The Impact of Insulin Resistance on Cardiovascular Control During Exercise in Diabetes

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MIZUNO, M., N. HOTTA, R. ISHIZAWA, H.-K. KIM, G. IWAMOTO, W. VONGPATANASIN, J.H. MITCHELL, and S.A. SMITH. The impact of insulin resistance on cardiovascular control during exercise in diabetes. *Exerc. Sport Sci. Rev.*, Vol. 49, No. 3, pp. 157–167, 2021. *Patients with diabetes display heightened blood pressure response to exercise, but the underlying mechanism remains to be elucidated. There is no direct evidence that insulin resistance (hyperinsulinemia or hyperglycemia) impacts neural cardiovascular control during exercise. We propose a novel paradigm in which hyperinsulinemia or hyperglycemia significantly influences neural regulatory pathways controlling the circulation during exercise in diabetes*. **Key Words:** insulin resistance, hyperglycemia, diabetes, exercise blood pressure, sympathetic nerve activity, exercise pressor reflex, central command

Key Points

- In patients with diabetes, exercise elicits an excessive increase in blood pressure (BP). As an exaggerated BP response to physical exertion increases the risk for the development of an unfavorable cardiovascular event, elucidating the mechanisms responsible is clinically important.
- Insulin resistance (hyperinsulinemia or hyperglycemia) is one of the pathophysiological characteristics of diabetes. As such, peripheral and central insulin resistance may contribute importantly to the development of abnormal autonomic cardiovascular control in diabetes.
- Sensitization of skeletal muscle sensory neurons by insulin or glucose as well as impairment of insulin transport to the central nervous system (decreasing the activity of the insulin signaling pathway in the brain) may potentiate the BP response to exercise.
- Identifying potential treatments that improve abnormally high exercise BP responses in diabetes may allow the safe prescription of physical activity as a beneficial therapeutic intervention in this disease.

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INTRODUCTION

In patients with diabetes mellitus or nondiabetics with insulin resistance, both dynamic and static exercise elicits an excessive increase in blood pressure (BP) (1–10). To date, the mechanism(s) underlying the exaggerated BP responsiveness to physical activity in this disease remains to be elucidated. As potentiated BP responses to physical exertion are associated with increased risk for adverse cardiovascular events during or immediately after exercise in individuals who are insulin resistant with or without diabetes mellitus (11–15), elucidating the mechanisms responsible is clinically and physiologically important. The aberrant circulatory response also limits the safety of exercise prescription as a nonpharmacological treatment for diabetes, which is problematic as habitual physical activity is known to be a viable therapy with demonstrated potential for lowering BP and improving overall cardiovascular health (16–18). Insulin is a peptide anabolic hormone secreted from pancreatic β cells that plays an important role in the control of blood glucose levels. Evidence suggests that insulin significantly contributes to activation of the sympathetic nervous system (19–21). In addition, high-glucose condition may cause sympathoexcitation that is independent of endogenous insulin in patients with diabetes (22). However, although insulin resistance is a pathophysiological characteristic of diabetes, the impact of insulin or insulin resistance on sympathetically mediated neural cardiovascular control, especially during exercise, is poorly understood. Thus, the global objective of this review article is to examine historical and recent evidence aimed at determining the mechanisms underlying the heightened BP response to exercise in diabetes. Although insulin modifies neural activity in the central nervous system (CNS) (23–26) or directly influences nociceptive ion channel function (27),

few studies have addressed directly the impact of insulin on neural cardiovascular control during exercise in diabetes. The key questions to be addressed are whether insulin or insulin resistance (*i.e.*, hyperinsulinemia or hyperglycemia) contribute to abnormal BP regulation during exercise after the pathogenesis of this disease.

Exaggerated Exercise BP in Diabetes

The Table summarizes evidence of abnormal exercise BP in individuals with insulin resistance or diabetes. In individuals with insulin resistance or type 2 diabetes mellitus (T2DM), both dynamic (1–3,6,9) and static (4,5,7,8,10) exercise elicits an excessive increase in BP. Likewise, in patients with type 1 diabetes mellitus (T1DM), the systolic and diastolic BP responses to exercise are abnormally heightened (9). It should be noted that as patients with T1DM do not have high insulin levels, evidence from T1DM supports the impact of hyperglycemia rather than insulin on the mechanism(s) underlying exaggerated exercise BP. Adding to this evidence, we recently investigated the relation between cardiovascular responses to exercise and insulin resistance–related factors in nondiabetic healthy men and women older than 60 yr (10). We found that hemoglobin A1c (HbA1c), an indicator for glycemic control, is an independent predictor of the diastolic BP response to dynamic handgrip exercise with muscle ischemia when using multivariate models that account for relevant variables and resting systolic BP (10). In addition, the presence of insulin resistance as evidenced by abnormal homeostatic model assessment of insulin resistance (HOMA-IR) was also determined to be associated with an augmented diastolic BP response to rhythmic dynamic handgrip with muscle ischemia (10). Despite this increasing evidence, the mechanism(s) underlying the exaggerated BP responsiveness to physical activity in diabetes remain largely elusive.

