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Improvement of vascular insulin sensitivity by downregulation of GRK2 mediates exercise-induced alleviation of hypertension in spontaneously hypertensive rats

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Xing W, Li Y, Zhang H, Mi C, Hou Z, Quon MJ, Gao F. Improvement of vascular insulin sensitivity by downregulation of GRK2 mediates exercise-induced alleviation of hypertension in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 305: H1111–H1119, 2013. First published August 2, 2013; doi:10.1152/ajpheart.00290.2013.—Exercise training lowers blood pressure and is a recommended nonpharmacological strategy and useful adjunctive therapy for hypertensive patients. Studies demonstrate that physical activity attenuates progression of hypertension. However, underlying mechanisms remain elusive. Vascular insulin resistance and endothelial dysfunction plays a critical role in the development of hypertension. The present study investigated whether long-term physical exercise starting during the prehypertensive period prevents the development of hypertension via improving vascular insulin sensitivity. Young (4 wk old) prehypertensive spontaneously hypertensive rats (SHRs) and their normotensive Wistar-Kyoto (WKY) control rats were subjected to a 10-wk free-of-loading swim training session (60 min/day, 5 days/wk). Blood pressure, mesenteric arteriolar vasorelaxation, G protein-coupled receptor kinase-2 (GRK2) expression and activity, and insulin-stimulated Akt/endothelial nitric oxide synthase (eNOS) activation were determined. SHRs had higher systolic blood pressure, systemic insulin resistance, and impaired vasodilator actions of insulin in resistance vessels when compared with WKY rats. Systolic blood pressure in SHRs postexercise was significantly lower than that in sedentary rats. Vascular insulin sensitivity in mesenteric arteries was improved after exercise training as evidenced by an increased vasodilator response to insulin. In addition, exercise downregulated vascular GRK2 expression and activity, which further increased insulin-stimulated vascular Akt/eNOS activation in exercised SHRs. Specific small interfering RNA knockdown of GRK2 in endothelium mimicked the effect of exercise-enhanced vascular insulin sensitivity. Likewise, upregulation of GRK2 by Chariot-mediated delivery opposed exercise-induced vascular insulin sensitization. Taken together, our results suggest that long-term exercise beginning at the prehypertensive stage improves vascular insulin sensitivity via downregulation of vascular GRK2 that may help to limit the progression of hypertension.

HYPERTENSION, DEFINED AS blood pressure (BP) at or above 140 mmHg systolic and/or 90 mmHg diastolic, remains one of the most significant modifiable risk factors for cardiovascular diseases, including coronary artery disease, stroke, and heart failure. Although several studies report controversial relationships between BP and physical activity, meta-analysis of randomized controlled trials shows chronic dynamic aerobic endurance training reduces BP (5). Therefore, regular physical exercise is broadly recommended by current European and American hypertension guidelines as first-line therapy. Endurance training decreases BP, in part, through reducing systemic peripheral vascular resistance. However, underlying or alternate mechanisms involved in the BP lowering effects of exercise remain largely elusive.

Physiological concentrations of insulin stimulate relaxation of resistance vessels via phosphatidylinositol 3-kinase (PI3K)/Akt/endothelial nitric oxide (NO) synthase (eNOS) pathways to promote production of NO from endothelium. Thus insulin plays an important role in regulating endothelial function, maintenance of vascular tone, and hemodynamic homeostasis (8, 22). Vascular insulin resistance, characterized by impaired insulin-stimulated production of endothelial-derived NO (vasodilator) or/and enhanced insulin-stimulated production of the vasoconstrictor endothelin-1, contributes to elevated peripheral vascular resistance in prehypertension as well as frank hypertension (17, 25, 33). Increased physical activity/exercise improves endothelial dysfunction in both conduit and resistance vessels of sedentary individuals characterized by enhanced endothelium-dependent vasorelaxation induced by acetylcholine (11). Exercise also increases whole body insulin sensitivity for glucose uptake and utilization as well as insulin-stimulated blood flow in cutaneous microvasculature in type 2 diabetic individuals (14). However, little is known about the effects of chronic exercise training on vascular insulin sensitivity in the prehypertensive condition and following.

