

Review Article

Sympathetic nerve activity in type 2 diabetes mellitus; a promising potential therapeutic target

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Abstract

Augmented sympathetic nerve activity (SNA) has an important effect on various diseases. SNA is significantly related to glucose metabolism in type 2 diabetes mellitus (DM). Type 2 DM causes cardiovascular complications such as heart failure, arrhythmia, and myocardial infarction. These complications are reported to be associated with increasing SNA. Previous studies have not shown a beneficial effect of insulin and conventional sulfonylurea therapy on cardiovascular mortality and morbidity. In previous studies, the principal therapeutic target in type 2 DM is recognized as lowering glycemic control. However, there is a lack of evidence for improvement of SNA and glycemic control in type 2 DM. Therefore, additional therapeutic strategy is required to prevent major cardiovascular complications in type 2 DM. In this review, we reconsidered effect of conventional anti-diabetic drugs on SNA and also discuss the risk and benefit of using beta blockade in the treatment of type 2 DM patients.

Introduction

Augmented sympathetic nerve activity (SNA) has an important effect on various diseases such as heart failure [1,2], hypertension [3], metabolic syndrome [4], and type 2 diabetes mellitus (DM) [5]. In heart failure patients, the sympathetic activation initially plays a compensatory role in acute decompensate state but increased SNA in chronic state is associated with adverse consequences at both cardiac and vascular levels which may aggravate the clinical status and negatively affect prognosis [6]. Sympathoexcitation induces also fatal arrhythmia [2,7]. It is well known that reducing SNA with beta blockade improve prognosis in heart failure. Beneficial effects of beta blockade have been reported. In CIBIS-II trial, bisoprolol showed 44 percent risk reduction of death [8]. In COPERNICUS trial, 35 percent decrease in the risk of death with carvedilol compared with placebo [9]. Likewise in type 2 DM, it is considered to be crucial to improve augmented SNA, which might contribute to better prognosis.

Type 2 DM causes cardiovascular complications that are related to mortality and morbidity. Previous studies have not shown a beneficial effect of insulin and conventional sulfonylurea therapy on cardiovascular mortality and morbidity [10,11]. Therefore, additional therapeutic strategy is required to prevent major cardiovascular events in type 2 DM, and one of the targets might be sympathetic nerve activity.

In this review, we reconsidered effect of conventional anti-diabetic drugs on SNA and also discuss the risk and benefit of using beta blockade in the treatment of type 2 DM patients.

Insulin Activates Sympathetic Nerve Activity

In type 2 DM patients sympathetic nerve activity is higher than normal subjects [12]. Anderson et al. reported that acute increase of plasma insulin elevated muscle sympathetic nerve activity (MSNA) in healthy young control [13]. There are three pathways by which insulin activates sympathetic nerve activity; one is a direct effect on

central nervous system [14], the others is hypoglycemia by insulin [15], and finally, feedback mechanism against vasodilatation induced by insulin [13]. Increased insulin resistance observed in the patient, such as obese, requires more insulin which activates sympathetic nerve activity.

Many types of anti-diabetic drugs are available to lower blood glucose. However, little is known about anti-diabetic drugs affect sympathetic nerve activity for treatment of type 2 DM patients.

Relationship Anti-Diabetic Drugs With Sympathetic Nerve Activity

Sulfonylurea

It was shown that sulfonylurea stimulate beta cell in pancreas, leading to lowering blood glucose. Sulfonylurea developed positive inotropic effect and increasing blood pressure without the mediation of glucagon, insulin, or adrenaline in dogs [16]. In human study, glibenclamide therapy is associated with greater responses of blood pressure and higher nocturnal blood pressures [17]. In the study, plasma insulin levels were significantly higher during glibenclamide treatment. The relationship blood pressure and plasma insulin was unclear, but hypoglycemia might induce the response. There is no report about the direct effect on central nervous system. However, sulfonylurea might increase the secretion of insulin, which might contribute to sympathoexcitation.

