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Modulation of Hepatic Gluconeogenesis: A Therapeutic Target for Diabetes

Lee IK* and Joen JH

Department of Internal Medicine, Kyungpook National University School of Medicine, Korea

***Corresponding author:** In-Kyu Lee, Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, Korea, E-mail: leei@knu.ac.kr

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Regulation of Hepatic Gluconeogenesis

Liver is the major organ responsible for the maintenance of glucose homeostasis under fasting conditions. Hepatic gluconeogenesis is tightly regulated by the complementary actions of insulin and glucagon, the principal hormones that respond to feeding status. In the fasted state, glucagon secreted from pancreatic alpha cells promotes the synthesis of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) through activation of adenylcyclase. The serine/threonine (Ser/Thr) kinase protein kinase A (PKA) is a heterotetramer that consists of two regulatory subunits and two catalytic subunits [1]. PKA is activated when cAMP binds to its regulatory subunits, thus exposing the catalytic subunits [2,3]. During the prandial phase, however, glucagon secretion is diminished, while insulin secretion from pancreatic beta-cells is enhanced, resulting in the inhibition of hepatic gluconeogenes is, in part through activation of the Ser/Thr kinase Akt/protein kinase B [4].

The opposing actions of insulin and glucagon on hepatic gluconeogenesis are tightly orchestrated and integrated by the transcription factor cAMP response element binding protein (CREB) [5] and its associated co-activators cAMP-regulated transcriptional co-activators (CRTCs) and CREB-binding protein (CBP)[5-9]. Upon glucagon stimulation, PKA catalytic subunits activate CREB by phosphorylation at Ser133 [10]. PKA also activates Ser/Thr phosphatases, such as protein phosphatase 2B (PP2B/calcineurin) and suppressor of MEK null (SMEK)/PP4C and, which dephosphorylate CRTCs [11,12], there by modulating their cellular location and activity. When hepatic CRTC2 is dephosphorylated by phosphatases, it translocates to the nucleus, where it binds to CREB and enhances its activity [13]. Conversely, insulin signaling antagonizes the effects of the cAMP-PKA-CREB pathway in the prandial state.

CRTC2 is inactivated by phosphorylation at Ser171 by AMP-activated protein kinase (AMPK) or salt-inducible kinase, as a result becoming sequestered in the cytoplasm through interactions with 14-3-3 proteins [13,14]. The critical role of CRTC2 in gluconeogenesis was revealed by a study with CRTC2-knockout hepatocytes [15]. In addition, the importance of CBP has been demonstrated recently; insulin or metformin treatment caused phosphorylation of CBP at Ser436, thereby triggering dissociation of the CREB-CBP-CRTC2 complex [16]. Furthermore, mice carrying a germ line mutation at this CBP phosphorylation site were resistant to the effects of insulin or metformin treatment, indicating that CBP is a critical co-activator of CREB, and thus a key regulator of hepatic gluconeogenesis [16]. The CREB-CBP-CRTC2 complex enhances transcription of key gluconeogenic enzymes, including pyruvate carboxylase, phosphoenolpyruvate carboxykinase 1, and glucose-6-phosphatase, thereby facilitating gluconeogenesis [17]. In addition, CREB activates peroxisome proliferator-activated receptor-γ co-activator 1α, members of the nuclear receptor subfamily 4 group A family, and fork head box protein O1, which are a series of key transcription factors that are responsible for activating gluconeogenesis upon prolonged fasting (Figure 1A & B) [1].

