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The effect of peptide tyrosine tyrosine (PYY_{3-36}), a selective Y2 receptor agonist on streptozotocin-induced diabetes in albino rats

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Objective. The aim of the present study was to assess the effect of the PYY_{3-36}, as a potential therapy for the type 2 diabetes mellitus (T2DM), induced by high fat diet (HFD) and an intraperitoneal (i.p.) administration of streptozotocin (STZ) in albino rats.

Methods. Forty adult male albino Wistar rats were divided into: 1) control group (C, in which the rats were fed with a standard diet and received vehicle; 2) diabetic group (D, in which T2DM was induced by feeding the rats with HFD for four weeks followed by a single i.p. injection of 35 mg/kg STZ, this group was also allowed to have HFD till the end of the study; and 3) D+PYY_{3-36} group (in which the diabetic rats were treated with 50 μg/kg i.p. PYY_{3-36} twice a day for one week). Food intake, water intake, body weight (b.w.), visceral fat weight (VFW), liver glycogen content, serum levels of glucose, insulin, and interleukin-6 (IL-6), were measured. Homeostatic-model assessment of insulin resistance (HOMA-IR) was estimated. The gene expression of the hypothalamic neuropeptide Y (NPY) and visceral nuclear factor kappa B (NF-κB) were assessed by a reverse transcription polymerase chain reaction (RT-PCR).

Results. The PYY_{3-36} administration to the diabetic group of rats significantly increased the serum insulin levels and liver glycogen content, decreased the body weight, VFW, food intake, water intake, serum levels of the glucose, IL-6, and HOMA-IR. It also decreased the expression of both the hypothalamic NPY and the visceral fat NF-κB.

Conclusion. With respect to the fact of improved insulin release and enhanced insulin sensitivity (an effect that may be mediated via suppressing accumulation of visceral fat and inflammatory markers), in the rats treated with PYY_{3-36}, the PYY_{3-36} might be considered for the future as a promising therapeutic tool in T2DM.

Key words: PYY, high fat diet, insulin resistance, NF-κB and NPY

Diabetes mellitus is a chronic disease affecting the carbohydrate metabolism and is manifested by hyperglycemia, due to the total or relative shortage of insulin release (Bobronnikova 2017). There are two major types of diabetes, type 1 and type 2. Type 1 diabetes, the juvenile type, is caused by autoimmune demolition of the β cells of the Islets of Langerhans. The type 2 diabetes (T2DM), the adult type, is caused by the resistance to insulin action (Girisha and Viswanathan 2017). Diabetes increases vulnerability for small vessels problems such as retinopathy, nephropathy, and neuropathy as well as large vessels problems such as cerebral and coronary disorders. The prevalence of diabetes is increasing worldwide,

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especially T2DM. These increases call for the need to develop a new effective treatment with the necessity of lifestyle changes that can help to reduce or delay the complications of diabetes (Dabelea et al. 2017).

PYY is a member of the pancreatic polypeptide family that also involves pancreatic polypeptide (PP) and neuropeptide Y (NPY). These peptides have similar chemical structure (possessing a carboxyl-terminal tyrosine amide). Each peptide is formed by 36 amino acids. However, the locations and actions of those amino acids differ among the PP family members (Nishizawa et al. 2017a,b). They bind to NPY receptors that include: Y_1, Y_2, Y_4, Y_5 and Y_6, which have been detected in rodents and rabbits (Nishizawa et al. 2017a,b). PYY is released from the lower portions of the gastrointestinal tract (L cells) and co-expressed in pancreatic islets with glucagon, somatostatin, and PP. In the circulation, PYY is present in two main forms: $PYY_{1–36}$ and $PYY_{3–36}$. $PYY_{1–36}$ is rapidly proteolyzed by dipeptidyl-peptidase IV enzyme (Torang et al. 2016). The cleaved product, $PYY_{3–36}$, is bioactive and performs its action particularly *via* Y_2 receptors (Abdalla 2017; Hassan et al. 2017). In addition to its peripheral action, $PYY_{3–36}$ has been found to cross the blood brain barrier (BBB) and performs its action by acting on central Y_2 receptors (Prinz and Stengel 2017).

