Biochemical and Biophysical Research Communications 430 (2013) 676–682

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

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

Chronic exercise enhances insulin secretion ability of pancreatic islets without change in insulin content in non-diabetic rats

Miho Tsuchiya [a,1], Yasuko Manabe [a,1], Kenichiro Yamada [a], Yasuro Furuichi [a], Masahiro Hosaka [b], Nobuharu L. Fujii [a,*]

[a] Department of Health Promotion Sciences, Graduate School of Human Health Sciences, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji, Tokyo 192-0397, Japan
[b] Division of Molecular and Cellular Biology, Department of Biotechnology, Akita Prefectual University, Kaidobata-nishi 241-438, Shimo-Shinjyo Nakano, Akita City 010-0195, Japan

ARTICLE INFO

Article history:
Received 23 October 2012
Available online 2 December 2012

Keywords:
Exercise
Insulin
Islet
Beta-cell
Type 1 diabetes
Skeletal muscle
Perifusion assay

ABSTRACT

We evaluated the effect of chronic exercise on insulin secretion in response to high-glucose by using a perifusion method with isolated pancreatic islets from normal rats. Male Wistar rats were assigned to one of two groups: a sedentary group and a trained group. Running exercise was carried out on a treadmill for one hour per day, five days per week, for six, nine, or 12 weeks. The chronic exercise significantly enhanced the insulin secretion ability of pancreatic islets in response to the high-glucose stimulation upon nine and 12 weeks of exercise. The insulin content in the pancreas and the weight of the pancreas did not change upon nine weeks of exercise. Potassium-stimulated insulin secretion was also increased in the islets isolated from rats that trained for nine weeks compared with that in sedentary rats, suggesting that insulin secretion events downstream of membrane depolarization are involved in targets of the exercise effect. These findings suggest that chronic exercise could be a useful strategy not only for the maintenance of peripheral insulin sensitivity but also for the promotion of islet function to secrete insulin in non-diabetics.

1. Introduction

Physical exercise is well recognized as an effective strategy to improve blood glucose control in both normal and diabetic individuals [1–3]. For example, chronic exercise improves overall glucose homeostasis by increasing the rate of whole-body glucose disposal. Many lines of evidence show that an increase in the sensitivity of skeletal muscle glucose transport to insulin is one of the mechanisms by which exercise produces this effect. On the other hand, whether chronic exercise affects the ability of the pancreas to secrete insulin is still poorly understood. Generally, chronic exercise is associated with a lowered basal insulin concentration in the circulation. This lower blood insulin level does not directly indicate an attenuated ability of the pancreas to secrete insulin, but is instead interpreted as a result of an increase in insulin sensitivity in peripheral tissues, such as skeletal muscle, due to exercise repetitions, which enables a reduction in the amount of insulin required to maintain glucose homeostasis [1–3].

Although the effect of exercise on insulin secretion has been of considerable interest to investigators, a number of conflicting results on this issue have been reported to date. When considering only studies that used rats as an animal model, physical exercise has been found to have no [4], negative [5–10], and positive [10–16] effects on the potential for insulin secretion from the pancreas, pancreatic islets, or beta-cells. One possible reason for this is variation in the method used to evaluate insulin secretion ability: hyperglycemic clamp *in vivo* [7,11,13,14], static incubation of isolated islets [9,10,17], single beta-cell assay [4,8], and perifusion of isolated islets [5,6,12,16].

Since its introduction, perifusion assay has been used as a reliable method to evaluate the insulin secretion potential of isolated pancreatic islets [18]. This is an effective and straightforward method to evaluate the ability of islets to secrete insulin against various secretagogues without an influence of the extracellular environment *in vitro*. To our knowledge, only three studies have used this method to determine the effects of chronic exercise on insulin secretion ability. In the early 1980s, it was reported that chronic exercise training with swimming [5] and voluntary wheel running [6] attenuates insulin secretion from isolated islets in normal rats in response to exposure to a high concentration of glucose. On the other hand, Delghingaro-Augusto et al. recently observed with the method that exercise prevents beta-cell failure in susceptible islets of Zucker diabetic rats [16]. As the perifusion method has been progressively improved for more than 30 years compared with the approach used in the 1980s, it might be worth re-evaluating the effect of chronic exercise on the insulin secretion ability of

* Corresponding author.
E-mail address: fujiin@tmu.ac.jp (N.L. Fujii).
[1] These authors contributed equally to this work.

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.11.092

islets. In this context, this study was designed to evaluate the effect of chronic exercise training on insulin secretion in response to high-glucose by using a perifusion method with isolated pancreatic islets of normal non-diabetic rats.

2. Materials and methods

2.1. Animal care and exercise training program

Male Wistar rats (Japan CLEA) with an initial body weight of approximately 120 g were housed in a cage in a temperature-controlled room at 23 °C with a 12-h (5:00 a.m.–5:00 p.m.) light–dark cycle. The animals were randomly assigned to one of two experimental groups: sedentary control and chronic exercise-trained groups. Prior to the chronic exercise protocol, the rats in the trained group were habituated to treadmill running for 15 min from 0 to 15 m/min for five days. After adaptation, the trained group was subjected to chronic exercise on a treadmill for 60 min at 25 m/min, five days per week, for six, nine, or 12 weeks. When the trained rats exercised, the sedentary rats were placed beside the treadmill and exposed to the same environment, but did not run on a treadmill. Trained rats were sacrificed 36 h or later after the last exercise session. All experiments conducted in this study were approved by the Animal Care Committee of Tokyo Metropolitan University.

