

:( )

\*

( )

$\beta$   
(GSIS)

:

( )

II

-

(nSTZ )

*Diabetes Mellitus and the Control of Cellular Energy Metabolism*

\*

Farzamib@sina.tums.ac.ir :

:/

// :

// :

[ ] (GSIS)

(EC. 2. 7.1.2)

[ ] GSIS

II [ ]  
[ ] ( II ) MODY-2

[ ]

[ ]

μM)

III II I

(Km =

(D IV )

( mM) Km (≈ KDa)

[ ]

[ ]

[ ]

[ ]

[ ]

[ ]

(GKRP)

[ ]

( )

[ ]

II

[ ]

[ ]

(nSTZ) II

[ ]

<sup>3</sup> β-cell dysfunction

<sup>1</sup> Translocation

<sup>2</sup> Fuel Hypothesis

( )

/ /

/

+

-

ELISA

DRG

mg/kg

( )

[ ]

[ ]

( )

-

*Leuconostoc mesenteroides*

NAD<sup>+</sup> NADH

Kontes

g

glass

/

( )

/

BSA

-

/

)

(

/

°C

(

)

<sup>1</sup> Rat

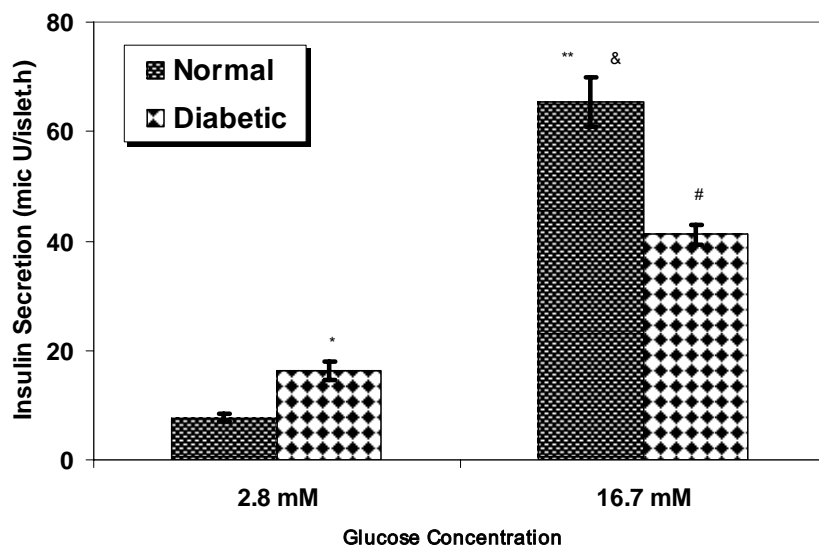
$\pm$   
 n . (Mean  $\pm$  SE)  
 SPSS  
 P-Value  
 ATP

STZ

( )

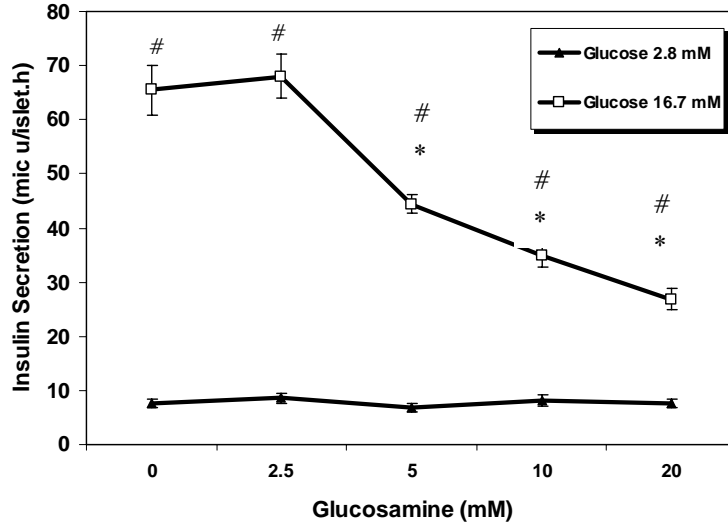
/ ( [ ] )

