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Effects of Passive Immunization against Peptide Tyrosine Tyrosine on the Growth Performance and Endocrine Hormone Levels in Blood Serum of Rats

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Abstract: The aim of this study was to determine the effects of immunization against Peptide tyrosine tyrosine (PYY) on the growth performance and endocrine hormone levels in the blood serum of rats. Sixty Sprague-Dawley rats were randomly assigned to four treatment groups, with five replicates in each group and three rats for each replicate. The antiserum of PYY was injected into the rats thrice every 8 days at the concentrations of 0 (control), 50, 100 and 200 μL. Throughout the experimental period, the rats were given free access to food pellets and water. The growth performance of the animals, including their average daily gain, average daily feed intake and feed/gain ratio, was recorded. The blood samples of PYY, Neuropeptide Y (NPY), leptin, gastrin and insulin concentrations were measured. The good effects of PYY antiserum on the growth performance and serum indexes of treat groups were observed in this trial, especially in group 3 rats. The average daily gain recorded for days 8-14 and 15-21 in group 3 increased by 7.23% ($p<0.05$) and 9.79% ($p<0.05$) respectively, compared with the control group. The feed intake in group 3 was also higher than that in the control group by 19.73% ($p<0.05$), 14.47% ($p<0.05$) and 12.09% ($p<0.05$) on days 0-7, 814 and 1521, respectively. However, no significant difference in feed/gain ratio between the treatment and control groups was detected. Moreover, the NPY, leptin, insulin and gastrin concentrations in group 3 significantly increased by 34% ($p<0.05$), 251% ($p<0.01$), 589% ($p<0.01$) and 31.93% ($p<0.01$) respectively, compared with the control group, whereas the level of PYY significantly decreased by 57.82% ($p<0.01$). In conclusion, the growth, ingestion and some metabolism-related hormones with good effects on the regulation of feed intake and energy metabolism can be improved by passive immunization against PYY rather than by causing immunological stress in animals.

Keywords: Endocrine hormone, growth, immunization, PYY

INTRODUCTION

Voluntary feed intake is mainly controlled by, but not limited to, the intricate and diverse afferent and efferent communication pathways, which transmit hormonal and neural messages throughout the body. A delicate balance between feed intake and its nutrient utilization exists to maintain nutritional homeostasis associated with food consumption, which is mainly controlled by a particular regulatory mechanism consisting of the appetite-stimulating effects of ghrelin, orexin and Neuropeptide Y (NPY) as well as the appetite-suppressing effects of leptin, cholecystokinin and Peptide tyrosine tyrosine (PYY). PYY plays an important physiological role in the regulation of feed intake and gastrointestinal function that tends to be more reflective of short-term energy stores within the body (Carroll and Allee, 2009). Research has shown that the mechanism of PYY mainly regulates feed intake by transmigrating across the blood-brain barrier and arriving at the hunger center of the lateral area and the satiety center of the ventromedial nucleus of the

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hypothalamus (Batterham *et al*., 2002). Therefore, PYY not only acts as a satiety signal to the central feeding system and inhibition of feeding but also serves as an important humoral mediator of the enterogastric feedback mechanism, thereby slowing down gastric emptying and small intestinal transit (Renshaw a Batterham, 2005; Chelikani *et al*., 2004). Prasanth *et al*. (2004) reported that the level of PYY in serum significantly increased after ingestion for several hours before reaching its maximum. A close dose-effect relationship between the decrease in feed intake and the dose of PYY injected peripherally in some rodents either in fasting treatment or in voluntary feed intake treatment exists (Challis *et al*., 2003) and it has been reported to usually lead to an increase in the feed intake and body mass indexes of white mice, rabbits and macaques (Koegler *et al*., 2005; Sileno *et al*., 2006). In fact, Le Roux *et al*. (2006) demonstrated that PYY reduced the secretion of some endocrine hormones, such as NPY and agouti-related protein by inhibiting neurons secreting them in the central feeding system.

