Excess Insulin as a Driver for Insulin Resistance, NAFLD and Type 2 Diabetes: Pathophysiological Mechanisms and Therapeutic Opportunities

A Thesis
Submitted
by

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For

The award of the degree of

Doctor of Philosophy

Under the supervision of

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Declaration by the Research Scholar

I hereby declare that the entire work embodied in the Thesis "**Excess Insulin as a Driver for Insulin Resistance, NAFLD and Type 2 Diabetes: Pathophysiological Mechanisms and Therapeutic Opportunities"** is the result of investigations carried out by me in the School of Basic Sciences, Indian Institute of Technology Mandi, under the supervision of **Dr. Prosenjit Mondal**, and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the finding of other investigators.

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Date: Name: **Abhinav Choubey**

Declaration by the Research Advisor

I hereby certify that the entire work in this thesis has been carried out by **Abhinav Choubey (Roll No D16069)**, under my supervision in the **School of Basic Sciences**, Indian Institute of Technology Mandi and that no part of it has been submitted elsewhere for any Degree or Diploma.

Signature: 

Name of the Guide: Dr. Prosenjit Mondal

Date : 16/06/2021

Consciously, this work is dedicated to "Lord Krishna" Animal Sacrificed, Teachers, Family, Beloved, Friends, Indian Farmers, and Soldiers.

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Preface

Type 2 diabetes (T2DM) and Non-alcoholic fatty liver (NAFLD) represents the most alarming dual epidemic concern of the 21st century. The prevalence/complexity of this looming epidemic is increasing severely and WHO predicts the incidence to double by 2030.T2DM is characterized by elevated blood glucose (hyperglycaemia) which is a result of peripheral insulin resistance where the body fails to use insulin and compensatory hyperinsulinemia where the pancreas is forced to secrete more insulin (in settings of insulin resistance). Hyperinsulinemia, a state of elevated circulatory insulin level is considered both a cause and consequence of insulin resistance, however the mechanism of how it causes insulin resistance is unknown. Several lines of evidence have shown that high insulin predisposes individuals toward metabolic illness. The two main causes of hyperinsulinemia are β-cell hypersecretion with or without an insulin-resistant state and decreased clearance of insulin from systemic circulation. Existing pieces of literature have also shown that T2DM, obesity, and its associated fatty liver can be reversed with a specific, partial reduction of insulin production. However, the lack of knowledge on how an excess of insulin drives insulin resistance and the unavailability of a proper pharmacological correction of circulatory high insulin put an immense area to look into. Thus, taking the need of current limitation, we deciphered the molecular mechanism on how high insulin induces systemic insulin resistance , NAFLD and also revealed that a low dose of naltrexone has a significant potential to protects against such states. Altogether these data provide evidence for the causal role of hyperinsulinemia in the progression of insulin resistance and fatty liver pathology and a low dose of naltrexone improves hyperinsulinemia mediated metabolic health