Insulin Regulatory Secretory Pathway: Role of Thyrotropin Releasing Hormone

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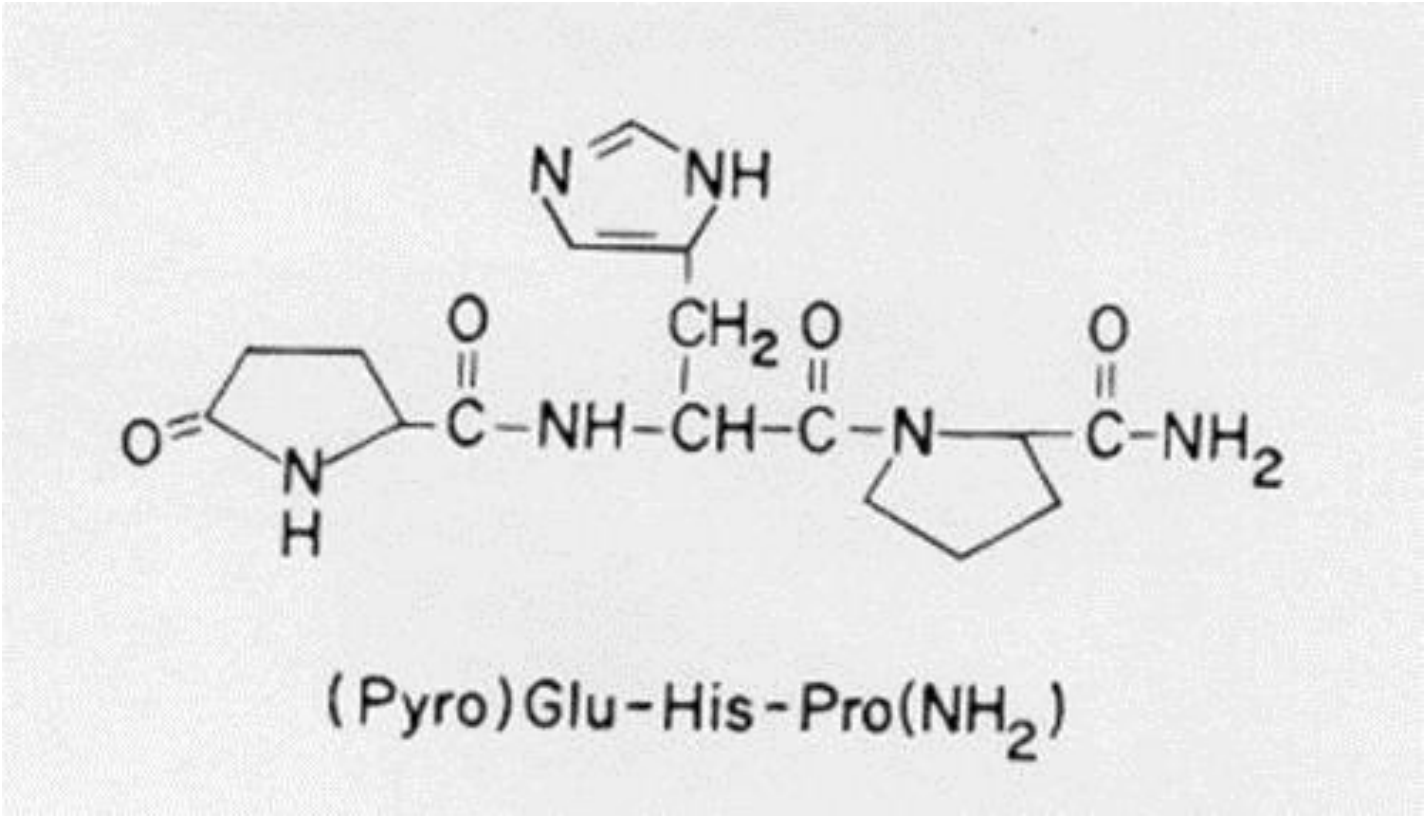
Type 2 DM

Various range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance

Could TRH be involved in its pathophysiology ?