Clinical Implications

The 2017 American College of Cardiology/American Heart Association high BP guidelines recommended that BP be consistently controlled in patients with high cardiovascular risks, including diabetes mellitus, as guided by home BP and 24-h BP monitoring during regular activity (28). Exercise has been shown to improve cardiovascular health (29). Moreover, exercise training is known to slow the progression of diabetes in prediabetic individuals (30), resulting in reductions in mortality rates associated with T2DM. However, there are risks associated with physical activity in T2DM that must be taken into account before its prescription (11–13). For example, transmission of BP surges to the cerebral circulation is dampened less effectively in patients with T2DM, in particular during high-intensity handgrip exercise, suggesting patients with T2DM at greater risk for cerebral events during such activities (31). Moreover, individuals exhibiting an exaggerated BP response to exercise, like patients with T2DM, are more likely to develop future hypertension and are at a greater risk for cardiovascular death (15). This suggests that early detection of the abnormal circulatory responses to physical activity in prediabetic or diabetic patients could also lead to the early treatment and prevention of hypertension in these individuals. Therefore, dissection of the mechanisms underlying the abnormal cardiovascular responses to exercise in diabetes may prove beneficial to the development of the novel therapeutic strategies targeted at reducing the risks associated with physical activity.

TABLE. Evidence of abnormal exercise BP in individuals with insulin resistance or diabetes

Reference	Subject	Age, yr	Glucose	Insulin	Exercise	Cardiovascular Response
Brett *et al.* (2000)	T2DM (M, n = 10)	45 ± 15	11 ± 5 $mmol \cdot L^{-1}$	23 ± 7 $\mu U \cdot mL^{-1}$	BIKE 50, 75, 100W	↑ DBP
Petrofsky *et al.* (2006)	T2DM (M, *n* = 5; F, *n* = 5)	38 ± 18	>126 $mg \cdot dL^{-1}$	—	SHG 40% MVC	↑ SBP/DBP
Petrofsky *et al.* (2005)	T2DM (*n* = 8)	38 ± 10	>126 $mg \cdot dL^{-1}$	—	SHG 40% MVC	↑ SBP/DBP
Matteucci *et al.* (2006)	T1DM (M, *n* = 16; F, *n* = 19)	36 ± 11	12 ± 5 $mmol \cdot L^{-1}$	—	BIKE 90% HR max	↑ SBP
Scott *et al.* (2008)	T2DM (M/F, *n* = 73)	54 ± 10	9 ± 3 $mmol \cdot L^{-1}$	18 ± 22 $mU \cdot L^{-1}$	RUN Submaximal	↑ Brachial/central BP
Papavasileiou *et al.* (2009)	Nondiabetes (M, *n* = 27; F, *n* = 40)	49 ± 5	99 ± 5 $mg \cdot dL^{-1}$	13 ± 2 $mU \cdot L^{-1}$	RUN Submaximal	↑SBP/DBP associated with glucose, insulin, HOMA-IR
Huot *et al.* (2011)	Nondiabetes (M, *n* = 163; F, *n* = 137)	35 ± 13	M, 5 ± 1 $mmol \cdot L^{-1}$ F, 5 ± 1 $mmol \cdot L^{-1}$	M, 61 ± 43 $pmol \cdot L^{-1}$ W, 64 ± 48 $pmol \cdot L^{-1}$	BIKE PWC150	↑ SBP correlated with insulin AUC
Holwerda *et al.* (2016)	T2DM (M, *n* = 9; F, *n* = 7)	50 ± 2	198 ± 22 $mg \cdot dL^{-1}$	11 ± 2 $\mu IU \cdot mL^{-1}$	SHG 30%, 40% MVC	↑ MBP, MSNA during exercise and PEMI MSNA correlated with glucose, HbA1c, HOMA-IR
Vranish *et al.* (2020)	T2DM (*n* = 17)	50 ± 2	206 ± 22 $mg \cdot dL^{-1}$	11 ± 2 $\mu IU \cdot mL^{-1}$	SHG 30%, 40% MVC	↑ MBP, MSNA onset of exercise MSNA correlated with glucose, HbA1c, HOMA-IR
Hotta *et al.* (2020)	Nondiabetes (M, *n* = 23; F, *n* = 22)	70 ± 6	96 ± 13 $mg \cdot dL^{-1}$	6 ± 4 $\mu IU \cdot mL^{-1}$	SHG/ischemic DHG 30% MVC	↑ DBP during ischemic DHG correlated with HbA1c and associated with HOMA-IR

AUC, area under curve; BIKE, cycling exercise; DBP, diastolic blood pressure; DHG, dynamic handgrip exercise; F, female; HR, heart rate; M, male; MBP, mean blood pressure; MSNA, muscle sympathetic nerve activity; MVC, maximal voluntary contraction; PEMI, postexercise muscle ischemia; PWC, physical work capacity; RUN, treadmill running; SBP, systolic blood pressure; SHG, static handgrip exercise.

