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The Classically Cardioprotective Agent Diazoxide Elicits Arrhythmias in Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND Type 2 diabetes mellitus (T2DM) is associated with an enhanced propensity for ventricular tachyarrhythmias (VTs) under conditions of metabolic demand. Activation of mitochondrial adenosine triphosphate-sensitive potassium (K_{ATP}) channels by low-dose diazoxide (DZX) improves hypoglycemia-related complications, metabolic function, and triglyceride and free fatty acid levels and reverses weight gain in T2DM.

OBJECTIVES In this study, we hypothesized that DZX prevents ischemia-mediated arrhythmias in T2DM via its putative cardioprotective and antidiabetic property.

METHODS Zucker obese diabetic fatty (ZO) rats (n = 43) with T2DM were studied. Controls consisted of Zucker lean (ZL; n = 13) and normal Sprague-Dawley (SprD; n = 30) rats. High-resolution optical action potential mapping was performed before and during challenge with no-flow ischemia for 12 min.

RESULTS Electrophysiological properties were relatively stable in T2DM hearts at baseline. In contrast, ischemia uncovered major differences between groups, because action potential duration (APD) in T2DM failed to undergo progressive adaptation to ischemic challenge. DZX promoted the incidence of arrhythmias, because all DZX-treated T2DM hearts exhibited ischemia-induced VTs that persisted on reperfusion. In contrast, untreated T2DM and controls did not exhibit VT during ischemia. Unlike DZX, pinacidil promoted ischemia-mediated arrhythmias in both control and T2DM hearts. Rapid and spatially heterogeneous shortening of APD preceded the onset of arrhythmias in T2DM. DZX-mediated proarrhythmia in T2DM was not related to changes in the messenger ribonucleic acid expression of Kir6.1, Kir6.2, SUR1A, SUR1B, SUR2A, SUR2B, or ROMK (renal outer medullary potassium channel).

CONCLUSIONS Ischemia uncovers a paradoxical resistance of T2DM hearts to APD adaptation. DZX reverses this property, resulting in rapid and heterogeneous APD shortening. This promotes reentrant VT during ischemia. DZX should be avoided in diabetic patients at risk of ischemic events. (J Am Coll Cardiol 2015;66:1144–56) © 2015 by the American College of Cardiology Foundation.

Type 2 diabetes mellitus (T2DM) is a multifactorial disease process that encompasses hyperglycemia, dyslipidemia, and hyperinsulinemia. Collectively, these factors produce a malignant environment marked by oxidative stress (1). Although patients with T2DM are more vulnerable to ischemic injury than nondiabetic people (2), the detailed electrophysiological substrate of T2DM hearts and their response to ischemia are poorly defined.

Because T2DM affects multiple organ systems, its pharmacological management is fraught with cardiovascular complications (3,4). One promising strategy is the use of the potassium channel agonist diazoxide (DZX), which improves the metabolic function of Otsuka Long-Evans Tokushima fatty rats by restoring their triglyceride and free fatty acid levels and reversing their weight gain and diabetes status (5). The antidiabetic efficacy of DZX is linked to preservation of pancreatic beta cells through promotion of

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beta cell rest and inhibition of apoptosis (5). These mechanistic studies in animal models are being rapidly translated to humans. In a proof-of-principle trial, healthy people who received oral DZX (4 mg/kg) exhibited a 30% decrease in glucose production, with no difference in the rate of glucose uptake compared with placebo-treated counterparts (6). Moreover, DZX reversed weight gain in prediabetic obese, hyperinsulinemic people (7,8). The therapeutic utility of DZX was also tested in patients with type 1 diabetes mellitus (T1DM) (9) and in those undergoing coronary bypass surgery (10). Radtke et al. (9) reported that treatment of newly diagnosed T1DM patients with DZX for 6 months improved their glycemic control without affecting their beta cell function. Finally, in a double-blinded randomized study, supplementation of cardioplegia with low-dose DZX protected cardiac mitochondria, metabolism, and function in patients undergoing cardiac bypass surgery (10).

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These highly encouraging clinical findings likely stem from the activation of cardioprotective signaling via mitochondrial adenosine triphosphate-sensitive potassium (mK_{ATP}) channels by DZX (11–19). However, at high concentrations (300 μmol/l), DZX was shown to promote arrhythmias in coronary-perfused atria and ventricles from failing and nonfailing human hearts by activating sarcolemmal (as opposed to mitochondrial) K_{ATP} channels (20).

