ISSN (Online) 2287-3406
Journal of Life Science 2024 Vol. 34. No. 1. 1~8 DOI : https://doi.org/10.5352/JLS.2024.34.1.1

Brain-type Natriuretic Peptide Ameliorates High-fat Diet–induced Hepatic Insulin Resistance

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Received November 8, 2023 /Revised November 28, 2023 /Accepted November 29, 2023

Brain-type natriuretic peptide (BNP) is a cardiac hormone that exerts cardiovascular and renal effects and regulates metabolic processes. In the current study, to determine the hepatic effects of BNP, we investigated whether it improves high-fat diet (HFD)–induced hepatic IR and characterized its possible mechanism. No significant differences in body weight, fat mass, or lean mass were observed between the saline- and BNP-treated groups of normal diet–and HFD-fed mice. During the clamp test, the BNP infusion into HFD-fed mice led to lower blood glucose levels and increased glucose infusion rates versus that into saline-treated HFD-fed mice. The BNP infusion also inhibited hepatic glucose production and decreased hepatic triglyceride levels concomitant with decreased expression of gluconeogenesis and lipogenesis-related genes, resulting in reduced levels of alanine aminotransferase and aspartate aminotransferase. BNP increased the phosphorylation of Akt and AMP-activated protein kinase (AMPK) in the livers of HFD-fed mice compared to saline-fed HFD mice. The incubation of AML12 murine hepatocytes with BNP increased the basal levels of phosphorylated Akt and AMPK and recovered the phosphorylated Akt and phosphorylated AMPK levels reduced by palmitate treatment. Furthermore, BNP incubation prevented palmitate-induced increases in lipogenesis gene expressions. Taken together, the current study's findings indicated that BNP ameliorates hepatic IR, resulting in reduced hepatic glucose production and hepatic steatosis.

Key words : AMP-activated protein kinase, brain-type natriuretic peptide, gluconeogenesis, hepatic insulin resistance, lipogenesis

Introduction

Natriuretic peptides (NPs), a family of structurally similar cardiac hormones, consist of three biologically active peptides: atrial natriuretic peptide (ANP), brain-type (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Each has cardiovascular and renal actions and are widely used cardiovascular biomarkers [6]. NPs bind to three receptors, NP receptor A (NPRA), NPRB, and NPRC, and regulate various physiological functions. ANP and BNP bind with high affinity to NPRA with specific guanylyl cyclase, which hydrolyzes guanosine triphosphate into cyclic guanosine monophosphate (cGMP) and activates various biological responses via cGMP-dependent protein kinases, including cGMP-gated ion channels or effector proteinases. CNP mainly binds to NP receptor B, a non-guanylyl cyclase receptor, and inhibits adenylyl cyclase or phospholipase C activation [6, 9]. NPs were recently shown to exert various effects on metabolic syndrome [1, 3, 7, 13]. They play a role in various metabolic processes, including fat oxidation in skeletal muscle [3], lipid mobilization in white adipose tissue [13], energy dissipation in brown adipose tissue [7], and browning of white adipocytes [1], which influences whole-body glucose homeostasis, free fatty acid metabolism, and insulin sensitivity.

BNP, a 32-amino-acid peptide hormone, is structurally similar to ANP and mainly produced and secreted by the ventricular myocardium as a prepro-BNP. Prepro-BNP is cleaved to pro-BNP and subsequently converted to 32-amino-acid BNP by a cardiac protease, namely corin or furin. BNP plays a cardioprotective role in cardiovascular diseases, including heart failure and hypertension [11]. Its administration to patients with chronic heart failure can improve left ventricular function owing to its prominent vasorelaxant, natriuretic, and diuretic activities. Furthermore, BNP and pro-BNP also play

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important roles in renal function and are used as biomarkers of cardiac dysfunction in chronic kidney disease. It was recently reported that chronic BNP infusion in obese diabetic db/db mice improved insulin sensitivity and glucose tolerance and reduced ectopic lipid accumulation [2]. However, little is known about the mechanisms underlying BNP-mediated insulin sensitivity.

Insulin acts on the skeletal muscle and adipose tissue and increases glucose uptake. Furthermore, it inhibits lipolysis of the adipose tissue and reduces circulating free fatty acid levels, thereby promoting glucose production [8]. The liver plays a central role in the systemic regulation of glucose and lipid metabolism. Insulin promotes anabolic metabolism in the liver by increasing glucose consumption and lipid synthesis. However, aberrant hepatic insulin action leads to excess glucose production and increased lipid accumulation, which is referred to as hepatic insulin resistance (IR). During the progression of hepatic IR, insulin fails to suppress hepatic glucose production (HGP) and continues to drive excess lipid synthesis, resulting in hyperglycemia and dyslipidemia, which are characteristic of type 2 diabetes mellitus [12]. Previous studies using genetic models of tissue-specific insulin receptor genes revealed their differing effects on IR in different tissues in the presence of systemic metabolic diseases [4, 5]. Muscle insulin receptor knockout mice and fat insulin receptor knockout mice still had normal blood glucose and insulin levels. In contrast, liver-specific insulin receptor knockout (LIRKO) mice show severe IR and fasting and postprandial hyperglycemia [5], suggesting that hepatic IR is the leading cause of fasting hyperglycemia, which might be a critical factor driving the development of type 2 diabetes mellitus.