The role of $PYY_{3–36}$ in glucose homeostasis remains contradictory. It has been reported that *in vivo* administration of $PYY_{3–36}$ may improve glucose tolerance and promote insulin secretion (Chandarana et al. 2013). However, it has also been reported that $PYY_{3–36}$ may suppress the insulin release from the immortalized islets of both the rodents and human, but *in vivo* administration did not produce any effect on glucose disposal or insulin secretion (Khan et al. 2016). In contrast, another study reported that $PYY_{3–36}$ did not provide significant effects on the insulin level or insulin sensitivity when it is administrated alone, but provided additive action when it was administrated in combination with glucagon like peptide-1 (GLP-1) (Tan et al. 2014). These conflicting findings were the reason for conducting the present study that is designed to test the effect of $PYY_{3–36}$ in the diabetic rats. Moreover, in our study, we focused on the effect of $PYY_{3–36}$ on liver glycogen content and inflammatory mediators such as NF-κB gene expression and serum IL-6.

Materials and methods

Ethical consent. The current study was conducted according to the guidelines for the use and taking care of experimental animals, which were approved by the Institutional Ethical Committee, Medicine Faculty, Minia University, Egypt which agree with the NIH Guide for taking care and use of laboratory animals (National Institutes of Health 1992).

Animals. Forty adult male albino Wistar rats 150–180 g of weight with ages ranged from 6 to 8 weeks, were used. The rats were preserved under normal standard lighting with normal laboratory food and water *ad libidum*. For all groups, the water was administrated in bottles fixed on the sides of the cages. One week before the onset of the study, they were left to be acclimated to the laboratory environment. They were divided into groups (n=10 for each) as follow: 1) Control groups (C, in which the rats were fed with a standard rat chow diet and received the vehicles, one group received saline as a vehicle and the other group received sodium citrate buffer as the vehicle) and 2) Diabetic group (D, in which diabetes was induced by feeding the rats with HFD for four weeks followed by a single i.p. injection of STZ at a dose of 35 mg/kg). One week later, the rats with blood glucose level higher than 200 mg/dl were considered diabetic. The rats were allowed to continue to feed HFD till the end of the experiment. 3) D+$PYY_{3–36}$ group, after diabetes induction as mentioned above, each rat received IP injection of 50 μg/kg $PYY_{3–36}$ twice daily for seven days while continuing HFD feeding.

Food system. The HFD composition used in this study was in agreement with the formula used by Hassan et al. (2015). It is composed of 46% fat (corn oil 25.5%, beef tallow 20.5%), 24% carbohydrates (6% corn starch and 18% sucrose), 20.3% proteins (20% casein and DL-0.3% methionine), 5% fibers, 3.7% salt mixture, and 1% vitamin mixture. This formula provided 4.6 kcal/g of diet.

Drug protocol. STZ (Sigma Aldrich, USA) was dissolved in 0.1 M sodium citrate buffer with pH adjusted at 4.5. $PYY_{3–36}$ (Sigma Aldrich, USA) was dissolved in saline solution. The doses of STZ and $PYY_{3–36}$ were selected on the basis of the previous studies (Mahmoud 2016; Panigrahi et al. 2016).

Assessment of body weight, food intake and water intake. The body weight and food intake were measured at the start of the experiment (after one-week of acclimatization, initial), before treatment with $PYY_{3–36}$ (5^{th} week), and after the treatment with $PYY_{3–36}$ (6^{th} week, final). Water intake was measured daily (the last week of the experiment). Body weight, food intake, and water intake were measured *via* digital electronic scale. The food and water consumptions were estimated by subtracting the weights of food and water bottles, which were measured at the beginning and at the end of 24 h.

Samples collection. After overnight fasting, all the rats were decapitated under light ether anesthesia and blood samples were gathered and centrifuged for 10 min at 5000 rpm. The serum layers were withdrawn, collected in Eppendorf tubes and stored at –20 °C till the time of glucose, insulin and IL-6 serum levels analysis. The IL-6 was determined using colorimetric kit (Biodiagnostic, Egypt) and the other two parameters were estimated by using rat enzyme linked immunosorbent assay (ELISA) kits (Sigma, USA). Homeostatic-model assessment-insulin resistance (HOMA-IR) was calculated according to Yada et al. (2008).

