Inhibition of peripheral NPY Y1 and Y2 receptors ameliorates the aberrant baroreceptor reflex sensitivity in streptozotocin induced diabetic rats

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Abstract: Neuropeptide Y (NPY), a sympathetic neurotransmitter, is highly associated with baroreflex dysfunction and multiple cardiac diseases such as diabetic myocardopathy. In the present study, we aimed to explore the role of peripheral NPY Y1 receptor (Y1R) and Y2 receptor (Y2R), which are dominantly present in peripheral cardiovascular control, in baroreflex sensitivity (BRS) of streptozotocin (STZ)-induced diabetic rats. Peripheral Y1R and Y2R were antagonized by specific antagonists (BIBP 3226 and BIIE 0246, respectively) from subcutaneously implanted ALZET mini-osmotic pump in STZ-induced diabetic rats for 4 weeks. Then baseline systolic blood pressure, heart rate, cardiac function, BRS, plasma NPY and lipid levels were evaluated. We found that STZ led to increased plasma NPY and lipid level. And the STZ-increased lipid levels were reduced by BIBP 3226 and BIIE 0246. BIBP 3226 ameliorated the aberrant BRS, but had little effect on the impaired cardiac function of the STZ rats. BIIE 0246 alleviated sodium nitroprusside (SNP)-induced but not phenylephrine (PE)-induced aberrant baroreflex control of heart rate in the STZ rats. In addition, BIIE 0246 alleviated the bradycardia, but further impaired cardiac contractility in the STZ rats. These results suggest that peripheral Y1R and Y2R play different roles in STZ-induced impairment of BRS.

Key words: neuropeptide Y; baroreflex sensitivity; BIBP 3226; BIIE 0246; diabetes mellitus
With the worldwide prevalence of diabetes mellitus (DM), increased morbidity and mortality in diabetic patients with cardiovascular complications become a challenging issue \[1\]. Clinical studies suggest that baseline cardiovascular autonomic dysfunction (CAD) results in 1.55 to 2.14 times the risk of mortality in diabetic patients \[2\], and mounting evidences emphasize that deranged baroreceptor reflex sensitivity (BRS), an indicator of CAD, is highly associated with life-threatening arrhythmias and even sudden death \[3, 4\]. Furthermore, both parasympathetic and sympathetic branches of the autonomic nervous system are impaired in patients with type 1 DM (T1DM) \[5, 6\] as well as in animals with streptozotocin (STZ)-induced DM \[7, 8\]. As a sympathetic neurotransmitter, neuropeptide Y (NPY) distributes widely in both central and peripheral system, and elevated plasma NPY level is found in various cardiovascular diseases including hypertension, myocardial ischemia and hypertrophy \[9–11\]. In addition, NPY has been proposed as a marker for evaluating the condition and prognosis in patients with acute myocardial ischemia, congestive heart failure and coronary diseases \[12–14\]. Further, long-term NPY administration in the periphery led to abnormal BRS, while reversed chronic stress-induced baroreflex hypersensitivity in rats \[15, 16\]. Nevertheless, whether chronic changes of the plasma NPY influences BRS in STZ-induced DM is still unclear.

Although the central effects of NPY on cardiovascular responses have been well documented \[17, 18\], our knowledge on the role of peripheral NPY receptors in the baroreflex circuits under T1DM is still fragmental. In addition, the slow onset and persistent action of NPY highlight the necessity of continuing intervention. Among the six identified receptors, NPY Y1 receptor (Y1R) and NPY Y2 receptor (Y2R) are determined as the dominant subtypes involving in the peripheral cardiovascular control \[19\]. Consequently, in the present study we focus on the roles of peripheral Y1R and Y2R in BRS of short-term (4 weeks) treatment of STZ-induced DM rats by subcutaneously implanted mini-osmotic pump filled with Y1R and Y2R specific peripheral antagonists (BIBP 3226 and BIIE 0246, respectively) \[20, 21\].

