Possible mechanisms underlying wheel-running-induced hypotensive effects

Susumu Sakata^{1*}, Akira Nakatani² and Hidefumi Waki³

¹ Graduate School of Health Science, Kio University, 4-2-2 Umami-naka, Koryo-cho, Kitakatsuragi-gun, Nara 635-0832, Japan

² Nara University of Education, Takabatake-cho, Nara, Nara 630-8528, Japan

³ Graduate School of Health and Sports Science, Juntendo University, 1-1 Hiraga-gakuendai, Inzai, Chiba 270-1695, Japan

Received: August 29, 2014 / Accepted: September 11, 2014

Abstract Physical activity of moderate intensity, like walking and jogging, can reduce the risk of developing metabolic syndrome and improve hypertension. However, such anti-hypertensive effects have yet to be fully studied. To explore the mechanisms underlying exercise-induced hypotensive effects, normotensive or hypertensive rats were subjected to voluntary wheel-running exercise. In consequence, daily wheel-running exercise appears to decrease resting blood pressure by multiple mechanisms. This short review focuses on possible mechanisms underlying the hypotensive effects of wheel-running exercise, i.e., hormonal control, nitric oxide control, sympathetic nervous control and central control in resting blood pressure regulation. To conclude, a voluntary wheel-running exercise-induced reduction in resting blood pressure may be accomplished via multiple mechanisms, i.e., a combination of 1) attenuated vasoconstriction by hormones, 2) hormone-induced reduction in blood volume, 3) hormone- and/or NO-induced vasodilation, and 4) diminished sympathetic nervous activity by body weight loss / less body weight gain, lower leptin levels and/or downregulation of serotonin 1A receptor gene in the nucleus tractus solitarii.

Keywords : wheel-running, blood pressure, hormone, nitric oxide, sympathetic nervous activity, nucleus tractus solitarii

Introduction

Obesity is considered as a major risk factor for metabolic syndrome, which is associated with an increased risk of developing type 2 diabetes mellitus and atherosclerotic cardiovascular disease^{1,2}. In addition to abdominal obesity, elevated blood pressure (BP), atherogenic dyslipidemia and elevated fasting blood glucose are widely regarded as possible risk factors for metabolic syndrome^{3,4}. Epidemiological human studies revealed that physical activity of moderate intensity, like walking, jogging and bicycling, can reduce not only the risk of developing metabolic syndrome, but also high BP⁵⁻⁷. In fact, moderate-intensity exercise equivalent to half maximum oxygen consumption was reported to lower resting BP in both normotensive and hypertensive individuals^{5,7-9}. However, such hypotensive effects of moderate-intensity exercise have not been fully studied as yet. Using cages equipped with a running wheel, likewise, the reducible effects of voluntary wheel-running (WR) on resting BP were reported in middle-aged normal fat rats¹⁰, spontaneously hypertensive rats (SHRs)¹¹⁻¹⁴ and transgenic rats that harbor a mouse Ren-2 renin gene (TG(mREN2)27)¹⁵.

In view of these studies, this short review focuses on possible mechanisms underlying the hypotensive effects of WR exercise, i.e., hormonal control, nitric oxide control, sympathetic nervous control and nucleus tractus solitarii (NTS) control in resting BP regulation.

Hormonal control of resting blood pressure in wheel-running rats

The renin-angiotensin system (RAS) is well-known for playing a major role in the control of resting BPs. Angiotensin II increases BP both by constricting peripheral vessels and by directly stimulating adrenal production of aldosterone. Voluntary WR for 10 weeks was found to prevent an increase in plasma angiotensin II and attenuate the elevation of systolic BP in young SHRs¹³. Similarly, we found that 3 week-WR rats show a significantly lower level of serum angiotensin II compared to sedentary rats, and have a significantly decreased systolic/diastolic BP at rest¹⁰. These WR rats showed a decrease in body weight (BW), waist circumference, mesenteric fat mass and adipocyte size, as compared with the control sedentary rats¹⁰. In adipose tissue of rats, angiotensinogen messenger RNA was identified and angiotensinogen was produced^{16,17}. Further, systolic BP was modulated by fasting and refeed-

*Correspondence: s.sakata@kio.ac.jp

ing parallel to adipocyte angiotensinogen expression¹⁷⁾. Moreover, in mice with targeted overexpression of angiotensinogen in adipose tissue¹⁸⁾ and with a deficiency of endogenous angiotensinogen in adipocytes¹⁹⁾, adipocyte-derived angiotensinogen was demonstrated to contribute to systemic angiotensinogen concentrations and BP control. Based on these results, it is conceivable that adipocyte-derived angiotensinogen plays an important role in controlling resting blood pressure not only in normal, but also in exercise physiology.