Biguanide

Metformin significantly increased insulin-stimulated glucose transport by 2.6 fold in rats, resulting in improvement in insulin resistance [18]. Intravenous administration of metformin decreased arterial pressure and sympathetic nerve activity [19]. With improvement in insulin resistance, metformin decreased blood pressure in diabetic hypertension patients [20]. Resting MSNA, total body and right renal norepinephrine spillover did not differ significantly after placebo and metformin treatment [21]. In

meta-analysis, metformin reduced systolic and diastolic pressure. Metformin treatment was associated with a significant improvement in cardiac sympathovagal balance [22].

Its effectiveness was seen especially in type 2DM patients with obesity. UKPDS study was performed in obese type 2 DM, cardiovascular event decreased in metformin group [11]. These results suggest that metformin affect not only diabetic profiles but also improvement in sympathetic activity, which contribute to favorable outcomes

Alpha-glucosidase inhibitor

STOP-NIDDM trial showed that acarbose treatment in patients with impaired glucose tolerance (IGT) is associated with a significant reduction in the risk of developing diabetes, hypertension, and cardiovascular complications [23]. Acarbose acts as an alpha-glucosidase inhibitor (GI) and slows the digestion of starch in the small intestine without reducing insulin release [24] or insulin sensitivity [25]. This study was performed in IGT subjects, so early intervention is associated with preventing progression of macro vascular disease. From our previous study, MSNA was significant higher in type 2 DM patient even treated with alpha-GI group compared to healthy control (Figure) [5].

Thiazolidinedion

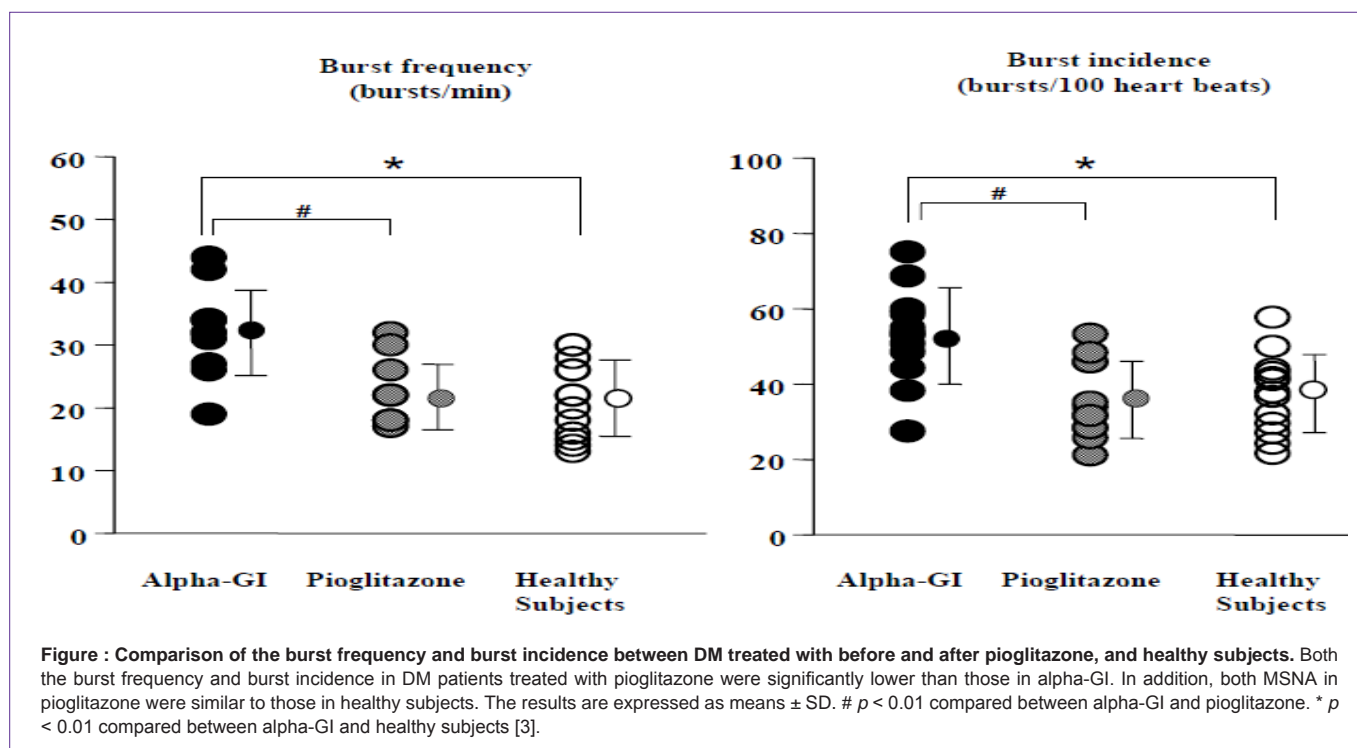
Proactive study showed that pioglitazone, which acts on peroxisome proliferator responsive elements, reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 DM at a high risk of macrovascular events [26]. One possible explanation for the reduction in cardiovascular events is thought to be the improved serum insulin level and insulin resistance. In our previous study, pioglitazone significantly decreased MSNA and