Role of Thyrotropin Releasing Hormone in regulation of insulin secretion

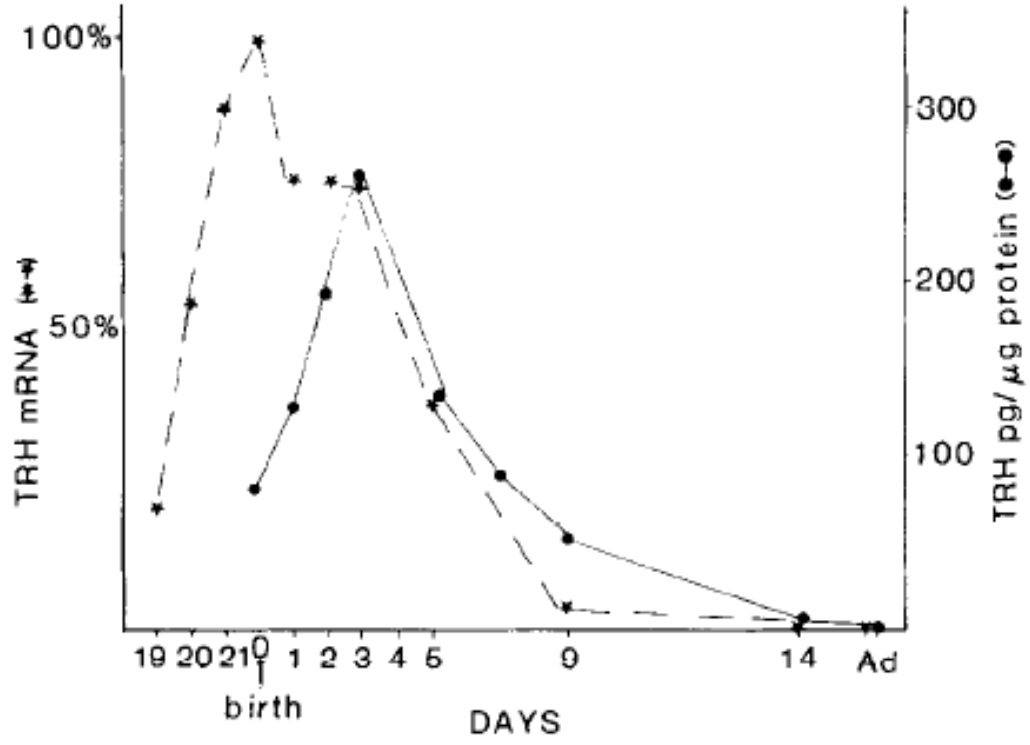
TRH -
Thyrotropin Releasing Hormone



Thyrotropin releasing hormone was first described as product of hypothalamic PVN regulating pituitary TSH secretion

Presence of TRH was later reported also in various organs outside the CNS including prostate, pancreas, heart, GIT

Dutour A, Giraud P, Kowalski C, Ouafik L, Salers P, Strbak V, Oliver C.
Ontogenesis of TRH mRNA in the rat pancreas.
Biochem Biophys Res Commun. 1987 Jul 15;146(1):354-60.



Ontogenesis of TRH mRNA (★--★) and TRH (●
concentrations in rat pancreas.

Period of high pancreatic TRH coincides with the perinatal maturation of the insulin secretory responsiveness to glucose and other nutrient secretagogues.

Poor secretory response to glucose challenge in the newborn rat involves a step in stimulus-secretion coupling.

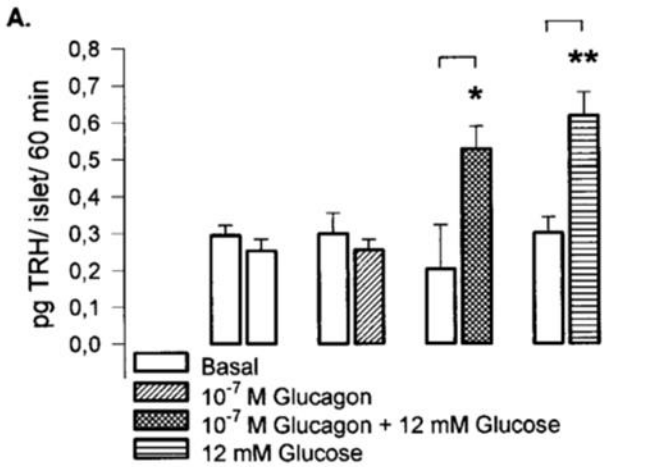
Grill et al. Generalized diminution in the response to nutrients as insulin-releasing agents during the early neonatal period in the rat. Diabetes 30,56-63, 1981

