

Review

Impact of Nitric Oxide and Insulin Resistance on the Pathophysiology of the Metabolic Syndrome: Possible Role of L-Arginine and Glutamate

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Dietary intervention could play a significant role in managing chronic diseases, including the metabolic syndrome (a cluster of nutrition-related diseases) that is increasing continually the world over. Although the pathogenesis of the metabolic syndrome is multifaceted, reports suggest significant impact of dysfunction in the nitric oxide-mediated pathway (notably from impaired nitric oxide synthesis) that could lead to insulin resistance. In nitric oxide synthesis, L-arginine is the major substrate whereas the excitatory activities of L-glutamate enhance the calcium-calmodulin complex formation that activates the neuronal and endothelial isoforms of the catalyzing enzyme (nitric oxide synthase). L-arginine and glutamate are abundant in natural foods, including nuts and tomatoes. Harnessed intake of L-arginine and glutamate-rich foods might enhance the optimal synthesis of nitric oxide resulting in the prevention of the metabolic syndrome. Thus, this review summarizes the roles of L-arginine and glutamate in the synthesis of nitric oxide that might affect the impact of nitric oxide and insulin resistance on the pathophysiology of the metabolic syndrome. The apparent insight from this review might help in designing suitable protocols and dietary interventions for the prevention, control and management of the metabolic syndrome.

Keywords: Nitric oxide, L-arginine, metabolic syndrome, L-glutamate, calcium ion, calcium-calmodulin complex.

INTRODUCTION

Metabolic syndrome (MES) is a clustering of abnormalities including obesity, lipid and glucose disorders that confer an increased risk of developing not only cardiovascular disease but also type 2 diabetes mellitus (Wilson et al., 2005) and currently colorectal cancer (Siddiqui, 2010; Pelucchi et al., 2010).

Dietary intervention could play a significant role in managing chronic diseases, including the metabolic syndrome that is increasing continually the world over. Although the pathogenesis of the metabolic syndrome is multifaceted, reports suggest significant impact from impaired nitric oxide synthesis that could lead to insulin resistance and, possibly, vice versa. Despite the fact that nitric oxide (NO) is the principal mediator of endothelium-dependent vasodilatation and could play an important

role in the host defense mechanism, many disease conditions in humans, including components of the metabolic syndrome, could occur as a result of either deficient or excessive production of NO (Lokhande et al., 2006).

In particular, Garlich et al. (2000) noted that MES might result from endothelial dysfunction characterized by a reduced availability of bioactive NO, perhaps following impaired endothelial-nitric oxide (NO)-mediated vasodilatation that may result in decreased blood flow to skeletal muscle. This may further suggest that reduced release of NO (a possible consequence of impaired NO synthesis) may contribute to the development of significant atherosclerosis and enhanced thrombus formation in the MES. Thus, the maintenance of optimum level of NO might have enormous benefit in the prevention and management of the MES.

In light of the above, ARG and GLU may be particularly useful because of their intricate role in the synthesis of

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NO (Moncada, 1991). In apparent support of this, effects of ARG (Nematbakhsh et al., 2008; Egbuonu et al., 2010a, b, c) and GLU (Bursnado, 2010) possibly mediated via NO synthesis were reported in rats, suggesting that ARG and GLU might affect NO-dependent effects in animals. Thus, harnessed intake of l-arginine and glutamate-rich foods might enhance the optimal synthesis of nitric oxide resulting in the prevention of the metabolic syndrome.

This review therefore summarizes the roles of l-arginine and glutamate in the synthesis of nitric oxide that might affect the impact of nitric oxide and insulin resistance on the pathophysiology of the metabolic syndrome. The apparent insight from this review might help in designing suitable protocols and dietary interventions for the prevention, control and management of the metabolic syndrome.

Metabolic syndrome

Meaning

The metabolic syndrome (MES) is a cluster of cardiovascular risk factors that is characterized by obesity, central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension (Deedwania and Gupta, 2006). The National Cholesterol Education Program (NCEP) (USA) (2001) defined metabolic syndrome as the presence of three or more of the following risk factors in the same individual: abdominal obesity or waist circumference greater than 102cm (40 in) (men) or greater than 88 cm (35 in) (women), serum triglycerides greater or equal to 150mg/dl, HDL cholesterol less than 40mg/dl (men) or less than 50mg/dl (women), systolic blood pressure greater than or equal to 130 mm Hg, diastolic blood pressure greater than or equal to 85 mm Hg, fasting blood glucose greater than or equal to 110 mg/dl.