In this study, we investigated the preventive effects of BNP on hepatic IR in high-fat diet (HFD)－induced obese mice using a hyperinsulinemic-euglycemic clamp. The infusion of BNP into HFD-fed mice improved HFD-induced hepatic IR, decreasing HGP and correcting hepatic steatosis through Akt and AMPK activation.

Materials and Methods

Animal experiments

Male C57BL/6 mice (8-10 weeks old; Jackson Labs, Bar Harbor, ME, USA) were fed an HFD (TD 93075; 55% kcal from fat; Envigo, Indianapolis, IN, USA) *ad libitum* for 10 weeks to induce obesity. The effects of HFD on body composition were monitored by the non-invasive measurement of whole-body fat mass and lean mass using ^{1}H magnetic resonance spectroscopy (Echo Medical Systems, Houston, TX, USA). All mice were housed under a controlled temperature (23℃) and light/dark cycle. The animal protocol used in this study was approved by the University of Massachusetts Medical School Institutional Animal Care and Use Committee for ethical procedures and scientific care (IACUC 2021-89).

Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity

Following the 10-week feeding period of a normal diet (ND) or HFD, survival surgery was performed 5-6 days before the clamp experiments to position an indwelling catheter in the jugular vein. To deliver BNP continuously into the body, we used mini-osmotic pumps (model 2001; Alzet Corporation, Cupertino, CA, USA) filled with 200 μl of BNP solution (AnaSpec; Fremont, CA, USA) to release 48 ng/day/body weight over 7 days. Saline was loaded for control, then implanted subcutaneously during the last 1 week of the HFD feeding in mice.

Cell culture

AML12 murine hepatocytes were obtained from American Type Culture Collection (Manassas, VA, USA) and cultured in Dulbecco’s modified Eagle medium/nutrient mixture F12 (Cytiva, Logan, UT, USA) containing 1% penicillin-streptomycin (Cytiva), insulin-transferrin-selenium (100X; Gibco, Waltham, MA, USA), 40 ng/ml dexamethasone (Sigma, St. Louis, MO, USA), and 10% fetal bovine serum (Cytiva) at 37°C in an incubator with 5% CO_2.

Western blot analysis

The AML-12hepatocytes were homogenized in lysis buffer (Pro-prep™ protein extraction solution (Intron Biotechnology, Seongnam, South Korea). Total protein was quantified using a bicinchoninic acid kit (ThermoFisher, Waltham, MA, USA), in which 20 μg/lane was loaded. Antibodies against Akt and phospho-Akt were obtained from Cell Signaling (Danvers, MA, USA), while AMPK and phospho-AMPK were purchased from Abclonal (Woburn, MA, USA). Glyceraldehyde-3-phosphate dehydrogenase, fatty acid synthase (FAS), and sterol regulatory element-binding transcription factor 1c (SREBP1c) were purchased from Santa Cruz Biotechnology (Dallas, TX, USA).

Table 1. Sequence of primers used for real-time PCR

Genes	Forward	Reverse
G6Pase	ACA TCC GGG GCA TCT ACA ATG	AAA GAG ATG CAG GCC CAA
Pepck	ATC ATC TTT GGT GGC CGT AG	ATC TTG CCC TTG TGT TCT GC
Fas	AGG TGG TGA TAG CCG GTA TGT	TGG GTA ATC CAT AGA GCC CAG
Srebp1c	TGGATTGCACATTTGAAGACAT	GCCAGAGAAGCAGAAGAG

Quantitative real-time polymerase chain reaction analysis

Total RNA was isolated from liver tissues and AML12 murine hepatocytes using TRIZOL® reagent (Invitrogen, Carlsbad, CA, USA) and cDNA synthesis was performed using TOPscript™ RT DryMIX (Enzynomics, Daejeon, South Korea), and subjected to quantitative real-time polymerase chain reaction (qPCR) using a SYBR Green master mix (SJ Bio Sciences, Daejeon, South Korea) with gene-specific primers (Table 1).