Brief Overview of Neural Control of the Circulation During Exercise

The sympathetic nervous system plays a crucial role in the regulation of the cardiovascular system during exercise. Adjustments in the autonomic nervous system regulating the cardiovascular response to physical activity are primarily mediated by integrating input from central command (CC), the exercise pressor reflex (EPR), the arterial and cardiopulmonary baroreflexes, and the arterial chemoreflex (32–35). Of these, CC and the EPR are engaged during exercise only. CC is a neural drive that originates in the cerebral cortex and regulates both locomotor and cardiovascular systems (34,36–38). The EPR generates somatosensory signals from working skeletal muscle that modulate autonomic activity (32,39,40). Skeletal muscle group III afferents are predominantly mechanically sensitive A-δ fibers that primarily mediate the muscle mechanoreflex component of the EPR (40). Skeletal muscle group IV afferents are primarily chemically sensitive C fibers associated with the muscle metaboreflex component of the EPR (40). Both group III and IV afferent fibers synapse in the dorsal horn of the spinal cord and subsequently project to the brainstem (41–44). Evidence suggests that the first site critical for the processing of EPR sensory information in the brainstem is the nucleus tractus solitarius (NTS) within the medulla oblongata (42,45–47). NTS GABAergic neurons communicate with neurons in the caudal ventrolateral medulla with subsequent interconnections with the rostral ventrolateral medulla (RVLM) (48–51). The RVLM generates basal sympathetic cardiac and vasomotor activity and is a critical synaptic relay for input from both CC and the EPR (52). The net result of these interactions is an increase in sympathetic outflow and decrease in parasympathetic activity during exercise.

Abnormal Exercise BP in Diabetic Animal Models

As stated previously, although increasing evidence suggests that the pressor response to exercise is exaggerated in diabetes, the underlying mechanisms causing this abnormality remain largely unknown. Specifically, the contributions of CC versus the EPR in mediating the augmented increase in BP in response to exercise in this disease have not been determined. Given this background, we have used a rat model of T2DM generated by administering a high-fat diet (HFD) in combination with a low dose (25–35 $mg \cdot kg^{-1}$) of streptozotocin (STZ). Using this model, we recently examined the impact of T2DM on CC and EPR function (53). Consistent with previous studies, the combination of an HFD and a low dose of STZ significantly increased fasting blood glucose and plasma insulin concentration (53). Importantly, the body weights of rats with T2DM were comparable with control animals eliminating the potential influence of obesity. In these studies, compared with healthy controls, the generation of T2DM markedly augmented the cardiovascular and sympathetic responses to the separate stimulation of both the mesencephalic locomotor region (a putative component of the CC pathway) and the EPR (53). Consistent with this, importantly, the effects of T2DM occurred in the absence of the development of hypertension, a diabetic comorbidity known to exaggerate CC (54,55) and EPR (56–62) activity. Our research group has extensively studied the altered cardiovascular responses to exercise induced by chronic high BP using nondiabetic spontaneously hypertensive rats (56–63). Given that spontaneously hypertensive rats are known to display peripheral insulin resistance and central insulin signaling defects (64), these previous findings in hypertensive animals have served as a major impetus for the investigation of the role insulin resistance plays in the abnormal regulation of the cardiovascular system during exercise in diabetes. It is likewise noted that potentiated EPR function has been observed in other models of diabetes mellitus such as University of California Davis T2DM rats (65) or STZ-induced T1DM (66,67). With regard to the latter, we have recently demonstrated that the sympathetic response to activation of the EPR, as well as its mechanically (*i.e.*, skeletal muscle mechanoreflex) and chemically (*i.e.*, skeletal muscle metaboreflex) sensitive components, was abnormally potentiated in STZ-induced T1DM (68).

MECHANISMS UNDERLYING ABNORMAL METABOREFLEX FUNCTION IN DIABETES

Sensitized Afferent Discharge to Chemical Stimulation as Well as Potentiated Skeletal Muscle Metaboreflex Activity in T1DM

In patients with T1DM, the systolic BP response to exercise is abnormally exaggerated (9). Moreover, it has been demonstrated in STZ-induced T1DM rats that the circulatory and sympathetic responses to intra-arterial administration of the transient receptor potential cation channel subfamily V member 1 (TRPV1) agonist, capsaicin, is significantly enhanced as compared with control animals (68). In addition, the response of group IV afferents to capsaicin exposure has been shown to be significantly greater in T1DM than in control (68). TRPV1 is a metaboreceptor widely expressed in muscle afferents (69), and recent human studies support that TRPV1 contributes to EPR function in healthy subjects (70,71). Importantly, a recent study (72) using a novel TRPV1 null mouse model to directly study the EPR demonstrated that the metaboreflex is, in part, mediated by activation of TRPV1 in skeletal muscle afferents, consistent with a large number of previous studies in healthy (73) and hypertensive rats (60), with some exceptions (74). Therefore, sensitization of muscle afferents by TRPV1 action may contribute to the abnormal circulatory responsiveness manifest in T1DM (Fig. 1). STZ-induced T1DM animals display hyperglycemia but not hyperinsulinemia because STZ treatment mitigates or eliminates pancreatic production of insulin. This suggests that hyperglycemia, rather than insulin, contributes to the generation of abnormal cardiovascular responses in T1DM. Hyperglycemia leads to the formation and accumulation of advanced glycation end products (AGE) (75) and the inflammatory cytokine high-mobility group box-protein 1 (HMGB1) (76). Both AGE and HMGB1 bind to the receptors for advanced glycation end products (RAGE) (75,77). RAGE is known to stimulate phosphorylation of protein kinase C (PKC) (77), leading to induction of peripheral neuronal damage (78). Interestingly, evidence suggests that TRPV1 is activated by PKC in sensory neurons (79,80). In a previous study from our laboratory, plasma HMGB1 was found to be significantly higher in rats with T1DM than in control, whereas plasma AGE did not differ (68). These findings are consistent with reports that HMGB1 levels are increased in the plasma (81) and skin (82) of patients and animals with T1DM. It is