### 1 MATERIALS AND METHODS

#### 1.1 Animals and establishment of STZ-induced diabetic model

Twenty-six male Wistar rats (weight 230–270 g) from the Animal Center of the Second Affiliated Hospital of Harbin Medical University (Harbin, Heilongjiang Province, China) were used and housed in a room with controlled temperature (23 °C ± 1 °C), humidity (55% ± 5%) and 12-h dark-light cycle (lights on at 07:00 A.M.). All rats were fed standard laboratory chow *ad libitum* with free access to drinking water. All experiments were conducted in accordance with the regulations of the ethics committees of Harbin Medical University (No. HMUIRB-2008-06). After 2-week adaptation, T1DM was induced in the 20 randomly chosen rats by intraperitoneal (i.p.) injection of 40 mg/kg of STZ (Sigma) in a 0.1 mol/L citrate buffer solution (pH 4.2) per day for 3 days after fasting for 12 h. The remaining six rats were given the same quantity of vehicle (citrate buffer). The fasting blood glucose (FBG) level was determined with a Grace glucometer (Grace Medical, Inc., USA) from the tail vein 72 h after the last injection of STZ. Eighteen of the STZ-induced rats with a FBG ≥16.7 mmol/L were used as established STZ-induced T1DM models.

#### 1.2 Treatments for different groups

Eighteen rats with STZ-induced T1DM were randomly divided into three equal groups: STZ-induced T1DM (STZ), STZ-induced T1DM with Y1R antagonist (STZ+antiY1R) and STZ-induced T1DM with Y2R antagonist (STZ+antiY2R). Y1R antagonist (BIBP 3226, Sigma-Aldrich, St. Louis, MO) or Y2R antagonist (BIIE 0246, Tocris, Ellisville, MO, USA) was administered for 4 weeks (85 μg per 30 days) using the ALZET mini-osmotic pump (DURECT Corporation, USA) after the confirmation of DM. The rats in STZ group were given pumps filled with equal quantity of vehicle (PBS), and the other six healthy rats were used as control (Ctl) group.

#### 1.3 Implantation of the ALZET mini-osmotic pump

After the mini-osmotic pumps were full filled with PBS, BIBP 3226 or BIIE 0246 with a volume enough for one-month continuous delivery and incubated in
sterile saline at 37 °C for 40 h, a small incision was made in the skin between the scapulae in rats, and a small pocket was formed through spreading the subcutaneous connective tissue apart with a hemostat, the pump was inlaid into the pocket. Then, the skin incision was closed with wound sutures.

1.4 In vivo cardiac function studies
Four weeks after the implantation of pumps, all rats were anesthetized with sodium pentobarbital (40 mg/kg) via i.p. injection. According to previous study[22], cardiac function of all rats was studied. Summarily, systolic blood pressure (SBP) and heart rate (HR) were monitored by inserting the catheter into the left ventricle through the right common carotid artery. Using a BL-420 Data Acquisition & Analysis System (Chengdu TME Technology Co., Ltd., China), left ventricular systolic pressure (LVSP) and the maximum rate of change in left ventricular pressure in the isovolumic contraction period (+dP/dt_max) were assessed to evaluate the systolic function of heart. Meanwhile, left ventricular end-diastolic pressure (LVEDP) and the maximum rate of change in left ventricular pressure during the isovolumic relaxation period (−dP/dt_max) were also studied as indexes of diastolic function of heart.

1.5 Surgical procedures
According to previous studies [23–25], rats were anesthetized initially via i.p. injection of sodium pentobarbital (40 mg/kg). Eye blinking and withdrawal reflex were used as indicators of the anesthetic condition. Supplemental doses of anesthetics (0.2 mg/kg sodium pentobarbital) were administered every 30 min to maintain the anesthetic state. The left femoral artery and the right femoral vein were exposed, then, tapered polyethylene catheters (0.5 mm-diameter tip) filled with heparinized saline were inserted into the exposed vessels. Arterial blood pressure (ABP) was recorded in the left femoral artery, and the vasoactive drugs were administrated through right femoral vein.

1.6 Baroreflex sensitivity study
A blood pressure transducer (MIT0699; AD Instruments, Australia) placed in the horizontal position level with the heart was connected to the blood pressure catheter, and then baseline mean arterial blood pressure (MABP), baseline HR and the changes in MABP responded to the serial challenges of vasoactive drugs were measured. ABP was measured automatically, and HR was evaluated by pulse pressure with the rate-meter function with the BL-420 Data Acquisition & Analysis System. After fresh dilution in 0.9 % NaCl, phenylephrine (PE) and sodium nitroprusside (SNP) were injected at different dosages as follows: 16, 32, 64, 128 and 256 µg/mL for PE; 10, 20, 40, 80 and 160 µg/mL for SNP (0.04 mL/100 g within 3–5 s). Baseline MABP and HR were recorded for 30 s before the first drug administration. The altered MABP and relative HR were monitored and averaged every second. The following challenge was applied when the ABP and HR reached a plateau. At each dose of PE or SNP administration, the MABP changes over the baseline ABP level (ΔMABP) and the maximal HR responses relative to the baseline HR level (ΔHR) were studied. To evaluate the BRS after PE or SNP addition, the averaged ratio of changes in HR over MABP (ΔHR/ΔMABP) was calculated. Dose-dependent curves of both ΔMABP and ΔHR/ΔMABP were plotted for all the groups, respectively. To show the maximal HR responses elicited by altered MABP, curves of ΔHR-ΔMABP were also plotted. All curves were fitted by Boltzmann equation [23, 26] with Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA).

