Increased risk of Torsades de Pointes in streptozotocin-induced diabetic rats.

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ABSTRACT

Insulin-dependent diabetes mellitus (type 1 diabetes) is associated with a variety of complications including cardiac rhythm anomalies. For instance, the prevalence of QT interval prolongation is higher in patients with type 1 diabetes. In this study, male Sprague-Dawley rats were administered two doses of 45 mg/kg streptozotocin to destroy their pancreatic beta cells. After 3 days post induction, the animals were implanted with subcutaneous osmotic pumps to maintain serum levels at 10 mmol/L of insulin. The animals were anesthetized weekly with isoflurane and carprofen and all rats were monitored for 6 weeks post-induction. ECGs were recorded using a 4 channel ECG system and the QT intervals were measured automatically for atrial and ventricular conduction intervals. Monitoring of blood glucose levels using OneTouch Verio IQ test strips showed that the glucose levels were either unchanged, or slightly lower in diabetic rats than in non-diabetic rats. In a parallel investigation, type-2 diabetes (insulin-resistant) was induced in adult male rats and ECG recordings were monitored weekly. After 6 weeks post induction, the QT intervals were measured using Van de Water’s formula, which were essentially identical (27 and 26 ms, respectively). Insulin-dependent regulation of genes expressing cardiac ion channel expression (Chen 2012) thus appear to be one of the mechanisms involved in QTc prolongation in diabetic patients.

INTRODUCTION

It has been reported that both type 1 and type 2 diabetes mellitus are associated with increased risk of sudden cardiac death independent of diabetes complications, hyperglycemia, hypertension or heart rate (Karm 1992). Indeed, diabetes mellitus type 1 is strongly associated with increased risk of sudden cardiac death (Veglio 2000). This means that current preclinical safety testing, as well as clinical early warning systems for cardiac arrhythmias, may not be sufficient to identify drug-induced QT interval prolongation in diabetic patients. Therefore, the aim of the present study was to establish the molecular mechanism by which streptozotocin (STZ) induces QT interval prolongation in type 1 diabetic rats.

METHODS

Induction of Type-2 Diabetes Mellitus in rats

Eight (8) adult, male Sprague-Dawley (Charles River) rats (average body weight 250 ± 50 g) were used for this study. Rats were anesthetized with sodium pentobarbital (50 mg/kg) and the left common carotid artery and the left external jugular vein were cannulated. After a 12-h fast, rats were injected with a single 45 mg/kg injection of streptozotocin (STZ). The animals’ diabetic state was assessed by daily monitoring of blood glucose levels using the Accu-Chek® test strips. Within 24 hours, blood glucose in STZ animals exceeded 33 mmol/L, and animals were provided with a 20% reconstituted Ensure® formula (Ross Laboratories, Columbus, Ohio) solution, set to disperse 2 units/day for approximately 30 days. This maintained blood glucose levels elevated within the range of detecting pathologically high blood glucose levels higher than 20 mmol/L were considered diabetic eligible for the study. These animals were maintained in a pathologically stable condition for 6 weeks post induction.

ECG recordings

ECGs were recorded using a 4 channel ECG system and the QT intervals were measured automatically for atrial and ventricular conduction intervals. Monitoring of blood glucose levels using OneTouch Verio IQ test strips showed that the glucose levels were either unchanged, or slightly lower in diabetic rats than in non-diabetic rats. In a parallel investigation, type-2 diabetes (insulin-resistant) was induced in adult male rats and ECG recordings were monitored weekly. After 6 weeks post induction, the QT intervals were measured using Van de Water’s formula, which were essentially identical (27 and 26 ms, respectively). Insulin-dependent regulation of genes expressing cardiac ion channel expression (Chen 2012) thus appear to be one of the mechanisms involved in QTc prolongation in diabetic patients.

DISCUSSION

Diabetes and prolonged QTc intervals

Clinical evidence is abundant in support of a cardiac conduction irregularities in diabetic patients. Repolarisation abnormalities, including mild prolongation of the QT interval have been described in patients with diabetes mellitus (Grum, 2001). Both type 1 and type 2 diabetes mellitus are associated with increased risk for sudden cardiac death (Gill, 2008), which is not attributable to general pathophysiological changes, such as atherosclerosis, hypertension or hyperlipidaemia, or other specific ion channels commonly observed in diabetes. The reduction of IKr and Icl in different diabetic animal models (Shimoz, 1999) can explain the prolongation of the QTc in diabetes mellitus, which may contribute to reduced repolarisation reserve in diabetes mellitus (Langel et al. 2007).

Diabetes-induced QTc prolongation in rats

The not a commonly used species in preclinical and toxicology assays, whereas a common used species in diabetes research is the rat. The rat is a commonly used diabetes model rat is insulin-deprived streptozotocin-induced diabetes (STZ-induced diabetes) model. This model is rat and diabetes model animals (Shimoz, 1999) can explain a prolonged QT interval (QTc) in type 1 diabetic rats, but failed to do so in type 2 diabetic rats.

Potential role of insulin in the differences between both rat models of insulin.

Since the presence of insulin is the source of the differences between the two types of diabetes (Henn, 1992), we suggest that its role in altering ion channel expression may play the absence of the potential role of insulin. In type 1 diabetic rats, the transient outflow current, and delayed rectifier currents, Icl, action potential and QTc interval. In contrast, in type 2 diabetic rats, Icl is unaltered, while Ikr is either unaltered, or slightly enhanced. The difference in QTc interval is prolonged, potentially as a result of autonomic disturbance and cardiac remodeling (Robl, 1994).

Insulin levels can be controlled in diabets in current variations in animal models (Shimoz, 1999), and the insulin levels in type 1 diabetic rats show a strong decline. The insulin levels in type 2 diabetic rats can be controlled by pancreatic insulin level and Icl. Therefore, the current variations in type 1 and type 2 diabetic rats can be controlled and type insulin of type 1 diabetic rats.

Importantt, EuR to may raise the dose-limiting QTc interval to a point where treatment is therefore dependant on the use of additional inhibitors to drugs, such as diabetic patients with a decreased repolarisation reserve.

Next steps

Characterization of the one and type 2 animal models will continue; insulin levels need to be controlled, as for the HbA1c levels (glycated hemoglobin). In addition to our current blood glucose measurements, further, our current expression pattern of insulin (mRNA) for pancreatic insulin will be quantified. The expression pattern in type 1 diabetic rats will continue with direct patch clamp assays on Ikr and Icl, and attempts to establish the molecular mechanism by which insulin to act the NERG inhibition, and QT prolongation, induced by multiple drugs.

REFERENCES