The hypertension advantage and natural selection: Since type 2 diabetes associates with co-morbidities and premature death, why have the genetic variants remained in the human genome?

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ABSTRACT

Type 2 diabetes is a major public health crisis around the world. It is estimated that more than 300 million people worldwide have type 2 diabetes. Furthermore, the World Health Organization estimates that deaths from the complications of diabetes will increase by two thirds between 2008 and 2030. Since type 2 diabetes is a major public health crisis, why have the genetic variants for diabetes not been removed from the genome by natural selection? We hypothesize that insulin resistance, a predisposition to type 2 diabetes, and the associated elevation in sympathetic nervous system activity and arterial blood pressure provided an advantage to humans who lived as hunter-gatherers. Specifically, sympathetic hyperactivity stimulates the renin-angiotensin aldosterone system, promotes sodium reabsorption, and increases blood volume, heart rate, stroke volume and peripheral vascular resistance, thus inducing hypertension. The hypertension in turn provides a hemodynamic advantage for hunter-gatherers. Specifically, sympathetic hyperactivity and increased blood pressure increases blood flow delivery to working muscles by increasing cardiac output and shunting blood from non-active tissue. This natural selection for hypertension occurred during the time in human evolutionary history when the lifespan of most individuals was probably 30–40 years, and morbidity and mortality from cardiovascular disorders was limited. Thus, the selection pressure for elevation in sympathetic nervous system activity and blood pressure provided an advantage for hunting and gathering that would be greater than the selection pressure exerted by the manifestations of cardiovascular disease in aged individuals.

Background to the hypothesis

Type 2 diabetes is destructive to health

Diabetes was the 7th leading cause of death in 2015 [1] and individuals with diabetes are at increased risk of blindness, renal failure, nerve damage [2], and cardiovascular disease [3–5]. Diabetes mellitus is characterized by reduced glycemic control resulting in elevated glucose levels due to impaired insulin secretion and/or action and its etiology includes two main types: insulin dependent diabetes mellitus (Type 1) and non-insulin dependent diabetes mellitus (Type 2) [6]. While type 1 diabetes is a result of complete beta-cell loss, type 2 diabetes arises from developed insulin resistance mostly concurrent with obesity (87.5% of diabetics are overweight or obese) and sedentary lifestyle (40.8% of diabetics get less than 10 min of moderate physical activity per week) [1,6,7]. However, while commonly described as a lifestyle-disease, type 2 diabetes also involves a genetic component and occurs in select individuals without adiposity due to its genetic predisposition [8–10]. The presence of a genetic contribution to type 2 diabetes suggests evolutionary conservation of genes contributing to insulin resistance. Importantly, preservation of these genes is not expected unless they provided a survival advantage. What is the survival advantage of type 2 diabetes?

The “thrifty genotype” and “carnivore connection” hypotheses

If diabetes is so destructive to health, shouldn’t the genetic variants for diabetes have been removed from the genome by natural selection? The most well-accepted hypothesis for the evolutionary conservation of genes resulting in diabetes was developed by University of Michigan geneticist James Neel in 1962. Neel described the evolutionary advantage of insulin resistance when humans were primarily hunters and
gatherers [11,12]. His “thrifty-gene” hypothesis suggests that insulin resistance was important for efficient use of nutritional resources during periods when food was scarce, specifically conservation of glucose after a feast and prevention of hypoglycemia during periods of famine [11]. Other hypotheses, e.g. the “carnivore connection,” suggest that insulin resistance developed due to the protein-rich diets in hunters and gatherers to accommodate low carbohydrate intake [13,14]. While these advantages may have ensured human survival as hunter-gatherers, continuation of this phenotype in modern societies may contribute to the epidemic of type 2 diabetes. The concept of evolutionarily conserved traits that can be disadvantageous in modern society is perhaps best illustrated by the sickle cell trait [11]. The sickle cell trait is an evolutionary advantage selected for its nearly 10-fold reduction in severe cases of malaria in individuals heterozygous for the sickle cell gene [15]. However, in modern societies where malaria is limited, mainly the negative aspects of sickle cell anemia remain.

