Abnormalities in gastric motility occur in 20-55% and up to 30% of patients with Type I (insulin-dependent) and Type II diabetes (non-insulin-dependent) respectively. Symptoms of diabetic gastropathy can range from mild dyspepsia to recurrent vomiting and abdominal pain. The pathogenesis of diabetic gastric dysfunction remains poorly understood. In addition, up to 80% of patients with diabetic gastroparesis are women, and the biological basis for this gender bias remains unknown.

Nitric oxide (NO), synthesized by neuronal nitric oxide synthase (nNOS) in the myenteric neurons is a major regulator of gastrointestinal motility in health. Several lines of experimental work also indicate a potentially important role for nitrergic dysfunction in the pathogenesis of diabetic gastroparesis.

Our preliminary data suggests that a significant impairment of nitrergic relaxation and delayed gastric emptying for solids was demonstrated selectively in female rats after diabetes induction with streptozotocin (STZ). Most importantly, we have also shown that changes in nitrergic relaxation in both healthy and diabetic rats correlates well with the state of dimerization of nNOSα but not with the expression of total nNOS (α, β and γ). BH4 is a cofactor for monoamine hydroxylases and all nitric oxide synthases. BH4 plays a critical role in controlling cardiovascular disease, hypertension, oxidative stress and acts as immunosuppressant. Nitric oxide-dysfunction is a hallmark of cardiovascular disease, including diseases which are considered as a major current public health concerns: hypertension, obesity, diabetes, malnutrition. Deficiency in BH4 leads to several neurological diseases and endothelial dysfunction. The results from my findings for the first time indicate that the pathogenesis of diabetic gastroparesis (delayed gastric emptying) may be different in males and females, with the latter being more vulnerable to changes in nitrergic regulation such as that caused by an acquired deficiency in the nNOS cofactor, BH4. Supplementation of BH4 may be beneficial in diabetic female patients with gastroparesis. I am in the process of examining whether supplementation of BH4 restores nNOS activity, NO synthesis and thus attenuate impaired gastric motility functions in diabetic female rats. These studies are important for the management of gastroparesis which is a challenging clinical syndrome in particular with diabetic women. The expression for GTPCH1, a first and rate-limiting enzyme in BH4 biosynthesis pathway is decreased in diabetic (human and rat) gastric tissues compared to controls. I also found that BH4 levels in gastric tissues from diabetic female rats are decreased. In addition, pilot studies indicate that BH4 supplementation restored the reduced levels of tumor necrosis factor-alpha (TNF-α) in female diabetic rat circulation and gastric IGF-1R expression. Currently, studies are in progress as to determine the role and regulation of BH4 on NO synthesis (R21 funding), oxidative stress and apoptosis in both in vivo and in vitro hyperglycemic conditions. In addition to the above studies, hypothesis driven experiments are initiated to investigate the role of BH4 in restoring NO synthesis in various experimental models such as preeclampsia, gestational diabetes, obesity and aging.
Dr. Pandu Gangula publications highlighted:
Antioxidant genes keep stomach (gastric) function intact
Gastroparesis – delayed emptying of the stomach that can cause indigestion, recurrent vomiting and abdominal pain – occurs more often in diabetic and idiopathic women than men. As a part of the Meharry-Vanderbilt Alliance, Dr. Gangula, Ph.D., Associate Professor of Physiology, MMC, was recently funded by the Diabetes Research Training Center at VU to investigate the role of oxidative stress in gastroparesis, along with VUMC collaborators Drs. Freeman and Sekhar. They report in Free Radical Biology & Medicine that NRF2 [a transcription factor that directs the expression of multiple antioxidant genes including GCLM (regulates glutathione synthesis)] or GCLM null mice have deficient nitric oxide-mediated gastric motility, and they characterize the functional & biochemical changes in the generation of nitric oxide. The findings suggest that antioxidant genes may be good therapeutic targets for gastroparesis. This and other DRTC-supported work by Dr. Gangula has been highlighted on the GI Motility Research Portal (www.gimotilityresearch.org), a website aiming to provide clinicians and researchers a centralized location for GI motility research.