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TITLE

# Diabetic Gastroparesis: Role of Tetrahydrobiopterin, a Cofactor For Neuronal Nitric Oxide Synthesis

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Gastroparesis is a disabilitating disease affecting predominantly young women. The biological basis of this disorder and its associated gender bias remains poorly understood. Recent studies have implicated a role for dysregulation of neuronal nitric oxide synthase (nNOS) in myenteric neurons and we surmised that gender differences in nitrergic control of gastric motility may possibly account for observed vulnerability of females to diabetic gastroparesis. Our data suggests that a significant impairment of nitrergic relaxation and delayed gastric emptying for solids was demonstrated selectively in females in the onset of diabetes. Most importantly, we have also shown that changes in nitrergic relaxation in both healthy and diabetic, oxidative stress and hyperlipidemia rodents correlates well with the state of dimerization of nNOSα but not with the expression of total nNOS (α, β and γ). Dimerization of nNOS is essential for activity of this enzyme but has not been previously studied in gastrointestinal tissue. In our laboratory, we have focused on the role of tetrahydrobiopterin (BH4), an essential cofactor for nNOS activity that is required to maintain the homodimeric structure of nNOS. BH4 levels in tissue in turn depend on the activity of GTP cyclohydrolase1 (GTPCH1), the rate limiting enzyme in the de novo synthesis of BH4. We have demonstrated that GTPCH1 mRNA and protein expression are down regulated in the diabetic female gastric tissues along with significantly reduced BH4 content, suggesting reduced synthesis of biopterins leading to decreased nitrergic relaxation. In support of this, the GTPCH1 inhibitor, 2, 4 diamino-6-hydroxypyrimidine (DAHP), reduced nNOSα dimerization, NO release and nitrergic relaxation of gastric tissue in normal female rodents in vitro. Conversely, the exogenous addition of BH4 to female gastric tissues in vitro reverses a hyperglycemia-induced decrease in nitrergic relaxation. In addition, *in vivo* BH4 or sepipaterin (a precursor for BH4 synthesis via salvage pathway) treatment attenuated reduced nNOS activity in diabetic or hyperlipidemia rodent gastric tissue. The data from these studies may lead to the discovery of novel therapeutic targets for the management of this challenging clinical syndrome.

## Biography

Pandu has completed his Ph.D at the age of 27 years from S.V University, India and postdoctoral studies from Vanderbilt Medical Center, Nashville, TN and UTMB, Galveston, TX. He is the Associate Professor of Department of Physiology, Meharry Medical College, Nashville, TN. He has published more than 45 papers in reputed journals and serving as an editorial board member of repute.