The hypertension hypothesis

We hypothesize that insulin resistance, a predisposition to type 2 diabetes, and the associated elevated in sympathetic nervous system activity and arterial blood pressure provided an advantage to humans who lived as hunter-gatherers. Insulin resistance causes sympathetic hyperactivity (Fig. 1). Sympathetic hyperactivity stimulates the renin-angiotensin aldosterone system, promotes sodium reabsorption, and increases blood volume, heart rate, stroke volume and peripheral vascular resistance, thus inducing hypertension. The sympathetic hyperactivity and hypertension provide a hemodynamic advantage for hunter-gatherers by increasing cardiac output and shunting blood from non-active to active tissues thus increasing blood flow delivery to working muscles. This natural selection for hypertension occurred during the time in human evolutionary history when the lifespan of most individuals was probably 30–40 years, and morbidity and mortality from cardiovascular disorders would be limited because the impact of hypertension and related cardiovascular diseases are pathologies of old age [16]. Moreover, since the detrimental effects of hypertension do not develop until after the reproductive years, the selection pressure for mechanisms that promote hunting and gathering would be greater than that exerted by the manifestations of cardiovascular disease in aged individuals [16].

Hypertension enhances exercise tolerance

An analysis of the literature supports the notion that inherited hypertension, resulting from exaggerated sympathetic activity at rest and during exercise, plays a beneficial role in exercise performance (Fig. 1). Increased sympathetic activity during exercise is necessary to maintain arterial blood pressure and increase perfusion pressure to working skeletal muscle that results in increased blood flow delivery [17,18]. This response is mediated by increases in cardiac output and vasoconstriction to non-active tissue that redistribute blood flow towards exercising muscle [18,19]. The importance of elevated perfusion pressure on skeletal muscle performance is well-demonstrated by a series of innovative experiments by McCloskey and colleagues. Utilizing supramaximal stimulation of the ulnar nerve via bipolar surface electrodes, isometric contractions were performed in the adductor pollicis muscle. During the exercising protocols, central blood pressure was measured and hydrostatic pressure was altered by positioning the hand above and below the heart. In one study, using this interesting technique, the authors demonstrated that the adductor pollicis muscle fatigue more quickly when the arm was elevated 45 cm and fatigued more slowly when lowered 45 cm [20]. The change in muscle performance was attributed to the change in perfusion pressure resulting from raising and lowering the hand relative to heart level. In subsequent work, a similar experiment was completed with subjects performing voluntary adductor pollicis muscle exercise at and above heart level on two separate days [21]. This exercise protocol involved 6 s sustained contractions at 50% of the maximum voluntary contraction (determined prior to protocol) with 4 s of rest between each contraction for a period of ten minutes. During the 4 s rest period, the ulnar nerve was stimulated to determine twitch strength and measure fatigue. The authors documented similar results of a reduced exercise performance when perfusion pressure was reduced by raising the hand above the heart compared to exercise performance when the hand was held at heart level. This study, using voluntary exercise, supports previous findings using electrically-induced contractions [21]. Moreover, in a subsequent study the authors extended these findings, documenting that increasing systemic blood pressure increases exercise performance [22]. Specifically, Wright and colleagues measured muscle fatigue in the adductor pollicis muscle at “normal” systemic blood pressure and demonstrated reduced fatigue after increasing systemic blood pressure by voluntary contraction of leg muscles. Contraction of this larger muscle mass increased sympathetic activity and resulted in elevated systemic blood pressure [22]. Taken together, the results from these studies document the critical role of perfusion pressure on muscle performance.