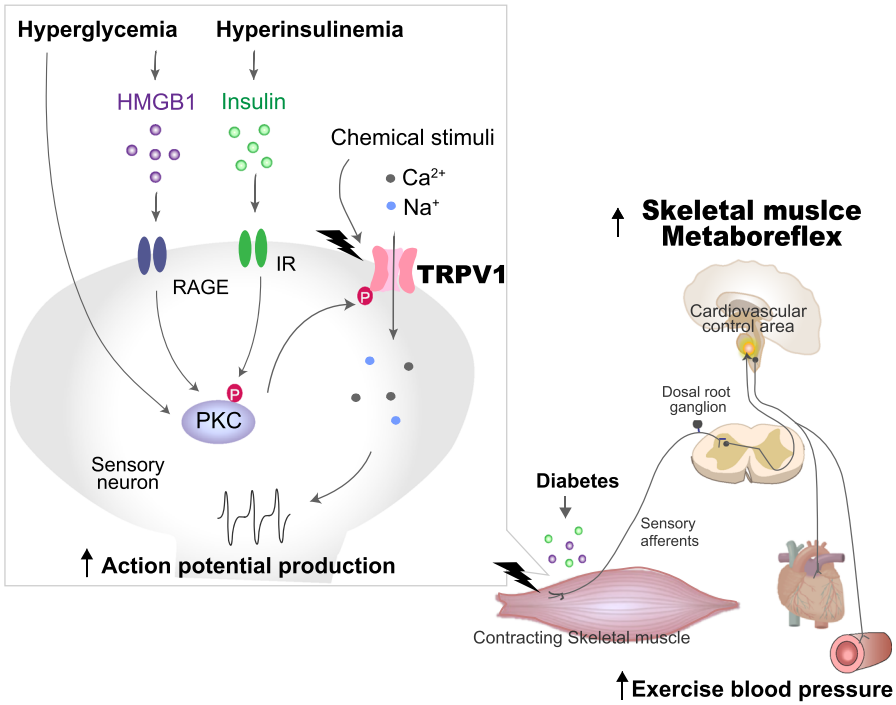

Figure 1. Peripheral mechanisms underlying exaggerated skeletal muscle metaboreflex function in diabetes. As depicted, it is proposed that potentiated skeletal muscle metaboreflex activity in diabetes is induced by the sensitization of transient receptor potential cation channel subfamily V member 1 (TRPV1) in skeletal muscle afferents. Hyperglycemia and hyperinsulinemia increase insulin, advanced glycation end products (AGE), and high-mobility group box-protein 1 (HMGB1). These substrates activate the protein kinase C (PKC)-TRPV1 pathway in sensory neurons. TRPV1 sensitization leads to an increase in Na^+/Ca^{2+} influx, which induces action potential firing in the afferent fiber. The action potentials in muscle afferents are transduced via the dorsal root ganglia (DRG) to the spinal cord and relayed to cardiovascular control areas in the brainstem, which, in diabetes, evokes an abnormal blood pressure (BP) response to exercise (*i.e.*, TRPV1-induced metaboreflex overactivity). IR, insulin receptor.

known that HMGB1 acts more rapidly to activate RAGE (77), whereas AGE must accumulate over time (75). In a previous investigation, we additionally observed that phosphorylated PKCα protein expression is upregulated in the dorsal root ganglia (DRG) of T1DM rats (68). Thus, in hyperglycemic T1DM, it is plausible to suggest that HMGB1 activation of RAGE rather than AGE contributes to the phosphorylation of PKC in DRG neurons, thereby contributing to augmentations in metaboreflex function.

Sensitized Afferent Discharge to Chemical Stimulation as Well as Potentiated Skeletal Muscle Metaboreflex Activity in T2DM