Research has shown that some gastrointestinal hormones released from the gut and small intestine, such as NPY, PYY, leptin, insulin and gastrin, might play a role in altering the eating behavior or material metabolism of animals (Cummings *et al*., 2002). As a neuron neurotransmitter, NPY is considered a strong inducing factor of feed intake and inhibiting factor of thermo genesis from brown adipose (Renshaw and Batterham, 2005). Similarly, feed intake has been found to increase significantly when NPY was injected into the ventricles and par ventricular nucleus of rat, with repeated injection leading to obesity (Stanley *et al*., 1986). On the other hand, leptin, a protein hormone expressed and secreted from mature white fat cells, is regarded as a feedback signal that regulates body weight and energy metabolism homeostasis (Margetic *et al*., 2002). Studies have demonstrated that leptin may exert its effects on feed intake through its interaction with NPY in the hypothalamus. Some evidence indicates that NPY administered via intraventricular injection can improve feed intake, white adipose tissue content and the levels of leptin, cortisol and insulin in plasma of mice (Baran *et al*. 2002; Xu *et al*., 2001). These findings suggest that NPY, feed intake and endocrine hormones in animals are closely related, but the data supporting this are still limited. As far as gastrointestinal physiology is concerned, research has indicated that the enterogastric feedback response, including gastric emptying, pancreatic secretion and insulin level, may contribute to regulating ingestion by influencing the level of PYY. In addition, PYY has a rather significant inhibitory effect on the secretion of gastric acid, secretin, insulin and gastrin that is closely related to the receptors and the level of PYY itself. For example, the significant inhibitory effect of PYY on pancreatic secretion was determined at the rates of 25 and 12.5 pmol/kg/h, respectively; however, it was influenced by the combination of receptors and PYY (Hoek *et al*., 2004). Hence, although the mechanisms underlying the influence of ingestion and enterogastric feedback in animals are poorly defined, PYY has been found to inhibit ingestion by affecting the plasma levels of endocrine hormones, such as NPY, leptin, insulin and gastrin, stimulating pro-opiomelanocortin neurons and increasing the level of melanocortin (Prasanth *et al*., 2004; Nematy *et al*., 2006).

We hypothesized that various processes, such as changes in appetite-stimulating or appetite-suppressing effects, the levels of endocrine hormones and gastrointestinal physiology define the mechanism of PYY in regulating feed intake. In addition, a close relationship between feed intake and the effects of PYY and endocrine hormone levels associated with metabolic status has been observed in rats and monkeys, but the role of immunization against PYY on growth and endocrine hormones remains largely unexplored. Therefore, the aim of the present study was to investigate the effects of immunization against PYY on feed intake and endocrine hormone levels in rats. It also assessed the relationship between the content of PYY in serum and its effects on feed intake and related hormones.

MATERIALS AND METHODS

Animal and experimental protocol: Sixty Sprague-Dawley mice weighing 87.77±1.61 g were obtained from the sub-center of the Chinese Academy of Sciences Laboratory Animal Center (Hunan, China). The mice were housed in a pathogen-free mouse colony (temperature, 25°C; relative humidity, 55-60%; light cycle, 12 h/day) and had free access to food and drinking water. The animals were randomly assigned to one of the following groups: group 1, 50 μL of PYY antiserum; group 2, 100 μL of PYY antiserum; group 3, 200 μL of PYY antiserum; control group, 0.9% physiological saline water. The PYY antiserum and saline were administered by intravenous injection thrice within 21 days (once every 8 days). All mice were injected with the PYY antiserum or saline on day 21 and then immediately killed, after which their serum was collected. All animal experiments were performed according to the guidelines of the Laboratory Animal Ethics Commission of the Chinese Academy of Sciences.

Data collection: The growth performance, including Average Daily Gain (ADG), Average Daily Feed Intake (ADFI) and Feed/Gain (F/G) ratio, of the mice in every replicate was calculated throughout the 21-day experimental period. Blood samples were collected into centrifuge tubes, centrifuged at 3000 rpm for 15 min and stored at -20°C for analysis of hormone levels using

enzyme-linked immunosorbent assay (CU-SABIO BIOTECH CO., LTD., Shanghai, China). The level of insulin was detected by sequential saturation analysis in a competitive inhibition reaction (Shanghai Institute of Biological Products, Shanghai, China). The NPY and leptin levels in the serum were determined by balancing in a homogeneous competitive restraining reaction, whereas the gastrin concentration was detected using special radial immunodiffusion kits (Shanghai Institute of Biological Products, Shanghai, China) according to the manufacturer's instructions.

Data were processed using Excel 2003 and analyzed by SPSS 16.0. The results were expressed as mean±Standard Deviation (SD).