The critical role of perfusion pressure on exercise performance has also been demonstrated during dynamic treadmill running. In 1998, Barbato and colleagues tested 11 different inbred strains of rats for aerobic treadmill running capacity and found a continuum in capacity [23]; the Dark Agouti (DA) strain of rats displayed the highest whereas the Copenhagen (COP) strain of rats displayed the lowest capacity for endurance running. Importantly, the DA rats had higher arterial pressure and heart rate during dynamic treadmill running. Furthermore, autonomic control of peripheral vascular function was also greater in the DA rats. Because endurance capacity is dependent on the exquisite matching of cardiac output and peripheral vascular tone, these phenotypic differences between DA and COP rats might be causative of the differences in aerobic capacity between the strains. The authors concluded that increased autonomic function and arterial blood pressure directly contributed to increased exercise performance [24].

Exercise performance is also enhanced in individuals with spinal cord injury by increasing arterial blood pressure. Specifically, cervical and thoracic spinal cord injury (SCI) causes loss of supraspinal control.
over sympathetic pre-ganglionic neurons. This leads to profoundly reduced sympathetic activity, hypotension, and a significantly reduced hemodynamic response to activities of daily living (ADL) as well as a reduced physical work capacity (PWC) [25–27]. To overcome restrictions to activities of daily living and reduced physical work capacity, some individuals with SCI have resorted to the practice of “boosting.” Boosting involves the intentional induction of autonomic dysreflexia (AD) [28,29]. Autonomic dysreflexia causes a profound increase in sympathetic activity and blood pressure [30,31]. AD-induced increases in sympathetic activity cause an increase in heart rate, blood pressure, cardiac output and oxygen transport to the working musculature thus increasing physical work capacity and delaying fatigue. Some paralympic athletes have also resorted to the banned practice of boosting to elevate arterial blood pressure and enhance (boost) exercise performance [32,33]. This example of boosting in individuals with spinal cord injuries further documents the profound benefits of elevated blood pressure on exercise performance.

**Statement of the hypothesis**

We posit that type 2 diabetes, and the associated elevation in sympathetic nervous system activity and arterial blood pressure, provides an advantage to humans who lived as hunter-gatherers by increasing exercise tolerance. Specifically, insulin resistance causes sympathetic hyperactivity (Fig. 1). Sympathetic hyperactivity stimulates the renin-angiotensin aldosterone system, promotes sodium re-absorption, and increases blood volume, heart rate, stroke volume and peripheral vascular resistance, thus inducing hypertension. The hypertension provides a hemodynamic advantage by increasing cardiac output, increasing blood flow delivery to working muscles and shunting blood from non-active tissue.

**Supporting data – presented as a test of the hypothesis**

A non-obese and non-sedentary genetic model of type 2 diabetes, the Goto-Kakizaki (GK) Rat (male, 8–10 months old) and age and sex-matched Wistar control rats were used to evaluate the initial hypothesis. All procedures were approved by the Michigan State University Institutional Animal Care and Use Committee and complied with The American Physiological Society’s “Guiding Principles in the Care and Use of Animals”. In all procedures performed, rats were chronically instrumented with a radio telemeter device to record arterial blood pressure and heart rate and a Doppler ultra-sonic flow probe around the popliteal artery to record muscle blood flow [34].

**Advantage during hunting and gathering; test of exercise tolerance**

An exercise tolerance test determined by voluntary treadmill running, without aversive stimuli, at a fixed submaximal rate to exhaustion (10 m/min [34]) demonstrated that the genetic GK type 2 diabetic rats ran longer (Fig. 2, Panel A), farther (Fig. 2, Panel B) performed more vertical work per gram muscle mass (Fig. 2, Panel C) and performed similar absolute vertical work compared to their genetic Wistar controls (Fig. 2, Panel D). An increased endurance exercise performance would have been an advantage for the nomadic lifestyles of hunter-gatherers. Although increased substrate availability likely contributes to increased exercise performance in the genetic GK type 2 diabetic rats [34], we posit that an elevated arterial blood pressure during exercise (see below) is also a major contributing factor.