STZ



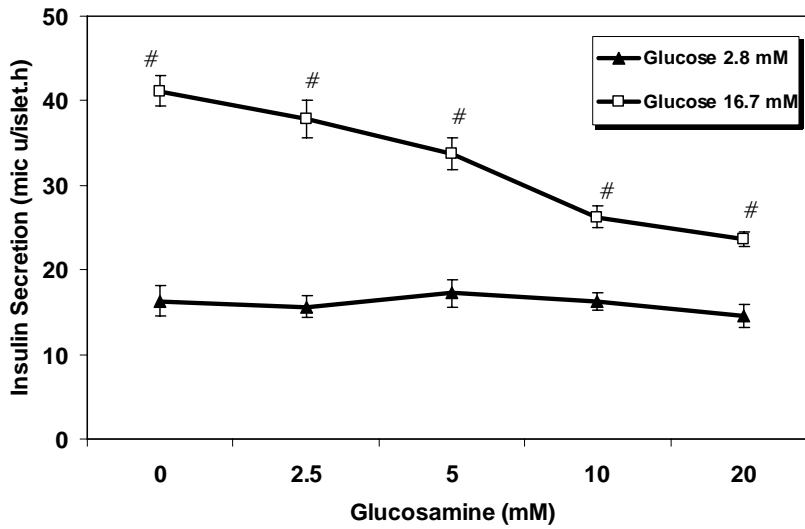
P< / \*\* .  
 P< / \* . n = n = . (Mean  $\pm$  SE)  
 P< / # . /

( )



(GSIS)

\* / + / P < / # . n = n = (Mean ± SE)  
(P < / )



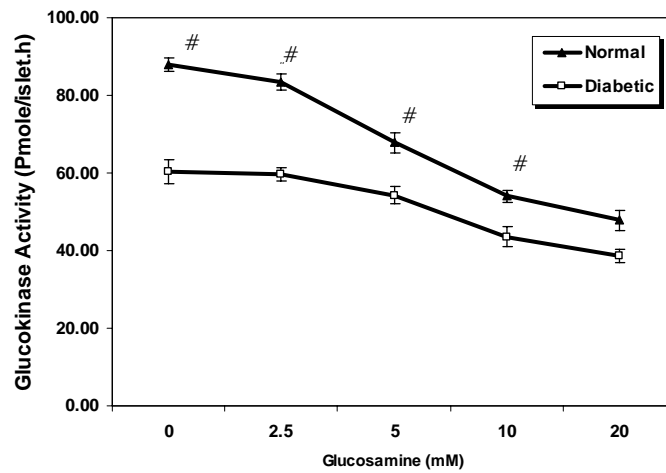
(GSIS)

+ / P < / # . n = n = (Mean ± SE)

/ /

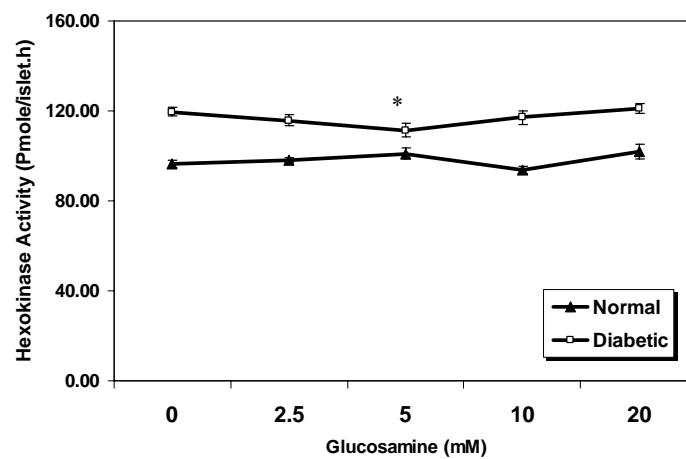
:

( / )  
 / (P< / )  
 (GSIS)  
 / ) (P< / )  
 (P<  
 r = / )  
 ( r = / (P< / )



نمودار ۴- اثر غلظت‌های مختلف گلوکز آمین بر فعالیت گلوکوکیناز پانکراس در موش‌های صحرایی سالم و دیابتی

(Mean  $\pm$  SE) n = . n = . # . (P< / )



نمودار ۵- اثر غلظت‌های مختلف گلوکز آمین بر فعالیت هگزوکیناز پانکراس در موش‌های صحرایی سالم و دیابتی

(Mean  $\pm$  SE) n = . n = . \* . (P> / )

( )

/  
/

(P< / )

r = / )

)

( r = /

(

/

(P< / )

[ ]

[ ] [ ]

[ ]

( )

(P< / )

[ ]

(GSIS)

/

[ ]

( )

GSIS

[ ]

II

GSIS

]

[ ]

[

II

( )

/

(II ) nSTZ

[ ]

[ ] [ ]

( )

[ ] [ ]

[ ]

/

(GSIS)

[ / ]

[ ]

)

)

(

[ ]

.(

[ ]

II

GSIS

[ ] [ ]

[ ]

[ ]

[ ]

[ ]

<sup>1</sup> Dose-dependent



GSIS

.[ ]