Measurement of biochemical parameters

During the clamping, glucose concentrations were measured using 10 μl of plasma by the glucose oxidase method on an Analox GM9 analyzer (Analox Instruments, Hammersmith, London, UK). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and triglyceride (TG) levels were measured using COBAS (Roche Diagnostics International AG, Rotkreuz, Switzerland).

Statistical analysis

All data were processed and analyzed using GraphPad software (version 9; GraphPad Software, Inc., La Jolla, CA, USA) and are presented as mean ± standard error of the mean. One-way analysis of variance with Tukey's multiple comparisons test was used for the analyses. Values of $p<0.05$ were considered statistically significant.

Results

BNP improved hepatic IR and activated insulin signaling in HFD-fed mice

HFD feeding for 10 weeks led to increased body weight and fat mass compared with ND feeding (Fig. 1A, 1B). The BNP infusion did not affect mean body weight or fat mass in either group (Fig. 1A, 1B). There were no differences in mean whole-body lean mass among the four groups (ND versus HFD supplied with saline or BNP) (Fig. 1C), suggesting that the BNP infusion did not affect adiposity in the ND or HFD condition.

To determine the effects of BNP on insulin sensitivity, a 2-h hyperinsulinemic-euglycemic clamp combined with a [^{3}H] glucose infusion was performed in conscious mice. The basal glucose levels were not significantly different among the four groups (Fig. 1D). During the clamp test, plasma glucose levels were significantly increased by HFD feeding (Fig. 1E); however, BNP infusion decreased HFD-induced glucose levels (Fig. 1E) to normal, although the HFD mice developed obesity. Glucose infusion rates (GINF) were determined in the four groups to determine insulin sensitivity. HFD feeding reduced GINF compared to ND feeding (Fig. 1F), suggesting that HFD leads to the development of systemic IR. However, the BNP infusion significantly increased GINF versus the saline infusion in the HFD-fed mice (Fig. 1F). BNP did not affect GINF in the ND-fed mice (Fig. 1F). Taken together, these results indicate that the BNP infusion improves whole-body insulin sensitivity of HFD-fed mice.

Hepatic insulin activity and glucose production were then determined during the clamp test. Basal HGP did not differ among the ND and HFD mice treated with saline or BNP (Fig. 2A). In contrast, HFD feeding increased HGP during clamping. However, the BNP infusion significantly blocked HFD-induced HGP in the HFD-fed mice (Fig. 2B). Furthermore, insulin-mediated suppression of blood glucose, referred to hepatic insulin action, was reduced by HFD, whereas the BNP infusion in HFD-fed mice significantly recovered hepatic insulin action (Fig. 2C). These results indicate that BNP ameliorates hepatic IR. Phosphoinositide-3-phosphate kinase (PI3K)/Akt pathway is the key signaling pathway that mediates the effects of insulin [8]. Akt phosphorylation is essential for insulin-induced HGP suppression. To characterize the signaling molecules associated with the improvement of hepatic IR by BNP, Akt phosphorylation was determined in BNP-treated HFD-fed mice. As shown in Fig. 2D, phosphorylated Akt was decreased in HFD- versus ND-fed mice; however, the BNP infusion significantly increased Akt phosphorylation.

Akt activation inhibits HGP by repressing gluconeogenesis genes including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) [8]. Thus, the expression of gluconeogenesis genes was examined in HFD-fed