**Benefits of hypertension during exercise**

Arterial blood pressure (Fig. 3, Panel A) and heart rate (Fig. 3, Panel B) were significantly higher during voluntary treadmill running at a fixed submaximal rate to exhaustion in the genetic GK type 2 diabetic rats compared with their genetic control. The higher blood pressure and heart rate in the genetic GK type 2 diabetic rats was associated with a higher exercising muscle blood flow (Fig. 3, Panel C) and lower exercising muscle vascular resistance (Fig. 3, Panel D). These results suggest that sympathetic hyperactivity increases blood flow delivery to working muscles by increasing heart rate and cardiac output and shunting blood from non-active tissue to exercising muscle.

Similarly, arterial blood pressure (Fig. 4, Panel A) and heart rate (Fig. 4, Panel B) were significantly higher during a graded (5, 10 and 15 m/min) exercise test in the genetic GK type 2 diabetic rats compared with their genetic control. The higher blood pressure and heart rate in the genetic GK type 2 diabetic rats was associated with a higher exercising muscle blood flow (Fig. 4, Panel C). Again, these results suggest that sympathetic hyperactivity increases blood flow delivery to working muscles by increasing heart rate and cardiac output and shunting blood from non-active tissue to exercising muscle. These data support the hypothesis since increased tissue perfusion as a result of increased arterial blood pressure would have been an advantage for the nomadic lifestyles of hunter-gatherers [35–37].

**Parasympathetic hyperactivity**

Lower resting heart rate and high autonomic vagal activity are strongly associated with increased exercise capacity. In fact, recent evidence suggests that the strength of cardiac vagal activity causally determines the ability to exercise [38,39]. A highly reproducible measure of vagal activity is the speed of heart rate recovery (HRR) after exercise. There is a strong causal relationship between the rate of HRR and exercise capacity. As an example, there is a dramatic absolute difference in HRR between athletes and individuals with heart failure [39]. The reduced resting heart rates in the GK animals (Fig. 4, Panel B) suggest increased parasympathetic activation compared with their genetic Wistar controls. In fact, the lower heart rate in the genetic GK type 2 diabetic rats compared with their genetic control was associated with a significantly enhanced parasympathetic tonus (Fig. 5, Panel A) [24,40,41]. In addition, HRR is mediated by the rate of vagal re-activation [38,42]. In agreement with the lower resting heart rate and higher parasympathetic tonus, HRR was faster in GK rats compared to genetic Wistar controls determined from change in heart rate during the first 20 s as well as during the first 3 min post-exercise cessation (Fig. 5, Panel B). The increases in vagal tone in GK animals support the increased exercise tolerance (Fig. 2) as increased vagal tone measured by HRR is documented to be the most effective predictor of exercise performance [38,39].

**Costs of hypertension during exercise**

The elevated blood pressure and heart rates during exercise caused a greater metabolic demand on the heart as measured by the rate pressure product (Fig. 6, Panels A and B). Indirect indices of myocardial oxygen consumption (rate pressure product, tension-time index, double product, and triple product) are used in clinical and experimental studies [43]. These indirect indices are highly correlated with direct measurements of myocardial oxygen consumption and energy demand of the heart [44]. The cost of increased sympathetic activity elevating blood pressure, heart rate and blood flow delivery to the working muscle resulted in an increased rate pressure product. This cost of exercise places a higher demand on the heart and would be a serious concern in modern society.

**Additional negative consequences of the “hypertension advantage”**

Increased cardiovascular reactivity, a marker for cardiovascular disease, was documented in the GK type 2 diabetic rats (Fig. 7). Specifically, a psychological stressor (restrainer stress [45]) was used to test cardiovascular reactivity in genetic GK type 2 diabetic rats and Wistar control rats. Restraint stress challenges the cardiovascular
Fig. 2. Voluntary treadmill running performance presented as time to exhaustion (A), distance to exhaustion (B), vertical work performed per gram muscle mass (C), and absolute vertical work performed (D). Values represent Mean ± SE. Genetic GK type 2 diabetic rats ran significantly longer and farther and performed more vertical work per gram muscle mass. (*P < 0.05, two-tailed t-test).