G protein-coupled receptor kinase-2 (GRK2) classically phosphorylates heptahelical receptors at specific serine residues facilitating β-arrestin-induced G protein-coupled receptor desensitization. Interestingly, GRK2 also plays a role in insulin’s metabolic signaling and action. GRK2 interacts with Gq/11 and functions as a key component in insulin-stimulated
hypertension by enhancing vascular insulin sensitivity and training beginning at the prehypertensive stage may mitigate progression to hypertension to previously reported.

Thus, in the present study, we used spontaneously hypertensive rats (SHRs) as a rodent model of prehypertension progressing to hypertension to 1) investigate whether exercise training beginning at the prehypertensive stage may mitigate hypertension by enhancing vascular insulin sensitivity and 2) examine whether this effect requires downregulation of vascular GRK2 expression.

MATERIALS AND METHODS

Reagents. Phenylephrine (PE), acetylcholine, sodium nitroprusside, insulin, N\textsuperscript{o}-nitro-l-arginine methyl ester (l-NAM), wortmannin, and dimethyl sulfoxide (DMSO) were purchased from Sigma (St. Louis, MO). GRK2 inhibitor methyl[5-nitro-2-furyl]vinyl][2-furoate was purchased from Calbiochem (La Jolla, CA). Stock solutions of each drug were prepared in distilled water except for wortmannin and GRK2 inhibitor (dissolved in DMSO). None of the vehicles used (including DMSO) at the final dilutions induced any significant vascular effects (assessed by appropriate controls in preliminary studies).

Animals. All experiments were performed in accordance with the National Institutes of Health “Guidelines on the Use of Laboratory Animals” and were approved by the Fourth Military Medical University Committee on Animal Care. Young (4 wk old) prehypertensive male SHRs and their age- and sex-matched normotensive Wistar-Kyoto (WKY) control rats were purchased from Vital River Laboratories (Beijing, China). Rats were housed in separate cages in a temperature-controlled room (22–24°C) under a 12-h:12-h light-dark cycle with free access to water and standard rat chow containing 11% fat, 24% proteins, 49% carbohydrate, 5% fiber, and 10% minerals. SHRs were randomly divided into the sedentary and 10-wk (from 4 to 14 wk old) exercise training groups. Systolic BP (SBP) was measured with a tail-cuff system. Rats were placed in a restraining chamber and warmed to an ambient temperature of 37°C, typically taking about 30 min. After rats were habituated to the procedure of inflating and deflating, SBP was measured five times on each occasion, and the average of the five measurements was calculated.

Exercise protocol. The swim training protocol was modified from a previously published procedure (16, 35). SHRs in the exercised groups were trained, free of loading, 5 days/wk for 10 wk in a 60 cm × 90 cm tank filled with ~50 cm depth of water at 33–35°C. Rats swam in groups of three. Rats swam for 15 min on the first day, and the swimming duration was then progressively increased to 60 min/day in a 1-wk period. All training sessions took place during the morning hours (9:00 AM–11:00 AM).

Measurement of insulin sensitivity. Fasting blood glucose and insulin levels were measured with the use of a blood glucose meter (Lifescan) and an RIA test kit (Peninsula Laboratories, Belmont, CA) (17), respectively. We measured insulin sensitivity using the quantitative insulin sensitivity check index (QUICKI). QUICKI was calculated using the following formula (2, 3): \text{QUICKI} = \frac{1}{1/\text{IO}_{2} + \log \text{G}_{\text{O}}}, where \text{IO}_{2} is fasting insulin (in \text{mU/mL}) and \text{G}_{\text{O}} is fasting glucose (in mg/dL).

Functional assessment of rat mesenteric arteries. Mesenteric arterioles were isolated from rats and cut into four ring segments 1 mm long. Arteriolar segments were mounted in a temperature-controlled myograph (model 610M, Danish Myo Technology) and perfused with physiological saline solution, containing (in mM) 118.99 NaCl, 4.69 KCl, 1.18 KH\textsubscript{2}PO\textsubscript{4}, 1.17 MgSO\textsubscript{4}, 5.00 CaCl\textsubscript{2}, 2.50 CaCl\textsubscript{2}, 0.03 EDTA, 25.0 NaHCO\textsubscript{3}, and 5.50 glucose and continuously gassed with a mixture of 95% O\textsubscript{2}-5% CO\textsubscript{2} (pH 7.4). An optimal passive tension (~2.5 mN) was applied for 1 h before the experiments were started. In certain preparations, the endothelium was removed by gentle mechanical abrasion. Mesenteric arteriolar segments were precontracted with 1 \text{µm} PE. A dose-response curve was obtained by cumulative addition of insulin (10\textsuperscript{-10} to 10\textsuperscript{-6} M). Relaxation at each concentration was measured and expressed as the percentage of force generated in response to PE. In some experiments, insulin dose response curves were repeated after pretreatment with l-NAM (a specific NO synthase inhibitor, 100 \text{µM}, 30 min), wortmannin (a PI3K inhibitor, 100 nM, 30 min) or GRK2 inhibitor (1 \text{µM}, 30 min).