2.2. Perifusion assays of isolated islets

Islets were isolated from Wistar rats by pancreatic duct injection of 1.33 mg/ml collagenase solution, followed by digestion at 37 °C for 9–12 min with gentle shaking, as reported previously [19]. Islets were picked up by hand selection under a dissecting microscope. A 2.5-ml syringe was cut to make its volume 700 μl, and the bottom was plugged with Sephadex G-25 gel (GE Healthcare). Fifty islets were placed on the gel in the handmade syringe column. This column was eluted with standard low-glucose Krebs–Ringer (KR) buffer (15 mM HEPES pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 24 mM $NaHCO_3$, 0.1% bovine serum albumin, and 2.8 mM glucose) at a constant flow rate of 1.0 ml/min for 30 min, which stabilized the basal insulin secretion from the islets. For glucose stimulation, islets were perifused with high-glucose KR buffer (16.7 mM) for 15 min, followed by low-glucose buffer for 10 min. For stimulation by high-potassium, islets were perifused with buffer containing 30 mM KCl plus 95 mM NaCl for 15 min, followed by low-glucose buffer for 20 min. During the entire perifusion period, samples were collected every minute or two for insulin assay. The insulin concentration of the sample buffer was measured by mouse insulin ELISA. Area under the curve of the perifusion assay was calculated using the obtained insulin concentration results.

2.3. Quantification of insulin content in pancreas

For the quantification of insulin content, the pancreases were exercised and weighed, and each was then cut into small pieces and frozen using liquid nitrogen. Insulin was extracted by homogenization using a glass-Teflon homogenizer (1300 rpm, 30 strokes) in an acid–ethanol solution (70% ethanol and 0.18 M HCl) and then by sonication for 20 s. After centrifugation at 3000*g* for 10 min, the immunoreactive insulin in the supernatant was measured.

2.4. Immunoblotting

Islet proteins (40 μg) were separated by SDS–PAGE and transferred to nitrocellulose membranes. The nitrocellulose membranes were blocked in Tris-buffered saline with either 5% milk or 5% bovine serum albumin and immunoblotted using antibodies against glucose transporter 2 (GLUT2; 07-1402, MILLIPORE), potassium inwardly rectifying channel, subfamily J, member 11 (Kir6.2; AB5495, MILLIPORE), calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (Cav2.1; AB5152, MILLIPORE), synaptosomal-associated protein 25 (SNAP25; ab5666, abcom), vesicle-associated membrane protein 2 (VAMP2; 104211, Synaptic Systems), and syntaxin 1 (S1172, Sigma–Aldrich). The blots were then incubated with secondary antibody (donkey anti-rabbit IgG horseradish peroxidase, Amersham Biosciences) for one hour at room temperature, followed by enhanced chemiluminescence (PerkinElmer). The intensity of the bands was quantified by densitometry.

2.5. Phenotypic characterization

For insulin tolerance test (ITT), human insulin (Humulin R; Eli Lilly) was injected intraperitoneally into the sedentary and trained rats in the eighth week of the training session (0.75 U/kg body weight). Blood samples were collected at 0, 15, 30, 60, 90, 120, 150, and 180 min after the injection of insulin. A drop of tail blood was applied to a One Touch Ultra glucometer (LifeScan Johnson & Johnson, CA) to measure blood glucose levels. Body weight, blood glucose level during the feeding period, and food intake were measured every two weeks until the eighth week of the nine-week exercise period. Since the ITT test was expected to influence the measurements, these variables were not measured in the ninth week.

2.6. Statistics

Data are expressed as means ± SEM. Statistical analysis of the data was performed using Student's *t*-test. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Effect of chronic exercise on high-glucose-stimulated insulin secretion in perifused islets

To evaluate the effect of chronic exercise on the ability of islets to secrete insulin, rats were subjected to treadmill running for one hour per day, five days per week, for six, nine, or 12 weeks. Pancreatic islets were isolated from sedentary and trained rats 36 h or later after the last exercise session, and were then used for the perifusion assay. As shown in Fig. 1 (left column), insulin secretion in response to high-glucose (16.7 mM) was enhanced in trained rats compared with that in sedentary rats for all exercise durations. Areas under the curve of insulin secretion obtained from the perifusion assay for the different exercise periods were significantly larger in the groups that trained for nine ($p < 0.01$) and twelve weeks ($p < 0.05$) than in the sedentary group (Fig. 1, right column). Even with six weeks of exercise, the area under the curve of perifusion analysis tended to be larger than in the sedentary group ($p = 0.07$). These results show that chronic exercise enhances the ability of islets to secrete insulin in response to high-glucose in normal rats. Since statistically significant differences were obtained for the area under the curve from nine weeks, we chose nine weeks of exercise for the subsequent analyses.