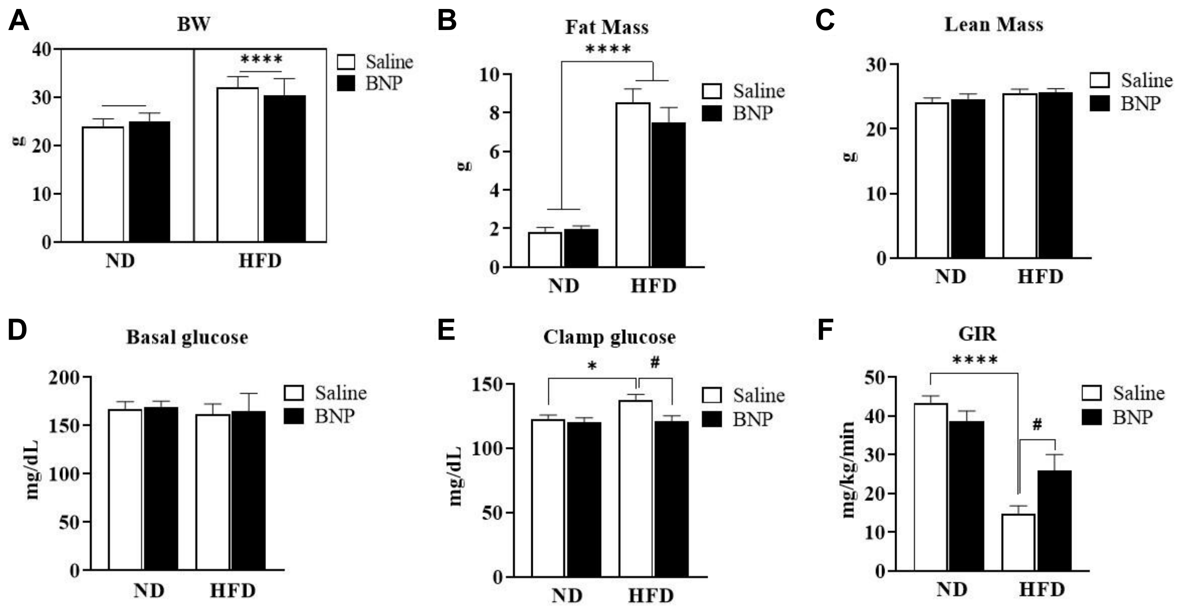

Fig. 1. BNP infusion improved the whole-body insulin sensitivity of HFD-fed mice. Following ND or HFD feeding, mini-osmotic pumps were used to deliver 200 µl of BNP continuously into the mice. (A) Body weight. ***p<0.001 versus HFD-fed mice. Body fat mass (B) and lean mass (C) were measured using ^{1}H magnetic resonance spectroscopy. ***p<0.001 versus HFD-fed mice. Basal glucose (D) and clamp glucose (E) levels were measured using an Analox GM9 analyzer. *p<0.05 versus HFD-fed mice, #p<0.05 versus HFD-fed mice + saline. (F) Glucose infusion rates were determined by 2-h hyperinsulinemic-euglycemic clamp test. ***p<0.001 versus HFD-fed mice, #p<0.05 versus HFD-fed mice + saline. The data are presented as mean ± standard error of the mean of 10 mice. BNP, B-type natriuretic peptide; HFD, high-fat diet; ND, normal diet; GINF, glucose infusion rate.

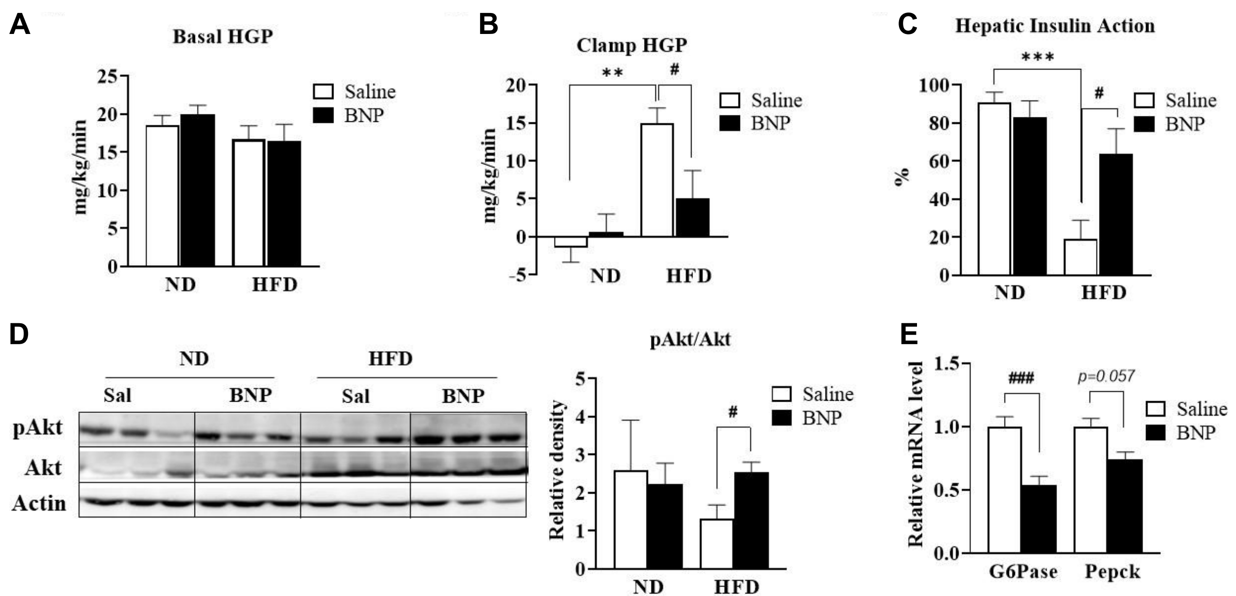

Fig. 2. BNP infusion ameliorated HFD-induced hepatic insulin resistance and activated Akt. (A) Basal hepatic glucose production. (B) Clamp hepatic glucose production. **p<0.01 versus HFD-fed mice, #p<0.05 versus HFD-fed mice + saline. (C) Hepatic insulin action. ***p<0.001 versus HFD-fed mice, #p<0.05 versus HFD-fed mice + saline. (D) Akt phosphorylation was determined in the livers of mice by western blotting. Representative images are shown. Densitometric analysis of western blots are given. #p<0.05 versus HFD-fed mice + saline. (E) Gluconeogenesis gene expression including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase was determined by quantitative real-time polymerase chain reaction. ###p<0.001 versus HFD-fed mice + saline. The data are presented as mean ± standard error for 10 mice. HGP, hepatic glucose production. BNP, B-type natriuretic peptide; HFD, high-fat diet; ND, normal diet