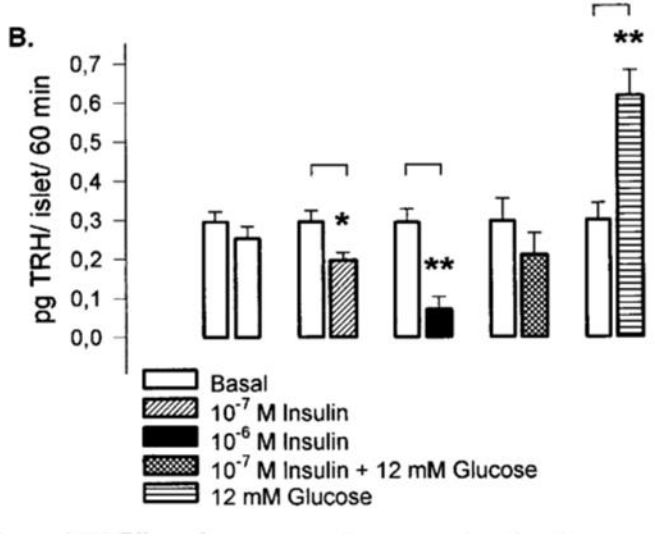
TRH is colocalized with insulin in the secretory granules of β cells

Leduque et al. Biology of the Cell 66:, 291-296, 1989

Secretion of TRH from pancreatic islets is stimulated by glucose and inhibited by somatostatin. Insulin inhibits both basal and glucose stimulated TRH release

Benicky and Strbak Eur J Endocrinol. 142: 60-65, 2000





(A) Effect of exogenous glucagon on basal and glucose-stimulated release of TRH. Islets (30 per tube) were incubated for two subsequent 60-min periods, the first in basal medium and the second in medium containing either glucagon alone (10^{1}7mol/l) or 10^{1}7mol/l glucagon plus 12mmol/l D-glucose, as indicated.

(B) Effect of exogenous insulin on the basal and glucose-stimulated release of TRH. Islets were incubated for two subsequent 60-min periods, the first in basal medium and the second in medium containing insulin alone (10^{1} 7 and 10^{1}6mol/l) or 10^{1}7 mol/l insulin plus 12mmol/l D-glucose. Results are expressed in pg TRH per islet (mean S.E.), *P<0.05, **P<0.01.

Benicky and Strbak Eur J Endocrinol. 142: 60-65, 2000

Different response of pancreatic TRH and insulin to perinatal STZ administration:

Neonatal STZ treatment results in parallel depletion of both insulin and TRH in the rat pancreas.
In contrast to the insulin, destruction of pancreatic TRH system was reported to be irreversible without spontaneous recovery.

Aratan-Spire et al. Endocrinology 114: 2369-2373, 1984
Leduque et al. Cell Tissue Res. 248:89-97. 1987

Absence of TRH system during neonatal period could play a role in disturbance of insulin control:

When administered neonatally, the acute effect of STZ is followed by spontaneous B-cell regeneration and return to normal glucose levels within about two weeks (Bonner-Weir et al. 1981). Nevertheless, a disturbance of the insulin response to glucose stimulation persists, thus providing a model for type 2 diabetes mellitus (Permutt et al. 1984).

MASANOBU YAMADA M et al.:

Tertiary hypothyroidism and hyperglycemia in mice with targeted disruption of the thyrotropin-releasing hormone gene.

Proc. Natl. Acad. Sci. USA, Vol. 94, pp. 10862–10867, September 1997
Medical Sciences

Prepro-TRH gene disruption in experimental mice results in hyperglycemia, accompanied by an impaired insulin response to glucose (Yamada et al. 1997). A similar disturbance of insulin secretion is observed in nSTZ animals (Briaud et al. 2000; Hemmings and Spafford 2000).

The role of TRH in this defect is therefore of interest.