As indicated in the Table, Holwerda *et al.* (7) demonstrated that BP and muscle sympathetic nerve activity responses were heighted during postexercise muscle ischemia, an experimental paradigm designed to isolate the muscle metaboreflex, in patients with T2DM. The study further revealed that the increases in muscle sympathetic nerve activity during skeletal muscle metaboreflex activation were significantly correlated with fasting glucose, HbA1c, and HOMA-IR (7). This suggests that a heightened metabolic component of the EPR seems to be related to the severity of T2DM. However, the exact mechanisms underlying the potentiation in metaboreflex function in T2DM remain to be fully elucidated. To address this gap, recent preliminary data from our laboratory demonstrated that, *in vivo*, the BP and sympathetic responses to intra-arterial administration of the TRPV1 agonist capsaicin were abnormally potentiated in rats with T2DM (83,84). Furthermore, *in vitro*, TRPV1-induced action potential discharge was markedly increased in skeletal muscle group IV fibers isolated from animals with T2DM (84,85). In addition, the expression of phosphorylated TRPV1 and PKCα in DRG were enhanced in diabetic animals (84,85). These findings provide the first evidence suggesting that the function/activation of TRPV1 is increased in the skeletal muscle afferents of animals with T2DM. Interestingly, neither AGE, nor HMGB1, nor RAGE was different between controls and rats with T2DM (84,85). Unlike reported in T1DM, TRPV1 sensitization in mildly hyperglycemic early-stage T2DM might not occur as a result of RAGE/PKC signaling, but rather a completely different pathway. Most importantly, the discharge response to capsaicin administration was significantly associated with fasting blood glucose (84,85). Bestall *et al.* (82) recently demonstrated that in DRG neural cells (50B11) exposed to high-glucose conditions for 24 h, phosphorylation of TRPV1 (S800 site) was increased compared with basal glucose conditions. Moreover, high glucose induced phosphorylation of PKC in DRG neurons *in vitro* (86). We also recently confirmed that the discharge to capsaicin was potentiated by acute exposure of group IV afferents to a high-glucose environment (84). Thus, in mildly hyperglycemic, early-state T2DM, glucose/PKC signaling may contribute to neuronal sensitization via TRPV1. Taken together, it is suggested that the alterations observed in rats with T2DM are associated with hyperglycemia and likely play a role in mediating the enhanced BP response characteristics of this disease.

Peripheral hyperinsulinemia also is a pathophysiological characteristic of T2DM. In pilot studies, using whole-cell patch-clamp techniques, we investigated the impact of insulin on chemically activated currents in DRG neurons in normal animals. The total charge transfer induced by capsaicin-activated

current was significantly higher after insulin exposure than that of control (87). These changes were blocked by pretreatment with the insulin receptor inhibitor GSK1838705 (87). Likewise, in a muscle-nerve preparation, insulin administration also significantly increased the response magnitude of 1 μM capsaicin (87). Given these initial findings, it is possible that insulin also could potentiate TRPV1 activity, significantly contributing to an exaggerated expression of the muscle metaboreflex in T2DM.

MECHANISMS UNDERLYING ABNORMAL MECHANOREFLEX FUNCTION IN DIABETES

Mechano-Gated Channels and the Skeletal Muscle Mechanoreflex

The mechanism of mechanotransduction in skeletal muscle sensory afferents remains to be determined, although several possibilities have been suggested. TRPV2 was recently demonstrated to be required for mechanical nociception and the stretch-evoked response in primary sensory neurons (88). It also is worth noting that insulin has been shown to facilitate capsaicin-evoked TRPV1 responses and translocation of TRPV1 and TRPV2 to the cell surface in DRG neurons (27) and pancreatic cells (89). Thermally and chemically sensitive TRPV1 is likewise proposed to be mechanosensitive because it responds to cell deformation induced by hypertonicity (90). Therefore, it is possible that the insulin/TRPV pathways could be associated with the sensitization of mechanosensitive muscle afferents. Recent evidence suggests that mechano-gated PIEZO2 channels contribute to the expression of the muscle mechanoreflex in normal rats (91), as well as in rat models of peripheral artery disease (92) and T1DM (66). The PIEZO2 channel has been shown to be directly gated by mechanical stimuli (93). However, to our knowledge, there is no study investigating the possible interactions between PIEZO2 ion channels and the insulin signaling pathway. Cleary, further investigation is required.

Mechanisms Underlying the Sensitization of the Skeletal Muscle Mechanoreflex in T1DM

As shown in the Table, the BP response to exercise is exaggerated in T1DM (9). As mentioned previously, it is likely that an overactive EPR contributes to the potentiated pressor response (67). Consistent with the pioneering work of Grotle *et al.* (67), we recently demonstrated in rats with STZ-induced T1DM that the BP and renal sympathetic nerve activity (RSNA) responses to passive muscle stretch (a maneuver designed to preferentially stimulate the mechanoreflex) were significantly augmented compared with control animals (68). In addition, using an isolated muscle-nerve preparation, it was determined that the response of mechanosensitive group IV afferents to mechanical stimulation was likewise significantly enhanced in T1DM (68). As mentioned, rats with T1DM exhibit hyperglycemia due to the lack of insulin production/secretion in the pancreas. Thus, it is probable that hyperglycemia, rather than insulin, plays a crucial role in the generation of abnormal cardiovascular responses to exercise in T1DM. High glucose (86) and elevated glucose-induced increases in HMGB1 (76,78,94) are known to activate PKC in sensory neurons. Importantly, PKC activates PIEZO channels, one of the known mechanoreceptors (95). Moreover, PIEZO2 channels contribute to the expression of the mechanical component of the EPR in normal rats (91) and T1DM (66). As mentioned, we have previously observed an upregulation of PKCα protein in the DRG of animals with induced T1DM (68) and T2DM (96). In addition, we have demonstrated that plasma HMGB1 is increased in T1DM (96). Although speculative, it is possible that the glucose/PKC/PIEZO2 pathway could sensitize mechanosensitive sensory afferents in T1DM. Additional studies in this area are warranted in the future.