3.2. Quantification of pancreatic insulin content

To test whether the enhancement of insulin secretion ability by exercise is due to increased insulin storage, insulin content of the pancreas was measured in rats trained for nine weeks and their sedentary counterparts. There was no significant difference in pancreatic insulin content between the sedentary and trained

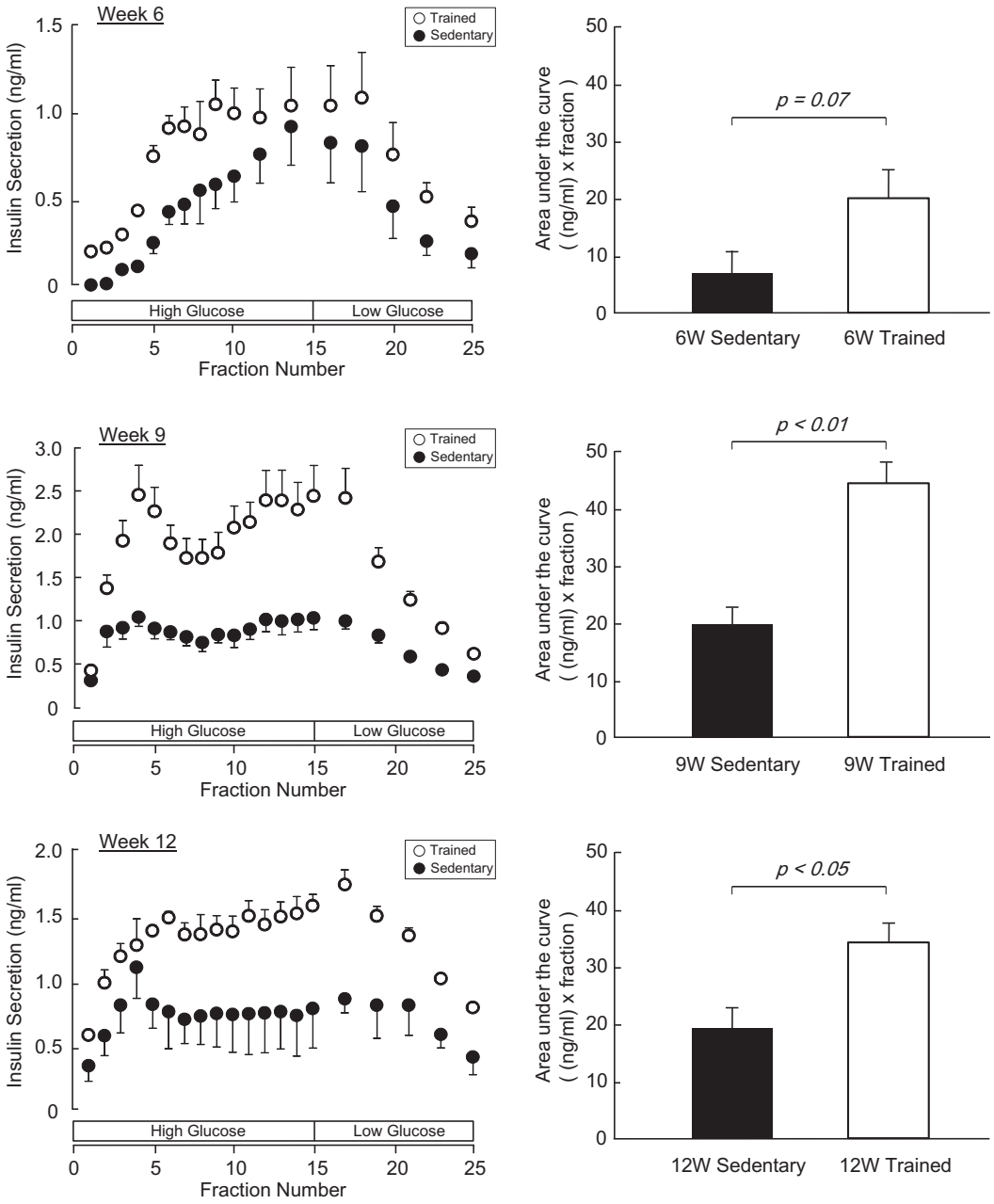

Fig. 1. (Left column) Insulin secretion by high-glucose stimulation in perfused islets. Insulin secretion was examined in islets isolated from trained rats (six, nine, or 12 weeks; open circles) and age-matched sedentary control rats (filled circles). After 30 min of stabilization by perifusion of standard low-glucose KR buffer (2.8 mM), islets were stimulated by high-glucose buffer (16.7 mM) for 15 min, followed by an additional 10 min with low-glucose buffer. Secreted insulin was measured in each fraction obtained upon the high-glucose stimulation and the subsequent low-glucose stimulation ($n = 4$, except for the control at 12 weeks ($n = 3$)). (Right column) Areas under the curve were calculated using the results of the perifusion assay for sedentary groups (filled bars) and trained groups (open bars). Data are presented as means ± SEM.

groups (Fig. 2(A)). The weight of the pancreas corrected by body weight also did not differ between the groups (Fig. 2(B)). Therefore, an increase in insulin storage by the pancreas is not the cause of exercise-enhanced insulin secretion in response to high-glucose.

