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ORIGINAL ARTICLE

Loperamide-induced Cardiac Depression Is Enhanced by Hyperglycemia: Evidence Relevant to Loperamide Abuse

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Background and Aims. Cardiac dysryhthmias and death are reported after loperamide abuse. The mechanism of death is not clear and cardiac depression may play a role in this mechanism. Loperamide is widely used as an agonist of the μ-opioid receptor (MOR) in clinical practice. In skeletal muscle, an increase in MOR in response to hyperglycemia is largely attributable to higher expression of the transducer and activator of transcription 3 (STAT3), which binds to the promoter of the MOR genes. Therefore, we investigated the changes in cardiac MOR caused by hyperglycemia both *in vivo* and *in vitro*.

Methods. Streptozotocin-induced type 1-like diabetic rats (STZ rats) were used to estimate cardiac performance and changes in cardiac MOR under the influence of loperamide. STAT3 was measured in cultured cardiomyocytes under high glucose (HG) to mimic the *in vivo* changes.

Results. Loperamide-induced reduction of cardiac performance was more marked in STZ rats than in normal rats. The increased MOR in the hearts of STZ rats was reversed by the reduction of hyperglycemia. Higher MOR expression paralleled the increase in STAT3 in cardiomyocytes under HG and was reversed by siRNA of STAT3. Stattic at a dose sufficient to inhibit STAT3 reduced MOR both *in vivo* and *in vitro*.

Conclusion. Cardiac depression induced by loperamide is enhanced by hyperglycemia due to higher MOR expression, which is associated with higher expression of STAT3 in the heart. These results suggest that loperamide abuse is particularly dangerous for individuals with hyperglycemia. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Cardiac performance, μ-opioid receptor, STAT3, siRNA, Stattic.

Introduction

Loperamide (Imodium®) is a synthetic phenylpiperidine with opioid-like action that is considered to have a low risk of abuse due to its limited influence on brain function (1,2). As the agonist of μ-opioid receptor (MOR), loperamide does not cause CNS effects at therapeutic doses due to active efflux from the CNS by p-glycoprotein (2,3). In clinical practice, loperamide acts to slow intestinal peristalsis to improve the symptoms of acute and chronic diarrhea (1). However, recent data show that some users take high doses of loperamide to self-medicate for symptoms of opioid withdrawal (4–6) or abuse loperamide to replace illicit opioids, causing safety concerns (7). Although loperamide can cause opioid-like action, there is a high risk of toxicity or death from cardiac depression at high doses (8,9).

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Additionally, opioid receptor (OR) subtypes including mu- (MOR), kappa- (KOR), and delta- (DOR) have been identified in heart tissue; MOR and DOR were found primarily in myocardial cells and on sparse individual nerve fibers, whereas KOR was observed predominantly in myocardial cells and intrinsic cardiac adrenergic cell-like structures (10). The expression of MOR in heart tissue was also confirmed using positron emission tomography imaging (11). Additionally, direct cardiac MOR stimulation with opioid agonists decreases cardiac contractility (12). Therefore, we propose that changes in MOR expression may be involved in death from cardiac depression in loperamide users.

Hyperglycemia is important in the pathogenesis of diabetes (13). Hyperglycemia- induced STAT3 signal pathway is an integral part of tissue damage, including myocardial dysfunction (14,15). Conditional STAT3 deletion mice showed mild hyperglycemia and hyperinsulinemia at the time of weaning and become hyperphagic immediately after weaning to exhibit impaired glucose tolerance (16). In clinical settings, the link of high glucose and STAT3 activation has been confirmed in tumor tissues from the cholangiocarcinoma patients with diabetes who exhibited higher STAT3 activation than those without diabetes (17). STAT3 seems to be the main factor for increased opioid receptor expression. STAT3 has been proven to bind to a site located at nucleotide −1583 on the promoter of the human μ-opioid receptor gene (18,19). STATs may transcriptionally regulate MOR genes (20). In skeletal muscle, the hyperglycemia-induced increase in MOR expression occurs due to increased expression of STAT3 (21). In this study, we examined whether a similar hyperglycemia-related increase in MOR expression occurs in the heart using hyperglycemic rats and cultured cardiomyocytes. These results may provide evidence that will report how clinicians counsel patients in risk of loperamide abuse.

Materials and Methods

Animal Model

Six-week-old male Wistar rats were obtained from the Animal Center of National Cheng Kung University Medical College. Diabetes was induced in the rats by intravenous (i.v.) injection of streptozotocin (65 mg/kg) into fasting animals as previously described (22). In accordance with previous studies, the animals were considered diabetic if they had plasma glucose concentrations >350 mg/dL (21,22). Plasma insulin levels in the STZ diabetic rats decreased to 1.37 ± 0.52 pmol/l from 257.6 ± 3.8 pmol/l measured in normal rats. All experiments were performed 9 weeks after diabetes induction. All animal procedures were performed according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. All invasive experiments were performed under anesthesia (2% isoflurane) to minimize animal suffering without altering the autonomic nervous system, according to previous reports (23,24). The experimental protocols used in this study were developed and approved in accordance with the guidelines for the care and use of laboratory animals at Chi-Mei Medical Center (No. 100052307). Additionally, the experiments conformed to the Guide for the Care and Use of Laboratory Animals as well as the guidelines of the Animal Welfare Act.

To correct hyperglycemia, STZ rats were injected intraperitoneally (i.p.) with long-lasting human insulin (1 IU/kg; Monotard® HM, Denmark) or phloridzin (1 mg/kg; Fluka Chemie AG, Switzerland), three times daily for 7 days as previously described (25). Age-matched rats were then divided into four groups (six rats per group): vehicle-treated normal rats, vehicle-treated STZ rats, insulin-treated STZ rats, and phloridzin-treated STZ rats.

Blood samples obtained from the rats were centrifuged at 12,000 g for 3 min and analyzed using glucose kit reagents (AppliedBio Assay Kits; Hercules, CA). Plasma glucose level was then estimated using an auto-analyzer (BioTek, Winooski, VT) and samples were run in duplicate.

Catheterization for Hemodynamics

The right femoral arteries of STZ diabetic rats were cannulated with polyethylene catheters (PE-50). Mean arterial pressure (MAP) and heart rate (HR) were recorded using a polygraph (MP35; BIOPAC, Goleta, CA). Animals were tracheally intubated for artificial ventilation (Small Animal Ventilator Model 683; Harvard Apparatus, Holliston, MA) at 50 breaths/min under a tidal volume of 8 mL/kg and a positive end expiratory pressure of 5 cm H_2O. After incision of the rat's chest at the third intercostal space to expose the heart, a small section (1 cm in length) of the ascending aorta was freed from the connective tissue. A Transonic Flowprobe (2.5PSB923; Transonic System Inc., Ithaca, NY) was implanted at the root of the ascending aorta and connected to a Transonic transit-time blood flowmeter (T403, Transonic System, Inc.). Cardiac output (CO) was calculated from the aortic blood flow, and the differences in CO were compared across groups.

The rats were injected intravenously with loperamide (1 mg/kg) (26) and/or with cyprodime (the selective MOR antagonist) (1 mg/kg) as previously described (27), and hemodynamic parameters were recorded continuously throughout the experiment.

Cell Culture and Treatment

H9c2 cells (BCRC No. 60096) were cultured according to a previously described method (28). In brief, H9c2 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.2; GIBCO-BRL Life Technologies, Gaithersburg, MD) supplemented with 10% fetal bovine serum.

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