Mechanisms Underlying the Sensitization of the Skeletal Muscle Mechanoreflex in T2DM

In pilot studies with rats with T2DM, mechanoreflex activation by passive stretch evoked significantly greater increases in BP and RSNA (96). The response to mechanical stimulation was likewise significantly greater in group IV afferents from T2DM as compared with those from control animals (96). Collectively, these findings suggest that T2DM exacerbated the cardiovascular and sympathetic responses to stimulation of the mechanoreflex. Peripheral hyperinsulinemia associated with insulin resistance is a pathophysiological characteristic of T2DM. Insulin receptors are known to be expressed on DRG neurons (97–100) and peripheral nerves (98,100). In the presence of insulin, the sensitivity of TRPV1 is increased and its activation threshold reduced, making it more responsive to stimuli (27). Furthermore, TRPV2 is expressed in mechanosensitive primary afferent neurons (101,102). Taken together, it is hypothesized that insulin potentiates the response of thin fiber afferents to mechanical stimuli. To test this hypothesis, we recently performed whole-cell patch-clamp studies obtaining recordings from cultured small DRG neurons, observing mechanically activated currents induced by mechanical stimuli applied to the cell surface (103). Using this experimental paradigm, it was determined that insulin injection significantly augmented the amplitude of mechanically activated currents and decreased the mechanical threshold (103). More importantly, pretreatment with the insulin receptor antagonist, GSK1838705, significantly suppressed the insulin-induced potentiation of the mechanical responses (103). We further examined the impact of insulin on thin fiber muscle afferent activity in response to mechanical stimuli using rat muscle-nerve preparation. Likewise, insulin increased the sensitivity of mechanosensitive group IV muscle afferents as evidenced by a significant reduction in the response threshold to mechanical stimuli (103). Although speculative in nature, the observed insulin-induced mechanical sensitization of somatosensory thin fiber afferents may contribute to an augmentation in muscle mechanoreflex activity in hyperinsulinemic T2DM (8).

CENTRAL MECHANISMS OF ABNORMAL EXERISE BP IN DIABETES

Pioneering work by Holwerda *et al.* (7) showed that the muscle sympathetic nerve response to a cold pressor test was potentiated in patients with T2DM. This suggests that a heightened central sympathetic reactivity may be involved in exaggerated cardiovascular responses to exercise in this disease.

Role of Brain Insulin in the Regulation of the Sympathetic Nervous System During Exercise

It was previously thought that insulin in the brain did not play a significant regulatory role especially in cardiovascular control during exercise. However, recent evidence suggests that insulin not only regulates glucose and lipid metabolism but also modulates neural activity in the brain. To date, whether brain insulin modulates EPR activity remains undetermined although likely. Insulin enters the CNS via a saturable transport system (104,105), and its receptors are widely expressed in the brain including the medulla oblongata, the site of both the NTS and RVLM (106). The binding of insulin to its receptor activates phosphoinositide 3-kinase (PI3K) phosphorylating PIP2 (phosphatidylinositol 4,5-bisphosphate) to form PIP3 (phosphatidylinositol (3,4,5)-trisphosphate) (107,108). PIP3 directly activates ATP-sensitive potassium (K_{ATP}) channels (109,110), resulting in hyperpolarization and decreased neuronal firing rate. PIP3 also indirectly activates Akt signaling (107,108), resulting in activation of nitric oxide synthase (NOS). The resultant nitric oxide (NO) produced also activates K_{ATP} channels in neurons (111). A more recent study demonstrated that activation of K_{ATP} channels in the RVLM decreases basal BP and RSNA (23,112). The NOS inhibitor, *N*-nitroarginine methyl ester, partially attenuates these sympathoinhibitory effects (23). As more direct evidence, insulin administration into the RVLM significantly attenuates BP and sympathetic responses to electrical stimulation of the RVLM in cats (113). Furthermore, insulin-stimulated production of NO (26) increases its bioavailability in the brain. An increase in NO bioavailability in the NTS and RVLM decreases BP and sympathetic nervous system activity (114). It is plausible that the insulin signaling pathway in the brain contributes to the modulation of the sympathetic and pressor responses to exercise via its actions on the NTS and RVLM in the brainstem.

Dysfunctional Brain Insulin Signaling in T2DM

Numerous studies demonstrate that brain insulin signaling is significantly altered in T2DM. For example, insulin binding to brain capillaries is reduced in genetically obese hyperinsulinemic Zucker rats as compared with lean Zucker rats (115). Furthermore, in dogs, increased adiposity induced by high-fat feeding is associated with reduced insulin delivery to the CNS (116). These reports suggest that the chronic peripheral hyperinsulinemia associated with insulin resistance in T2DM results in hypoinsulinemia in the CNS (115,116). In contrast, insulin receptor expression in the brain is unlikely to be affected by T2DM (117,118). However, its downstream signaling cascade is impaired. For example, downregulation of key enzymes in the insulin signaling pathway, such as PI3K, Akt, and NOS, have been observed in human (118) and rat studies (64,117). Furthermore, insulin has been shown to activate K_{ATP} channels in hypothalamic neurons of lean but not obese rats (25). In addition, normotensive patients with T2DM exhibit sympathetic hyperactivity at rest, which is likely contributory to the development of essential hypertension (119). Together, these alterations in brain insulin signaling in T2DM may contribute to the exaggerated cardiovascular response to exercise.