Visceral fat (whole gastro-colic omental fat) was removed (Jiang et al. 2008), weighed instantly *via* digital electronic scale then stored at –80 °C until used for the measurement by the real time reverse transcription polymerase chain reaction (RT-PCR). The liver samples were taken away from all groups, weighed, and then stored at –80 °C for assay of the glycogen content. Then, each rat head was dissected to remove the brain and isolate the hypothalamus for the measuring of the NPY mRNA levels.

Liver glycogen assay. The liver tissues were homogenized in 5 ml trichloroacetic acid reagent and then boiled in water bath for 15 min followed by a centrifugation. One ml of the supernatant was added to 3 ml of concentrated sulfuric acid and boiled in a water bath for 6.5 min, then cooled. Glycogen concentration was measured by a spectrophotometer at 502 nm. The standard curve was prepared at the same time to deduce glycogen concentration. This was done in accordance with the method reported by Ibrahim and Aziz (2016).

Quantification of NPY and NF-κB by RT PCR. Total RNA extraction of NPY from homogenized hypothalamus samples and NF-κB from visceral adipose tissue was done by using ribozol RNA extraction reagent according to the producer's instructions (Amresco, Solon, USA). cDNAs were formed *via* using revert aid™ first strand cDNA synthesis kit (Fermentas, Life Sciences). Then reverse transcription of cDNA was done from 5 µg of mRNA in transcription buffer, 200 U M-MuLV reverse transcriptase, 20 U RNase inhibitor at 42 °C for 60 min then instant cooling on ice was done. RT PCR was finished by using 50 ng cDNA per reaction using 25 µl of SYBR Green QPCR Mix (Solis BioDyne) containing 20 µM of specific primers in the RT PCR detection system. Analysis of the SYBR green data was done in comparison with the reference gene, GAPDH (glyceraldehyde-3-phosphate dehydrogenase). The groups of used primers were following:

NPY forward, 5'-GACATGGCCAGATACTACTCCG-3', NPY reverse, 5'-AAGGGTCTTCAAGCCTTGTTCT-3; NF-κB sense, 5'-ACAACCCCTTCCAAGTTCCCT-3', NF-κB antisense, 5'-TGGTCCCGTGAAATACACCT-3; GAPDH forward, 5'-GTCGGTGTGAACGGATTTG-3', GAPDH reverse 5'-CTTGCCGTGGGTAGAGTCAT-3'.

At 7500 fast, all reactions were done. RT PCR System (Applied Bio systems) under the following circumstances: 95 °C for 15 min, followed by 40 cycles of 94 °C for 15 s, 55 °C for 30 s, and 72 °C for another 30 s. The formula $2^{(-\Delta\Delta Ct)}$ was used to estimate the relative expression level of each gene in comparison with the control (the value equal 1) which was in agreement with VanGuilder et al. (2008). The results were presented in graphs for all experimental groups.

Statistical analysis. The statistical difference among the studied groups in the measured parameters was assessed by one-way analysis of variance (ANOVA) test using Graph pad Prism program, version 7 and the data was presented in the form of mean ± standard error of the mean (mean ± SEM). The probability value (p-value) ≤0.05 was considered statistically significant.

Results

No significant differences in all measured parameters were observed between the two control groups, one receiving saline and the other one sodium citrate buffer as a vehicle. Therefore, only ten rats were chosen to represent the control group.

The influence of PYY_{3-36} on body weight, visceral fat weight (VFW), food intake and water intake. The final body weight, VFW, food intake, and water intake in diabetic (D) group were significantly higher than in the control (C) group. Treatment of diabetic group with PYY_{3-36} (D+PYY_{3-36}) resulted in a significant decrease of the final body weight, VFW, and food intake as compared with the diabetic non-treated (D group). But all of these parameters were still significantly higher than the C group, except water intake, which reached the control group value (Table 1).