Western blot analysis. Protein samples were separated by electrophoresis on SDS-PAGE and transferred to a polyvinylidene difluoride membrane. The membranes were blocked with 5% BSA and incubated overnight with the appropriate primary antibodies, respectively, i.e., anti-phospho (p)-GRK2 (Ser670, 1:1,000, Millipore, Temecula, CA), anti-GRK2 (1:500, Santa Cruz Biotechnology), anti-p-Akt (Ser473, 1:1,000), anti-p-eNOS (Ser1177, 1:1,000), and anti-eNOS (1:1,000, BD Biosciences, CA), followed by incubation with the corresponding secondary antibodies. The blots were visualized with ECL-plus reagent. GAPDH was used as the internal loading control. GRK2 activity was assessed by phosphorylation of GRK2 at Ser670 and was shown as the reciprocal of the p-GRK2 expression (27).

Vascular organ culture. We used a well-established method for the experiment as described by Merrick et al. (21). Briefly, mesenteric arterioles were cleaned of loosely adhering fat and connective tissue and cut into segments of 1 mm in length. The segments were placed in 1 ml DMEM supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin and incubated at 37°C with 5% CO\textsubscript{2}-95% room air.

Small interfering RNA transfection and chariot-mediated antibody delivery. For gene silencing assay, small interfering RNA (siRNA) specifically targeting GRK2 mRNA was purchased from Santa Cruz Biotechnology. Arteriolar tissues were transfected with siRNA specific to GRK2 or scrambled control by Lipofectamine 2000 (Invitrogen, Carlsbad, CA) following the manufacturer’s instructions (29, 33). At 48 h after transfection, arteriolar segments were treated with 10\textsuperscript{-7} M insulin for 30 min. To increase GRK2 expression, a macromolecular protein delivery system, Chariot (Active Motif, Carlsbad, CA), was used following the manufacturer’s instructions as described by Taguchi et al. (29). Briefly, protein was first incubated with the protein delivery agent Chariot (1:1 vol/vol) at room temperature for 30 min to allow the complex to form. The arteriolar segments were transferred to a sterile 24-well cell culture plate, overlaid with 200 \text{µL} of Chariot/protein complex, and mixed gently. DMEM (300 \text{µL}) was added, and the tissues were incubated for 1 h at 37°C. Additional DMEM (500 \text{µL}) containing 10% fetal bovine serum was then added, and tissues were further incubated for 2 h at 37°C. After that,
EXERCISE IMPROVES VASODILATOR ACTIONS OF INSULIN

H1113

Fig. 1. Effect of 10-wk exercise training on blood pressure (BP) and systemic insulin sensitivity of rats. A: systolic BPs of Wistar-Kyoto (WKY) rats, spontaneously hypertensive rats (SHRs) kept under sedentary conditions for 10 wk (SHR-SED), and SHRs subjected to a 10-wk exercise training (SHR-EX). B: quantitative insulin sensitivity check index (QUICKI) in WKY, SHR-SED, and SHR-EX rats at the end of the training protocol. All values are presented as means ± SE; n = 8 independent experiments. *P < 0.05; **P < 0.01 vs. WKY; #P < 0.05 vs. SHR-SED.