1.7 Measurement of plasma biochemical indexes and NPY concentration
After in vivo cardiac function and BRS studies, blood samples of all rats were collected from heart and separated to analyze total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C) using the appropriate kit (Shanghai Rong-sheng Biotech Co., Ltd., China) according to the manufacturer’s instructions, and the concentration of plasma NPY was determined with the kit (Phoenix Pharmaceutical Company Belmont, CA, USA).

1.8 Statistical analysis
Data were expressed as mean ± SEM and analyzed by one-way ANOVA using SPSS 11.0 software. Statistical comparison between two groups was performed using Student’s t test. P < 0.05 was considered significant. Figures were plotted and constructed with GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA).

2 RESULTS
2.1 NPY antagonist blocked the STZ-induced increase of TG level
Compared with that in control group, the level of plasma NPY was obviously elevated in rats of STZ group
(6.14 ng/mL ± 0.74 ng/mL vs 10.09 ng/mL ± 0.89 ng/mL, P < 0.05). As illustrated in Table 1, TC level showed no statistical significance among all four groups. STZ significantly increased the TG as well as LDL-C level (P < 0.01 vs Ctl), and reduced the HDL-C level (P < 0.05 vs Ctl). Although Y1R antagonist attenuated the STZ-induced elevation of TG (P < 0.05 vs STZ) and LDL-C (P < 0.05 vs STZ), the two indexes were still markedly higher than those in control group (P < 0.01 vs Ctl). No obvious differences of HDL-C level were observed between STZ and STZ+antiY1R groups. Though Y2R antagonist blocked the STZ-induced increase in TG level (Table 1, P > 0.05 vs Ctl; P < 0.01 vs STZ), it failed to ameliorate the STZ-induced aberrant HDL-C (P < 0.05 vs Ctl; P > 0.05 vs STZ) and LDL-C (P < 0.01 vs Ctl; P > 0.05 vs STZ).

### 2.2 NPY antagonists had no effect on SBP but Y2R antagonist reversed the STZ-induced bradycardia

Baseline SBP showed an overt fall in all three STZ-treated groups in contrast to control group (P < 0.01 vs Ctl, Fig. 1A). Compared with STZ group (64.12 mmHg ± 3.10 mmHg), no significant difference of baseline SBP was found in both STZ+antiY1R (64.50 mmHg ± 3.31 mmHg) and STZ+antiY2R (62.65 mmHg ± 4.21 mmHg) groups (Fig. 1A). As for baseline HR, Y2R antagonist reversed the bradycardia elicited by STZ (Fig. 1B). However, STZ+antiY1R group showed no difference from that in STZ rats.

### 2.3 Y1R antagonist improved baroreflex control of HR in STZ rats following PE administration

The ABP showed a dose-dependent increase when challenged by PE in Ctl, STZ, STZ+antiY1R and STZ+antiY2R rats (Fig. 2A1, 2B1). Furthermore, the dose-dependent curves were plotted to value the changes of ΔMABP over various PE doses. The augmentations of ΔMABP following different PE dosages were less pronounced in the STZ rats when compared with the control rats, but was partly reversed in STZ+antiY1R group (P < 0.05, Fig. 2A2) rather than STZ+antiY2R group (Fig. 2B2).

To assess BRS, ΔHR/ΔMABP ratio against PE doses was also illustrated. As shown in Fig. 2A3 and Fig. 2B3, the curves in all groups displayed a smooth increase trend. Notably, the ΔHR/ΔMABP values were obviously increased in the STZ rats compared with the control rats (P < 0.05). These aberrant values were ameliorated in STZ+antiY1R group (P < 0.05, Fig. 2A3), which could not be achieved in the STZ+antiY2R group (Fig. 2B3).

