteric artery with intact neurovascular supply was exteriorized and both ends were ligated to

Download English Version:

https://daneshyari.com/en/article/4302476

Download Persian Version:

https://daneshyari.com/article/4302476

Daneshyari.com