In addition to angiotensin II, our WR rat serum showed lower concentrations of aldosterone, endothelin-1 and vasopressin, and higher concentrations of brain natriuretic peptide (BNP), as compared with the sedentary rat serum¹⁰⁾. Thus, the voluntary WR for 3 weeks altered the circulating levels of several BP-related hormones, which play pivotal roles in controlling BP. Vasopressin and endothelin-1, like angiotensin II, are well-known as potent vasoconstrictors that contribute to hypertension. On the other hand, aldosterone and vasopressin promote the body's retention of water and increase the blood volume, resulting in hypertension. Moreover, BNP with natriuretic effect is well-known to cause not only a reduction in blood volume, but also vasodilation, and, consequently, to lower systemic BP. In view of these results, it seems most likely that resting BP lowered by WR exercise is attributable mainly to both vasodilatation and a reduction in blood volume, which would be induced by changed concentrations of these circulating hormones, as shown in Table 1.

Nitric oxide control of resting blood pressure in wheel-running rats

It is well known that vasodilation is induced not only by hormones, but also by endothelial nitric oxide (NO) formation. In rats^{20,21)} and humans²²⁾, short-term running on a

treadmill or acute physical exercise was reported to stimulate the formation of endothelial NO, resulting in reduced BP. In addition, endothelial NO synthase (eNOS) mRNA and protein expression were elevated in rats with exercise training on the treadmill²³⁾. Voluntary WR, as well as treadmill running, was found to increase NO formation and to decrease plasma angiotensin II concentration, and consequently attenuated the elevation of systolic BP in SHR¹³⁾. Further, positive immunostaining for phospho-specific eNOS in cross sections of white gastrocnemius muscle was increased in Otsuka Long-Evans Tokushima Fatty (OLETF) rats with voluntary WR²⁴⁾. Thus, a WR-induced reduction in resting BP appears to be ascribable in part to peripheral vascular resistance decreased by enhanced endothelium-dependent vasodilation, which is mediated via the NO signaling pathway.

Sympathetic nervous control of resting blood pressure in wheel-running rats

In standard chow-fed¹⁰⁾ and high-fat diet-fed rats²⁵⁾, and hyperphagic OLETF rats²⁶⁾, voluntary WR caused a gradual loss or less gain in BW during the exercise period, presumably, resulting from a significant reduction in visceral and subcutaneous fat pad mass. In addition, the mRNA expression of adipokine leptin was significantly decreased in adipose tissue by WR exercise^{25,27)} and, consequently, serum leptin concentrations were lowered in the WR rats^{10,25-27)}. There was a fairly good positive correlation between leptin protein^{25,27)} or mRNA expression²⁵⁾ and fat pad mass.

In humans, BW gain-induced sympathetic nervous activation was reported to be tightly linked to BW gain-induced BP elevation²⁸⁾. In reverse, therefore, the BW loss or less BW gain caused by the WR exercise might have lowered resting BP through diminished sympathetic nervous activity (SNA). In fact, the reduction both in rest-

Table 1. Circulating hormone levels in rats with voluntary wheel-running exercise

Hormone	Physiological action	Circulating levels
Angiotensin II	Vasoconstriction Aldosterone production	↓
Endothelin-1	Vasoconstriction	↓
Vasopressin	Vasoconstriction Increase in blood volume	↓
Aldosterone	Increase in blood volume	↓
Brain natriuretic peptide	Vasodilation Decrease in blood volume	↑

ing BP and in plasma norepinephrine concentrations that reflect SNA were found in patients with essential hypertension who were subjected to moderate-intensity aerobic exercise therapy for 10 or 20 weeks^{8,9}. In SHR, moreover, moderate-intensity exercise training on a treadmill for 12-18 weeks decreased the heart rate (HR) and cardiac output and, consequently, lowered the resting BP^{29,30}.