The influence of PYY_{3-36} on HOMA-IR and serum levels of glucose, insulin, and IL-6. As shown in Table 2, a significant decrease in serum insulin level was shown in D group accompanied by a significant increase of glucose and IL-6 serum levels as compared to C group. In D+PYY_{3-36} group, PYY_{3-36} treatment resulted in a significant increase in serum insulin level and a significant decrease in the serum levels of glucose and IL-6 as compared to D group, but it remained significantly different from

Table 1
Effect of PYY_{3-36} treatment on body weight, food intake, water intake and visceral fat weight in different groups

Parameters	Groups		
	C	D	D+PYY_{3-36}
BW (g)			
Initial	166.7±1.7	165.7±1.4	164.7±1.5
5th week	205.5±2.4	231.2±2.4^{A}	230±2.9^{A}
Final	208.7±1.7	236±3.4^{A}	221.2±0.5^{AB}
Food intake (g)			
Initial	11.82±0.11	12.1±0.28	12±0.1
5th week	13.5±0.32	20.8±0.55^{A}	21.3±0.49^{A}
Final	15.1±0.21	21±0.23^{A}	15.3±0.16^{B}
VFW (g)	0.93±0.02	2.06±0.06^{A}	1.35±0.07^{AB}
Water intake (ml/day)	57.6±0.8	76.1±1.07^{A}	61±0.5^{B}

Abbreviations: C – control; D – diabetic; PYY_{3-36} – peptide tyrosine tyrosine$_{3-36}$; BW – body weight; VFW – visceral fat weight. Data are expressed as mean±SEM of 10 rats per group. $^{A}p\leq0.05$ vs. control group; $^{B}p\leq0.05$ vs. diabetic group.

Table 2
Effect of PYY_{3-36} treatment on HOMA-IR, serum levels of glucose, insulin, and IL-6 in different groups

Parameters	Groups		
	C	D	D+PYY_{3-36}
Serum glucose (mg/dl)	82.8±0.8	303.8±3.3^{A}	123.8±1.4^{AB}
Serum insulin (μIU/ml)	28.5±0.6	12.5±0.7^{A}	20.8±1.07^{AB}
Serum IL-6 (pg/ml)	32.03±0.4	51.08±1.1^{A}	38.5±0.9^{AB}
HOMA-IR	5.96±0.09	9.6±0.5^{A}	6.4±0.2^{B}

Abbreviations: C – control group; D – diabetic group; PYY_{3-36} – peptide tyrosine tyrosine$_{3-36}$; IL-6 – interleukin-6; HOMA-IR – homeostatic-model assessment-insulin resistance; HOMA-IR=serum glucose (mg/dl) X serum insulin (μIU/ml)/405. Data are expressed as mean±SEM of 10 rats per group. $^{A}p\leq0.05$ vs. control group; $^{B}p\leq0.05$ vs. diabetic group.

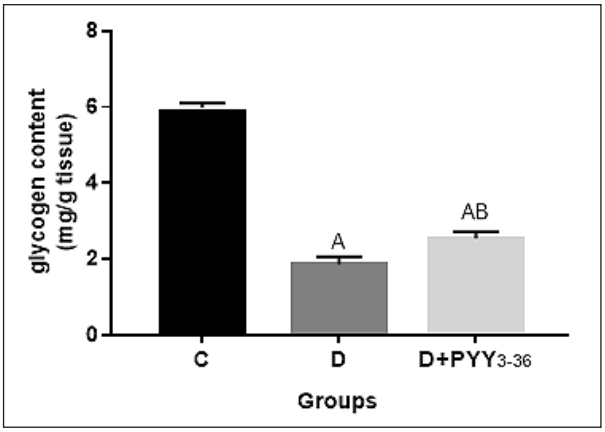

Figure 1. Liver glycogen content in different groups. Abbreviations: C – control group; D – diabetic group; PYY_{3-36} – peptide tyrosine tyrosine 3–36 group. $^{A}p\leq0.05$ vs. control group; $^{B}p\leq0.05$ vs. diabetic group.