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### Table 1. The effect of chronic neuropeptide Y (NPY) receptor blockers administration on blood biochemical indexes in rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>TC (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctl</td>
<td>1.24 ± 0.09</td>
<td>0.57 ± 0.04</td>
<td>0.57 ± 0.06</td>
<td>0.18 ± 0.01</td>
</tr>
<tr>
<td>STZ</td>
<td>1.42 ± 0.18</td>
<td>1.77 ± 0.23</td>
<td>0.39 ± 0.02</td>
<td>0.50 ± 0.04</td>
</tr>
<tr>
<td>STZ+antiY1R</td>
<td>1.17 ± 0.15</td>
<td>1.12 ± 0.15</td>
<td>0.31 ± 0.05</td>
<td>0.36 ± 0.04</td>
</tr>
<tr>
<td>STZ+antiY2R</td>
<td>1.36 ± 0.12</td>
<td>0.46 ± 0.03</td>
<td>0.28 ± 0.06</td>
<td>0.53 ± 0.04</td>
</tr>
</tbody>
</table>

Mean ± SEM, n = 6. *P < 0.05, **P < 0.01 vs Ctl group; *P < 0.05 vs STZ group. TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein; LDL-C: low density lipoprotein. Ctl: control group; STZ: STZ group; AntiY1R: Y1R antagonist, BIBP 3226; AntiY2R: Y2R antagonist, BIIE 0246.
Fig. 2. Effects of Y1R and Y2R antagonists on BRS of STZ-induced diabetic rats following phenylephrine (PE) administration. **A**: Y1R antagonist ameliorates the impaired baroreflex control of heart rate induced by STZ during PE administration. 

**A1**: Increment of blood pressure is induced by PE application at 16, 64, and 128 µg/mL in control (Ctl), STZ, STZ+antiY1R groups.

**A2–A4**: Y1R antagonist improves the decreased ΔMABP (**A2**), ΔHR/ΔMABP (**A3**) and ΔHR to ΔMABP (**A4**).

**B**: Y2R antagonist displays no effect on the impaired baroreflex control of heart rate induced by STZ during PE administration. **B1**: Increment of blood pressure is induced by PE application at 16, 64, and 128 µg/mL in Ctl, STZ, STZ+antiY2R groups.

**B2–B4**: Y2R antagonist does not affect the decreased ΔMABP (**B2**), ΔHR/ΔMABP (**B3**) and ΔHR to ΔMABP (**B4**). Mean ± SEM, n = 6. *P < 0.05 vs Ctl, †P < 0.05 vs STZ.
Fig. 3. Effects of Y1R and Y2R antagonists on BRS of STZ-induced diabetic rats following sodium nitroprusside (SNP) application. 

A: Y1R antagonist has weak effect on the impaired baroreflex control of heart rate induced by STZ during SNP administration. 

A1: Decrease of blood pressure is induced by SNP application at 10, 40, and 80 µg/mL in control (Ctl), STZ, STZ+antiY1R groups. 

A2–A4: Y1R antagonist does not affect the decreased ΔMABP (A2), ΔHR/ΔMABP (A3) and ΔHR to ΔMABP (A4).

B: Y2R antagonist ameliorates the impaired baroreflex control of heart rate induced by STZ during SNP administration. 

B1: Decrease of blood pressure is induced by SNP application at 10, 40, and 80 µg/mL in Ctl, STZ, STZ+antiY2R groups. 

B2–B4: Y2R antagonist ameliorates the decreased ΔMABP (B2), ΔHR/ΔMABP (B3) and ΔHR to ΔMABP (B4). Mean ± SEM, n = 6. *P < 0.05 vs Ctl, †P < 0.05 vs STZ.
As another index of BRS, the maximal ΔHR to the maximal ΔMABP elicited by increased doses of PE was also recorded (Fig. 2A, Fig. 2B). The maximal ΔMABP was dropped from 43.99 mmHg in Ctl group to 31.43 mmHg by STZ treatment, but was marginally improved in both STZ+antiY1R (33.66 mmHg) and STZ+antiY2R groups (34.44 mmHg).

2.4 Y2R antagonist improved baroreflex control of HR in STZ rats after SNP administration

As depicted in Fig. 3A and Fig. 3B, ABP gradually decreased by the increased doses of SNP injections despite the margins of falls varied. STZ dramatically suppressed the increase of ΔMABP induced by each dose of SNP (P < 0.05; Fig. 3A, Fig. 3B), but ΔMABP was almost invariable in STZ+antiY1R group (Fig. 3A). Notably, the inhibition of ΔMABP by STZ was ameliorated to some extent in STZ+antiY2R group (P < 0.05 vs STZ group; Fig. 3B).