mice treated with saline or BNP. As shown in Fig. 2E, qPCR revealed that the expressions of gluconeogenesis genes, including G6Pase and PEPCK, were downregulated by the BNP versus saline infusion in the HFD-fed mice. Taken together, these results indicate that BNP activates the Akt pathway, which leads to the downregulation of gluconeogenesis gene expression, resulting in HGP suppression.

BNP attenuated HFD-induced hepatic steatosis and activated AMPK

Hepatic IR is associated with hepatic steatosis, a better predictor of hepatic IR [12]. To investigate whether BNP also attenuates hepatic steatosis by improving hepatic IR, hepatic TG level was determined in HFD-fed mice infused with BNP or saline. Hematoxylin and eosin staining showed that BNP reduced HFD-induced large lipid droplets versus saline (Fig. 3A). Oil Red O (ORO) staining was increased in HFD infused with saline versus ND mice infused with saline. However, BNP infusion blocked this increase in ORO staining (Fig. 3A). Furthermore, the HFD group demonstrated increased hepatic TG levels versus the ND group (Fig. 3B); however, the BNP infusion markedly reduced the hepatic TG level of the HFD group. To investigate whether the improvement in hepatic steatosis was associated with reduced lipogenesis, the expression of lipogenesis genes, including serum responsive binding protein 1c (SREBP1c) and fatty acid synthase (FAS), was determined in HFD-fed mice. As shown in Fig. 3C, BNP markedly reduced the HFD-induced expression of lipogenesis genes in HFD-fed mice. Moreover, liver toxicity was analyzed to determine whether improved hepatic insulin protects against HFD-induced liver toxicity. HFD feeding increased circulating ALT and AST levels compared to ND feeding; however, BNP reduced them (Fig. 3D). These results indicate that BNP attenuates HFD-induced hepatic steatosis.

AMPK reportedly inhibits lipogenesis [10]. Therefore, to identify another signaling molecule involved in the effect of BNP, AMPK phosphorylation was determined in BNP-treated HFD mice. Phosphorylated AMPK levels were decreased in the livers of HFD-fed versus ND-fed mice; however, the BNP infusion significantly increased AMPK phosphorylation (Fig. 3E). These results suggest that AMPK activation may be involved in BNP-mediated suppression of lipogenesis.