Fig. 2. The vasorelaxation effect of insulin in rats. A: dose-response curves for insulin-induced relaxation were obtained from mesenteric arteries of WKY, SHR-SED, and SHR-EX rats. Data are expressed as percentage of the contraction to phenylephrine. Conc, concentration. B: effects of wortmannin (Wm), Nω-nitro-l-arginine methyl ester (l-NAME), and removal of endothelial cell (E-) on insulin-induced relaxations of mesenteric arteries from WKY, SHR-SED, and SHR-EX rats. Data are shown as relaxation to 10⁻⁶ mol/l insulin. All values are presented as means ± SE; n = 6 independent experiments. **P < 0.01 vs. WKY; #P < 0.05 vs. SHR-SED; λP < 0.05.
exercise opposed enhancement of GRK2 activity in SHR as assessed by phosphorylation of GRK2 at Ser670 (a proxy for enzyme activation).

**Insulin-stimulated vascular Akt/eNOS signaling.** Since GRK2 regulates the Akt/eNOS pathway, we further examined the effect of exercise-mediated GRK2 downregulation on insulin-stimulated Akt/eNOS signaling. As shown in Fig. 4, insulin-evoked phosphorylation of vascular Akt at Thr308/Ser473 and phosphorylation of eNOS at Ser1177 was markedly decreased in SHR-SED when compared with samples from WKY rats. Conversely, insulin-induced phosphorylation of both vascular Akt and eNOS were enhanced in SHR-EX.

**Effects of GRK2 inhibition on vascular insulin sensitivity in SHRs.** To investigate the casual relationship between decreased GRK2 and exercise-induced improvement of vascular insulin sensitivity, we used siRNA for selective suppression of GRK2 in cultured mesenteric arterioles. As shown in Fig. 5, A and B, GRK2 expression was significantly decreased by siRNA treatment. At the same time, responses to insulin of mesenteric arterioles from SHR-SED were significantly improved. Moreover, GRK2 knockdown by siRNA significantly increased insulin-stimulated Akt and eNOS phosphorylation (Fig. 5, C–E). Treatment with scrambled siRNA had no effect on either GRK2 expression or insulin's vasorelaxation and signaling (Fig. 5). Similarly, preincubation with a relatively specific GRK2 inhibitor also enhanced the vasodilator actions of insulin as well as insulin-stimulated Akt and eNOS activation in arterioles from the SHR-SED group (Fig. 6). Thus GRK2 inhibition by several methods mimicked the effect of exercise to improve vascular insulin sensitivity in SHRs.

**Effects of GRK2 upregulation on vascular insulin sensitivity in SHRs subjected to exercise training.** To provide further evidence for a casual relationship between GRK2 and exercise-induced improvement vascular insulin sensitivity, we used Chariot for delivering GRK2 to cultured mesenteric arterioles. As shown in Fig. 7, A and B, the augmentation of insulin-induced vasodilation in SHR after 10-wk exercise training was opposed by delivery of GRK2 to the arteriole segments that presumably resulted in overexpression of GRK2. Importantly, after Chariot-mediated delivery of GRK2, insulin-induced activation of Akt and eNOS were also significantly reduced (Fig. 7, C–E). Treatment with Chariot alone as a control had no effect on either vascular GRK2 expression or insulin signaling or vasodilator actions (Fig. 7). Thus GRK2 overexpression opposed the effect of exercise on improving vascular insulin sensitivity in SHRs and provides further evidence that GRK2 is mediating the effects of exercise to improve vasodilator actions of insulin that help to reduce BP.

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**Fig. 3. Western Blot analysis of G protein-coupled receptor kinase-2 (GRK2) expression and activity in mesenteric arteries of WKY, SHR-SED, and SHR-EX rats.** A, top: representative blots for GRK2 protein. A, bottom: statistical data obtained from quantitative densitometry of GRK2 blots. B: GRK2 activity in mesenteric arteries of WKY, SHR-SED, and SHR-EX rats. All values are presented as means ± SE; n = 6 independent experiments. **P < 0.01 vs. WKY; ##P < 0.01 vs. SHR-SED.