RESULTS

The results on the growth performance of the mice from all study groups are shown in Table 1. The ADGs of group 3 rats, which were injected with 200 μL of PYY antiserum, were higher by approximately 7.23% ($p<0.05$) in week 2 and 9.79% ($p<0.05$) in week 3 compared with the control group. Moreover, the consumption of feed increased by 19.73% ($p<0.05$), 14.47% ($p<0.05$) and 12.09% ($p<0.05$) on days 0-7, 8-14 and 15-21, respectively, compared with the control group. These results indicate that a dose-effect relationship between the level of PYY antiserum and growth performance, such as daily weight gain and feed intake, exists; however, the difference in F/G ratio between groups was not statistically significant (Fig. 1 to 3, Table 1).

To understand the reasons for the effects of the PYY antiserum on growth performance, we measured the levels of some hormones related to ingestion, metabolism and digestive function (Table 2). Different levels of regulatory effects on the contents of serum hormones were observed in the rats. For example, the change in gastrin level was much better than those in other hormones compared with the control group (Fig. 4). In addition, compared with NPY, insulin and PYY, the concentration of leptin, following that of gastrin, in serum significantly changed (Fig. 5). Collectively, the levels of NPY and insulin did significantly exceed those in the control group ($p<0.01$; Fig. 5 and 6). As shown in Table 2, the NPY, leptin, gastrin and insulin concentrations, especially in group 3, increased by 34% ($p<0.05$), 251% ($p<0.01$), 589% ($p<0.01$) and 31.93% ($p<0.01$), respectively, compared with the control group, whereas the level of PYY decreased by 57.82% ($p<0.01$). However, no significant difference between the other treatment groups was noted ($p>0.05$).

DISCUSSION

Effects of PYY immunization on the growth performance of rats: The objective of this study was to investigate the effects of passive immunization against PYY on growth and endocrine hormone levels. Its primary challenges were whether the effects of passive immunization against PYY in animals would be observed and if the immune technique or administration of antibody including antiserum or egg yolk antibody would be feasible. Under normal circumstances, sufficient feed intake of nutrients during critical periods, such as weaning, lactation and growth, is crucial for the performance, health and welfare of animals (Gourdine *et al*., 2006). Research has demonstrated that PYY immunization improved ingestion in a few animals, including rats, New Zealand white rabbits and monkeys (Sileno *et al*., 2006; Papanimitriou *et al*., 2007). We found that ADG and feed consumption significantly increased with a change in the PYY antiserum, indicating that a dose-effect relationship between the level of PYY antiserum and the growth performance of mice exists. The results showed that the ADG values in group 3 increased by 7.23% ($p<0.05$) and 9.79% ($p<0.05$) on days 8-14 and 15-21, respectively, compared with the control group. Similarly, the feed intake in group 3 was also higher than that in the control group by 19.73% ($p<0.05$), 14.47% ($p<0.05$) and 12.09% ($p<0.05$) on days 0-7, 8-14 and 15-21, respectively (Table 1). These findings are consistent with those of Sileno *et al*. (2006) and Papanimitriou *et al*. (2007), who reported the suitability of PYY immunization in mammals. In the present study, the results on the effects of PYY antiserum on ADG and ADFI indicated that the elimination or weakening of the appetite-suppressing effects of PYY by immunization improved the feed intake and growth rate of mice. However, the effects of PYY immunization on F/G ratio and Feed Conversion Rate (FCR) were not observed, suggesting that the utilization of nutrients from the diet was not only affected by the antiserum but also regulated by such other factors as endocrine hormones, which changed with PYY immunization.

In addition, immunization has also been shown to cause immunological stress because of the increases in epinephrine and nor epinephrine, which trigger the decomposition of glycogen and fat. Hence, the feed consumption and growth performance of animals would often decrease to a certain degree. For example, Van Heugten *et al*. (1994) observed that the feed intake of piglets decreased by 97% 1 day after injection of 200 g/kg lip polysaccharides compared with the control group. Similar findings were reported for piglets and chicks in that the immunological stress caused by exogenous substances, such as lip polysaccharides and pathogenic microorganisms, inhibited the appetite of animals and decreased their performance (Webel *et al*., 1998a, b). However, whether the slight stress reaction associated with the injection of PYY antiserum in the present study showed effects similar to those observed