Features

The features of metabolic syndrome include insulin resistance (the diminished ability of cells to respond to the action of insulin in promoting the transport of sugar (glucose) from blood to muscles and other tissues), hypertension (high blood pressure), cholesterol abnormalities, obesity and an increased risk for clotting (Mathur, 2010). Earlier, metabolic syndrome predicted type 2 diabetes (Resnick et al., 2003; Sattar et al., 2004), cardiovascular disease (Hunk et al., 2004; Ruther et al., 2004) and nonalcoholic fatty liver disease, a spectrum of disorders ranging from simple hepatic steatosis to cirrhosis and liver failure (Marchesini et al., 2003). Subsequently, markers of liver damage were associated with metabolic syndrome variables, including type 2

diabetes (Sattar et al., 2004; Liangpunsakul and Chalasani, 2005; Hanley et al., 2004).

Prevalence

Globally, the prevalence of MES is high (Gotto et al., 2008) and about 20-30% of adult population was reported to have MES (Grundy, 2008). Presently, the figure may be higher since the prevalence of the syndrome is increasing (Chaabo et al., 2010). Although the prevalence of MES was higher in the urban areas, it was appreciably high in the rural areas and more prevalent in females than in males (Mangat et al., 2010). MES may therefore aggravate the poverty-related health burden (associated with infections and nutrition) of millions of people in developing countries (Mohan and Deepa, 2006) especially the female gender reported to be among the independent risk factors for MES (Ravikiran et al., 2010). Furthermore, components of MES (insulin resistance and type 2 diabetes) were among the reported major disorders of childhood and adolescence linked to increasing prevalence of obesity in the pediatric population (Kohen-Avramoglu et al., 2003), seemingly indicating that MES is not peculiar to adult alone.

Etiology and Risks

Apart from genetic factors, environmental factors, sedentary lifestyle and progressive weight gain may contribute significantly to the risk of developing the metabolic syndrome. In addition, MES was associated with liver and kidney damage, obstructive sleep apnea, polycystic ovary syndrome, increased risk of dementia with aging, and cognitive decline in the elderly (Mathur, 2010).

Pathophysiology of the metabolic syndrome: Impact of Nitric Oxide and Insulin Resistance

Endothelial dysfunction

Patients with metabolic syndrome represent a group with extensive cardiovascular risk factors for the development of atherosclerosis, probably preceded by impaired endothelial function due to reduced availability of bioactive nitric oxide, the principal mediator of endothelium-dependent vasodilation (Garlich et al., 2000). Evidence of diminished NO bioavailability in the pathophysiology of MES variables were inferred from research reports.

For instance, Calver et al. (1993) recognized that a rise in blood pressure or vasospasm in a vessel might not be due to increased vasoconstrictors but due to a loss of the basal dilator tone mediated by nitric oxide. In the

periphery of the myocardium, endothelial NO acts as a potent vasodilator by stimulating guanyl cyclase, which then generates cyclic guanyl monophosphate, inducing smooth muscle relaxation (Just et al., 1994) and a change in myocardial contractibility comparable to that of the baroreceptors (Mohan et al., 1996).

Insulin resistance

Insulin is the key hormone in the regulation of glucose homeostasis. Insulin resistance was recognized as the main pathogenic factor in the development of type 2 diabetes and the main feature of obesity hence could play a pivotal role in initiating and perpetuating the pathologic manifestations of the metabolic syndrome, including hypertension and dyslipidemia (Lann and LeRoith, 2007). Furthermore, higher levels of white blood cell count associated with insulin resistance was independently associated with the presence of nonalcoholic fatty liver disease, a hepatic manifestation of insulin resistance, and other components of metabolic syndrome (Lee, 2010).

It was reported that visceral fat accumulation, a consequence of insulin resistance via hepatocyte fatty degeneration, might ultimately result in triacylglyceride accumulation (Pessayre, 2007). In addition, triacylglyceride accumulation was implicated in beta-cell dysfunction associated with increased basal insulin release and impaired glucose-stimulated insulin secretion by beta-cells (Nascimento et al., 2010). Thus, the liver (a major site for amino acid metabolism) might be a key target organ for insulin resistance and the development of the metabolic syndrome (Grundey, 2007). Subsequently, elevated alanine aminotransferase (ALT) activity, a biomarker of hepatic inflammation, significantly correlated with indicators of MES, increased with the metabolic syndrome components (Mojiminiyi et al., 2010), and was prevalent in patients with at least one component of MES (Koller et al., 2010; Gunji et al., 2010).