Overexpression

GKRP

.[ ]

Km

.[ ]

( )

.[ ]

[ ]

1. Matschinsky FM. Glucokinase as glucose sensor and metabolic signal generator in pancreatic  $\beta$ -cells and hepatocytes. *Diabetes* 1990; 39: 647 – 652.
2. Pilkis SJ, Weber IT, Harrison RW, Bell GI. Glucokinase: Structural analysis of a protein involved in susceptibility to diabetes. *J Biol Chem* 1994; 269: 21925 – 21928.
3. Vandercammen A, Van Schaftingen E. Species and tissue distribution of the regulatory protein of glucokinase. *Biochem J* 1993; 294: 551 – 556.
4. Shiota C, Coffey J, Grimsby J, Grippo JF, Magnuson MA. Nuclear import of hepatic glucokinase depends upon glucokinase regulatory protein, whereas export is due to a nuclear export signal sequence in glucokinase. *J Biol Chem* 1999; 274: 37125-37130.
5. Bell GI, Pilkis SJ, Weber IT, Polonsky KS. Glucokinase Mutations, insulin Secretion, and diabetes mellitus. *Ann Rev Physiol* 1996; 58: 171 – 186.
6. Matschinsky FM, Glaser B, Magnuson MA. Pancreatic  $\beta$ -cell glucokinase. *Diabetes* 1998; 47: 307 – 315.
7. Gloyn AL et al. Glucokinase (GCK) mutations in hyper and hypoglycemia: maturity – onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemia of infancy. *Hum Mutat* 2003; 22: 353 – 362.
8. Hattersley AT et al. Linkage of type 2 diabetes to the glucokinase gene. *Lancet* 1992; 339: 1307 – 1310.
9. Grimsby J, Sarabu R, Corbett WL, Haynes N-E, Bizzarro FT, Coffey JW, et al. Allosteric activators of glucokinase: potential role in diabetes therapy. *Science* 2003; 301: 370 – 374.
10. Brocklehurst KJ, Payne VA, Davies RA, Carroll D, Vertigan HL, Wightman HJ, et al. Stimulation of hepatocyte glucose metabolism by novel small molecule glucokinase activators. *Diabetes* 2004; 53: 535 – 541.
11. Lenzen S, Tiedge M, Panten U. Glucokinase in pancreatic B-Cells and its inhibition by alloxan. *Acta Endocrinologica* 1987; 115: 21 – 29.
12. Tiedge M, Lenzen S. Effects of glucose refeeding and glibenclamide treatment on glucokinase and GLUT-2 gene expression in pancreatic B-Cells and liver from rats. *Biochem J* 1995; 308: 139 – 144.
13. Kaneto H, Xu G, Song K-H, Suzuma K, Bonner – Weir S, Sharma A, Weir GC. Activation of the hexosamine pathway leads to deterioration of