Fig. 3. Mean ± SE mean arterial pressure (A), heart rate (B), triceps surae blood flow (C), and triceps surae vascular resistance (D) for Wistar and GK rats during running to exhaustion. MAP, HR, and triceps surae blood flow were each significantly higher in GK rats while triceps surae vascular resistance was significantly reduced. (*P < 0.05, one-tailed t-test (A,B); two-tailed t-test (C,D)).
system with a mental stressor and documents an emotional psychological hemodynamic response. Genetic GK type 2 diabetic rats demonstrated elevated arterial blood pressure response (Fig. 7, Panel A) to restraint stress. Exaggerated arterial pressure responses to stress are deleterious to cardiovascular health and are significant cardiovascular disease risk factors. Specifically, an elevated arterial blood pressure response to mental stress is a cardiovascular disease risk factor [46,47] and high blood pressure reactivity to mental stressors has been linked to an increased incidence of myocardial ischemia and greater risk for untoward cardiac events [48–51]. As an example, white coat hypertension, an elevation in arterial blood pressure from feelings of anxiety in a medical environment, is associated with increased cardiovascular risk [52,53]. Similarly, an elevated arterial blood pressure response to mental arithmetic is associated with increased cardiovascular risk [47].

Other measures of cardiovascular disease risk factors at rest in the GK type 2 diabetic rats included ~14% increased pulse wave velocity compared with Wistar controls indicating reduced vascular compliance. Pulse wave velocity (PWV), an index of aortic compliance and macrovascular disease, was determined at rest by measuring time from the foot of the arterial blood pressure pulse recorded in the arch of the aorta to the foot of the blood flow pulse recorded in the hindlimb [54,55]. PWV provides information about the elastic properties of the arterial system and is defined as the velocity at which the pressure waves, generated by the systolic contraction of the heart, propagate along the arterial tree. The higher PWV corresponds to lower vessel compliance and, therefore, to higher arterial stiffness [56,57]. PWV was increased in GK type 2 diabetic rats compared to Wistar control rats (615.8 ± 16.8 versus 542.5 ± 38.8 cm/s) consistent with arterial stiffness and cardiovascular disease. Individuals with type 2 diabetes are documented to have 20–30% faster PWV and mortality risk is increased by 8% per 1 m/s increase in PWV [58]. Taken together, results document enhanced CVD risk factors in animals with genetically-induced type 2 diabetes. This natural selection for hypertension and the resulting increased CVD risk factors occurred during the time in human evolutionary history when the lifespan of most individuals was probably 30–40 years [16], and morbidity and mortality from cardiovascular disorders was limited. Thus, the selection pressure for elevation in arterial blood pressure provided an advantage for hunting and gathering that was greater than the selection pressure exerted by cardiovascular disease in aged individuals [16].

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**Fig. 4.** Mean ± SE mean arterial pressure (A), heart rate (B), triceps surae blood flow (C), and triceps surae vascular resistance (D) during rest and graded exercise at 5, 10, and 15 m/min. Arterial pressure was increased in GK rats and heart rate showed a group x treadmill speed interaction (*P < 0.05, group difference two-way repeated measures ANOVA; #P < 0.05, group x treadmill speed interaction two-way repeated measures ANOVA).