Evidence of involvement of nitric oxide and insulin resistance on the pathophysiology of the metabolic syndrome

Several researchers reported that the induction of diabetes mellitus by alloxan in animals produced a marked fall in plasma nitric oxide (NO) and insulin but a simultaneous elevation in glucose, lactate, ketone bodies and lipid peroxide levels (Mohan and Das, 1998). The reports appear to support, at least in part, the intricate involvement of nitric oxide and insulin resistance in the pathophysiology of the MES. Thus, insulin resistance and nitric oxide-dependent endothelial dysfunction seems the main pathophysiological feature of the metabolic

syndrome. Reduction in NO may contribute to insulin resistance and vice versa, but this is unsubstantiated.

L-Arginine

L-arginine is considered a conditionally essential amino acid because endogenous L-arginine synthesis may not be sufficient to meet metabolic needs, especially during growth (infants and children) (Wu et al., 2004) and during highly catabolic conditions such as sepsis and burns.

ARG could enhance the production and release of glucagon and insulin (Harold, 2004), reduce hypertension (Alexander et al., 2004), increase lipid peroxidation level (Lubec et al., 1997) and induce vasodilation (Rang et al., 2003). ARG inhibited the oxidation of low-density lipoproteins to oxidized LDL, which is an early step in atherogenesis (Rang et al., 2003) and reduced hypercholesterolemic effect in animals (Carroll and Kurowska, 1995).

In addition, ARG plays a key role in many metabolic processes in health and disease (van Waardenburg et al., 2007) including the synthesis of nitric oxide (Morris, 2006). Luiking et al. (2003) had associated critical illnesses with a strong inflammatory response that were related to increase in NO production and arginase activity, but a decrease in renal de novo arginine synthesis, suggesting that exogenous supply of ARG may play an important limiting role in critical illnesses. Plasma L-arginine concentration was lowered during the acute phase of critical illness in children but normalized again during recovery (van Waardenburg et al., 2007), suggesting upregulated utilization (or diminished synthesis) of L-arginine in critical illnesses.

ARG administration (in vitro and in vivo) improved endothelium function in diabetes mellitus models (Pieper et al., 1997). Additionally, L-arginine decreased oxidative stress by reducing the vascular superoxide anion production and improved endothelial function in hypercholesterolaemic subjects (Kawano et al., 2002). L-arginine may also increase polyamines production in the pancreas of diabetic rats resulting in enhanced recovery of the endocrine pancreatic function (Mendez and Arreola, 1992). Furthermore, the tendency to normalize lipid, lipoprotein and apoprotein levels in diabetic rats treated with L-arginine were explained by the antilipolytic, antioxidant and antiapoptotic roles of L-arginine-derived polyamines (Lovaas, 1995). Furthermore, El-Missiry et al. (2004) showed that exogenously administered ARG decreased oxidative stress and clinical manifestation of diabetes mellitus in rat model. This supported the beneficial effect of ARG, which they, partly, attributed to direct NO-dependent antioxidant capacity of ARG.

The augmentation of NO production/release induced by L-arginine may act as an antioxidant (Kawano et al., 2002) possibly through NO-mediated pathway. In earlier studies, NO terminated oxidant stress in tissues by

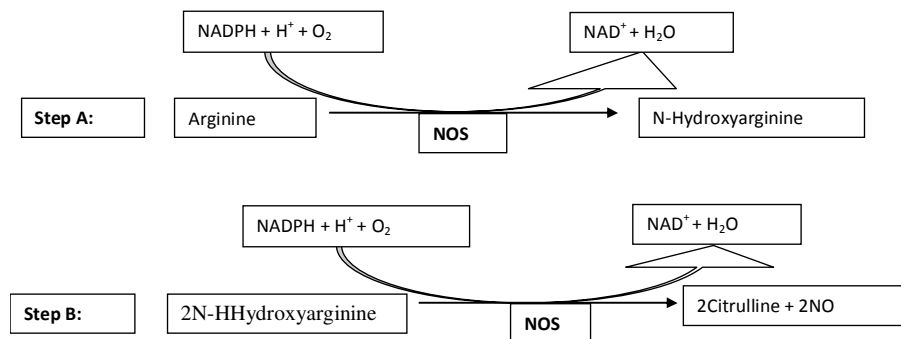


Figure 1: Synthesis of nitric oxide from arginine

suppressing iron-induced generation of hydroxyl radical (OH \cdot) via the Fenton reaction, interrupting the chain reaction of lipid peroxidation, augmenting the antioxidative potency of the reduced glutathione (GSH) and inhibiting cysteine protease (Chiueh, 1999). The molecular mechanism of NO, polyamines and their precursor ARG in stimulating insulin synthesis and release, activating insulin receptors and endogenous antioxidants, is critical in diabetes mellitus – a major component of MES.