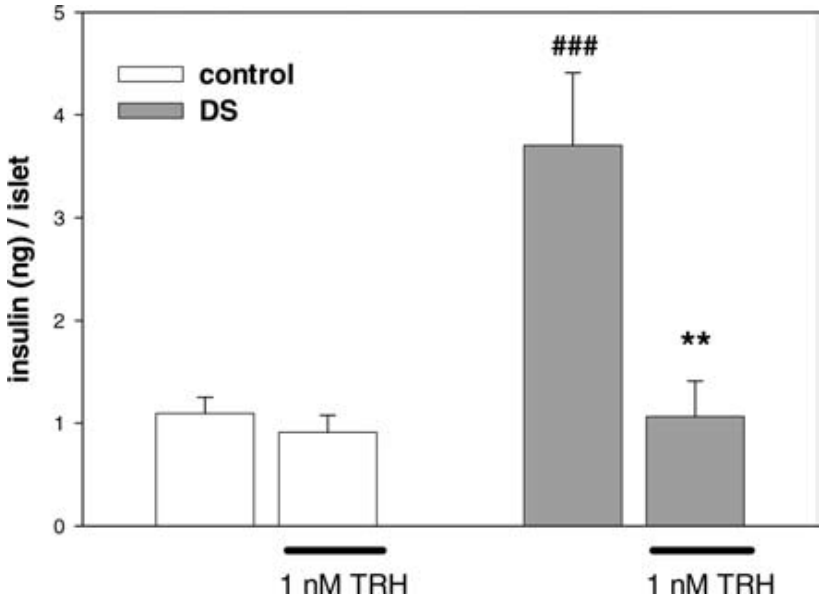
How could TRH affect insulin secretion?

Has TRH immediate effect on insulin secretion from TRH depleted pancreatic islets?

Disulfiram (DS) is an effective tool for reducing peptide amidation and an accumulation of bioactive TRH *in vitro* and *in vivo*. DS acts as a selective inhibitor of peptidyl-glycine alfa-amidating monooxygenase (PAM), enzyme catalyzing the last step of biosynthesis of alpha-amidated peptides, including TRH.

In the presented study, we blocked the terminal step of the post-translational maturation of the amidated peptides by DS treatment for 5 days *in vivo* and then tested *in vitro* (isolated pancreatic islets) - how the insulin secretion was affected.

Effect of thyrotropin-releasing hormone (TRH) on basal insulin secretion from islets from control and disulfiram (DS)-treated rats.



Inhibition of TRH biosynthesis

in rat *in vivo* results in

high basal insulin secretion by

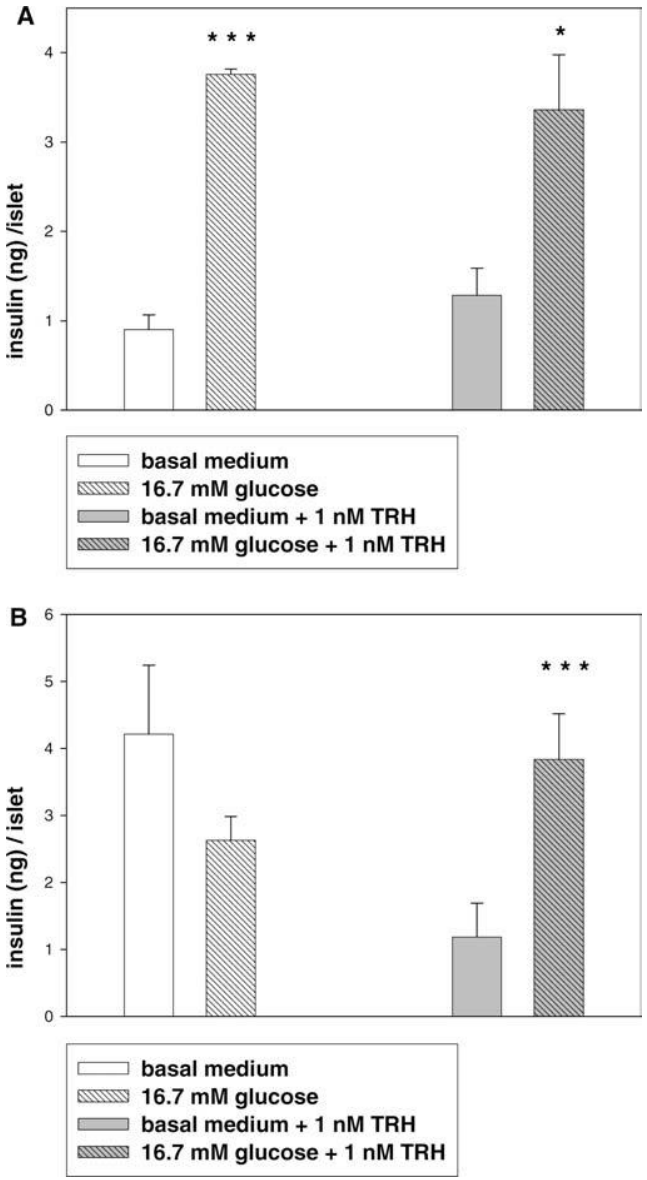
pancreatic islets when tested *in vitro*