Compared with Ctl group, the value of ΔHR/ΔMABP induced by each dosage of SNP was increased in STZ group (P < 0.05; Fig. 3A, 3B). Furthermore, such increments were augmented in both STZ+antiY1R (P < 0.05; Fig. 3A) and STZ+antiY2R (P < 0.05; Fig. 3B) groups.

In accordance with ΔHR/ΔMABP values against SNP doses, the maximal ΔMABP collapsed from 57.02 mmHg in the control rats to 19.54 mmHg in the STZ rats (Fig. 3A and Fig. 3B), between which the values of STZ+antiY1R (23.43 mmHg) and STZ+antiY2R (39.83 mmHg) groups were found.

2.5 Different effects of the two NPY antagonists on cardiac function

As shown in Fig. 4A, STZ decreased the LVSP from (15.53 ± 1.22) kPa to (12.34 ± 0.43) kPa (P < 0.05), while Y1R antagonists did not affect this reduction (STZ+antiY1R vs Ctl, P < 0.01). Furthermore, the collapse of LVSP in STZ+antiY2R group was even more obvious compared with the decreased parameter in STZ group (P < 0.01).

The LVEDP in STZ group was increased from (−0.82 ± 0.12) kPa to (0.32 ± 0.15) kPa compared with Ctl group (P < 0.05, Fig. 4B), which was partly reversed in STZ+antiY1R group (P < 0.05) but not in STZ+antiY2R group.

**Fig. 4.** Quantitative analysis of parameters of cardiac function in different rat groups. A: The effect of Y1R antagonist and Y2R antagonist on the decreased LVSP induced by STZ in rats. B: The effect of Y1R and Y2R antagonists on the increased LVEDP induced by STZ in rats. C and D: Both +dp/dt\_max and −dp/dt\_max of STZ+antiY2R group are significantly decreased compared with those of both control and STZ groups. Mean ± SEM, n = 6. *P < 0.05, **P < 0.01 vs Ctl group; *P < 0.05, **P < 0.01 vs STZ group.
As demonstrated in Fig. 4C, no statistical difference of $\frac{+dp}{dt_{\text{max}}}$ was observed among Ctl, STZ and STZ+antiY1R groups. However, $\frac{+dp}{dt_{\text{max}}}$ in the STZ+antiY2R rats experienced a significant drop compared with that in the control rats ($P < 0.05$).

The STZ+antiY2R group showed a substantial impairment of $\frac{+dp}{dt_{\text{max}}}$ when compared with those of Ctl and STZ groups ($P < 0.05$, Fig. 4D). Nevertheless, the $\frac{-dp}{dt_{\text{max}}}$ values in STZ and STZ+antiY1R groups showed no significant differences from that in Ctl group.

### 3 DISCUSSION

In the present study, we examined the role of peripheral Y1R and Y2R in BRS and heart function by implanting the mini-osmotic pumps filled with Y1R antagonist (BIBP 3226) and Y2R antagonist (BIIE 0246) in STZ-induced diabetic rats with elevated plasma NPY level for 4 weeks. We found that BIBP 3226 improved the aberrant BRS, but exerted no obvious effect on the cardiac function in STZ-induced diabetic rats. Though BIIE 0246 alleviated SNP-induced aberrant baroreflex control of heart rate in STZ rats, it failed to improve PE-induced aberrant baroreflex control of heart rate. In addition, BIIE 0246 alleviated the bradycardia, but further inhibited cardiac contractility in the STZ rats. What’s more, both BIBP 3226 and BIIE 0246 influenced the lipid metabolism despite the extent varied.

Consistent with our speculation, the concentration of circulating NPY strikingly increased in 4-week STZ induced diabetic rats. It is reported that Y1R sustained the strong antilipolytic effect of NPY and facilitated leptin secretion, both of which could be antagonized by BIBP 3226 [27]. Moreover, Kuo’s group found that the release of NPY and the activation of Y2R resulted in abdominal obesity and a metabolic syndrome-like condition by stimulating fat angiogenesis as well as proliferation and facilitating the differentiation of new adipocytes [28]. Based on these studies, considering that abnormal metabolism of lipid is a key characteristic of diabetic patients and increase of NPY level in normal rats could alter the lipid level [15], we then evaluated the effects of BIBP 3226 and BIIE 0246 on lipid metabolism. We found that BIBP 3226 partially repressed elevated LDL-C and TG induced by STZ, however, BIIE 0246 failed to prevent the increase of LDL-C but ameliorated the aberrant TG. The data reaffirmed the results reported by above mentioned studies. Although the precise mechanism behind Y1R/Y2R-elicited alteration of lipid level is still unclear, these reports along with our results delineated the underlying relationship between peripheral Y1R/Y2R and lipid metabolism.

