

**An executive summary of the final report of work done on the Minor Research Project of Dr Asha Abraham entitled “Evaluate the role of Norepinephrine in leptin production and secretion *in vitro*” sanctioned by UGC, vide sanction letter No. 1448-MRP/14-15/KAMA002/UGC-SWRO, and dt 04/02/2015**

Leptin, an adipocyte hormone is recognized to have a crucial role in regulating food intake and maintaining metabolic homeostasis. Contemporary research suggests that leptin, may be an important factor linking obesity, the metabolic syndrome, and cardiovascular disorders. Virtually nothing is known about the cellular pathway(s) involved in Leptin secretion, *i.e.*, whether Leptin secretion *per se* is regulated or is merely constitutively secreted at a rate proportional to its synthesis. Preliminary studies from my lab have revealed that High fat simple carbohydrate (HFSC) feeding to C57BL/6J mice resulted in an increase in the hypothalamic as well as plasma Norepinephrine (NE) levels. Also hyperleptinemia and leptin resistance were noted in the above mice. Therefore in the present study, we have attempted to understand if NE influenced leptin production and/ secretion. *In vitro* leptin secretion study revealed that the basal leptin levels were higher in test mice after 5 months of feeding HFSC diet, which is in agreement to our findings *in vivo*. Also, we noted that NE was able to stimulate leptin release both in control, and test mice. The extent of stimulation was more pronounced in test mice compared to age matched control. In order to understand the mechanism of this NE stimulated leptin release, we used various adrenergic receptor antagonists. From our studies we conclude that NE acting *via* alpha adrenergic receptors tends to inhibit leptin secretion while NE acting *via* beta adrenergic receptors tends to stimulate leptin secretion in control mice. However in HFSC fed test mice there seems to be a derailment of adrenergic receptor functioning. Further, gene expression studies were carried out to understand the role of leptin gene expression in the presence and absence of Norepinephrine and adrenergic blockers. Leptin gene expression was higher in test adipose tissue explants confirming the basal leptin secretion results. Blocking  $\alpha$  adrenergic receptor enhanced leptin gene expression even though leptin secretion was inhibited while blocking  $\beta$  adrenergic receptor resulted in down regulation of leptin gene expression as well as secretion in control. However, the pattern of leptin gene expression in HFSC fed test mice showed that blocking  $\alpha$  adrenergic receptor downregulated the leptin gene expression and blocking  $\beta$  adrenergic receptor resulted in up regulation of leptin gene expression. Further studies on the expression profiles of adrenergic receptors on adipose explant will help understand the complex interrelationships of NE and leptin secretion in control and HFSC fed test mice.

This study shows that Norepinephrine stimulates leptin production and secretion. Intake of High Fat Simple Carbohydrate diet seems to affect the signaling mechanisms leading to leptin resistance. The study enables the understanding of the etiology of metabolic syndrome which is becoming very prevalent in the recent times. Further, it would help to develop suitable therapeutic interventions to combat metabolic syndrome in future.

### **Presentations in National and International Conferences**

1. Namitha N Kharvi, Alin Maria Jacob, Shruthi K, Neena Roy and Asha Abraham. Norepinephrine mediates Leptin secretion via beta adrenergic receptors in obese C57BL/6J mice: An age related study. Abstract as Proceedings in “Recent Advances in molecular biology [RAMB- 2016] held in Kannur University from March 9-11, 2016.
2. Pinto C, Krishna K.R, Roy N and Abraham A. Evaluation of Adrenergic Control of Lipolysis in the Normal and Obese C57BL/6J Mice Adipose Explants in vitro at International Conference on Green Chemistry & Nanotechnology opportunities and Challenges-2017 held at SAC, Mangaluru.