High basal insulin secretion is immediately corrected by adding TRH

Into medium

M. Najvirtova, Z. Bacova, A. Mateffyova. V. Strbak: A role of thyrotropin-releasing hormone in insulin secretion by isolated rat pancreatic islets.
Pflugers Arch – Eur J Physiol (2005) 449: 547–552

Effect of thyrotropin-releasing-hormone (TRH) on basal insulin secretion from islets from control and disulfiram (DS)-treated rats – glucose



Intact islets – upper panel:

TRH in incubation medium does not change response to glucose

DS- islets – lower panel:

Islets with inhibited TRH synthesis have high basal insulin secretion and do not react to glucose stimulation

TRH in incubation medium corrects both; lowers basal insulin secretion and normalizes its response to glucose stimulation.

M. Najvirtova, Z. Bacova, A. Mateffyova. V. Strbak: A role of thyrotropin-releasing hormone in insulin secretion by isolated rat pancreatic islets. Pflugers Arch – Eur J Physiol (2005) 449: 547–552

Absence of TRH (DS islets) results in high islet insulin content after glucose stimulation

Table 1 Insulin content (nanograms/islet) in islets from control and disulfiram (*DS*)-treated rats after in vitro stimulation. Islets were stimulated in vitro by 16.7 mM glucose or 30% hyposmolarity in absence and presence of 1 nM thyrotropin-releasing hormone (*TRH*)

In vivo treatment	In vitro stimulation								
	Glucose		Glucose + TRH		30% Hyposmolarity		30% Hyposmolarity + TRH		
	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE	*n*	Means ± SE	*n*	*P*
Control	6.5 ± 0.5	6	8.3 ± 1.6	7	9.1 ± 1.8	8	8.7 ± 0–9	9	
DS	18.2 ± 2.7*	7	9.6 ± 1.2*	7	10.8 ± 1.7	5	10.4 ± 3.2	5	* < 0.01
P	< 0.001								

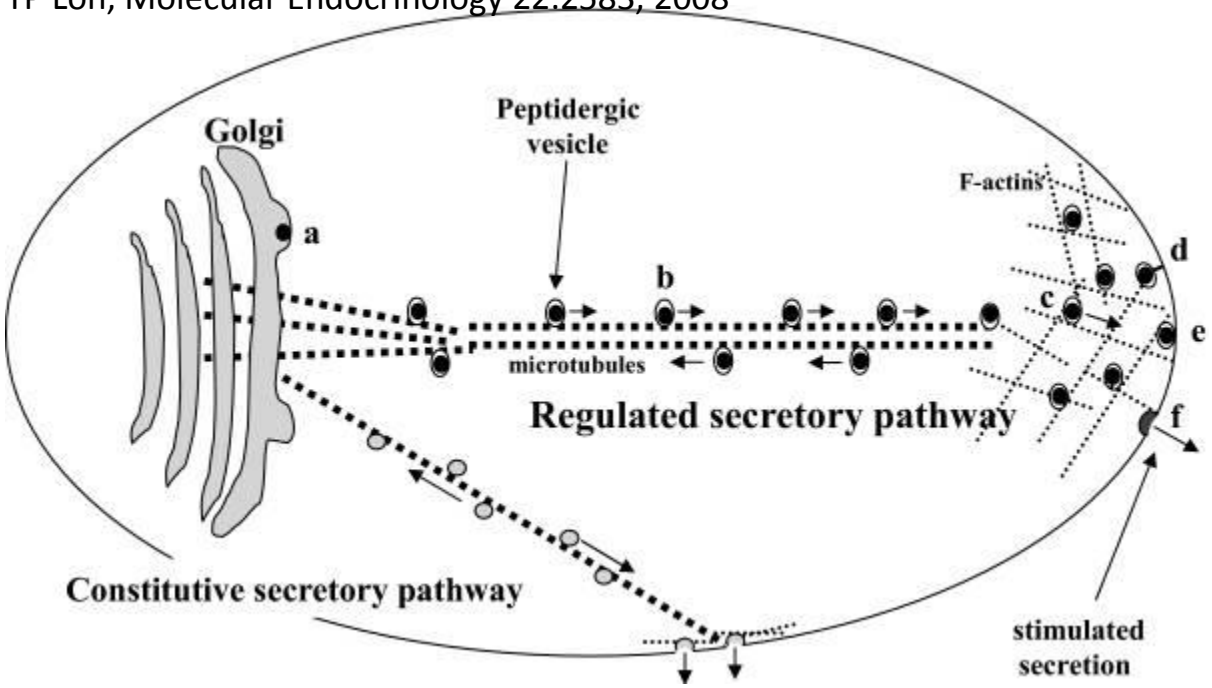
*$P < 0.01$ for comparison between two groups with *asterisk*