We hypothesized that owing to its dual nature as an antidiabetic and cardioprotective agent, low-dose (30 μmol/l) DZX may be particularly useful in suppressing ischemia-related arrhythmias in T2DM without altering basal electrophysiology. Contrary to our original hypothesis, we uncovered a potent proarrhythmic effect of DZX exclusively in T2DM hearts during challenge with ischemia. Our findings raise major concerns regarding the safety profile of mK_{ATP} channel activation in T2DM patients at risk of ischemic injury.

METHODS

EXPERIMENTAL RAT MODEL OF T2DM. All procedures involving animal handling were approved by the Animal Care and Use Committee of the Icahn School of Medicine at Mount Sinai and adhered to the *Guide for the Care and Use of Laboratory Animals* published by the U.S. National Institutes of Health. All animals were purchased from the Charles River Laboratory (Wilmington, Massachusetts). We used 12- to 16-week-old male Zucker obese diabetic fatty (fa/fa) rats (ZO) (n = 43) as a standard model of established insulin resistance and T2DM. This model faithfully recapitulates hallmark features of the clinical disease, including hyperinsulinemia, dyslipidemia, and hyperglycemia (21). Age- and sex-matched Zucker lean (ZL) (n = 13) and normal Sprague-Dawley (SprD) (n = 30) rats were also used. In a subset of experiments involving 6 ZL and 7 SprD rats, we found no significant differences in electrophysiological parameters, including action potential duration at 50%, 75% (APD_{75}), and 90% of repolarization and conduction velocity (CV). Marked hyperglycemia and weight gain in the absence of hypertrophy were confirmed in T2DM compared with control rats (Table 1).

OPTICAL ACTION POTENTIAL MAPPING OF EX VIVO PERFUSED HEARTS. Hearts were excised rapidly and Langendorff perfused with Tyrode's solution containing 121.7 mmol/l NaCl, 25.0 mmol/l $NaHCO_3$, 2.74 mmol/l $MgSO_4$, 4.81 mmol/l KCl, 5.0 mmol/l dextrose, and 2.5 mmol/l $CaCl_2$ (pH 7.40; 95% O_2/5% CO_2). Atria were removed to avoid competitive stimulation of the ventricles. Perfusion pressure was maintained at 60 to 70 mm Hg by regulating coronary perfusion flow.

Preparations were placed in a custom-built tissue bath and pressed gently against a glass imaging window by a stabilizing piston (22–26). Movement was suppressed by perfusion with blebbistatin 10 μmol/l for 10 to 15 min. To avoid surface cooling, preparations were immersed in the coronary effluent maintained at a physiological temperature by a heat exchanger assembly (22). Cardiac rhythm was monitored continuously via silver electrodes connected to an electrocardiogram amplifier. Cardiac rhythm, perfusion pressure, and flow were monitored continuously during each experiment.

TABLE 1 Average BW, HW, Ratio of BW to HW, and Blood Glucose Levels of T2DM and Control Animals

	T2DM	Control
BW (g)	410 ± 65	283 ± 29
HW (g)	1.6 ± 0.1	1.2 ± 0.1
HW/BW, mg/g	3.9 ± 0.3	4.3 ± 0.2
Glucose, mg/dl	408 ± 119	128 ± 14
Age, weeks	13–16	13–14

BW = body weight; HW = heart weight; T2DM = type 2 diabetes mellitus.

ABBREVIATIONS AND ACRONYMS

APD = action potential duration

APD_{75} = action potential duration at 75% of repolarization

CV = conduction velocity

DZX = diazoxide

K_{ATP} channel = adenosine triphosphate-sensitive potassium channel

mK_{ATP} = mitochondrial adenosine triphosphate-sensitive potassium

mRNA = messenger ribonucleic acid

PCL = pacing cycle length

PCR = polymerase chain reaction

ROMK = renal outer medullary potassium channel

SprD = Sprague-Dawley

T1DM = type 1 diabetes mellitus

T2DM = type 2 diabetes mellitus

VT = ventricular tachyarrhythmia

ZL = Zucker lean (rat)

ZO = Zucker obese diabetic fatty (rat)