Journal of Diabetes and Metabolism
ISSN: 2155-6156

Matrougui, J Diabetes Metab 2014, 5:1
DOI: 10.4172/2155-6156.1000323

Short Communication Open Access

Diabetes and Microvascular Dysfunction

Khalid Matrougui*

Department of Physiological Sciences, Eastern Virginia School of Medicine, USA

Microvascular reactivity is an important mechanism that regulates local blood flow and therefore tissue perfusion. The reactivity (vasorelaxation and vasoconstriction) of microvessels is mainly regulated by mechanical factors (shear stress for relaxation and blood pressure for myogenic tone, which is a vasoconstriction of microvessels in response to increase in intraluminal blood pressure) and neuro-hormones. We previously showed that epidermal growth factor receptor tyrosine kinase (EGFRtk) is an important factor in the regulation of myogenic tone in microvessels. In fact, pressure-induced myogenic tone in resistance arteries is regulated by the mechanism that involves metalloproteinases 2 and 9 activation with subsequent Heparin-Binding-EGF release and EGFRtk transactivation [1]. This mechanism appears to be specific to myogenic tone, since the contractions to angiotensin and KCl are independent of EGFRtk transactivation. We previously reported that diabetes is associated with microvascular dysfunction [1,2]. We observed reduced microvascular endothelium-dependent relaxation and aberrant increase in pressure-induced myogenic tone in type 2 diabetes [3,4]. The impairment in microvascular function in type 2 diabetes is, in part, caused by the enhanced EGFRtk activity. In a murine model of type 2 diabetic mice, we found an increase of EGFRtk phosphorylation in microvessels. Interestingly, the inhibition of EGFRtk improves vascular function in type 2 diabetes independently of the diabetes and obesity [4]. We also demonstrated that advanced glycation end products cause microvascular dysfunction in type 2 diabetes through the enhance in oxidative stress [3]. In another study, we demonstrated an increase in poly (ADP-ribose) polymerase 1 (PARP-1) and nuclear factor-κB activity in microvessels isolated from type 2 diabetic compared to control [2,5,6]. Interestingly, the inhibition of PARP-1 and NFκB pathways improves microvascular function in type 2 diabetic mice [2,6] indicating that PARP-1 and NFκB are important factors in microvascular dysfunction in type 2 diabetes. The aberrant increase in PARP-1 and NFκB activity is caused by the augmented EGFRtk activity [2,7]. Thus, we determined that the inhibition of EGFRtk activity improved microvascular function by PARP-1 and NFκB-dependent mechanism [2,7] suggesting that EGFRtk is up stream to PARP-1 and NFκB signaling. The aberrant increase in NFκB and PARP-1 activity impairs microvascular function in type 2 diabetes by Sp-1 and COX-2-dependent mechanism. In summary, our studies delineated the mechanism of type 2 diabetes induced microvascular dysfunction. Therefore, the EGFRtk, oxidative stress, NFκB and PARP-1 pathways could be potential targets for novel therapeutic strategies to overcome diabetes-induced microvascular dysfunction.

Sources of Funding

National Institutes of Health (HL095566; PI: Dr. Matrougui).

References

1. Lucchesi PA, Sabri A, Belmadani S, Matrougui K (2004) Involvement of metalloproteinases 2/9 in epidermal growth factor receptor transactivation in pressure-induced myogenic tone in mouse mesenteric resistance arteries. Circulation 110: 3587-3593.
2. Kassan M, Choi SK, Galán M, Bishop A, Umezawa K, et al. (2013) Enhanced NF-Î°B activity impairs vascular function through PARP-1-, SP-1-, and COX-2-dependent mechanisms in type 2 diabetes. Diabetes 62: 2078-2087.
3. Su J, Lucchesi PA, Gonzalez-Villalobos RA, Palen DI, Rezk BM, et al. (2008) Role of advanced glycation end products with oxidative stress in resistance artery dysfunction in type 2 diabetic mice. Arterioscler Thromb Vasc Biol 28: 1432-1438.
4. Belmadani S, Palen DI, Gonzalez-Villalobos RA, Boulares HA, Matrougui K (2008) Elevated epidermal growth factor receptor phosphorylation induces resistance artery dysfunction in diabetic db/db mice. Diabetes 57: 1629-1637.
5. Matrougui K (2010) Diabetes and microvascular pathophysiology: role of epidermal growth factor receptor tyrosine kinase. Diabetes Metab Res Rev 26: 13-16.
6. Choi SK, Galán M, Kassan M, Partyka M, Trebak M, et al. (2012) Poly(ADP-ribose) polymerase 1 inhibition improves coronary arteriole function in type 2 diabetes mellitus. Hypertension 59: 1060-1068.
7. Galan M, Kassan M, Choi SK, Partyka M, Trebak M, et al. (2012) A novel role for epidermal growth factor receptor tyrosine kinase and its downstream endoplasmic reticulum stress in cardiac damage and microvascular dysfunction in type 1 diabetes mellitus. Hypertension 60: 71-80.

***Corresponding author:** Khalid Matrougui, Department of Physiological Sciences, Eastern Virginia Medical School, Norfolk, Virginia 23501, USA, Tel: (757)-446-5278; E-mail: matrouk@evms.edu

Received December 20, 2013; **Accepted** January 08, 2014; **Published** January 14, 2014

Citation: Matrougui K (2014) Diabetes and Microvascular Dysfunction. J Diabetes Metab 2: 323. doi:10.4172/2155-6156.1000323