M. Najvirtova, Z. Bacova, A. Mateffyova. V. Strbak: A role of thyrotropin-releasing hormone in insulin secretion by isolated rat pancreatic islets. Pflugers Arch – Eur J Physiol (2005) 449: 547–552

Regulated secretory pathway

a- vesicle budding, b- microtubule-based transport, c- actin based transport, d- vesicle tethering, e- docking, f- fusion

• From JJ Park and YP Loh, Molecular Endocrinology 22:2583, 2008



Absence of TRH (DS islets)

High basal secretion and inability to release insulin in response to glucose stimulation suggest that in absence of TRH insulin is directed from the regulatory to constitutional secretory pathway

Addition of TRH restores regulatory secretory pathway

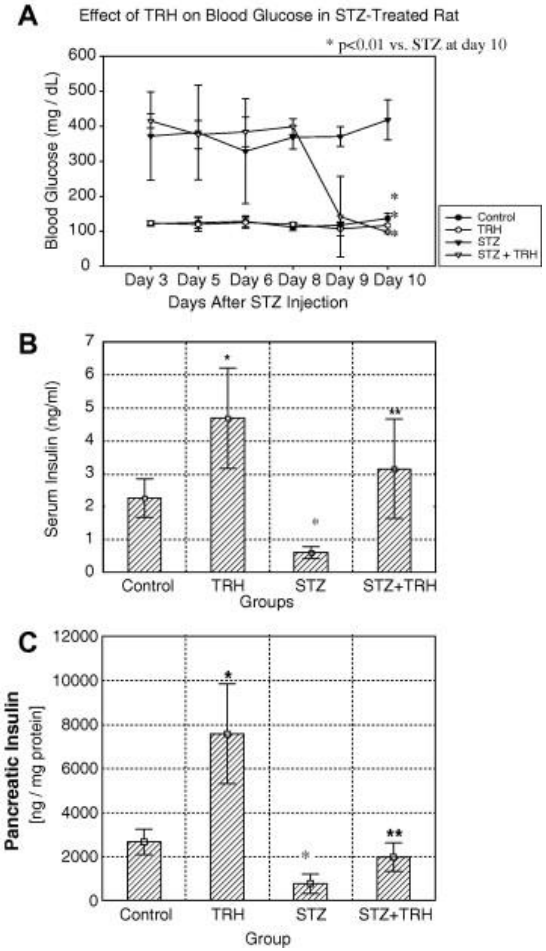
M. Najvirtova, Z. Bacova, A. Mateffyova. V. Strbak: A role of thyrotropin-releasing hormone in insulin secretion by isolated rat pancreatic islets. Pflugers Arch – Eur J Physiol (2005) 449: 547–552

TRH is essential for adequate insulin response to glucose stimulation

Diabetes mellitus type II

1. **Does TRH play a role in its pathopysiology?**
2. **Could treatment with TRH improve insulin response to glucose?**

LuGuang Luo, John Z.Q. Luo and Ivor M.D. Jackson: Thyrotropin-releasing hormone (TRH) reverses hyperglycemia in rat Biochemical and Biophysical Research Communications Volume 374, Issue 1, 12 September 2008, Pages 69-73