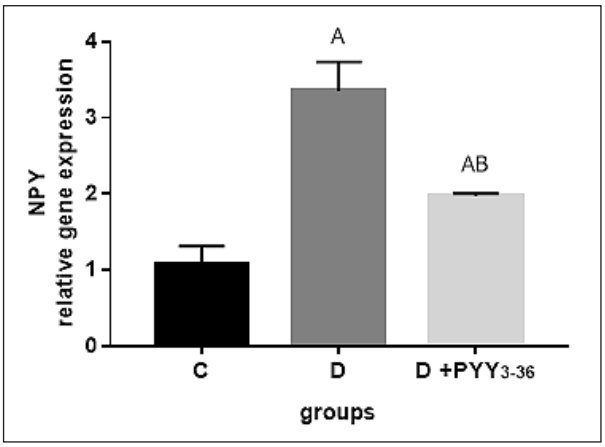

Figure 2. Relative gene expression of neuropeptide Y (NPY) in the hypothalamus in different groups. Abbreviations: NPY – neuropeptide Y; C – control group; D – diabetic group; PYY_{3-36} – peptide tyrosine tyrosine 3–36 group. $^{A}p\leq0.05$ vs. control group; $^{B}p\leq0.05$ vs. diabetic group.

the C group. HOMA-IR was significantly higher in D group as compared to C group. In D+PYY_{3-36} group, it was significantly lower than D group and reached the control level.

The influence of PYY_{3-36} on liver glycogen content. The results revealed a significant decrease in liver glycogen content in D group as compared to C group. PYY_{3-36} resulted in an increase of liver glycogen content in D+PYY_{3-36} group as compared with D group but it was still significantly lower as compared to C group (Figure 1).

The influence of PYY_{3-36} on NPY and NF-κB gene expression. As shown in Figures 2 and 3, the hypothalamic NPY mRNA (Figure 2) and visceral fat NF-κB mRNA (Figure 3) were significantly higher in the D group as compared to C group. In D+PYY_{3-36} group, the NPY mRNA and visceral fat NF-κB mRNA expression was significantly suppressed as compared to the D group, but they was still significantly higher than in the C group.

Discussion

In this study, diabetes was induced by combination of HFD with STZ, which resulted in metabolic characteristics of human T2DM including elevated serum glucose, decreased serum insulin, and insulin resistance (IR), which was also described by Pari and

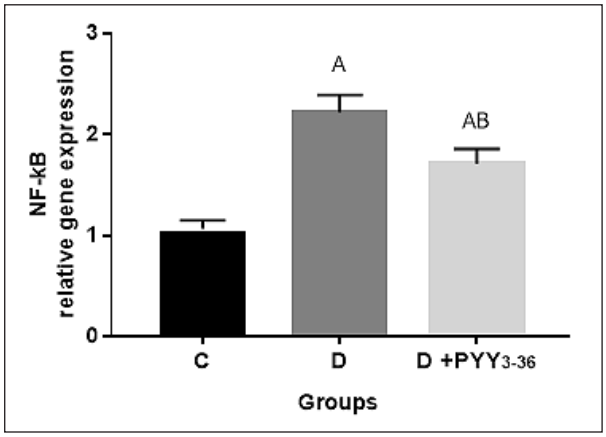

Figure 3. Relative gene expression of NF-κB in visceral fat in different groups. Abbreviations: NF-κB – nuclear factor kappa B; C – control group; D – diabetic group; PYY_{3-36} – peptide tyrosine tyrosine 3–36 group. $^{A}p \leq 0.05$ vs. control group; $^{B}p \leq 0.05$ vs. diabetic group.

Chandramohan (2017). HFD was used to develop IR, but STZ was used to develop hyperglycemia or diabetes. STZ effect is dependent on its dose and the mass of β cells which are still functioning. Low dose of STZ affects β cells and causes mild deterioration of insulin secretion which is similar to T2DM at the late stage. It has been reported that small dose of STZ had an ability to prevent cellular mitosis and/or enhanced β cells dysfunction (Nagarchi et al. 2015). This is compatible with the decreased serum insulin level and the increased serum glucose level found in the diabetic (D) group in the current study.

