Abnormal regulation of nitric oxide synthesis by advanced glycation end products as pathogenic mechanisms for diabetic complication.

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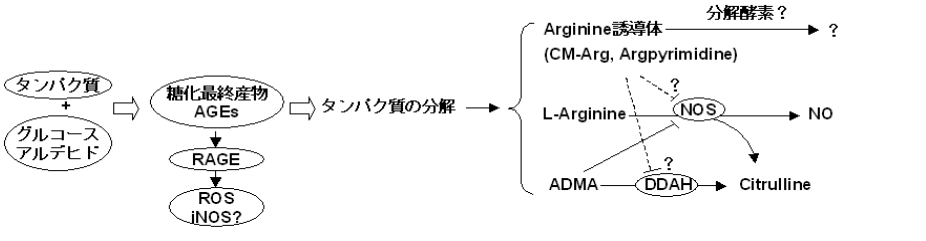
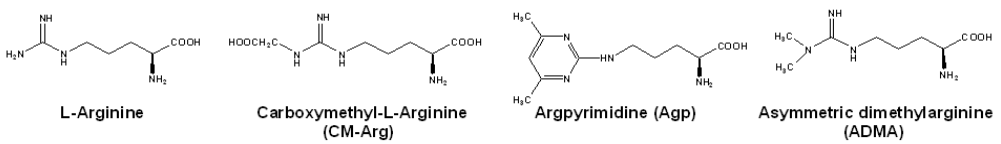
Advanced glycation end products (AGEs) are formed via a non-enzymatic reaction between reducing sugars (such as glucose) and amino residues of proteins. In diabetes mellitus, accumulation of AGEs induced by prolonged hyperglycemia in various tissues has been implicated in development of diabetic complications. However, the molecular mechanism behind this association remains to be clarified.

Nitric oxide (NO) is an important signal molecule formed from arginine in the reaction catalyzed by nitric oxide synthases (NOS). Asymmetric dimethylarginine (ADMA) is synthesized by methylation of protein arginine residues, and is a competitive inhibitor of nitric oxide synthases resulting in decreased NO availability. ADMA is eliminated by renal excretion or is metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to citrulline and dimethylamine. Plasma concentrations of ADMA are markedly increased in patients with chronic renal failure, leading to increased risk for hypertension, heart failure, and atherosclerosis.

Glyoxal and methylglyoxal derived from glucose degradation react with arginine residues in proteins to form glycation adducts, which have been identified as carboxymethyl-arginine (CMA), argpyrimidine (Agp) and carboxyethyl-arginine (CEA). Furthermore, it has been reported that serum CMA levels were significantly elevated in diabetic patients compared to those in normal subjects. The arginine-derived glycation adducts are structurally-analogous with potent endothelial NOS inhibitor of ADMA. For these reasons, we are examining whether CMA, Agp and CEA inhibit enzymatic activities of NOS, DDAH, and other arginine-metabolizing enzymes.





L-Arginine | Carboxymethyl-L-Arginine (CM-Arg) | Argpyrimidine (Agp) | Asymmetric dimethylarginine (ADMA)