Table 1: Effects of different doses of PYY antiserum on growth performance

	ADG (g/d)			ADFI (g/d)			F/G		
Treat	0-7 days	8-14 days	15-21 days	0-7 days	8-14 days	15-21 days	0-7 days	8-14 days	15-21 days
Control	12.69±0.14a	17.83±0.69a	24.41±1.58a	82.18±6.35a	100.88±11.51a	111.97±1.94a	0.93±0.06a	0.81±0.12a	0.66±0.05a
Treat 1	12.56±0.32a	18.08±0.62a	25.37±0.99ab	90.81±7.34ab	110.05±6.46ab	118.49±7.95a	1.03±0.09a	0.86±0.04a	0.67±0.03a
Treat 2	12.72±0.10a	18.28±0.31ab	25.96±0.60bc	91.20±5.05ab	114.64±7.04ab	128.38±4.02b	0.93±0.28a	0.90±0.07a	0.71±0.03a
Treat 3	12.62±0.09a	19.12±0.98b	26.80±0.10c	98.40±5.57b	115.48±5.96b	132.81±2.42b	1.12±0.07a	0.87±0.06a	0.71±0.01a

Data are expressed as mean±S.D. values in a row without a common letter differ at p<0.05

Table 2: Effects of different doses of PYY antiserum on serum hormone indexes

Treat	NPY (pg/mL)	Leptin (pg/mL)	PYY (pg/mL)	胃泌素 (pg/mL)	胰岛素 (μg/mL)
Control	128.35±12.34a	20.24±5.500Aa	6.14±2.19Bb	30.14±4.11Aa	22.77±1.44Aa
Treat 1	125.02±21.99a	31.08±10.57Aab	6.16±1.23Bb	42.29±22.29ABa	26.05±0.44ABab
Treat 2	132.02±7.52ab	49.07±15.89ABbc	3.71±0.78ABa	169.58±85.62ABb	29.76±1.89Bb
Treat 3	171.98±37.49b	71.11±26.33Bc	2.59±0.48Aa	207.78±103.69Bb	30.04±4.79Bb

Data are expressed as mean±S.D. values in a row without a common letter differ at p<0.05 (lowercase) and p<0.01 (uppercase)

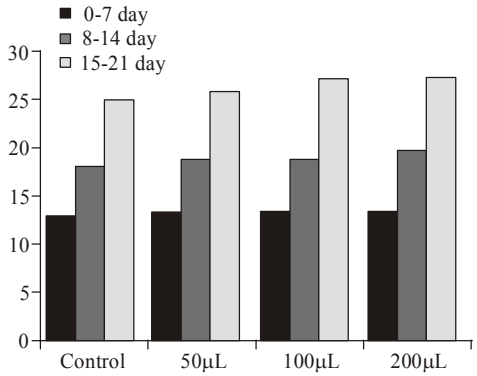

Fig. 1: Daily weight gain in the study groups (n = 15 each)

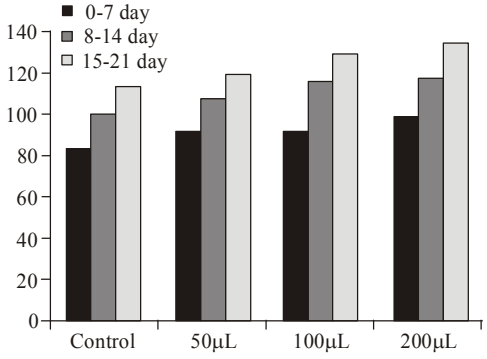

Fig. 2: Feed intake in the study groups (n = 15 each)

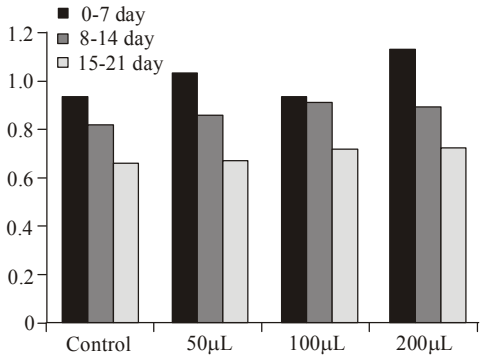

Fig. 3: Feed/gain ratio in the study groups (n = 15 each)

