World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:11, No:06, 2017

Homeostatic Analysis of the Integrated Insulin and Glucagon Signaling Network: Demonstration of Bistable Response in Catabolic and Anabolic States

Authors : Pramod Somvanshi, Manu Tomar, K. V. Venkatesh

Abstract : Insulin and glucagon are responsible for homeostasis of key plasma metabolites like glucose, amino acids and fatty acids in the blood plasma. These hormones act antagonistically to each other during the secretion and signaling stages. In the present work, we analyze the effect of macronutrients on the response from integrated insulin and glucagon signaling pathways. The insulin and glucagon pathways are connected by DAG (a calcium signaling component which is part of the glucagon signaling module) which activates PKC and inhibits IRS (insulin signaling component) constituting a crosstalk. AKT (insulin signaling component) inhibits cAMP (glucagon signaling component) through PDE3 forming the other crosstalk between the two signaling pathways. Physiological level of anabolism and catabolism is captured through a metric quantified by the activity levels of AKT and PKA in their phosphorylated states, which represent the insulin and glucagon signaling endpoints, respectively. Under resting and starving conditions, the phosphorylation metric represents homeostasis indicating a balance between the anabolic and catabolic activities in the tissues. The steady state analysis of the integrated network demonstrates the presence of a bistable response in the phosphorylation metric with respect to input plasma glucose levels. This indicates that two steady state conditions (one in the homeostatic zone and other in the anabolic zone) are possible for a given glucose concentration depending on the ON or OFF path. When glucose levels rise above normal, during post-meal conditions, the bistability is observed in the anabolic space denoting the dominance of the glycogenesis in liver. For glucose concentrations lower than the physiological levels, while exercising, metabolic response lies in the catabolic space denoting the prevalence of glycogenolysis in liver. The non-linear positive feedback of AKT on IRS in insulin signaling module of the network is the main cause of the bistable response. The span of bistability in the phosphorylation metric increases as plasma fatty acid and amino acid levels rise and eventually the response turns monostable and catabolic representing diabetic conditions. In the case of high fat or protein diet, fatty acids and amino acids have an inhibitory effect on the insulin signaling pathway by increasing the serine phosphorylation of IRS protein via the activation of PKC and S6K, respectively. Similar analysis was also performed with respect to input amino acid and fatty acid levels. This emergent property of bistability in the integrated network helps us understand why it becomes extremely difficult to treat obesity and diabetes when blood glucose level rises beyond a certain value.

Keywords : bistability, diabetes, feedback and crosstalk, obesity
Conference Title : ICSPH 2017 : International Conference on Systems Physiology and Homeostasis
Conference Location : San Francisco, United States
Conference Dates : June 07-08, 2017