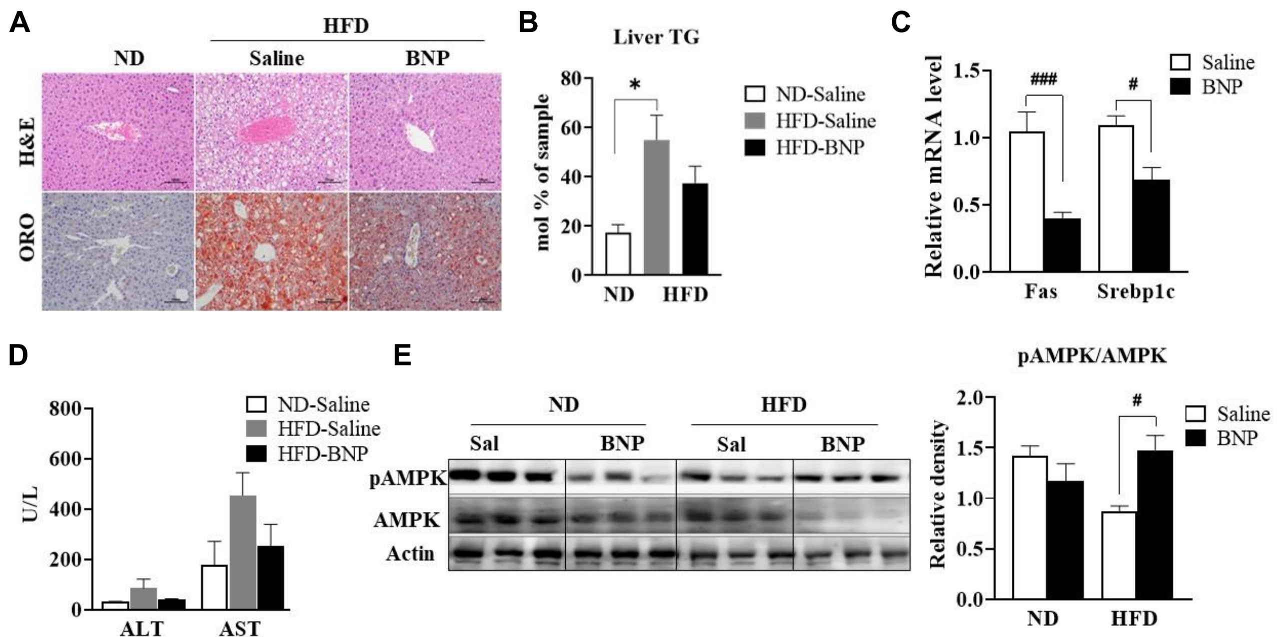

Fig. 3. BNP prevented HFD-induced hepatic steatosis and activated AMPK. (A) Oil Red O and hematoxylin and eosin staining of the liver tissues. Scale bar, 50 μm. (B) The amount of hepatic TG was measured using a kit. $^{*}p<0.05$ versus HFD-fed mice. (C) The expression of lipogenesis genes including fatty acid synthase and sterol regulatory element-binding transcription factor 1c was determined by quantitative real-time polymerase chain reaction. $^{\#}p<0.05$, $^{\#\#\#}p<0.001$ versus HFD-fed mice + saline. (D) Alanine aminotransferase and aspartate aminotransferase levels were measured by kits. (E) AMPK phosphorylation was determined by western blotting. Representative images are shown. Densitometric analysis of western blots are given. $^{\#}p<0.05$ versus HFD-fed mice + saline. The data are presented as mean ± standard error of the mean of 10 mice. BNP, B-type natriuretic peptide; HFD, high-fat diet; ND, normal diet

BNP increased Akt and AMPK phosphorylation and inhibited lipogenesis gene expression in AML12 murine hepatocytes

To confirm the ameliorative effect of BNP on hepatic IR noted *in vivo,* we examined whether BNP activated insulin signaling and AMPK in AML12 murine hepatocytes. Following the incubation of AML12 murine hepatocytes with BNP and insulin, phosphorylated Akt and AMPK were analyzed by western blotting. As shown in Fig. 4A, BNP treatment increased the basal levels of phosphorylated Akt similar to insulin but did not show a synergistic effect with insulin. We further examined the effect of BNP on Akt phosphorylation under IR conditions. AML12 murine hepatocytes were treated with palmitate and incubated with BNP. As shown in Fig. 4A, the phosphorylated Akt level was decreased by palmitate treatment; however, co-treatment with palmitate and BNP increased Akt phosphorylation, similar to the effect of insulin.

Next, we determined whether BNP also activated AMPK in palmitate-treated AML12 murine hepatocytes. As shown in Fig. 4B, BNP increased the basal levels of phosphorylated AMPK in AML12 murine hepatocytes. In addition, BNP recovered the palmitate-mediated reduction of phosphorylated AMPK in palmitate-treated AML12 murine hepatocytes. Taken together, these results indicate that BNP activates insulin signaling and AMPK in AML12 murine hepatocytes. We then examined the effect of BNP on the expression of lipogenesis genes in AML12 murine hepatocytes. As shown in Fig. 4C, western blotting and qPCR revealed that palmitate increased the expressions of lipogenesis genes, including FAS and SREBP1c; however, co-incubation with BNP prevented this increase (Fig. 4C).

Discussion

Hepatic IR failed to inhibit HGP and increases ectopic lipid accumulation, resulting in hepatic steatosis [12]. BNP is a natriuretic peptide known for its cardiovascular function [6]. It was recently reported to play a role in metabolic processes [1, 3, 7, 13]. However, little is known about the effects of BNP on hepatic IR. The current study investigated the effect of BNP on HFD-induced hepatic IR and hepatic steatosis using a hyperinsulinemic-euglycemic clamp and confirmed BNP's effects on AML12 murine hepatocytes *in vitro*.