3.3. Effect of chronic exercise on potassium-stimulated insulin secretion in perifused islets

Membrane depolarization of islet beta-cells is one of the critical events for insulin secretion induced by high-glucose stimulation. Once glucose is transported into the cells through GLUT2, the intracellular ATP concentration increases by the promotion of glucose oxidation. Depolarization is triggered by the closure of ATP-sensitive potassium channels (K_{ATP}), which occurs as a consequence of the increase in intracellular ATP concentration. Subsequent entry of extracellular Ca^{2+} through voltage-dependent calcium channels and an increase of cytosolic Ca^{2+} concentration produce exocytosis on insulin-containing granules and insulin secretion. Therefore, we used potassium for further investigation of the effect of chronic exercise on increased insulin secretion ability. Insulin secretion in response to potassium (30 mM) was also enhanced by nine weeks of chronic exercise (Fig. 2(C)), similarly to the case with high-glucose stimulation (Fig. 1). The area under the curve of insulin secretion was significantly larger in the trained group than in

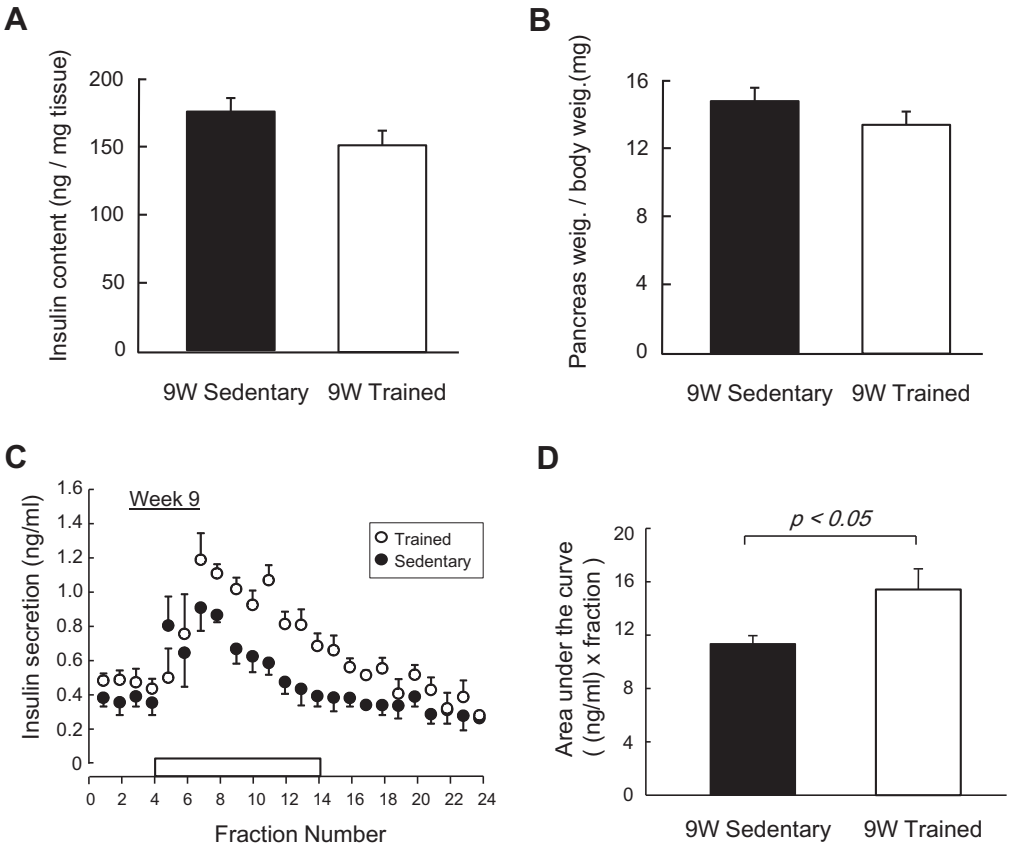

Fig. 2. Insulin content, pancreas weight, and insulin secretion by potassium stimulation in perifused islets. (A) Total insulin content in the pancreas was measured in the rat group with nine weeks of training (open bar, $n = 8$) and an age-matched sedentary rat group (filled bar, $n = 8$). (B) Weight of pancreas corrected for body weight ($n = 8$). (C) Insulin secretion by potassium stimulation in perifused islets. Insulin secretion was examined in islets isolated from rats trained for nine weeks (open circles) and age-matched sedentary control rats (filled circles). The islets were stabilized by 30 min of perifusion of standard low-glucose buffer (2.8 mM), and then stimulated using buffer containing 50 mM KCl for 10 min, followed by standard low-glucose buffer for 10 min ($n = 4$). The perifused buffer fractions were collected every minute in the last four minutes of the stabilization phase and the subsequent perifusion phase. (D) Areas under the curve were calculated using the results of the perifusion assay for sedentary group (filled bar) and trained group (open bar). Data are presented as means ± SEM ($n = 4$).

the sedentary group (Fig. 2(D)). This result indicates that enhancement of post-depolarization events is involved in the effect of exercise on high-glucose-stimulated insulin secretion.

3.4. Expression level of insulin secretion-related proteins in pancreatic islets

We also determined the effect of chronic exercise on the protein expression of key molecules that have been reported to contribute to the insulin secretion in pancreatic islets (Fig. 3). GLUT2 (glucose transport into beta-cells), Kir6.2 (a major subunit of K_{ATP}), Cav2.1 (an alpha 1A subunit of voltage-dependent calcium channel), and SNAP25, VAMP2, and syntaxin 1 (components of the SNARE complex and regulators of the exocytosis of insulin granules) were chosen for this analysis. As shown in Fig. 3, the expression levels of these molecules were not significantly different between sedentary and trained groups. Therefore, nine weeks of chronic exercise does not change the levels of expression of GLUT2, Kir6.2, Cav2.1, SNAP25, VAMP2, syntaxin 1 and these molecules can be excluded from the mechanisms of chronic exercise-enhanced insulin secretion ability in islets.