L-Glutamate

GLU occurs naturally in protein-containing food such as milk, tomatoes, mushrooms, meat, fish and many vegetables. It is an excitatory amino acid (Cotman et al., 1995) and a precursor of the neurotransmitters-glutamine and gamma amino butyric acid (Harold, 2004) hence is involved in the excitatory central nervous system (CNS) transmission (Rang et al., 2003; Cotman et al., 1995).

Busnardo et al. (2010) hypothesized that a local NO - guanylate cyclase interaction mediates cardiovascular effects of GLU microinjection into the paraventricular nucleus (PVN) of rats and the results of their study suggest that GLU-evoked cardiovascular responses in rats involve a local production of NO and activation of guanylate cyclase.

Synthesis of Nitric Oxide: Roles of L-Arginine and Glutamate

Nitric oxide, a free radical gas and local messenger molecule with a very short half-life, could inhibit mononuclear cell adhesion and platelet aggregation thereby promoting vasodilation (Boger and Bode-Boger, 2001). It could boost glucose transport and metabolism (Young et al., 1997). Under normal conditions, NO could enhance balance in several physiological functions

(Moncada et al., 1991). However, in pathological conditions, including diabetes mellitus – a component of MES, impaired NO production may result, perhaps by the overstimulation of glutamate receptors forming peroxynitrites (Dawson et al., 1992) which may inhibit NO synthesis by way of diminished bioavailability of calcium ion (Ca²⁺). Generally, decreased NO generation is attributed to uncoupling of receptor-mediated signal transduction, a deficiency of the nitric oxide synthase (NOS), substrate L-arginine or a decreased availability of one or more cofactors essential for optimal functioning of NOS (Moncada et al., 1991). ARG and GLU could fill most of these deficiencies as shown below.

L-arginine is the exclusive substrate (precursor) for nitric oxide (NO) synthesis in the body (Vallance, 2000; Davignon and Ganz, 2004). In a nitric oxide synthase (NOS) catalyzed monooxygenation reactions that require molecular oxygen (O₂) and reduced nicotinamide adenosine di-nucleotide phosphate, L-arginine is sequentially converted to nitric oxide. As depicted in Figure 1, L-arginine is hydroxylated (in the first step) to generate N-hydroxyarginine which is subsequently oxidized in the second step to yield NO and citrulline. Citrulline, the byproduct of NO synthesis, is re-converted into L-arginine *via* the reactions of the urea cycle (Knowles and Moncada, 1994).

NOS has three isoforms: neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS). These NOS isoforms differ on the basis of their location, dependence for activity on increased cytosolic Ca²⁺ concentration, duration of action and whether inducible or constitutive.

Generally, the NOS is activated only after binding to a calcium-calmodulin complex, and it is the excitatory neurotransmission activity of GLU that enhances the influx of Ca²⁺ into cells to form the calcium-calmodulin complex (Moncada et al., 1991). In contrast, NO could activate soluble guanylate cyclase in the target tissue by binding to heme protoporphyrin producing cyclic guanylate monophosphate (cGMP), which in turn

phosphorylates cGMP-dependent protein kinase consequently reducing intracellular Ca^{2+} concentrations. Although peroxynitrite formed after NO reaction with superoxide mediates the action in physiological concentration, it nevertheless highlights the significant role of GLU in NO synthesis. In addition, increased reaction of NO with superoxide, and the subsequent formation of peroxynitrite (ONOO^-), may contribute to endothelial cell damage and endothelial dysfunction in patients with coronary artery disease (Landmesser et al., 2000) probably indicating physiological consequence of impaired bioavailability of Ca^{2+} and further highlighting the significance of the role of GLU in Ca^{2+} mobilization.

CONCLUSION

Thus, impaired regulation of NO synthesis together with insulin resistance may have significant impact on the pathophysiology of the metabolic syndrome. The intricate roles of ARG and GLU in the synthesis of NO suggest that regulating the exogenous supply of ARG and GLU could enhance optimized production of NO consequently improving insulin resistance and ultimately exert favorable impact on the metabolic syndrome. The apparent insight from this review coupled with the abundance of arginine and glutamate in common foods may help in designing protocols and dietary interventions for the prevention, control or management of the metabolic syndrome. Studying the effects on the markers of the metabolic syndrome of ARG either alone or in combination with GLU might throw further insight in this regard hence is warranted.

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