Administration of PYY_{3-36} to D group could enhance the insulin secretion. The enhanced insulin secretion with PYY_{3-36} could explain the mechanism of improved serum glucose level and amelioration of thirst sensation in D group (decreased water intake). This has been assured by a study showing that i.p. injection of PYY_{3-36} in mice improved nutrient-stimulated glucose tolerance and enhanced insulin secretion indirectly *via* glucagon like peptide-1(GLP-1) release (Chandarana et al. 2013; Gautier-Stein and Mithieux 2013). However, another *in vitro* research of Ramracheya et al. (2016) have confirmed that PYY_{3-36} could enhance insulin secretion *via* a direct action on mouse islets, which were restored structurally and functionally.

NPY, an orexigenic peptide, is spreading widely in the central nervous system (CNS) of rats and humans, where it plays a remarkable role in the control of energy intake and BW (Ye et al. 2017). Previous studies have reported that central injection of NPY may induce obesity and glucose metabolic disorder in rats (Long et al. 2015; Park et al. 2017). In the current study, the attenuation of NPY gene expression in D group treated with PYY_{3-36} may be explained by the peripheral enhancing effect of PYY_{3-36} on insulin release as insulin can cross the BBB and interact with insulin receptors that are broadly disseminated in the ARC nucleus of the hypothalamus expressed on NPY neurons inhibiting NPY expression (Shpakov et al. 2015; Loh et al. 2017). This inhibitory tone of the peripheral insulin on NPY is supported by the upregulation of NPY expression found in our study and other rodents' models of STZ-induced diabetes (Gelling et al. 2006). On the other hand, several researches have confirmed that PYY_{3-36} acts directly on Y_2 receptors expressed on NPY neurons (Hassan et al. 2017) that act as presynaptic auto-receptors inhibiting endogenous NPY release as well as its gene expression (Dum et al. 2017; Al-Baldawi et al. 2017). There was a positive correlation between the increased hypothalamic NPY gene expression and the increased food intake and BW in D group which was reversed by PYY_{3-36} administration as found by Mahmoud (2016) who also have shown that PYY-null mice exhibited hyperphagia and increased adiposity.

The decrease of visceral fat weight in diabetic rats treated with PYY_{3-36} found in the present study can be explained by several mechanisms, such as 1) the direct effect of PYY_{3-36} to enhance fat utilization (Gautier-Stein and Mithieux 2013; Hassan et al. 2015; Mahmoud 2016; Nishizawa et al. 2017a,b); 2) stimulation of Y_2R in visceral fat by PYY_{3-36} (Chatree et al. 2017); 3) the attenuated NPY gene expression in diabetic rats caused by PYY_{3-36} administration may be a possible central mechanism of action to suppress visceral fat accumulation as Park et al. (2017) have reported that NPY promoted adiposity when it was administered exogenously or overexpressed. This may be related to its stimulatory action on adipogenesis and inhibitory action on lipolysis in adipose tissue and these effects have been elucidated by Zhang et al. (2014) who reported that the hypothalamic NPY inhibited the peripheral sympathetic action on adipose tissue through hypothalamus-sympathetic nervous system-adipose tissue innervation and adipose tissue-hypothalamus feedback loops. This was confirmed by Park et al. (2014) who have mentioned that NPY antagonism reduces adiposity and attenuates the imbalance of adipose tissue metabolism. Chao et al. (2011) have also reported that knockdown of NPY expression in the dorsomedial hypothalamus decreased adiposity and prevented diet-induced obesity. The overexpressed hypothalamic NPY inducing

hyperphagia in D group in this study may be a reason for increased VFW in this group as found by Hassan et al. (2015) who have reported that excess HFD feeding inhibited oxidation of fatty acid and increased fat synthesis and storage in the adipose tissue.