3.5. Insulin tolerance test

Blood glucose concentrations were monitored for 180 min after intraperitoneal insulin injection in rats in the eighth week of the nine-week exercise period. As shown in Fig. 4(A), eight weeks of exercise did not significantly change the level of insulin tolerance. This result suggests that the enhancement of the insulin secretion ability of pancreatic islets could be generated earlier than the peripheral adaptation in terms of insulin tolerance. Chronic exercise did not significantly change body weight (Fig. 4(B)), fed blood glucose level (Fig. 4(C)), and food intake (Fig. 4(D)) in the eighth week of the exercise period.

4. Discussion

In the current study, it has been clearly shown that chronic exercise training significantly enhances the insulin secretion ability of pancreatic islets upon high-glucose stimulation in normal non-diabetic rats. The insulin secretion of isolated islets determined by perifusion assay tended to increase upon six weeks of treadmill running, and significantly increased upon nine and 12 weeks of exercise. This effect of exercise was observed without changes in the total amount of pancreatic insulin and the weight of the pancreas, suggesting that an increase in the insulin content of islets does not contribute to the enhancement of insulin secretion ability upon exposure to a high concentration of glucose. Although the expression levels of some proteins that are considered to regulate insulin secretion, namely, GLUT2, Kir6.2, Cav2.1, and SNAP25, VAMP2, and syntaxin 1, were quantified by immunoblotting, no increase in protein level could be found. However, enhancement of potassium-stimulated insulin secretion was

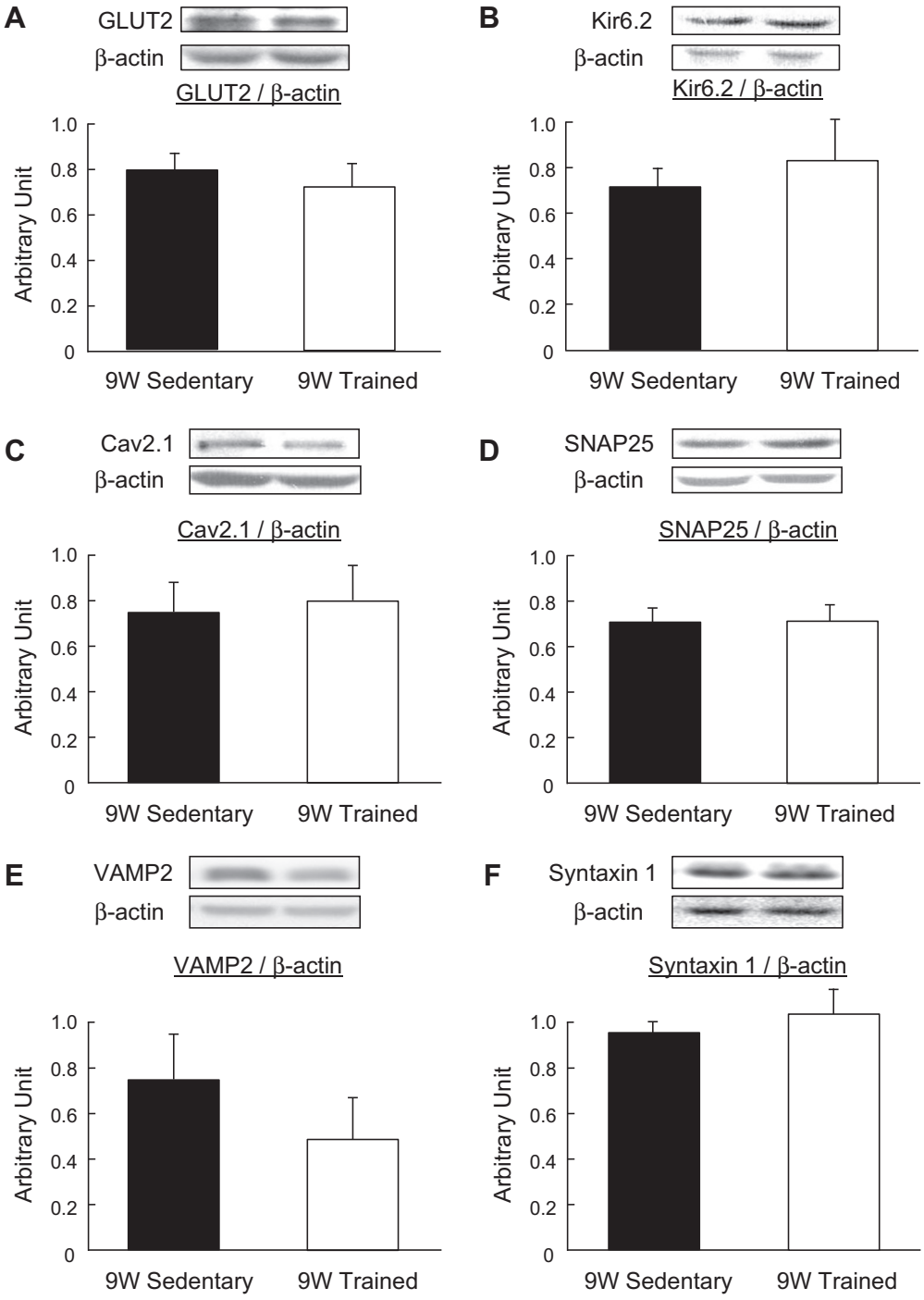

Fig. 3. Immunoblotting of islet lysates from rats trained for nine weeks (open bars, $n = 4$) and age-matched sedentary rats (filled bar, $n = 4$). Quantification of (A) GLUT2, (B) Kir6.2, (C) Cav2.1, (D) SNAP25, (E) VAMP2, (F) syntaxin 1 is displayed. Representative immunoblots of these proteins are shown above the bar graphs. Data are presented as means ± SEM.

concomitantly observed in the islets isolated from the trained rats, the same as with the high-glucose-stimulated insulin secretion, so it is possible that insulin secretion events downstream of membrane depolarization are sensitized by chronic exercise.