In Sprague-Dawley rats, on the other hand, acute intravenous infusion of leptin increased SNA to the kidney, hindlimb and adrenal gland³¹, and, furthermore, chronic leptin infusion induced sustained increases in HR and mean arterial pressure³². Therefore, lowered serum leptin levels in the WR rats^{10,25-27} might have caused the fall in resting BP by decreased SNA. Thus, in obese animals and humans with hypertension, leptin may play a crucial role not only in energy expenditure but also in cardiovascular regulation via the sympathetic nervous system.

Nucleus tractus solitarius control of resting blood pressure in wheel-running rats

The basal level of SNA is also regulated by the baroreceptor reflex, which is a fundamental mechanism to maintain cardiovascular homeostasis. Laterza et al.³³ recently demonstrated that a decrease in basal SNA through exercise training in patients with hypertension is likely mediated by an improved baroreceptor reflex. In the case of an animal model of hypertension, Moraes-Silva et al.³⁴ also demonstrated that treadmill exercise training reduced the basal level of SNA and improved the baroreceptor reflex function to levels similar to those of normotensive animals. Although it remains unknown whether WR exercise in hypertensive rats alters the baroreflex function, we predict that the training-induced hypotensive effects in WR animals may also be mediated, at least in part, by an improved baroreceptor reflex³⁵.

The NTS is the central termination site for baroreceptor input. The NTS also receives numerous inputs from other brain areas which are related to the central command³⁶⁻³⁸ and projections from spinal dorsal horn neurons, which transmit afferent inputs from skeletal muscle³⁹. Therefore, it is considered to be a central site that integrates descending and ascending inputs while regulating baroreceptor function during exercise. This suggests that the NTS is likely to be one of the cardiovascular centers where functional and neuroanatomical plasticity occurs by exercise training. The potential neural mechanisms underlying the exercise training-induced hypotensive effects are discussed in our recent review³⁵. In short, our data from the microarray study demonstrated that WR exercise training in SHR altered the expression levels of the serotonin 5-hydroxytryptamine_{1A} (5-HT_{1A}) receptor gene³⁵ in the NTS. We confirmed that serotonin microinjected into the NTS decreases BP and HR as previously reported⁴⁰. The depressor and bradycardia responses are known to be mediated mainly by the 5-HT_{2A} receptor, which is a

Gq/G11-protein coupled receptor that induces excitatory neurotransmission and may be expressed in barosensitive second-order (or higher order) neurons in the NTS⁴⁰. On the other hand, it has been reported that the 5-HT_{1A} receptor mediates inhibitory neurotransmission through activation of the Gi/Go proteins. Moreover, it may act as an autoreceptor⁴¹. Considering the 5-HT_{1A} receptor counteracts the actions of the 5-HT_{2A} receptor, we hypothesized that downregulation of 5-HT_{1A} receptors in the NTS may potentiate the serotonergic effects in the NTS and participate in the central mechanism of the anti-hypertensive effects of exercise³⁵, although further investigation is required to confirm this hypothesis.

Conclusion

In rats, a voluntary WR exercise-induced reduction in resting BP may be accomplished via multiple mechanisms, i.e., a combination of attenuated vasoconstriction by hormones, hormone-induced reduction in blood volume, hormone- and/or NO-induced vasodilation, and diminished SNA by BW loss/less BW gain, lower leptin levels and/or downregulation of serotonin 1A receptor gene in the NTS.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Acknowledgments

This work was supported in part by Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS) (20590215 and 24590290 to S. Sakata).

References

- 1) Kahn SE, Hull RL and Utzschneider KM. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 444: 840-846.
- 2) Van Gaal LF, Mertens IL and De Block CE. 2006. Mechanisms linking obesity with cardiovascular disease. *Nature* 444: 875-880.
- 3) Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA and Costa F. 2005. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112: 2735-2752.
- 4) National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). 2001. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 285: 2486-2497.
- 5) Bassuk SS and Manson JE. 2005. Epidemiological evidence