**Fig. 4. Activation of insulin-stimulated signaling in mesenteric arteries of WKY, SHR-SED, and SHR-EX rats after insulin incubation.** A, top: representative blots of total and insulin-stimulated phosphorylation (p) of Akt at Thr308. A, bottom: ratio of Akt phosphorylation at Thr308 to total Akt expression. B, top: representative blots of total and insulin–stimulated phosphorylation of Akt at Ser473. B, bottom: ratio of Akt phosphorylation at Ser473 to total Akt expression. C, top: representative blots of total and insulin–stimulated phosphorylation of endothelial nitric oxide (NO) synthase (eNOS). C, bottom: ratio of eNOS phosphorylation to total eNOS expression. All values are presented as means ± SE; n = 6 independent experiments. **P < 0.01 vs. WKY; #P < 0.05 vs. SHR-SED.
DISCUSSION

In the present study, we demonstrated for the first time that exercise mitigates hypertension through improving vascular insulin sensitivity of resistance vessels. More importantly, our data provide direct evidence that GRK2 expression is causally linked to the ability of exercise to enhance the vasodilator actions of insulin that help to ameliorate hypertension.

Physical activity, a major component of lifestyle modification, is a first-line therapy for reducing high BP, lowering medication for BP, and delaying end-organ damage (6). This is supported by both animal experiments and human studies and further consolidated by the finding that low-exercise capacity results in hypertension and insulin resistance (32, 34). Our present study showed that SHRs subjected to regular physical exercise had significantly reduced SBP when compared with their sedentary counterparts. In fact, in the exercised group, they did not reach their genetically programmed elevation of BP, indicating the beneficial effect of exercise on prevention and treatment of hypertension. This is in agreement with the previous data that long-term swimming reduces BP and heart rate of SHRs from our and other laboratories (9, 16). Our findings that exercise training starting at the prehypertensive stage attenuates the progression from prehypertension to hypertension is clinically relevant to the prevention of hypertension, especially in light of the awareness that prehypertensive individuals are more likely to progress to established hypertension and to experience premature clinical cardiovascular disease.
Insulin stimulates PI3K, resulting in phosphorylation and activation of Akt that then phosphorylates eNOS at Ser1177 but not the inhibitory sites at Thr495 or Ser113 in endothelium, resulting in increased activity of eNOS with subsequent production of NO. Therefore, PI3K-dependent insulin signaling in vascular endothelium promotes vasorelaxation of resistance vessels and thereby plays a role in regulating endothelial function and maintenance of vascular tone. Our previous studies demonstrate that young normotensive SHRs have blunted insulin-induced vasorelaxation and impaired insulin signaling (PI3K/Akt/eNOS) and decreased NO production in the vasculature. This suggests that vascular insulin resistance is a risk factor preceding phenotypic manifestation of hypertension (17, 33). Impaired insulin action and signaling in the vascular endothelium contributes to elevated vascular tone and vascular inflammation in hypertensive and high fat-diet rodent models (15, 17). Exercise training improves insulin sensitivity related to metabolic regulation in metabolic insulin-target organs such as skeletal muscle and adipose tissue (23, 24). However, whether exercise training impacts vascular tone by improving insulin sensitivity of resistance vessels in the progression of hypertension is less well understood. In the present study, we provide the first direct experimental evidence that after 10 wk of exercise training, vasodilator responses to insulin in mesenteric arteries from SHRs were significantly improved. Exercise training for 10 wk enhanced insulin-induced Akt/eNOS activation in vascular endothelium, suggesting that exercise-induced improvement of vascular insulin sensitivity plays an important role in attenuating development of hypertension in SHRs. Although we have not directly assessed NO production in our present study, this is supported by our previous report that exercise protects endothelial function and insulin’s vasodilation via increasing eNOS activation and NO production in aorta in aging-associated insulin resistance (16). Importantly, our finding that vascular insulin resistance of mesenteric arterioles was reversed by exercise training is of particular importance in attempting to understand the way to prevent hypertension, since small arteries rather than conduit arteries are more physiologically relevant to the peripheral vascular resistance that underlies the development of hypertension. Taken together, exercise training alleviates an increase in BP in SHRs, which is at least partly attributable to attenuated vascular resistance mediated by improved vascular insulin sensitivity.