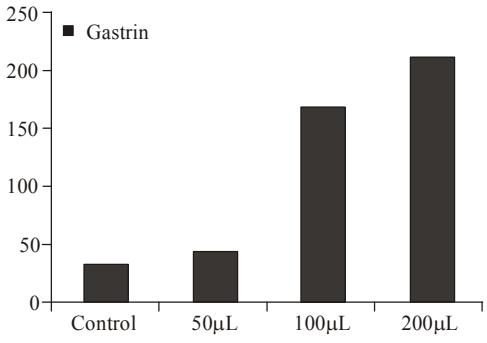

Fig. 4: Content of PYY in the PYY antiserum group at three levels. Each group (n = 15) was injected with antiserum three times throughout the experimental period and the serum was collected on the 21st day

in previous study remains unknown. The results of this study indicated that the effects of the administration of PYY antiserum on the growth of mice differed from those caused by immunological stress, with the former mainly eliminating the appetite-suppressing effects of PYY and stimulating the ingestion of animals (Fig. 1 and 2).

Effects of PYY immunization on the levels of serum hormones: Endocrine hormones (including the appetite stimulators ghrelin, orexin and NPY as well as the appetite suppressants PYY, leptin and urocotin), metabolism-related hormones (such as insulin) and gastrointestinal hormones (such as gastrin) play a key role in regulating feed intake in various ways (Carroll and Allee, 2009). Conversely, the metabolism of animals influences ingestion and there exists a complex interaction between feed consumption, the regulatory mechanism of endocrine hormones, nutrient metabolism and the physiological regulation of the gastrointestinal tract. For instance, research has shown that the effect of insulin on feed intake is often associated with a defect of the blood-brain barrier in the

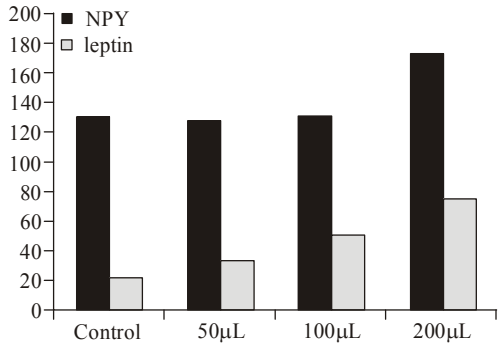

Fig. 5: Contents of NPY and leptin in the PYY antiserum group at three levels. Each group (n = 15) was injected with antiserum three times throughout the experimental period, and the serum was collected on the 21st day

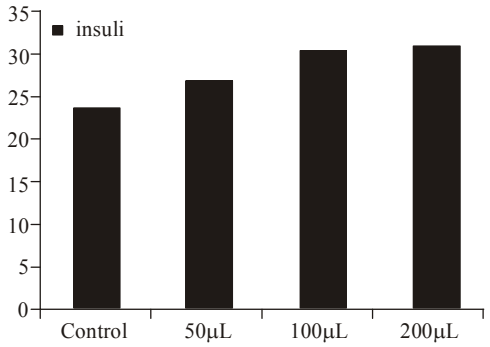

Fig. 6: Content of insulin in the PYY antiserum group at three levels. Each group (n = 15) was injected with antiserum three times throughout the experimental period and the serum was collected on the 21st day

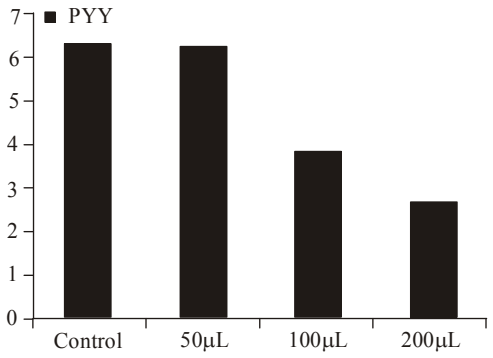

Fig. 7: Content of gastrin in the PYY antiserum group at three levels. Each group (n = 15) was injected with antiserum three times throughout the experimental period and the serum was collected on the 21st day

median eminence and posterior hypothalamus and that insulin may exert its effect on the ingestion of animals by interacting with its receptor such that it could influence the activity of neurons in the hypothalamus via the transition of nerve fibers (Le Megnen, 1983). Similar results were observed for NPY, PYY, gastrin and leptin in this study (Table 2). We found that the level of insulin and ingestion increased following an increase in the level of PYY antiserum, suggesting that the consumption of feed is indeed positively correlated with the insulin content in the serum of mice (Fig. 6, Table 2). Moreover, changes in the level of insulin were inhibited and influenced by PYY itself-for example, the level of insulin further increased with increasing PYY antiserum dose (Table 2). However, as for the inhibitory mechanism of PYY, limited information indicated that the receptor Y1 played an important role by decreasing the level of insulin and weakening the effect thereof through a reduction in the content of intracellular cyclic adenosine monophosphate or an inhibition of the activity of β cells (Van Houten and Posner, 1981).