**Fig. 5.** Markers for vagal activity: Mean ± SE resting parasympathetic tonus (A) and heart rate recovery (HRR) following exercise to exhaustion (B). Parasympathetic tonus was significantly elevated in GK rats compared to controls and HRR was significantly faster when measured at approximately 20 s and 3 min after exercise (*P < 0.05, one-tailed t-test).
The capacity to enhance a sympathetically driven hypertensive response would be an advantage to hunters and gatherers. Hunters and gatherers evolved under environmental conditions in the hot African savannah that posed a threat of circulatory collapse [16,59]. Specifically, hunters and gatherers were exposed to acute extracellular fluid losses from injury-induced hemorrhage and water and sodium loss via perspiration. Restoring extracellular volume and maintaining blood pressure was difficult especially during a prolonged dry season. This challenge required adaptations that maintained blood volume and blood pressure. Accordingly, we propose the capacity to enhance a sympathetically driven hypertensive response evolved to meet this challenge. However, today, this environmentally and activity triggered phenotypic adaptation contributes to the pathogenesis of hypertension.

**Significance of the hypothesis**

The capacity to enhance a sympathetically driven hypertensive response would be an advantage to hunters and gatherers. Hunters and gatherers evolved under environmental conditions in the hot African savannah that posed a threat of circulatory collapse [16,59]. Specifically, hunters and gatherers were exposed to acute extracellular fluid losses from injury-induced hemorrhage and water and sodium loss via perspiration. Restoring extracellular volume and maintaining blood pressure was difficult especially during a prolonged dry season. This challenge required adaptations that maintained blood volume and blood pressure. Accordingly, we propose the capacity to enhance a sympathetically driven hypertensive response evolved to meet this challenge. However, today, this environmentally and activity triggered phenotypic adaptation contributes to the pathogenesis of hypertension.

**Phenotypic similarities of the genetic GK type 2 diabetic rats and exercise training**

The primary purpose of the cardiovascular system is to supply tissues with adequate blood flow and oxygen delivery to match metabolic demand and support aerobic respiration. In skeletal muscle, especially during whole body dynamic exercise, the limitation to aerobic respiration is adequate supply of oxygen. As reviewed by Bassett and Howley (2000), the limit to metabolic demand as determined by
measuring the maximal oxygen consumption (VO2Max) is related to one of four mechanisms that play a role in oxygen dynamics: 1) pulmonary diffusing capacity, 2) cardiac output, 3) O2 carrying capacity, or 4) skeletal muscle uptake [60]. In subjects with normal lung function and blood hemoglobin, the limitation to VO2Max is inadequate cardiac output to perfuse all active tissue [61–66]. Thus the most significant adaptation improving oxygen delivery is increased maximal cardiac output in trained athletes [67,68]. Aerobic exercise training results in an elevated cardiac output by several mechanisms including an increase in heart size [69,70], contractility [67,71], and blood volume [72,73]. Interestingly, the genetic GK type 2 diabetic rats in the present work showed similar functional adaptations. Specifically, the genetic type 2 diabetic rats presented with increased heart mass to body mass ratio (0.28 ± 0.01 versus 0.20 ± 0.01%, P < 0.05 two-tailed t-test) and increased heart rates during exercise (Fig. 3, Panel B; Fig. 4, Panel B) suggesting increased cardiac output. Furthermore, while blood volume was not measured in these animals, the mechanisms resulting in hypertension (Fig. 1) closely resemble mechanisms increasing blood volume following exercise training. Exercise training increases blood volume, in part, via increased sympathetic nervous activity activating the renin-angiotensin aldosterone system (RAAS) that results in increased sodium reabsorption and renal water retention [72]. Similarly, increased sympathetic activity associated with hypertension directly stimulates the RAAS and increases water retention thus expanding blood volume [16]. Further adaptations to aerobic exercise training that permit increased oxygen delivery include alterations to vessel structure, number, and reactivity to increase perfusion capacity to the musculature [74,75]. Although previous studies in the GK rat demonstrate altered vascular structure, number and reactivity [76–78], at the exercise intensities invoked in the current work perfusion to exercising muscle was elevated (Fig. 3, Panel C; Fig. 4, Panel D) suggesting adequate vessel responses. Taken together, the cardiovascular adaptations in the GK rat closely resemble adaptations to endurance exercise training and support increases in treadmill exercise performance (Fig. 2).