homeostasis model assessment of insulin resistance index (HOMA-IR) in DM patients compared with alpha-GI (Figure) [5]. In addition, a significant relationship was found between the absolute change in MSNA and HOMA-IR. These results indicate that improvement in insulin resistance is associated with reduction in sympathetic nerve activity.

Incretin related drugs

Glucagon like polypeptide-1 (GLP-1) is one of the incretin hormones, which act on pancreas to secrete insulin. In human, GLP-1 was reported to increase MSNA but did not affect cardiac sympathetic and parasympathetic indices, as assessed by spectral analysis [27]. Two types of incretin related drugs are developed; one is GLP-1 mimetic, the other is dipeptidyl peptidase-4 (DPP-4) inhibitor. Recently, Saxagliptin, one of DPP-4 inhibitors, did not improve the rate of cardiovascular events [28]. There is no study about how these drugs effect on sympathetic nerve activity. However, insulin secretion is promoted by these drugs, so that it is likely that SNA might be increased.

In terms of insulin secretion, these drugs are assumed to be divided into two groups. Sulfonylurea and incretin related agents are categorized as the drugs which stimulate insulin secretion. They might have a potential ability of sympathoexcitation via elevation of serum insulin. Metformin and pioglitazone are included in the drugs that improve the insulin resistance and the reducing requirement of insulin. Alpha-GI inhibits the overshoot of postprandil hyperglycemia, and does not affect insulin secretion or insulin sensitivity. So far, there is no report that former group improve cardiovascular event in the treatment of type 2 DM. Thus, it is important to consider the interaction of SNA and insulin.



The role of beta blockade in DM

The augmentation of sympathetic nerve activity in type 2 DM patients is mainly caused by elevated serum insulin induced by insulin resistance. From the point of view, thiazolidinedion or biguanide that improve insulin resistance are thought to be superior to the drugs which secrete insulin. Taken together, the role of beta blockade in treatment with DM is warranted to be reconsidered as potential therapeutic agents as well as diabetic agent. In fact, beta blockade negatively affects glucose metabolism. Insulin release is suppressed by blocking of beta 2 receptor. Blood flow of skeletal muscles is decreased by vasoconstriction with relative alpha effect. Insulin resistance is increased by decline of metabolism in the tissues in association with reduced blood flow to peripheral muscles. Kjekshus et al reported that beneficial effect of beta blockade on one-year mortality was greater in MI patients with diabetes than without diabetes [29]. This fact indicated that the treatment with beta blockade provide an additional favorable effect in DM patients complicated with heart failure or ischemic heart disease. Insulin resistance was elevated by almost types of beta blockade. For avoiding these adverse effects to glucose metabolism, beta 1 selective type blockade was reported to be promising. Agent with alpha blockade effect is also thought to be better. Actually, in Glycemic Effects in Diabetes Mellitus; Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, haemoglobin A1c elevated in metoprolol time dependently [30]. However, in carvedilol haemoglobin A1c did not change and improved insulin resistance. In COMET, new onset diabetes was lesser in carvedilol group than metoprolol group [31].

Conclusion

It is important to recognize that we should treat type 2 DM for the purpose of not only reducing blood glucose but also improving SNA. The anti-diabetic agent should be selected with considering insulin resistance related with sympathoexcitation. We also emphasized that beta blockade provide favorable outcomes to treat type 2 DM patients complicated with cardiovascular diseases.

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