A hyperinsulinemic-euglycemic clamp study was performed in HFD-fed mice in which BNP was delivered by an osmotic pump for 1 week. BNP infusion in HFD-fed mice did not affect body weight, fat mass, lean mass, or basal glucose levels. However, BNP reduced the clamp blood glucose level and increased the glucose infusion rate, suggesting that

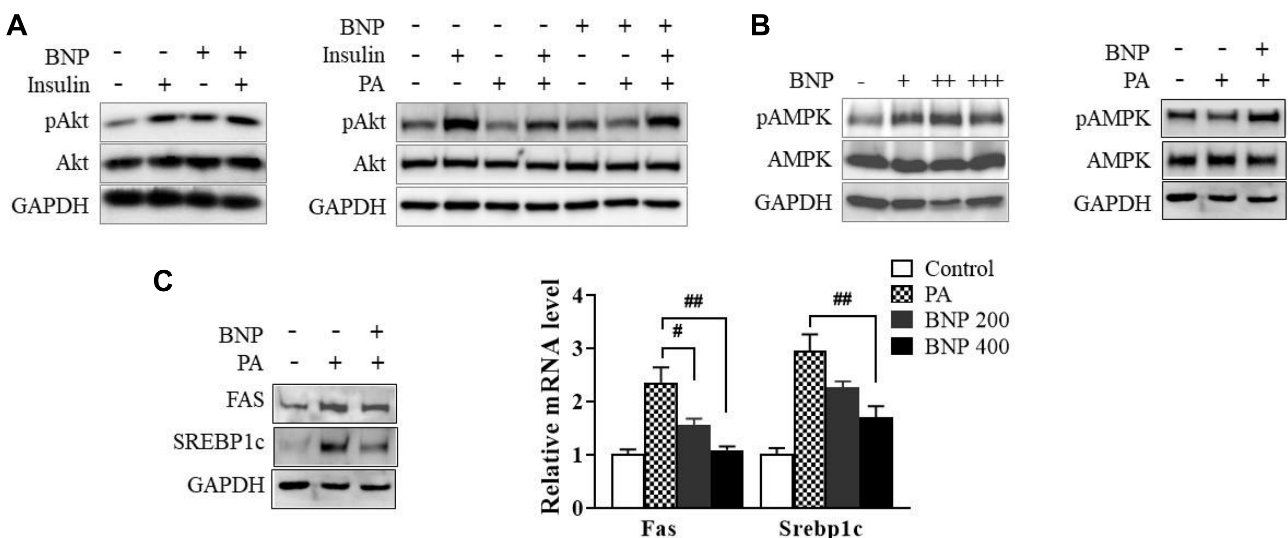

Fig. 4. BNP activated both Akt and AMPK in AML12 murine hepatocytes. AML12 murine hepatocytes were treated with BNP or insulin in the presence or absence of palmitate. (A) Akt phosphorylation was determined by western blotting. (B) AML12 murine hepatocytes were treated with BNP in different concentrations. AMPK phosphorylation was determined by western blotting. (C) Lipogenesis gene expression, including fatty acid synthase and sterol regulatory element-binding transcription factor 1c, was measured by western blotting and quantitative real-time polymerase chain reaction. Values are mean ± standard error of the mean from triplicate experiments. $^{\#}p<0.05$, $^{\#\#}p<0.01$ versus PA treatment. BNP, B-type natriuretic peptide; HFD, high-fat diet; ND, normal diet; PA, palmitate

it improves HFD-induced IR throughout the body. Whole-body IR conventionally refers to impaired glucose uptake via glucose transporter 4 in the skeletal muscle and adipose tissue. A previous study revealed that knockout of the insulin receptor in the skeletal muscle and adipose tissue is not sufficient to induce IR [4]. However, LIRKO mice showed severe IR, glucose tolerance, fasting hyperglycemia, and hyperinsulinemia [5]. These studies suggest that hepatic IR may be a critical factor leading to the development of fasting hyperglycemia. Thus, we investigated whether BNP improves hepatic IR and inhibits HGP. The current results indicate that HFD lowered insulin-induced glucose disposal in the liver; however, BNP infusion significantly recovered this reduction. Furthermore, the HFD increased HGP. However, the BNP infusion significantly prevented the HFD-induced HGP. HGP is primarily caused by gluconeogenesis. Thus, we examined the expression of gluconeogenesis genes in the HFD-fed mice. Our results revealed that BNP versus saline administration efficiently reduced gluconeogenesis gene expression. These results suggest that BNP ameliorates hepatic IR and prevents HFD-induced HGP.

Paradoxically, hepatic IR reportedly enhances TG accumulation, resulting in hepatic steatosis [12]. Hepatic lipid accumulation mainly results from increased hepatic *de novo* lipogenesis and an influx of blood free fatty acids and TG while reducing free fatty acid oxidation and TG export via very low-density lipoprotein [12]. Therefore, here we investigated whether the BNP-induced hepatic IR improvement reduces hepatic TG accumulation. The ORO and hematoxylin and eosin staining and hepatic TG level measurements revealed that BNP infusion prevented HFD-induced hepatic TG accumulation. Furthermore, BNP infusion reduced the expression of lipogenic genes, including SREBP and FAS, versus saline infusion in HFD mice. Collectively, these results suggest that BNP ameliorates HFD-induced hepatic IR and prevents HFD-induced hepatic steatosis.