**Cardiac vagal activity is strongly associated with exercise capacity**

Endurance exercise training is well established to alter autonomic nervous system activity, resulting in an apparent increase in cardiac parasympathetic tone. In fact, resting bradycardia is a well-established consequence of exercise training [79–82]. In this context, the resting heart rate in elite endurance athletes is low due to exceptionally high parasympathetic vagal tone in these select individuals [83,84]. Thus, resting vagal activity directly relates with exercise training [85–87]. Importantly, the genetic type 2 diabetic rats had a lower resting heart rate (Fig. 4, Panel B) and higher parasympathetic tone (Fig. 5, Panel A).

Parasympathetic tone and heart rate recovery have recently been identified as the greatest predictors of exercise capacity [38,39]. Specifically, Machhada and colleagues (2017) determined the role of parasympathetic control of the heart on exercise capacity by targeting dorsal vagal preganglionic neurons (vagal projections modulating ventricular function [88]) in rats using a reversible inhibitor [39]. Before inhibition, experimental and control groups had similar exercise capacities determined by shock grid-motivated treadmill running to exhaustion. On a separate day, after inhibiting dorsal vagal preganglionic neurons, exercise capacity was reduced by 80% compared to baseline. Furthermore, on a separate day, exercise capacity returned to baseline levels after reversal of inhibition. These data document that vagal activity plays a direct role in enhancing exercise performance.

Interestingly, the GK rat demonstrates similar phenotypes in vagal activity. Specifically, GK rats showed increased vagal activity as determined from reduced resting heart rate (Fig. 4, Panel B), increased parasympathetic tonus (Fig. 5, Panel A), and increased heart rate recovery (Fig. 5, Panel B). Each of these independent measures of increased vagal activity demonstrate increased parasympathetic control of the heart and agree with increased exercise capacity in the GK rat.

**Genetic determinants of cardiac vagal tone**

Evolutionary conservation of diabetes and hypertension is evident in the literature. Similarly, a high degree of cardiac vagal activity is determined by genetics [38]. Although vagal activity increases with exercise training, it was also shown that approximately 60% of HRR is determined by genetics. This was determined by studying 225+ sets of twins and comparing maximum exercise capacity and HRR [89]. In accordance with the studies performed with twins, two separate studies using genome-wide association studies (GWAS) identified several independent genes that directly relate to HRR and increased vagal activity [90,91]. The genetic contribution to vagal activity is particularly interesting as in the current context. Specifically, the genetically developed GK rats are genetically predisposed to diabetes, hypertension, and increased parasympathetic activity. The role of each of these factors in improving exercise capacity and characteristics intrinsic to survival for hunters and gatherers suggest they may be inherited in concert.

**Summary**

The genetic GK type 2 diabetic rats have high sympathetic activity, are hypertensive and have significant cardiovascular disease risk factors. Thus type 2 diabetes is destructive to health and a major public health concern! However, if type 2 diabetes is a major public health crisis, why have the genetic variants for diabetes not been removed from the genome by natural selection? We hypothesize that insulin resistance, a predisposition to type 2 diabetes, and the associated elevation in sympathetic nervous system activity and arterial blood pressure provided an advantage to humans who lived as hunter-gatherers by enhancing exercise capacity. In fact, the genetic GK type 2 diabetic rats run longer and farther than their genetic controls. Importantly, this hypertension exercise advantage evolved at a cost in that these diabetic animals also had higher rate-pressure products and pulse wave velocity than their genetic controls. However, this natural selection for hypertension occurred during the time in human evolutionary history when the lifespan of most individuals was probably 30–40 years, and morbidity and mortality from cardiovascular disorders was limited [16]. Thus, the selection pressure for elevation in sympathetic nervous system activity and blood pressure provided an advantage for hunting and gathering that would be greater than the selection pressure exerted by the manifestations of cardiovascular disease in aged individuals [16].

**Declaration of Competing Interest**

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

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**Appendix A. Supplementary data**

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**References**