To the best of our knowledge, this is the first report to show the effect of chronic running exercise (treadmill running exercise, one hour per day, five days per week, nine or 12 weeks in total) on enhancement of the insulin secretion ability of pancreatic islets by the perifusion method in normal rats. This result suggests that the generally observed hypoinsulinemia induced by chronic exercise training is not due to decreased insulin sensitivity of beta-cells against glucose. Rather, the presence of feedback regulation from increased insulin sensitivity of peripheral tissues can be supposed. Indeed, Farrell et al. observed increased insulin secretion of islets perifused by high-glucose buffer in trained normal rats, although the exercise that they adopted involved hindlimb resistance exercise for four days [11]. In contrast, two previous studies reported a negative effect of chronic exercise on insulin secretion ability with exercise training, by using the islet perifusion method in normal rats [5,6]. Specifically, in 1981, Galbo et al. observed that

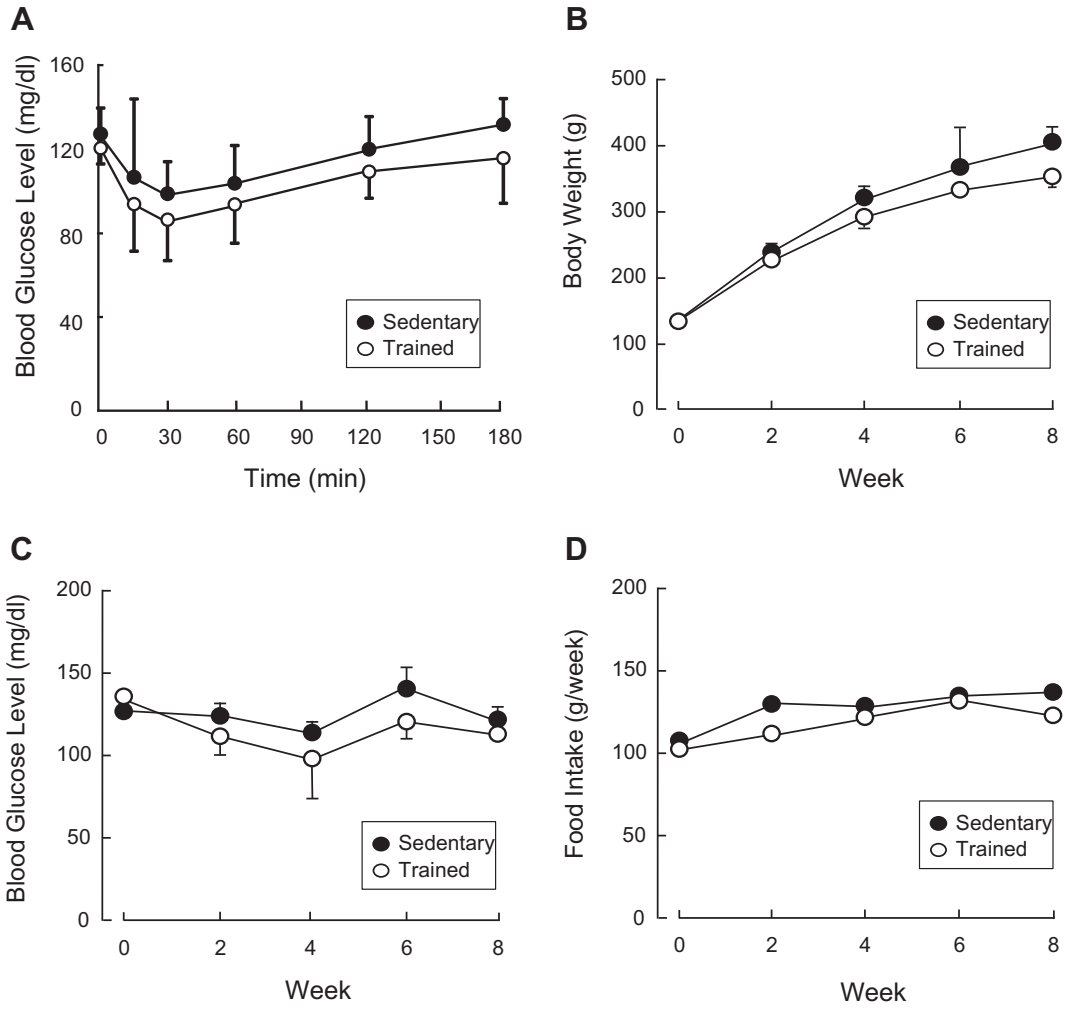

Fig. 4. Insulin tolerance test (ITT) and basic physiological parameters. (A) ITT was performed in the eighth week of the experiment in the rats trained for nine weeks (open circles) and age-matched sedentary rats (filled circles). Blood glucose level was measured at time points 0, 15, 30, 60, 120, and 180 min after the insulin injection. No significant difference was observed between the two groups at each point ($n = 8$). Changes in (B) body weight, (C) blood glucose, and (D) food intake in rats trained for nine weeks (open circles, $n = 8$) and age-matched sedentary rats (filled circles, $n = 8$). Data are presented as means ± SEM.