FUTURE PERSPECTIVES

An increasing number of studies in diabetic patients and various animal models of diabetes suggest that EPR and CC dysfunction contributes significantly to the potentiated hemodynamic responsiveness during physical activity characteristic of the disease. To date, evidence elucidating both central and peripheral mechanisms underlying the pathogenesis of abnormal exercise BP in diabetes is just beginning to emerge. Aerobic exercise is more commonly prescribed in clinical practice rather than forms of resistance exercise. However, diabetes mellitus is an independent risk factor for low muscular strength. As such, a position statement by the American Diabetes Association recommends resistance training (*e.g.*, static/ischemic) as well for patients with T2DM (120). Combining endurance exercise with resistance exercise may provide greater improvements (121), and high-intensity interval training may be superior to continuous aerobic training in adults with diabetes (122). In addition, this is clinically important because isometric contractions are a component of many daily activities and are capable of inducing marked increases in BP even when performed with a small muscle mass (123). Therefore, dissection of the mechanisms underlying the abnormal cardiovascular response to both static and dynamic exercise in T2DM may prove beneficial to the development of novel therapeutic strategies targeted at reducing the risks associated with physical activity. This could lead to the prescription of exercise of greater frequency, intensity, and duration, allowing the benefits of exercise training to be fully realized in this disease.

Specifically, studies have demonstrated that EPR overactivity in diabetes is mediated, in part, by insulin, insulin resistance, or hyperglycemia. Continuous research likely will be beneficial to the development of novel therapies targeted at reducing the risks associated with physical activity in this disease. For example, it has been demonstrated recently that desensitization of TPRV1 in cardiac afferent neurons by resiniferatoxin exhibits protective effects against autonomic dysfunction in heart failure animals (124,125). Furthermore, ablation of cardiac afferent nerves by resiniferatoxin at the level of the upper thoracic DRG can prevent the development of hypertension in spontaneously hypertensive rats (126). We previously demonstrated that blockade of TRPV1, which contributes significantly to EPR activation (73), significantly reduced pressor and sympathetic responses to suprastimulation of the metaboreflex (via ischemic hindlimb muscle contraction) in spontaneously hypertensive rats (60). Therefore, further investigation as to whether antagonism of hyperinsulinemia/hyperglycemia-induced sensitization of TRPV and mechano-gated channels ameliorates abnormal EPR function in diabetes may prove valuable in facilitating favorable clinical outcomes when physical activity is part of the prescribed treatment regimen (Figs. 1, 2). Hyperglycemia activates superoxide production (127,128). Increasing evidence suggests that oxidative stress in the exercising muscle modulates the EPR function in disease states associated with excessive oxidative stress such as hypertension (129), heart failure (130), and peripheral arterial disease (131). Further investigation is needed to examine if hyperglycemia-induced oxidative stress potentiates EPR function in diabetes.

Evidence suggests that central insulin resistance is a potentially important factor in the pathophysiology of obesity, systemic insulin resistance (a common comorbidity of T2DM),

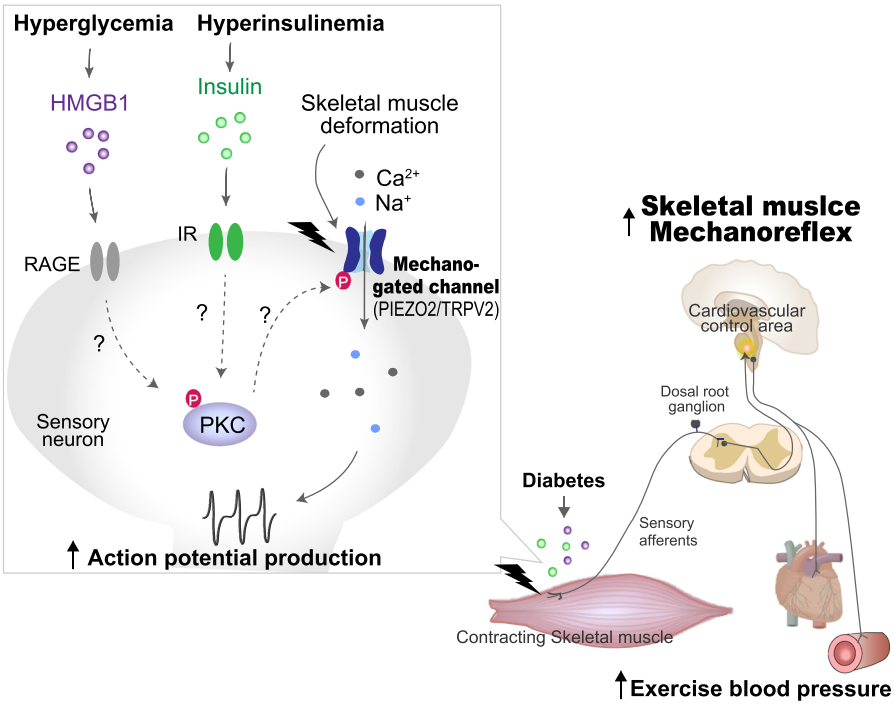

Figure 2. Peripheral mechanisms underlying exaggerated skeletal muscle mechanoreflex function in diabetes. As depicted, it is proposed that augmented skeletal muscle mechanoreflex activity in diabetes is induced by the sensitization of mechano-gated channels in skeletal muscle afferents. Hyperglycemia and hyperinsulinemia increase insulin and high-mobility group box-protein 1 (HMGB1). These substrates may activate protein kinase C (PKC) phosphorylated mechanoreceptors in sensory neurons. The sensory signals generated by activation of mechanoreceptors (PIEZO and TRPV2) in skeletal muscle are transduced via the dorsal root ganglia (DRG) to the spinal cord and relayed to cardiovascular control areas in the brainstem, which, in diabetes, evokes an abnormal BP response to exercise (*i.e.*, TRPV1-induced mechanoreflex overactivity). IR, insulin receptor.