Excess of visceral fat accumulation could compress its own blood supply inducing hypoxia. Hypoxia enhances the activity and gene expression of NF-κB in visceral fat in diabetic rats. NF-κB gene expression enhances the transcription of pro-inflammatory cytokines and increases their circulating level. The proinflammatory cytokines could act as inducers of NF-κB activation and gene expression in adipose tissue creating a positive feedback mechanism that augment adipose tissue inflammation resulting in more expansion of adipocytes. This is in-agreement with the increased NF-κB gene expression in visceral fat and increased serum level of IL-6 in D group in the present study (Tourniaire et al. 2013; Ghosh 2014; Litvinova et al. 2014). Insulin resistance (IR), appeared in D group in the present study, may be related to IL-6 induction of serine phosphorylation and reduction of tyrosine phosphorylation of insulin receptor, leading to inhibition of insulin signaling (Gutierrez-Rodelo et al. 2017). This indicated that there is a positive correlation between serum IL-6 level and fat accumulation and a negative correlation between it and insulin action. The previous findings are in agreement with the hypothesis that inflammation has a role in the development of IR and T2DM. Thus, the connection between IR and inflammatory process suggested that the anti-inflammatory therapeutic strategies may be a promising therapeutic tool in diabetes (Castro et al. 2017).

Administration of PYY_{3-36} to D group reduced IR in our work. This could be attributed to its ability to decrease VFW which resulted in reduction of the circulating level of proinflammatory cytokines. This is compatible with the decreased serum level of IL-6 with PYY_{3-36} in the present study. The decreased serum level of IL-6 may be due to PYY_{3-36} ability to attenuate transcription of NF-κB as found in the present study and reported by Robinson et al. (2006). Moreover, the inhibitory effect of PYY_{3-36} on food intake may be considered as another possible mechanism of reduced IR. It has also been known that lipotoxicity with long-term HFD feeding may be involved in altering of the cell membrane structure, hence interfere with insulin binding (Hassan et al. 2015).

The inhibitory effect of PYY_{3-36} on NPY expression found in the present study may be an additional reason of improved IR and decreased serum glucose level (Gautier-Stein and Mithieux 2013; Hassan et al. 2015; Mahmoud 2016; Nishizawa et al. 2017a,b). It has been suggested by Li et al. (2016) that the hypothalamic NPY neurons *via* efferent vagal nerves innervating the liver abolished the inhibitory effect of insulin on glucose production. This has been confirmed by a study documented that the β cells function and insulin action were under control of hypothalamic neurons. This has been confirmed by induction of c-Fos expression (the marker of neurons activity) in hypothalamic neurons after peripheral glucose injection (Mobbs 2016). Thus, this may provide an evidence that PYY_{3-36} improved IR and enhanced insulin action on glucose elimination through hypothalamic Y_2 receptors (van den Hoek et al. 2007). The evidence that PYY regulate insulin sensitivity has been provided by Loh et al. (2017) who have reported that PYY knockout mice became glucose intolerant. Enhancement of insulin release and improvement of IR stimulate peripheral glucose utilization and enhance glycogenesis with concomitant decrease in glycogenolysis and gluconeogenesis (Saleh et al. 2014). This is compatible with the increased liver glycogen content with PYY_{3-36} administration as compared to D group in the current study.

Several studies have shown various results from the current study. It has been reported that PYY_{3-36} had no effect on glucose homeostasis and did not improve insulin secretion or IR when it was administrated alone (Tan et al. 2014). Another study has documented that *in vivo* administration of PYY_{3-36} did not affect glucose disposal or insulin secretion after peripheral glucose administration. However, *in vitro*, PYY_{3-36} inhibited glucose, alanine, and GLP-1 stimulated insulin secretion from mouse and human islets by blocking the changes of the membrane potential and elevation of cyclic adenosine monophosphate (cAMP) (Khan et al. 2016). A recent *in vitro* study has shown that through a paracrine mechanism, PYY may inhibit insulin secretion from rat and mouse islets (Loh et al. 2017). The different strains and experimental protocols used may explain the different findings among different studies (Acuna-Goycolea and van den Pol 2005).

Conclusions

With respect to the fact of improved insulin release and enhanced insulin sensitivity (an effect that may be mediated *via* suppressing accumulation of visceral fat and inflammatory markers), in the rats treated with $PYY_{3-36,}$ the PYY_{3-36} might be considered for the future as a promising therapeutic tool in T2DM.

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