swimming training (five days per week, for a total of 12 weeks; the swimming time per day was gradually increased, until after the eighth week, when the rats swam for six hours a day) lowered the rate of insulin release from perifused islets with several doses of glucose [5]. Similarly, in 1982, Zawalich et al. found a decrease of insulin release by 40–50% by free-access wheel cage exercise (4–6 miles/day, total 36 ± 4 days) [6]. In these two reports, it was hypothesized that hypoinsulinemia induced by exercise training is due to a decrease in the insulin sensitivity of beta-cells against glucose. We do not have any solid evidence to explain the different results between the current study and these previous works. However, these discrepancies may be due to differences in the duration of exercise training sessions and/or the type of exercise employed. It may also be worth considering the potential effects of the progression in islet perifusion methodology and the improvement in sensitivity of insulin measurement over recent decades.

Although the mechanism by which exercise affects the insulin secretion ability of islets is unclear given these past reports, the importance of physical exercise for the management of blood glucose in type 1 diabetes has been suggested since the 1950s [20]. In a randomized study of type 1 diabetic subjects, attendance of an exercise program, one or three times per week, for six months, significantly reduced the glycosylated hemoglobin (HbA1c) and insulin requirements [21]. Moreover, a cross-sectional study of over 19,000 children with type 1 diabetes showed that regular physical activity is one of the most important factors influencing HbA1c [22]. In fact, using the insulin-clamp method, several groups have observed that exercise training partially improves diminished insulin secretion in pancreatectomized rats *in vivo* [11,13,14]. Additionally, Huang et al. recently reported that impaired insulin secretion of isolated islets from streptozotocin (a toxin to islet beta-cells)-treated type 1 diabetic rats evaluated by static incubation of the beta-cells was partially, but significantly, improved by six weeks of voluntary running exercise in a wheel cage in basal conditions (i.e. in the presence of low-glucose) [17]. Unfortunately, no observation has directly indicated the role of exercise in dysfunctional islets in the current study. Therefore, it would be interesting to adapt our chronic exercise protocol and islet perifusion assay for use with diabetic rats in future.

It has been demonstrated that glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin secretion and lowers blood glucose in patients with diabetes [23]. Recently, Ellingsgaard et al. showed that interleukin-6 (IL-6) is an important mediator of the effect of GLP-1 on insulin secretion [24]. They demonstrated that IL-6 mediates an increase in GLP-1 secretion from the intestinal L cells and the pancreatic alpha-cells, which leads to improvement of beta-cell function, insulin secretion, and blood glucose control. Since it has been proposed that IL-6 increases whole-body

insulin sensitivity [25] and IL-6 is one of the most recognized myokines the concentration in the circulation of which is elevated by exercise [26], the IL-6 and GLP-1 axis can be a network that connects exercise and islet function. In fact, their report confirmed that treadmill running increases plasma GLP-1 level the same as the plasma IL-6 level in wild-type mice, and the increase in plasma GLP-1 level is inhibited in IL-6-deficient mice [24]. Moreover, it may be possible to determine the exercise training type, period, frequency, and/or intensity that enhance islet function in terms of secreting insulin by monitoring plasma IL-6 and GLP-1 levels. Therefore, further investigations are anticipated to elucidate the mechanism behind the exercise-mediated effect on islet function.

In conclusion, we showed in the current study that chronic exercise enhances the insulin secretion ability of islets upon high glucose stimulation evaluated by perifusion analysis in normal rats. This enhancement is accompanied by an increase in insulin secretion induced by potassium stimulation, suggesting that events downstream of membrane depolarization are involved in the mechanism. These results suggest the possibility of using exercise as a preventive strategy not only to maintain peripheral insulin sensitivity, which has been well confirmed by various approaches, but also to promote the function of islets to secrete insulin.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science (KAKENHI 21700657 to Y.M. and KAKENHI 21240063 to N.L.F.) and by the Cabinet Office, Government of Japan (Funding Program for Next Generation World-Leading Researchers LS102 to N.L.F.).

