

Weekly Colloquium

Tuesday, 1/23/2018, 12:30pm, Billings Building – Rosedale Conference Room

“Control of Insulin Secretion by Cytochrome c and Calcium: Wagging the Dogma”

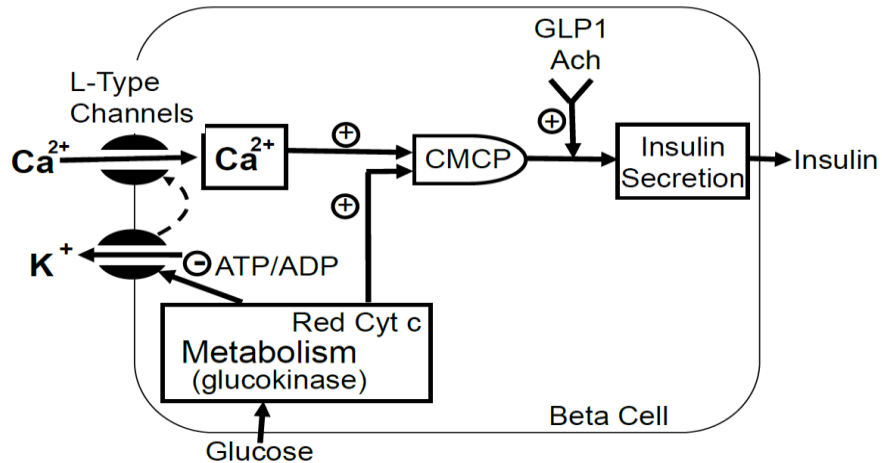
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Summary. The data highlight the need for modifying the “Consensus Model” to include the dual role of the metabolic factor cytochrome c and L-type calcium channels to stimulate insulin secretion, where each regulatory factor alone is insufficient to activate exocytotic machinery. The essentiality of cytochrome c reduction in the model accounts for the inability of non-nutrient potentiators of insulin secretion such as GLP-1 and acetylcholine to stimulate the release of insulin in the absence of hyperglycemia, a teleological imperative that is not predicted by the Consensus Model. The remarkable findings that calcium stimulation occurs normally in models of impaired energetics will be discussed with respect to KATP channels, as will the strong correlation between deficit of reduced cytochrome c and insulin secretion rate.

Conclusions. Reduced cytochrome c and its translocation to the cytosol are essential control steps in the regulation of insulin secretion. A possible pathogenic role for cytochrome c in the development of diabetes is supported by the observed deficit of reduced cytochrome c and its translocation in islets with impaired insulin secretion. Notably, the impaired islets retained normal calcium signaling capacity. Our data suggest developing therapeutics to enhance insulin secretion in patients with Type 2 diabetes that target cytochrome c signaling.



REFERENCES

1. Jung, S. R., Kuok, I. T., Couron, D., Rizzo, N., Margineantu, D. H., Hockenbery, D. M., Kim, F., and Sweet, I. R. (2011) Reduced cytochrome C is an essential regulator of sustained insulin secretion by pancreatic islets. *J Biol Chem* **286**, 17422-17434
2. Jung, S. R., Reed, B. J., and Sweet, I. R. (2009) A highly energetic process couples calcium influx through L-type calcium channels to insulin secretion in pancreatic beta-cells. *Am J Physiol Endocrinol Metab* **297**, E717-727
3. Rountree, A. M., Neal, A. S., Lisowski, M., Rizzo, N., Radtke, J., White, S., Luciani, D. S., Kim, F., Hampe, C. S., and Sweet, I. R. (2014) Control of insulin secretion by cytochrome C and calcium signaling in islets with impaired metabolism. *J Biol Chem* **289**, 19110-19119