- pancreatic  $\beta$ -cell function through the induction of oxidative stress. *J Biol Chem* 2001; 276: 31099 – 31104.
14. Yoshikawa H, Tajiri Y, Sako Y, Hashimoto T, Umeda F, Nawata H. Glucosamine – induced  $\beta$ -cell dysfunction: a possible involvement of glucokinase or glucose – transporter type 2. *Pancreas* 2002; 24: 228 – 234.
  15. Postic C, Shiota M, Magnuson MA. Cell – specific roles of glucokinase in glucose homeostasis. *Recent Prog Horm Res* 2001; 56: 195 – 217.
  16. Zawulich WS, Dye ES, Matschinsky FM. Metabolism and insulin – releasing capabilities of glucosamine and N-acetylglucosamine in isolated rat islets. *Biochem J* 1979; 180: 145 – 153.
  17. Zawulich WS, Zawulich KC. Glucosamine – induced desensitization of  $\beta$ -cell responses: possible involvement of impaired information flow in the phosphoinositide cycle. *Endocrinology* 1992; 130: 3135 – 3142.
  18. Balkan B, Dunning BE. Glucosamine inhibits glucokinase in vitro and produces a glucose – specific impairment of in vivo insulin secretion in rats. *Diabetes* 1994; 43: 1173 – 1179.
  19. Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes* 1967; 16: 35 – 39.
  20. Liang Y, Najafi H, Matschinsky FM. Glucose regulates glucokinase activity in cultured islets from rat pancreas. *J Biol Chem* 1990; 265: 16863-16866.
  21. Bonner – Weir S, Trent DF, Honey RN, Weir GC. Responses of neonatal rat islets to streptozotocin: limited  $\beta$ -cell regeneration and hyperglycemia. *Diabetes* 1981; 30: 64 – 69.
  22. Poitout V, Robertson PR. An Integrated view of  $\beta$  – Cell dysfunction in type-II diabetes. *Annu Rev Med* 1996; 47: 69-83.
  23. Matschinsky FM. Banting Lecture 1995: A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. *Diabetes* 1996; 45: 223 – 241.
  24. Piston DW, Knobel SM, Postic C, Shelton KD, Magnuson MA. Adenovirus mediated knockout of a conditional glucokinase gene in isolated pancreatic islets reveals an essential role for proximal metabolic coupling events in glucose stimulated insulin secretion. *J Biol Chem* 1999; 274: 1000 – 1004.
  25. Chen C, Thorens B, Bonner – Weir S, Weir GC, Leahy JL. Recovery of glucose – induced insulin secretion in a rat model of NIDDM is not accompanied by return of the  $\beta$ -cell GLUT<sub>2</sub> glucose transporter. *Diabetes* 1992; 41: 1320 – 27.
  26. Portha B, Giroix M-H, Serradas P, Welsh N, Hellerstrom C, Sener A, Malaisse WJ. Insulin production and glucose metabolism in isolated pancreatic islets of rats with NIDDM. *Diabetes* 1988; 37: 1226 – 33.
  27. Liu YI, Nevin PW, Leahy JL.  $\beta$ -cell adaptation in 60% pancreatectomy rats that preserves normoinsulinemia and normoglycemia. *Am J Physiol Endocrinol Metab* 2000; 278: E68 – E73.
  28. Weir GC, Clorere ET, Zmachinski CJ. Bonner – Weir: Islet Secretion in a new experimental model for non – insulin – dependent diabetes. *Diabetes* 1981; 30: 590 – 595.
  29. Dachicourt N, Serradas P, Giroix M-H, Gangnerau M-N, Portha B. Decreased glucose – induced cAMP and insulin release in islets of diabetic rats: reversal by IBMX, glucagons, GIP. *Am J Physiol* 1996; 271: E725 – E732.
  30. Ashcroft SJH, Crossley JR, Crossley PC. The effect of N-acetyl glucosamine on the biosynthesis and secretion of insulin in the rat. *Biochem J* 1976; 154: 701 – 707.
  31. Liang Y, Bonner – Weir S, Wu Y-J, Berdanier CD, Berner DK, Efrat S, Matschinsky FM. In situ glucose uptake and glucokinase activity of pancreatic islets in diabetic and obese rodents. *J Clin Invest* 1994; 93: 2473 – 2481.
  32. Chen C, Hosokawa H, Bumbalo LM, Leahy JL. Mechanism of compensatory hyperinsulinemia in normoglycemic insulin – resistant spontaneously hypertensive rats. *J Clin Invest* 1994; 94: 399 – 404.
  33. Giroix M-H, Sener A, Pipeleers DG, Malaisse WJ. Hexose metabolism in pancreatic islets: inhibition of hexokinase. *Biochem J* 1984; 223: 447 – 453.
  34. Koopitwut, Zraika S, Thorburn AW, Dunlop ME, Darwiche N, Kay TW, Proietto J, Andrikopoulos S. Comparison of insulin secretory function in two mouse models with different susceptibility to  $\beta$ -cell failure. *Endocrinology* 2002; 143: 2085 – 2092.
  35. Milburn JL, Hirose H. Pancreatic  $\beta$ -cells in obesity. *J Biol Chem*. 1995; 270: 1295 – 1299.
  36. Khan A, Chandramouli V, Ostenson CG, Low H, Landau BR, Efendic S. Glucose cycling in islets from healthy and diabetic rats. *Diabetes* 1990; 39: 456 – 459.
  37. Khan A, Efendic S. Evidence that increased glucose cycling in islets of diabetic ob/ob mice is a primary feature of the disease. *Am J Physiol* 1995; 269: E 623 – 626.
  38. Sreenan SK, Cockburn BN. Adaptation to hyperglycemia enhances insulin secretion in glucokinase mutant mice. *Diabetes* 1998; 47: 1881 – 1888.
  39. Sturis J, Kurland IJ. Compensation in pancreatic beta – cell function in subjects with glucokinase mutations. *Diabetes* 1994; 43: 718 – 723.
  40. Becker TC, Noel RJ. Differential effects of over expressed glucokinase and hexokinase I in isolated islets. *J Biol Chem* 1996; 271: 390 – 394.
  41. Hosokawa H, Hosokawa YA, Leahy JL. Upregulated hexokinase activity in isolated islets from diabetic 90 % pancreatectomized rats. *Diabetes* 1995; 44: 1328 – 1333.