With regard to appetite regulation, NPY has been associated with a number of physiological activities, especially appetite stimulation in animals, such as poultry, sheep and pigs (Barb *et al*., 2006). The fact that NPY was reported to be a more potent stimulator of feed intake than orexin in rodents and subsequent research showing that NPY gene expression in the hypothalamus was up-regulated following food deprivation in animals confirms that NPY plays a role in appetite stimulation (Colmers and E1, 2003). Interestingly, we observed a common elevation to a certain degree among NPY, insulin and leptin in the serum of rats (Table 2), which demonstrated that there was some complex regulatory mechanism between these three hormones. Several studies showed that leptin could regulate the content of body fat and energy metabolism by acting on the arcuate nucleus of the hypothalamus and decreasing ingestion or promoting energy consumption (Mercer *et al*., 1996). The weakening or elimination of the inhibitory role of leptin has been found to lead to an increase in the activity of NPY and overeating or obesity, although how this interaction between leptin and NPY is completed remains unclear (Clement *et al*., 1998).

Several studies have indicated that a bidirectional regulatory effect exists between leptin and insulin (Wang *et al*., 2003). In the present study, leptin and insulin were positively correlated because the level of insulin in serum maintained good synchronization with the content of leptin in mice (Fig. 5 and 6; Table 2). Kastin and Akerstrom (2001) and Ishii *et al*. (2002) demonstrated that insulin promoted the rapid secretion of leptin from Ob cells, increased the expression of mRNA and improved the contents in serum within the physiological range of insulin itself. Conversely, leptin could inhibit the secretion of insulin by increasing the permeability of the β-cell ATP-dependent potassium channel and islet β-cell hyper polarization (Wang *et al*., 2003). Moreover, the inhibition of leptin on the gene expression of NPY mRNA through its receptors was reported to cause a reduction in ingestion and an

increase in energy consumption and metabolism, which led to a decrease in the secretion of insulin (Ishii *et al*., 2002). As for the regulatory mechanism between leptin and insulin, two operating pathways are associated with their complex interaction: Adipose tissue could secrete leptin stimulated by insulin and activate the activity of obesity gene receptors, thereby inhibiting the production of NPY in the hypothalamus and then leading to inhibited secretion of insulin by reducing the activity of the parasympathetic nerve (Baskin *et al*., 1999). In addition, leptin binds with obesity gene receptors and existing islet cells, activates ATP-sensitive K^+ channels and induces pancreatic islet β-cell hyper polarization, which lead to a reduction in Ca^+-dependent protein kinase C and inhibition of insulin secretion (Kieffer *et al*., 1997). However, the levels of insulin and leptin continued to increase simultaneously and no correlation between them was detected in this trial (Table 2), indicating that a complex mechanism of hormone regulation but no significant relationship exists between the two hormones. A major problem in this experiment was that although a synergistic effect did exist between leptin and insulin to a certain degree, their activities were lower than the sum of their effects.

This study also found that gastrin, which is secreted from islet cells, exerts many effects on the regulatory function of the gastrointestinal tract, delays gastric emptying and promotes insulin release. The level of gastrin in the serum of mice also retained a certain degree of synchronism with the changes in other endocrine hormones, including NPY, PYY, insulin and leptin (Fig. 6 and 7; Table 2). However, the level of gastrin increased following a change in the dose of PYY antiserum, which indicated that PYY may influence the secretion of gastrin to a certain degree; moreover, the increasing range of gastrin compared with the control group was much higher than those of the other hormones. Furthermore, this experiment observed that FCR did not improve with increasing PYY antiserum level, which was similar to the results obtained for gastrin (Table 1 and 2). These results indicate that the reduction in FCR in mice can be attributed to an excessively high level of gastrin and thus warrant further investigation of the relationship between the two.

CONCLUSION

This study has demonstrated that PYY immunization improved the growth performance of rats and that a significant dose-effect relationship between the level of PYY antiserum and growth existed. PYY regulated feed intake by influencing the contents and the ratios between NPY, leptin, insulin and gastrin. An unknown relationship among these hormones likely exists, leading to a complex regulatory mechanism of ingestion of PYY.

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