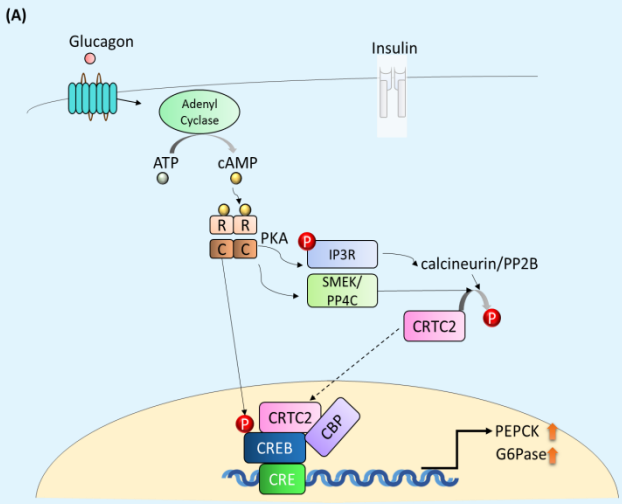

Figure 1(A): Suggested mechanism by which hepatic gluconeogenesis is enhanced upon glucagon stimulation in diabetes or during fasting. Dephosphorylation of CBP and CRTC2 is required for their nuclear localization and subsequent complex formation with CREB. These co-activators potentiate the transcriptional activity of CREB thereby increase hepatic gluconeogenesis upon glucagon stimulation.

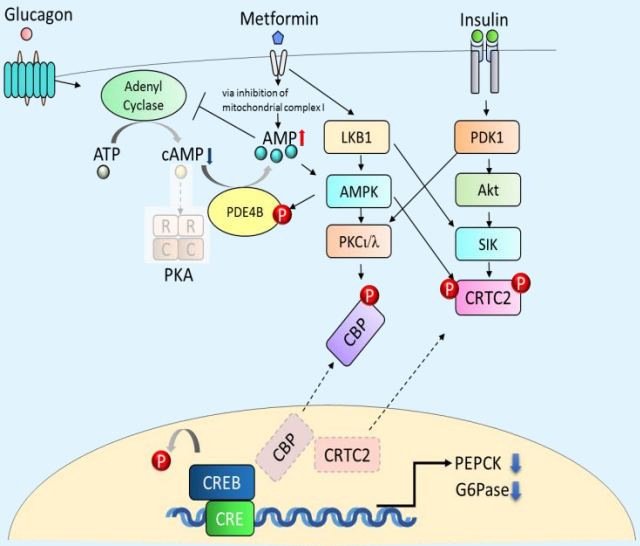

Figure 1(B): Metformin and Insulin inhibits hepatic glucogeneogensis by modulating various gluconeogenic signaling. Insulin phosphorylates CRTC2 at Ser171by activation of PDK1-Akt-SIK pathway as well as CBP at Ser436 by activation of PKCι/λ. Metformin phosphorylates CBP at Ser436 by stimulation of LKB1-AMPK pathway. In addition, increased hepatic AMPK activity by AMPK activators promotes phosphorylation of PDE4B which eventually blocks cAMP accumulation in the liver. High-dose of metformin increases cellular AMP level via inhibition of mitochondrial complex I. Increased AMP level inhibits adenyl cyclase activity thereby lowers cAMP level in the liver. CREB, cAMP response element binding protein; CRTC2, cAMP-regulated

Modulation of Gluconeogenic Signaling: A Therapeutic Target for Diabetes

The signaling mechanisms regulating gluconeogenesis that have been discussed above may represent therapeutic targets for diabetes, given that hyperglucagonemia induced by increased pancreatic alpha cell activity has emerged as one of the main pathophysiological features of type 2 diabetes [18].

Metformin, one of the most frequently prescribed oral anti-diabetic agents, attenuates hepatic gluconeogenesis in a number of ways. The therapeutically effective concentration (≤ 80 μM) of metformin was sufficient to activate AMPK, leading to CBP phosphorylation and inhibition of the cAMP-PKA-CREB pathway [19]. However, when higher concentrations are used, metformin inhibits mitochondrial complex I, thereby increasing intracellular AMP in mouse hepatocytes [20]. This results in inhibition of adenyl cyclase activity, thus reducing intracellular cAMP concentrations. Furthermore, a very recent paper showed that a small-molecule AMPK activator inhibits gluconeogenesis by activation of phosphodiesterase 4B [21]. Taken together, these findings indicate that AMPK activators attenuate gluconeogenesis by modulation of cAMP-PKA-CREB pathway.

In summary, regulation of the hepatic cAMP-PKA-CREB pathway using small molecule inhibitors might be an attractive option for future therapy of diabetes in cases where glucagon action is inappropriately enhanced.

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