High glucose, nitric oxide, and adenosine: a vicious circle in chronic hyperglycaemia?

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This editorial refers to ‘Nitric oxide reduces SLC29A1 promoter activity and adenosine transport involving transcription factor complex hCHOP–C/EBPa in human umbilical vein endothelial cells from gestational diabetes’ by M. Farias et al., pp. 45–54, this issue.

Diabetes mellitus is characterized by accelerated atherosclerosis and increased risk of cardiovascular disease. Metabolic factors associated with the diabetic state itself, such as hyperglycaemia, are likely to contribute to the increased cardiovascular risk in diabetic patients. Endothelial dysfunction is recognized as a major cardiovascular risk factor, being a key determinant of atherosclerosis. Among the number of factors involved in maintaining proper vascular wall homeostasis, nitric oxide (NO) is of pivotal relevance in guaranteeing physiological endothelium-mediated vasodilation observed in diabetic patients, it is still a matter of controversy whether and in which way the imbalance of glucose metabolism might affect NO synthesis and bioavailability.

The pathways involved in these transcriptional events are still unknown. On the contrary, the mechanism that, through hCHOP–C/EPB complex formation, leads to reduced hENT1 expression in HUVEC from gestational diabetic pregnancies has been elucidated by Farias et al. This phenomenon is clearly mediated by increased NO levels, which could be due to the activation of the ALANO pathway, although it is still unclear whether and in which way this pathway could be part of the increased eNOS expression in HUVEC from gestational diabetic pregnancies.

In this respect, the identification of the molecular mechanism underlying the decreased hENT1 expression in gestational diabetes may open up intriguing scenarios and potentially enlarge our understanding of the ability of high glucose to impair endothelial functions in diabetes through the adenosine/-arginine/NO (ALANO) pathway, which was recently identified by San Martin and Sobrevia.

It may be proposed that in gestational diabetes, increased NO release by HUVEC could occur via activation of the ALANO pathway. NO increases formation of the hCHOP–C/EBPa complex, which, in turn, causes the decrease in hENT1 expression (Figure 1). As a consequence, the extracellular accumulation of adenosine, due to the reduction of hENT1 functions, results in increased l-arginine transport via human cationic amino acid transporters (hCATs) and enhanced NO synthesis by increased eNOS activity. The up-regulation of the endothelial l-arginine/NO pathway by adenosine is associated with increased transcription of eNOS and SLC7A1, leading to increased eNOS and hCAT-1 mRNA levels, respectively.

The study by Farias et al. provides the first evidence of NO-dependent down-regulation of SLC29A1 expression by the hCHOP–C/EPB complex in HUVEC from gestational diabetic pregnancies. The authors have identified the repression of SLC29A1 promoter activity by the transcription factor hCHOP–C/EBPa complex as a potential mechanism of the reduced hENT1 expression in human foetal endothelial cells from gestational diabetes. The SLC29A1 promoter region contains consensus sequences for several transcription factors, including C/EBP homologous protein 10 (hCHOP), a member of the CCAAT/enhancer-binding protein family that forms heterodimers with C/EBP-activating transcription factors. Notably, hCHOP expression is up-regulated in cultured HUVEC by high glucose as well as in diabetic patients. In this respect, the identification of the molecular mechanism underlying the decreased hENT1 expression in gestational diabetes may open up intriguing scenarios and potentially enlarge our understanding of the ability of high glucose to impair endothelial functions in diabetes through the adenosine/-arginine/NO (ALANO) pathway, which was recently identified by San Martin and Sobrevia.

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In this regard, although limited information is available on cellular mechanisms associated with increased endothelial eNOS levels in...
hyperglycaemia, it is worth emphasizing that high glucose may independently modulate eNOS at transcriptional, post-transcriptional, and post-translational levels. This suggests that chronic hyperglycaemia might permanently modify gene expression in vivo, likely through high glucose-dependent epigenetic regulation of eNOS (Figure 1). Thus, hyperglycaemia might represent the primum movens within this context by increasing eNOS levels and NO production, which, in turn, can induce hCHOP-C/EBPa complex formation, leading to reduced hENT1 expression (Figure 1). In addition, since ENT1 is widely expressed in several cell types and its expression may be modulated in vivo and in vitro by high glucose concentrations, HUVEC from gestational diabetes may be taken as a model to investigate mechanism(s) leading to endothelial dysfunction in chronic hyperglycaemia. Nevertheless, the possibility that the ‘ALANO pathway’ is functional in other endothelial cells and that it is influenced by hyperglycaemia needs to be further investigated. In this respect, it has to be pointed out that since impaired endothelial function in diabetes is associated with reduced vascular NO availability, it will be of great interest to determine whether in HUVEC from gestational diabetes NO bioavailability is altered because of oxidative inactivation by excessive accumulation of high glucose-induced superoxide anion.

In conclusion, the article by Farias et al. broadens our vision of hyperglycaemia-induced endothelial dysfunction dynamics by uncovering a vicious circle in which high glucose might take the role of scene director, whereas NO and adenosine might play parts of co-protagonists.

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References