GRK2 has attracted great interest as a ubiquitous GRK family member that may play a central, integrative role in signal-transduction pathways known to modulate intracellular effectors involved in cardiovascular function (1). GRK2 was initially identified as a serine/threonine kinase that participates, together with β-arrestins, in the regulation of multiple G protein-coupled receptors. Increased vascular expression and activity of GRK2 have been manifestly associated with human and numerous experimental models of hypertension (4, 13). Hypertensive patients have elevated GRK2 activity and protein expression without concomitant changes in GRK5, GRK6, PKA, or β-arrestins, suggesting selective variation of GRK2 in this condition (12). These findings indicate that GRK2 may be
a valuable therapeutic target for the treatment of hypertension. Interestingly, GRK2 is also increased in insulin-resistant conditions. In vitro studies using liver cells and adipocytes show that GRK2 inhibits basal and insulin-stimulated glycogen synthesis and insulin-mediated glucose transport (27, 31). Recent data highlight the important role of GRK2 in endothelial dysfunction in obese and diabetic rodent models (28, 29). However, it is largely unclear whether GRK2 participates in exercise-associated improvement of vascular insulin sensitivity in hypertension. In the present study, we found that exercise training for 10 wk significantly reduced GRK2 expression and activity in SHRs. This is consistent with the reports that GRK2 was downregulated by physical exercise in the heart and kidney (20, 26). Importantly, we implicated a causal role for GRK2 by overexpression and knockdown or inhibition of GRK2 in organ culture of mesenteric arteries. Inhibition of GRK2 via either GRK2 inhibitor preincubation or transfection with GRK2 siRNA significantly enhanced insulin-induced relaxation in the mesenteric arteries of SHR-SED, mimicking the effect of exercise training on vascular insulin sensitivity. Moreover, GRK2 inhibition enhanced Akt and eNOS activation. Conversely, overexpression of GRK2 by Chariot-mediated GRK2 delivery opposed the beneficial effects of exercise training on improving insulin signaling and vasodilator actions. Taken together, results from our experiments of both overexpression and knockdown/inhibition of GRK2 are fully consistent with a causal relationship between exercise-induced GRK2 downregulation and enhancement of vascular insulin sensitivity that helps to

Fig. 7. Improved insulin-induced vasorelaxation and insulin signaling of mesenteric arteries by exercise were abolished by upregulating of GRK2 expression. A: Western blot analysis showing GRK2 level after Chariot-mediated delivery of GRK2 in SHR-EX. B: dose-response curves for insulin-induced relaxation were obtained from mesenteric arteries of SHR-EX rats after GRK2 delivery. C, top: representative blots of total and phosphorylated Akt at Thr308. C, bottom: ratio of insulin-stimulated Akt phosphorylation at Thr308 to total Akt expression after delivery GRK2 by Chariot. D, top: representative blots of total and phosphorylated eNOS. D, bottom: ratio of insulin-stimulated eNOS phosphorylation to total eNOS expression after delivery GRK2 by Chariot. E: proposed mechanism of exercise attenuates the vascular insulin resistance and reduces blood pressure. Exercise induces GRK2 downregulation and thus enhances insulin-evoked Akt-dependent NO production. All values are presented as means ± SE; n = 6 independent experiments. δP < 0.05 vs. SHR-EX; &P < 0.05 vs. SHR-EX + Chariot.
mediate amelioration of hypertension. Recent studies suggest potential mechanisms by which GRK2 may influence development of insulin resistance. Increased GRK2 coupled with loss or dysfunction of β-arrestin-2 results in deficiency of a signal complex containing insulin receptor, c-Src, and Akt and disturbance of insulin signaling (19, 29). Formation of dynamic GRK2/insulin receptor substrate 1 (IRS1) complexes may be an additional mechanism underlying the inhibition of insulin signaling by GRK2 in adipocytes (10). GRK2 also mediates IRS1 serine/threonine phosphorylation and inhibits IRS1 tyrosine phosphorylation (30). A lack of Akt activation is also observed when GRK2 directly interacts with and inhibits Akt (18). Taken together, these findings suggest the key role of GRK2 in negative regulation of vascular insulin signaling pathways.

In summary, our findings demonstrate for the first time that exercise training beginning at the prehypertensive stage in SHRs ameliorates hypertension via opposing development of vascular insulin resistance that is at least partly attributable to exercise-induced downregulation of GRK2 in resistance vessels in SHRs (Fig. 7F). Therefore, lifestyle interventions, including physical activity, that improve vascular insulin sensitivity and/or reduce GRK2 expression or activity may have significant value in the prevention and treatment of hypertension.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

W.X., H.Z., and F.G. conception and design of research; W.X., Y.L., C.M., Z.H., M.J.Q., and F.G. approved final version of manuscript.

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