In the present study, STZ treatment could induce hypotension and bradycardia, which is consistent with previous report [29]. However, BIBP 3226 did not restore the decreased baseline ABP and HR induced by STZ, which is in line with reported study [30]. Since microinjections of NPY or Y1R agonist into the nucleus tractus solitarii (NTS) could lead to vasodepressor and bradycardic response [31, 32], and BIBP 3226 could not cross the blood brain barrier [21], we speculate that the regulatory effect of BIBP 3226 on baseline ABP and HR is due to its peripheral effects but not its function in NTS. It is well known that Y1R mediates peripheral vasoconstrictor response directly by its own activation and indirectly by potentiating noradrenaline (NE)-induced vasoconstriction [35] which was further verified in blood vessels isolated from Y1R-deficient animals [34]. Therefore, it seems that Y1R antagonist might potentially lead to vasodilatation and subsequent decrease in baseline ABP rather than constant as we observed. The discrepancies might be explained as follows. On the one hand, the decreased baseline ABP induced by STZ had dropped to such a low level that it could not respond to the further prohypotensive effect of Y1R antagonist. On the other hand, the action of BIBP 3226 administered may be not strong enough to overcome the relative compensatory responses. Undoubtedly, the precise underlying mechanism deserves further study.

In terms of Y2R antagonist, despite of little contribution to the decreased baseline ABP, BIIE 0246 compensated the repressed baseline HR in the STZ rats. This was consistent with previous report that Y2R knockout mice had a tendency to be tachycardia [35]. Regrettably, the potential central effect in these Y2R knockout mice could not be obviated. As to the peripheral role, the function of BIIE 0246 was probably relied on inhibiting prejunctional Y2R-suppressed NE release in heart, and hence indirectly increased the baseline HR by facilitating NE release [34]. To explore the exact mechanism behind, further work should be done in the future.

In accordance with our previous study [37], the amplitudes of the increased $\Delta$HR/$\Delta$MABP in response to both PE and SNP administration were more augmented in the rats of STZ group when compared with that in Ctl group. In the present study, we found that BIBP 3226 partially improved the aberrant BRS following various
PE and SNP injections. It is well known that NPY, as a local neurotransmitter of heart, could produce inotropic and chronotropic effects through Y1R of cardiomyocytes and hence influence the contraction and beating rate of heart [33]. In addition, the blockade of Y1R in smooth muscle cells and endothelial cells might influence the blood flow and vasoconstriction of blood vessels [33]. Considering the action of BIBP 3226 on the diabetic heart function, we thought that the protective effects of BIBP 3226 on impaired BRS in STZ rats might largely account for its action on Y1R in vascular smooth muscle cells but not cardiomyocytes. However, the exact mechanism behind is an interesting topic deserving of further study.

On the other hand, previous studies are likely to support the hypotheses that Y2R exerts apparent function in the baroreflex circuits: multiple reports document that NPY represses cardiac vagal activity via action on prejunctional Y2R on cholinergic nerves peripherally [33, 38, 39]; Y2R agonist NPY (13-36) rather than Y1R prejunctional Y2R on cholinergic nerves peripherally [33]. Considering the action of BIBP 3226 on impaired BRS in STZ rats, it failed to improve PE-induced aberrant baroreflex control of heart rate induced by STZ rats, it failed to improve PE-induced aberrant baroreflex control of heart rate induced by STZ. Based on the seriously deteriorated contractile function was found in STZ+antiY2R rats, we speculate that the absent effect of chronic BIIE0246 treatment on baroreceptor reflex might result from the decreased heart function which is difficult to response to exogenous stimulations. Undoubtedly, more elaborated researches are necessary to unveil the facts.

In summary, the present study provides new insight into the role of peripheral Y1R and Y2R in BRS and cardiac function of short-term STZ-induced diabetic rats, and provides sound evidence for further therapeutic strategies for diabetic heart disease targeting at peripheral Y1R and Y2R.

REFERENCES


