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Niclosamide blocks glucagon phosphorylation of serine 552 on β-catenin leading to a reduction in cyclin D1 and c-Myc expression in primary rat hepatocytes via PKA signaling

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Recently it has been found that glucagon is able to activate the β-catenin signaling pathway leading to increased cyclin D1 and c-Myc expression in liver. Therefore, the main aim of this study is to determine if the effect of glucagon activating β-catenin signaling leading to increased target gene expression is mediated through cAMP activation of protein kinase A. Primary rat hepatocytes were incubated with insulin, glucagon or epinephrine and a range of inhibitors of PI 3-kinase, Wnt, mitochondrial uncoupler (niclosamide) or PKA inhibitors to dissection out the pathway leading to increased serine 552 phosphorylation of β-catenin following glucagon exposure. Western blot and real-time PCR were used. In primary rat liver cells, we found that short exposure of glucagon or epinephrine caused a rapid increase in serine-552 phosphorylation on β-catenin that leads to increased cyclin D1 and c-Myc expression. Both glucose and insulin had no effect on this pathway. A range of PI 3-kinase and Wnt inhibitors were unable to block the effect of glucagon phosphorylating β-catenin. Interestingly, both niclosamide and the PKA inhibitor H89 blocked the glucagon effect on β-catenin signaling leading to a reduction in the target genes expression. We have identified a new pathway via glucagon signaling that leads to increased β-catenin activity that can be reversed with the antihelminthic drug niclosamide which has recently shown promise as a potential treatment of type-2 diabetes (T2D). This novel finding could be useful in liver cancer treatment particularly in the context of T2D with increased β-catenin activity.

Biography

Md Kamrul Hasan Chowdhury has completed his Bachelor of Pharmacy from the University of Development Alternative (UODA), Bangladesh. Following his Bachelor's degree, he has received a scholarship for studying Master of Science (MSc) in Pharmacogenomics at Inje University, College of Medicine, South Korea. After graduating from Inje University, he successfully obtained a competitive PhD Scholarship UIPA (University International Postgraduate Award) from the University of New South Wales Australia, Australia.

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