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**REGULATION OF GLUCOSE HOMEOSTASIS BY MUNC18c
AND SYNTAXIN 4**

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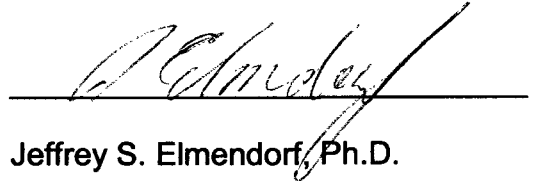
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ABSTRACT

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REGULATION OF GLUCOSE HOMEOSTASIS BY MUNC18c AND SYNTAXIN 4

Glucose homeostasis is a coordinated, highly regulated complex process that involves the commitment from various tissues to maintain proper levels of glucose. Three essential features involved are insulin-stimulated glucose uptake into peripheral skeletal muscle and adipose tissues, glucose-stimulated insulin secretion from the pancreatic β -cell and insulin suppression of hepatic glucose. Two of these processes involve the translocation of GLUT4 storage vesicles or insulin secretory granules from intracellular storage pools to the plasma membrane and are regulated by a SNARE-mediated mechanism. The target membrane SNARE, Syntaxin 4 and its high affinity binding partner Munc18c have been identified as the proteins responsible for proper glucose regulation *in vitro*. To determine whether these proteins are essential in both glucose uptake and insulin secretion *in vivo* and their effect on glucose homeostasis, mice were engineered with a tetracycline-repressible promoter to over-express either Munc18c or Syntaxin 4 protein. Munc18c transgenic mice displayed whole body insulin resistance and impaired insulin secretion and this deficiency was reversed upon down regulation of the transgene by tetracycline or by simultaneous over-expression of Syntaxin 4. Concomitantly, Syntaxin 4 over-expression enhanced insulin-stimulated glucose uptake in skeletal muscle which could be attributed to a 2-fold increase of GLUT4 translocation to the plasma membrane. Moreover, this improved insulin sensitivity was also normalized upon feeding of tetracycline.

Furthermore, numerous over-expression studies have implicated Syntaxin 4 as a positive effector of insulin secretion. Therefore, islets from Syntaxin 4 heterozygous knockout mice were subjected to perfusion analysis and data indicated that islets secreted 50% less insulin during first phase upon glucose stimulation than wild-type littermates and this defect was restored upon the replenishment of recombinant Syntaxin 4. Remarkably, islets isolated from transgenic mice displayed 3-fold higher levels of Syntaxin 4 relative to wild-type and secreted 2-fold more insulin during both phases of insulin secretion. Together, these data provide evidence that Syntaxin 4 and Munc18c are critical regulators of multiple processes key to maintaining whole body glucose homeostasis.

Maureen A. Harrington, Ph.D. – Chair

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