- for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol* 99: 1193-1204.
- 6) Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE and Manson JE. 1999. Walking compared with vigorous physical activity and risk of type 2 diabetes in women. A prospective study. *JAMA* 282: 1433-1439.
 - 7) Jennings G, Nelson L, Nestel P, Esler M, Korner P, Burton D and Bazelmans J. 1986. The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. *Circulation* 73: 30-40.
 - 8) Kiyonaga A, Arakawa K, Tanaka H and Shindo M. 1985. Blood pressure and hormonal responses to aerobic exercise. *Hypertension* 7: 125-131.
 - 9) Urata H, Tanabe Y, Kiyonaga A, Ikeda M, Tanaka H, Shindo M and Arakawa K. 1987. Antihypertensive and volume-depleting effects of mild exercise on essential hypertension. *Hypertension* 9: 245-252.
 - 10) Sakata S, Hanaoka T, Ishizawa R, Iwami K, Imagita H, Mine-matsu A, Waki H and Nakatani A. Voluntary wheel-running exercise decreases blood pressure through hormonal control and increases endurance exercise capacity in middle-aged normal fat rats. (*Submitted*)
 - 11) Overton JM, Tipton CM, Matthes RD and Leininger JR. 1986. Voluntary exercise and its effects on young SHR and stroke-prone hypertensive rats. *J Appl Physiol* 61: 318-324.
 - 12) LaPier TLK, Swislocki ALM, Clark RJ and Rodnick KJ. 2001. Voluntary running improves glucose tolerance and insulin resistance in female spontaneously hypertensive rats. *Am J Hypertens* 14: 708-715.
 - 13) Kohno H, Furukawa S, Naito H, Minamitani K, Ohmori D and Yamakura F. 2002. Contribution of nitric oxide, angiotensin II and superoxide dismutase to exercise-induced attenuation of blood pressure elevation in spontaneously hypertensive rats. *Jpn Heart J* 43: 25-34.
 - 14) Waki H, Gouraud SS, Bhuiyan MER, Takagishi M, Yamazaki T, Kohsaka A and Maeda M. 2013. Transcriptome of the NTS in exercise-trained spontaneously hypertensive rats: implications for NTS function and plasticity in regulating blood pressure. *Physiol Genomics* 45: 58-67.
 - 15) Kinnick TR, Youngblood EB, O'keefe MP, Saengsirisuwan V, Teachey MK and Henriksen EJ. 2002. Selected contribution: modulation of insulin resistance and hypertension by voluntary exercise training in the TG(mREN2)27 rat. *J Appl Physiol* 93: 805-812.
 - 16) Campbell DJ and Habener JF. 1987. Cellular localization of angiotensinogen gene expression in brown adipose tissue and mesentery: quantification of messenger ribonucleic acid abundance using hybridization in situ. *Endocrinology* 121: 1616-1626.
 - 17) Frederich RC, Kahn BB, Peach MJ and Flier JS. 1992. Tissue-specific nutritional regulation of angiotensinogen in adipose tissue. *Hypertension* 19: 339-344.
 - 18) Massiera F, Bloch-Faure M, Ceiler D, Murakami K, Fukamizu A, Gasc J-M, Quignard-Boulange A, Negrel R, Ailhaud G, Seydoux J, Meneton P and Teboul M. 2001. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. *FASEB J* 15: 2727-2729.
 - 19) Yiannikouris F, Karounos M, Charnigo R, English VL, Rateri DL, Daugherty A and Cassis LA. 2012. Adipocyte-specific deficiency of angiotensinogen decreases plasma angiotensinogen concentration and systolic blood pressure in mice. *Am J Physiol Regul Integr Comp Physiol* 302: R244-R251.
 - 20) Sun D, Huang A, Koller A and Kaley G. 1994. Short-term daily exercise activity enhances endothelial NO synthesis in skeletal muscle arterioles of rats. *J Appl Physiol* 76: 2241-2247.
 - 21) Sun MW, Qian FL, Wang J, Tao T, Guo J, Wang L, Lu AY and Chen H. 2008. Low-intensity voluntary running lowers blood pressure with simultaneous improvement in endothelium-dependent vasodilatation and insulin sensitivity in aged spontaneously hypertensive rats. *Hypertens Res* 31: 543-552.
 - 22) Jungersten L, Ambring A, Wall B and Wennmalm A. 1997. Both physical fitness and acute exercise regulate nitric oxide formation in healthy humans. *J Appl Physiol* 82: 760-764.
 - 23) Spier SA, Delp MD, Meininger CJ, Donato AJ, Ramsey MW and Muller-Delp JM. 2004. Effects of ageing and exercise training on endothelium-dependent vasodilatation and structure of rat skeletal muscle arterioles. *J Physiol* 556: 947-958.
 - 24) Mikus CR, Rector RS, Arce-Esquivel AA, Libla JL, Booth FW, Ibdah JA, Laughlin MH and Thyfault JP. 2010. Daily physical activity enhances reactivity to insulin in skeletal muscle arterioles of hyperphagic Otsuka Long-Evans Tokushima Fatty rats. *J Appl Physiol* 109: 1203-1210.
 - 25) Gollisch KSC, Brandauer J, Jessen N, Toyoda T, Nayer A, Hirshman MF and Goodyear LJ. 2009. Effects of exercise training on subcutaneous and visceral adipose tissue in normal- and high-fat diet-fed rats. *Am J Physiol Endocrinol Metab* 297: E495-E504.
 - 26) Laye MJ, Rector RS, Warner SO, Naples SP, Perretta AL, Uptergrove GM, Laughlin MH, Thyfault JP, Booth FW and Ibdah JA. 2009. Changes in visceral adipose tissue mitochondrial content with type 2 diabetes and daily voluntary wheel running in OLETF rats. *J Physiol* 587: 3729-3739.
 - 27) Zachwieja JJ, Hendry SL, Smith SR and Harris RBS. 1997. Voluntary wheel running decreases adipose tissue mass and expression of leptin mRNA in Osborne-Mendel rats. *Diabetes* 46: 1159-1166.
 - 28) Masuo K, Mikami H, Ogihara T and Tuck ML. 2000. Weight gain-induced blood pressure elevation. *Hypertension* 35: 1135-1140.
 - 29) Tipton CM, Sebastian LA, Overton JM, Woodman CR and Williams SB. 1991. Chronic exercise and its hemodynamic influences on resting blood pressure of hypertensive rats. *J Appl Physiol* 71: 2206-2210.
 - 30) Veras-silva AS, Mattos KC, Gava NS, Brum PC, Negrao CE and Krieger EM. 1997. Low-intensity exercise training decreases cardiac output and hypertension in spontaneously hypertensive rats. *Am J Physiol* 273: H2627-H2631.
 - 31) Haynes WG, Sivitz WI, Morgan DA, Walsh SA and Mark AL. 1997. Sympathetic and cardiorenal actions of leptin. *Hypertension* 30: 619-623.
 - 32) Shek EW, Brands MW and Hall JE. 1998. Chronic leptin infusion increases arterial pressure. *Hypertension* 31: 409-414.
 - 33) Laterza MC, de Matos LD, Trombetta IC, Braga AM, Roveda F, Alves MJ, Krieger EM, Negrao CE and Rondon MU. 2007. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension* 49: 1298-1306.
 - 34) Moraes-Silva IC, De La Fuente RN, Mostarda C, Rosa K, Flues K, Damaceno-Rodrigues NR, Caldini EG, De Angelis

