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COMMENTARY

Tuning in to the 'right' calcium channel regulation in experimental models of diabetes

M Sturek

Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence
Michael Sturek, Department of Cellular and Integrative Physiology, Indiana University School of Medicine, 635 Barnhill Drive, Room 385, Indianapolis, IN 46202-5120, USA. E-mail: msturek@iupui.edu

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Elucidation of cellular and molecular mechanisms underlying vascular disease is of fundamental importance to the development of pharmacological agents to target these pathways. Pinho *et al.* in this issue of the *BJP* provide highly compelling evidence that the δ isoform of phosphatidyl inositol 3-kinase (PI3K δ) was upregulated and accounted for the increase in L-type, voltage-gated, Ca channel current in aortic vascular smooth muscle (VSM) cells of a mouse model of type 1 diabetes. There are several key issues of broad fundamental significance to this work. Firstly, what is the 'right' answer about calcium channel regulation in diabetes? Conflicting reports of increased and decreased Ca channel current may be due to specificity of the vascular bed and species. Then, the time course of diabetic vasculopathy may influence the expression of contractile versus proliferative phenotypes of VSM. Also the metabolic characterization of diabetes may enlighten or confound any study of diabetic vascular disease. These issues need attention to move forward work in this area.

LINKED ARTICLE
This article is a commentary on Pinho *et al.*, pp. 1458–1471 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2010.00955.x

Abbreviations
PI3K, phosphatidyl inositol 3-kinase; VSM, vascular smooth muscle

It is widely known that vascular disease is a major complication in patients with diabetes and poor glycaemic control. Elucidation of cellular and molecular mechanisms underlying vascular disease therefore is of fundamental importance to the development of pharmacological agents to target these pathways. Indeed, adjunct pharmacotherapy to ameliorate vascular complications would be especially beneficial because the large majority of type 1 diabetic patients do not achieve optimal glycemic control (Buse *et al.*, 2007). In this issue of the *BJP*, Pinho *et al.* (2010) provide highly compelling evidence that phosphatidyl inositol 3-kinase δ (PI3K δ) was upregulated and accounted for the increase in L-type voltage-gated Ca channel current in aortic vascular smooth muscle (VSM) cells of a mouse model of type 1 diabetes. Robustly increased contractions to high K^+-induced depolarization and phenylephrine occurred in parallel in aorta of diabetic mice. A selective pharmacological inhibitor of the PI3K δ isoform, LY294002, applied *in vitro* and antisense oligonucleotides to PI3K δ applied *in vivo* normalized Ca currents and contractile responses of aorta from diabetic mice. These results raise several important issues in the wider context of diabetic vascular complications.

1. What is the 'right' answer about calcium channel regulation in diabetes?

There are conflicting reports of increased (Navedo *et al.*, 2010) and decreased (Witczak *et al.*, 2006)

L-type voltage-gated Ca channel current in VSM in diabetes. It seems that specificity of the vascular bed and species may be involved, as increased Ca current was found in mouse cerebral artery (Navedo *et al*., 2010) and aorta (Pinho *et al*., 2010), while decreased Ca current was found in pig coronary conduit artery VSM (Witczak *et al*., 2006). Overall, studies in large animal models more closely mimicking humans that have clearly separated hyperglycaemia from other factors in the diabetic milieu, such as lipids, have shown that hyperglycaemia alone did not elicit macrovascular atherosclerosis (Gerrity *et al*., 2001; Mokelke *et al*. 2003). However, it is clear from large-scale clinical trials in humans that hyperglycaemia more strongly predicts microvascular disease (Brown *et al*., 2010). Do mouse arteries more accurately represent the human microvasculature, thus the sensitivity to hyperglycaemia-induced dysfunction in diabetics? This debate will not be resolved in this commentary, but should be considered in future studies.

2. Time course of diabetic vasculopathy

The impairment of endothelium-dependent relaxation is virtually a hallmark of diabetic vascular disease. Data from Pinho *et al*. (2010) showing lack of impairment might be viewed as a divergence from the large number of earlier reports, thus clouding the overall picture of diabetic vascular disease in their model. The authors are to be complimented on reporting this, especially, as they noted, it was accompanied by increased vasoconstrictor responses. In this context it is absolutely essential to refer to a detailed systematic comparison showing that increased, no change and decreased endothelium-dependent relaxation was completely dependent on the duration of diabetes (Pieper, 1999). The implication is that analogous divergence of VSM function and Ca channel regulation could occur in Pinho's study. Alternatively, is the increased contractile phenotype and VSM Ca channels, in the Pinho *et al*. study, a precursor of decreased VSM Ca channels (Witczak *et al*., 2006) and VSM de-differentiation to a more proliferative phenotype (Owens *et al*., 2004), that may, ultimately, lead to classical macrovascular atherosclerosis?

3. Metabolic characterization of diabetes

Translation of findings from animal models of diabetes to humans is never perfect, but every effort must be made to mimic the 'diabetic milieu', which requires close attention to the metabolic state. Although every study is not performed using sophisticated glucose clamps (Wasserman *et al*., 2009), attention simply must be paid to fasting glucose and body weight as metabolic indices. The level of blood glucose in Pinho's diabetic mice (19 mM) is very high and generally may result in a severe catabolic state, which can leave significant doubt whether the effects of untreated diabetes were due to body wasting, that is, starvation, or hyperglycaemia. Indeed, the somewhat catabolic state of the mice (23% lower body weight) potentially limits the relevance to the clinical course of diabetes in humans, because the majority of type 1 diabetic humans with poor glycemic control (average blood glucose >10 mM) have either normal or elevated body weight (Chaturvedi *et al*., 1995). Any data, regardless of the profoundness and novelty of the data, collected from animals undergoing body wasting may further confuse the story on mechanisms of diabetic vascular disease. Thus, the metabolic state of the diabetic mice may not mimic completely the milieu underlying the true pathogenesis of diabetic vascular complications in humans. Again, Pinho *et al*. are to be complimented for acknowledging this critical issue.

Exciting and novel mechanisms of diabetic vascular dysfunction must be based on close attention to fundamental metabolic characterization, vascular biology, and overall study design. Pinho *et al*. have, in their report, definitely given us more to consider regarding pharmacological targets for vascular disease in diabetes.

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