References

[1] L.J. Goodyear, B.B. Kahn, Exercise, glucose transport, and insulin sensitivity, Annu. Rev. Med. 49 (1998) 235–261.
[2] J.R. Zierath, Invited review: exercise training-induced changes in insulin signaling in skeletal muscle, J. Appl. Physiol. 93 (2002) 773–781.
[3] T.E. Jensen, E.A. Richter, Regulation of glucose and glycogen metabolism during and after exercise, J. Physiol. 590 (2012) 1069–1076.
[4] J. Lamontagne, P. Masiello, M. Marcil, V. Delghingaro-Augusto, Y. Burelle, M. Prentki, C.J. Nolan, Circulating lipids are lowered but pancreatic islet lipid metabolism and insulin secretion are unaltered in exercise-trained female rats, Appl. Physiol. Nutr. Metab. 32 (2007) 241–248.
[5] H. Galbo, C.J. Hedeskov, K. Capito, J. Vinten, The effect of physical training on insulin secretion of rat pancreatic islets, Acta Physiol. Scand. 111 (1981) 75–79.
[6] W. Zawalich, S. Maturo, P. Felig, Influence of physical training on insulin release and glucose utilization by islet cells and liver glucokinase activity in the rat, Am. J. Physiol. 243 (1982) E464–E469.
[7] P.A. Farrell, Decreased insulin response to sustained hyperglycemia in exercise-trained rats, Med. Sci. Sports Exercise 20 (1988) 469–473.
[8] P.A. Farrell, A.L. Caston, D. Rodd, J. Engdahl, Effect of training on insulin secretion from single pancreatic beta cells, Med. Sci. Sports Exercise 24 (1992) 426–433.
[9] V.C. Calegari, C.C. Zoppi, L.F. Rezende, L.R. Silveira, E.M. Carneiro, A.C. Boschero, Endurance training activates AMP-activated protein kinase, increases expression of uncoupling protein 2 and reduces insulin secretion from rat pancreatic islets, J. Endocrinol. 208 (2011) 257–264.
[10] C.C. Zoppi, V.C. Calegari, L.R. Silveira, E.M. Carneiro, A.C. Boschero, Exercise training enhances rat pancreatic islets anaplerotic enzymes content despite reduced insulin secretion, Eur. J. Appl. Physiol. 111 (2011) 2369–2374.
[11] P.A. Farrell, A.L. Caston, D. Rodd, Changes in insulin response to glucose after exercise training in partially pancreatectomized rats, J. Appl. Physiol. 70 (1991) 1563–1568.
[12] J.D. Fluckey, W.J. Kraemer, P.A. Farrell, Pancreatic islet insulin secretion is increased after resistance exercise in rats, J. Appl. Physiol. 79 (1995) 1100–1105.
[13] S. Park, S.M. Hong, J.E. Lee, S.R. Sung, Exercise improves glucose homeostasis that has been impaired by a high-fat diet by potentiating pancreatic beta-cell function and mass through IRS2 in diabetic rats, J. Appl. Physiol. 103 (2007) 1764–1771.
[14] S. Park, S.M. Hong, S.R. Sung, Exendin-4 and exercise promotes beta-cell function and mass through IRS2 induction in islets of diabetic rats, Life Sci. 82 (2008) 503–511.
[15] C.A. Oliveira, M.F. Paiva, C.A. Mota, C. Ribeiro, J.A. Leme, E. Luciano, M.A. Mello, Exercise at anaerobic threshold intensity and insulin secretion by isolated pancreatic islets of rats, Islets 2 (2010) 240–246.
[16] V. Delghingaro-Augusto, S. Decary, M.L. Peyot, M.G. Latour, J. Lamontagne, N. Paradis-Isler, M. Lacharite-Lemieux, H. Akakpo, O. Birot, C.J. Nolan, M. Prentki, R. Bergeron, Voluntary running exercise prevents beta-cell failure in susceptible islets of the Zucker diabetic fatty rat, Am. J. Physiol. Endocrinol. Metab. 302 (2012) E254–E264.
[17] H.H. Huang, K. Farmer, J. Windscheffel, K. Yost, M. Power, D.E. Wright, L. Stehno-Bittel, Exercise increases insulin content and basal secretion in pancreatic islets in type 1 diabetic mice, Exp. Diabetes Res. 2011 (2011) 481427.
[18] K. Jain, J. Logothetopoulos, Secretion of insulin in a perifusion system and conversion of proinsulin to insulin by pancreatic islets from hyperglycemic rats, Diabetes 26 (1977) 650–656.
[19] T. Izumi, H. Yokota-Hashimoto, S. Zhao, J. Wang, P.A. Halban, T. Takeuchi, Dominant negative pathogenesis by mutant proinsulin in the Akita diabetic mouse, Diabetes 52 (2003) 409–416.
[20] K. Robertson, P. Adolfsson, G. Scheiner, R. Hanas, M.C. Riddell, Exercise in children and adolescents with diabetes, Pediatr. Diabetes 10 (Suppl. 12) (2009) 154–168.
[21] M.A. Salem, M.A. Aboelasrar, N.S. Elbarbary, R.A. Elhilaly, Y.M. Refaat, Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial, Diabetol. Metab. Syndr. 2 (2010) 47.
[22] A. Herbst, R. Bachran, T. Kapellen, R.W. Holl, Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus, Arch. Pediatr. Adolesc. Med. 160 (2006) 573–577.
[23] D.J. Drucker, Development of glucagon-like peptide-1-based pharmaceuticals as therapeutic agents for the treatment of diabetes, Curr. Pharm. Des. 7 (2001) 1399–1412.
[24] H. Ellingsgaard, I. Hauselmann, B. Schuler, A.M. Habib, L.L. Baggio, D.T. Meier, E. Eppler, K. Bouzakri, S. Wueest, Y.D. Muller, A.M. Hansen, M. Reinecke, D. Konrad, M. Gassmann, F. Reimann, P.A. Halban, J. Gromada, D.J. Drucker, F.M. Gribble, J.A. Ehses, M.Y. Donath, Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells, Nat. Med. 17 (2011) 1481–1489.
[25] A.L. Carey, G.R. Steinberg, S.L. Macaulay, W.G. Thomas, A.G. Holmes, G. Ramm, O. Prelovsek, C. Hohnen-Behrens, M.J. Watt, D.E. James, B.E. Kemp, B.K. Pedersen, M.A. Febbraio, Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase, Diabetes 55 (2006) 2688–2697.
[26] B.K. Pedersen, M.A. Febbraio, Muscle as an endocrine organ: focus on muscle-derived interleukin-6, Physiol. Rev. 88 (2008) 1379–1406.