The PI3K/Akt pathway is a key signaling pathway associated with the effects of insulin [8]. Insulin-induced Akt activation inhibits gluconeogenesis through multiple downstream pathways including FoxO1 [8]. FoxO1 stimulates the expression of gluconeogenesis genes including *PEPCK* and *G6Pase*. Insulin activates Akt, which phosphorylates and inactivates FoxO1, leading to nuclear exclusion and inhibition of PEPCK and G6Pase expression [8]. The current study revealed that HFD reduced Akt phosphorylation and downregulated PEPCK and G6Pase expressions; however, the BNP infusion increased Akt phosphorylation and reduced the HFD-induced PEPCK and G6Pase expressions. The effects of BNP on Akt phosphorylation and gluconeogenesis gene expressions were further confirmed in AML12 murine hepatocytes. BNP treatment increased basal Akt phosphorylation and recovered phosphorylated Akt levels reduced by palmitate treatment in AML12 murine hepatocytes. Consistent with the Akt phosphorylation results, BNP treatment inhibited palmitate-induced gluconeogenesis gene expression.

AMPK reportedly improves insulin sensitivity and inhibits lipogenesis [10]. The mTOR/S6K1 pathway promotes IR via the inhibitory serine phosphorylation of IRS1. AMPK phosphorylates mTOR/SK6, an inducer of IR, via the inhibitory serine phosphorylation of IRS1 and inactivates mTOR/SK6. Thus, AMPK-mediated inhibition of mTORC1/S6K1 could alleviate hepatic IR. Furthermore, AMPK phosphorylates acetyl-CoA carboxylase 1 (ACC1) at Ser79, a key rate-controlling enzyme in the synthesis of malonyl-CoA, a critical precursor for fatty acid biosynthesis, inhibiting its enzymatic activity. Thus, AMPK-mediated ACC1 phosphorylation inhibits the enzymatic activity of ACC1 and suppresses lipogenesis. Moreover, AMPK inhibits lipogenesis by downregulating SREBP1c, which stimulates lipogenesis genes including *FAS* and *SCD1*. Therefore, AMPK activation may be a promising strategy for alleviating hepatic steatosis. The current results revealed that BNP increased AMPK phosphorylation that was reduced by HFD. Furthermore, the *in vitro* study revealed that BNP treatment increased the basal levels of phosphorylated AMPK in AML12 murine hepatocytes and significantly recovered the AMPK phosphorylation that was reduced by palmitate treatment. These results suggest that AMPK may play a role in BNP-mediated insulin sensitivity and hepatic steatosis. In conclusion, the current study demonstrated that BNP ameliorates HFD-induced hepatic IR, inhibiting HGP and preventing hepatic steatosis.

Acknowledgement

This work was supported by a 2-Year Research Grant of Pusan National University.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : Brain-type natriuretic peptide (BNP)의 고지방 식이 유도에 의한 인슐린 저항성 개선 효과

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Brain-type natriuretic peptide (BNP)은 뇌나트륨이뇨펩티드로, 좌심실의 심근세포에서 분비되는 호르몬으로, 심장과 신장에 작용하여 혈관 확장과 나트륨 이뇨 작용 등을 하는 것으로 알려져 있으나, 최근에는 다양한 조직에서 대사 작용을 조절하는 것으로 보고된다. 본 연구에서는 간 조직에서 BNP의 영향을 알기 위해 BNP가 고지방식이에 의해 유도되는 인슐린 저항성을 개선하는지를 조사하였다. BNP을 주입한 쥐와 control로서 saline을 주입한 쥐들 간에는 몸무게, 체지방양(fat mass), 제지방량(lean body mass)의 변화는 없었다. 고인슐린혈증 정상혈당 글루코스 클램프(Hyperinsulinemic Euglycemic Glucose Clam) 동안, BNP를 주입한 고지방 식이 쥐들은 saline을 주입한 고지방식이 쥐에 비해 혈당(blood glucose)은 감소하였으며, 포도당 주입 속도(glucose infusion rate)는 증가하였다. 또한 BNP은 포도당 신생 및 중성지방 합성 관련 유전자들의 발현을 감소시켜, 간에서 포도당 생성과 중성지방의 양을 감소시켰다. BNP는 saline을 주입한 쥐에 비해 간 조직에서 Akt와 AMP-activated protein kinase (AMPK)의 인산화를 증가시켰는데, 이는 BNP을 처리한 AML12 간세포에서도 BNP는Akt와 AMPK 인산화를 증가시켰다. 이상의 결과는 BNP가 간에서 인슐린 저항성을 개선하여 포도당 생성과 중성 지방 생성을 억제함을 알 수 있었다.