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**Title of the thesis: "Studies on the mechanisms of acute mental stress-induced gastropathy and impairment of mitochondrial biogenesis in gastric mucosa"**

## ABSTRACT

Mental stress has a profound impact on gastric health, which includes gastric mucosal ulceration, hyperacidity, and associated gastric complications, collectively called gastropathy. However, the molecular mechanisms of how mental stress imparts gastropathy are not very clear. This work investigated the molecular and subcellular events in acute stress-induced gastropathy using a rat model of acute stress. This study identified that mental stress impairs the electron transport chain (ETC) and mitochondrial biogenesis in the gastric mucosa, leading to disruption in ATP production and mitochondrial homeostasis. Impaired ETC function further led to excessive production of reactive oxygen species (ROS), exacerbating oxidative stress and contributing to mitochondrial damage. Induction of cold-restraint stress on rats led to downregulation of mitochondrial biogenesis regulators, including PGC-1α, NRF1, and TFAM, resulting in bioenergetic failure and associated gastric mucosal damage. The study also revealed that stress-induced activation of the glucocorticoid receptor (GR) pathway led to ubiquitination-mediated degradation of PGC-1α, resulting in compromised mitochondrial function, impaired mitochondrial biogenesis, and disrupted lipid metabolism. Elevated corticosterone levels and altered expression of key catabolic genes, such as Klf15 and Fbxo32, contributed to mitochondrial dysfunction, reinforcing the connection between stress and impaired gastric energy metabolism. To counteract the mitochondrial and metabolic dysfunction induced by acute psychological stress, this study systematically evaluated three mechanistically distinct therapeutic strategies: (1) antioxidant supplementation using quercetin-3-glucoside (Q3G), (2) central modulation of stress perception through the administration of olanzapine, and (3) direct antagonism of glucocorticoid receptor (GR) signalling via RU486. Q3G, a bioavailable antioxidant flavonoid, significantly restored the expression of genes involved in oxidative phosphorylation, fatty acid oxidation, and glucose metabolism, as confirmed by transcriptomic and qRT-PCR analyses. It preserved mitochondrial function by stabilizing key regulatory proteins such as PGC-1α and TFAM. Olanzapine effectively attenuated systemic corticosterone elevation and suppressed GR-driven catabolic gene expression (Klf15, Fbxo32), partially restoring mitochondrial biogenesis and ATP production. RU486, a competitive GR antagonist, offered the most robust protection by directly blocking GR-mediated transcriptional pathways, thereby preserving mitochondrial bioenergetic function despite elevated corticosterone levels. Collectively, these interventions highlight the therapeutic potential of targeting mitochondrial integrity, redox homeostasis, and neuroendocrine stress pathways in the prevention of stress-induced gastric mucosal injury.

In conclusion, this study provides novel insights into the molecular mechanisms underlying stress-induced gastropathy while emphasizing mitochondrial dysfunction as a central contributor of gastric injury. By demonstrating that stress disrupts mitochondrial biogenesis, ETC function, and metabolic homeostasis, the findings reinforce the importance of targeting mitochondrial pathways in stress-related gastric disorders. Importantly, the study highlights the therapeutic promise of three targeted intervention strategies: antioxidant supplementation with Q3G, central modulation of stress perception via olanzapine, and direct inhibition of GR signalling using RU486. This research work paves the way for innovative strategies to combat stress-induced gastric disorders. By shedding light on mitochondria-targeted therapies, it opens new avenues for the development of cutting-edge interventions that could revolutionize the treatment of stress-related gastrointestinal diseases.

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