- Fig. 1. TRH reverses STZ induced high blood glucose. (A) After 3 days STZ injection ip induced hyperglycemia, TRH (10 μg/kg body weight, ip) was administered to rats. On the day 8, TRH-treated STZ animal glucose started to decline to reach a normal level ($^{*}p < 0.01$ vs. STZ group, $n = 6$); (B) TRH reversed the decline in serum insulin level resulting from STZ treatment on day 10 ($^{*}p < 0.05$ vs. control; $^{**}p < 0.05$ vs. STZ $n = 6$). (C) Quantities of insulin content by ELISA from rat pancreas extract on day 10 (simultaneously collected in frozen section for immunohistochemistry, Fig. 2A) (results normalized by total protein, $^{*}p < 0.05$ vs. control; $^{**}p < 0.05$ vs. STZ $n = 6$).

TRH has the potential to prevent apoptosis and promotes Insulin-Producing Cell Proliferation.

LuGuang Luo. John CQ Luo and Ivor Jackson,

Current Aging Science 6: 8-13, 2013

W. Perpaoli: **Aging-Reversing Properties of Thyrotropin-Releasing Hormone**. **Aging-Reversing Properties of Thyrotropin-Releasing Hormone.** ***Current Aging Science, 2013, 6, 92-98***

Treatment of aging mice with TRH show clear aging-delaying and even aging-reversing effects of the neuropeptide :

maintenance or even reconstitution of testes structure and function,

protection for the kidneys from amyloid and hyalin infiltration of tubuli and glomeruli

TRH, like melatonin, is an anti-aging agent with a broad spectrum of activities

Conclusions

TRH

1. Plays a role in stimulated insulin secretion with possible role in diabetes mellitus
2. Has potential to prevent apoptosis and stimulate proliferation
3. Has aging-reversing properties

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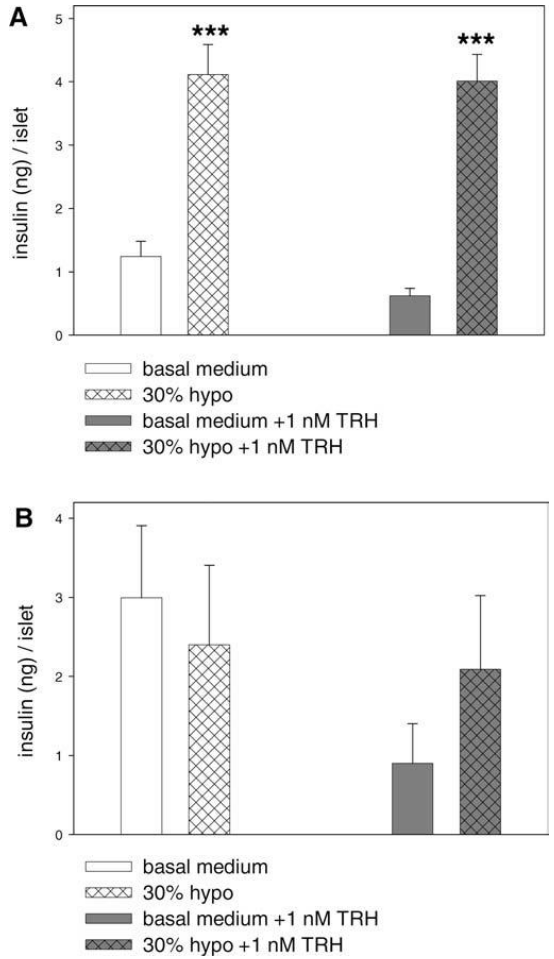
- Bratislava


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Thank you for your attention



Effect of thyrotropin-releasing hormone (TRH) on basal insulin secretion from islets from control and disulfiram (DS)-treated rats –hyposmotic stimulation



Intact islets:

Hyposmotic-induced insulin secretion

DS islets:

High basal insulin secretion and absence of hyposmotic stimulation

TRH in medium restored basal secretion and response to hypoosmotic stimulation

M. Najvirtova, Z. Bacova, A. Mateffyova. V. Strbak: A role of thyrotropin-releasing hormone in insulin secretion by isolated rat pancreatic islets. Pflugers Arch – Eur J Physiol (2005) 449: 547–552