and cognitive impairments (*e.g.*, Alzheimer disease). Intranasal delivery of insulin is a noninvasive technique that bypasses the blood-brain barrier and delivers insulin from the nasal cavity to the CNS via intraneuronal and extraneuronal pathways. Intranasal administration of insulin to the brain greatly impacts cognitive function and peripheral metabolism (132). For example,

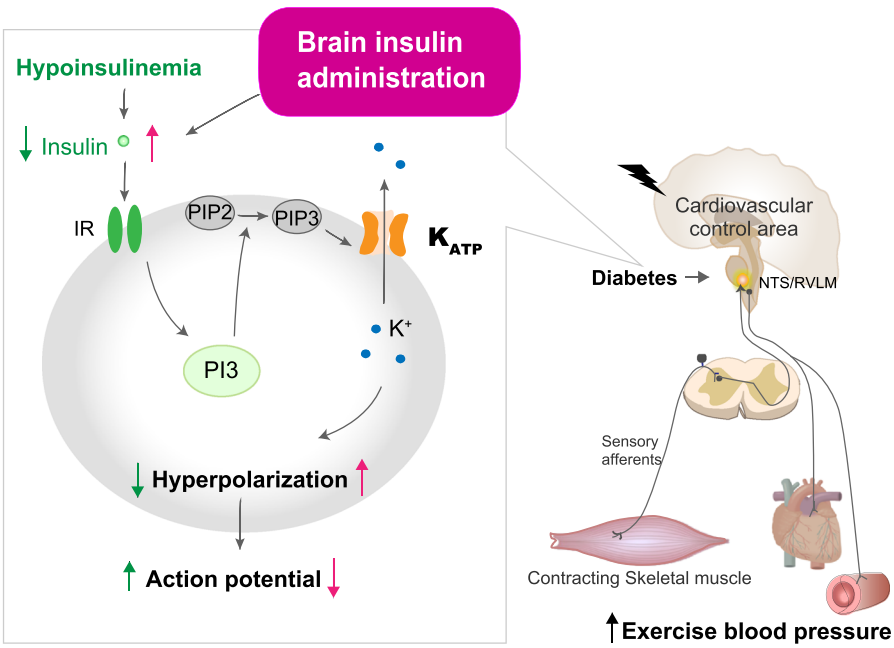

Figure 3. Central mechanisms of exaggerated cardiovascular responses to exercise in diabetes. As depicted, it is proposed that the brain insulin signaling pathway contributes to the modulation of the blood pressure (BP) responses to exercise in diabetes. The binding of insulin to IR activates phosphorylating PIP2 to form PIP3. PIP3 directly activates K_{ATP} channels, resulting in hyperpolarization and decreased neuronal firing rate. Central hypoinsulinemia induced by diabetes, therefore, may lead to the pathogenesis of abnormally enhanced cardiovascular responses to physical activity via the central nervous system (CNS). Administration of insulin to the whole brain or the NTS/RVLM may be effective in ameliorating this exaggerated exercise BP response in diabetes. IR, insulin receptor.

intranasal insulin treatment for 21 d improves cognition for adults with mild cognitive impairment or early-stage Alzheimer disease dementia (133). In animal studies, long-term treatment with intranasal insulin ameliorates cognitive impairment in an STZ-induced Alzheimer rat model (134). To date, there is no report suggesting that nasal insulin treatment improves insulin resistance–induced autonomic nervous system dysfunction in T2DM. However, it is logical to suggest that central insulin treatment may attenuate the overactive exercise BP in T2DM by improving brain insulin signaling (Fig. 3). Pilot studies in our laboratory have demonstrated that the pressor and sympathetic responses to activation of the EPR were significantly attenuated 2 h after intracerebroventricular injection of insulin in T2DM but not control animals (63). This finding suggests that brain insulin contributes to the modulation of the BP response to EPR activation in T2DM. Moreover, central delivery of insulin ameliorates CC and EPR overactivity in T2DM. It is of note that pilot data were obtained using an acute delivery of insulin centrally, and the impact of a more chronic administration needs to be investigated. In addition, further study is required to determine which brain regions (*e.g.*, NTS and RVLM) are involved in this response. As recent studies suggest that glutamatergic *N*-methyl-D-aspartate (135) or melanocortin receptor 3/4 (136) in the hypothalamic paraventricular nucleus contributes to insulin-induced sympathetic responses, these receptors could be specific targets for central insulin treatment in this disease. It has been reported that lumbar but not renal sympathetic nerve is particularly sensitive to insulin in rodents (21). It is physiologically and clinically relevant to clarify impacts of central insulin on differential sympathetic outflow to internal organs or exercising skeletal muscle especially during exercise.

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