- K, Krieger EM and Irigoyen MC. 2010. Baroreflex deficit blunts exercise training-induced cardiovascular and autonomic adaptations in hypertensive rats. *Clin Exp Pharmacol Physiol* 37: e114-e120.
- 35) Waki H, Takagishi M and Gouraud SS. 2014. Central mechanisms underlying anti-hypertensive effects of exercise training. *J Phys Fitness Sports Med* 3: 317-325.
- 36) Dampney RA, Horiuchi J and McDowall LM. 2008. Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour. *Auton Neurosci* 142: 3-10.
- 37) Matsukawa K. 2012. Central command: control of cardiac sympathetic and vagal efferent nerve activity and the arterial baroreflex during spontaneous motor behaviour in animals. *Exp Physiol* 97: 20-28.
- 38) Michelini LC and Stern JE. 2009. Exercise-induced neuronal plasticity in central autonomic networks: role in cardiovascular control. *Exp Physiol* 94: 947-960.
- 39) Potts JT. 2006. Inhibitory neurotransmission in the nucleus tractus solitarius: implications for baroreflex resetting during exercise. *Exp Physiol* 91: 59-72.
- 40) Raul L. 2003. Serotonin₂ receptors in the nucleus tractus solitarius: characterization and role in the baroreceptor reflex arc. *Cell Mol Neurobiol* 23: 709-726.
- 41) Hjorth S, Bengtsson HJ, Kullberg A, Carlzon D, Peilot H and Auerbach SB. 2000. Serotonin autoreceptor function and antidepressant drug action. *J Psychopharmacol* 14: 177-185.