Antisense Inhibition of β₁-Adrenergic Receptor mRNA in a Single Dose Produces a Profound and Prolonged Reduction in High Blood Pressure in Spontaneously Hypertensive Rats

Yuan Clare Zhang, BS; Jonathan D. Bui, PhD; Leping Shen, BS; M. Ian Phillips, PhD, DSc

Background—β-Blockers are the first line of therapy for hypertension. However, they are associated with side effects because of central nervous system (CNS) effects and β₂-adrenergic antagonism. To overcome these problems and provide a long-term β₁-blockade, antisense oligonucleotides against rat β₁-adrenergic receptor (β₁-AR) mRNA (β₁-AS-ODN) were designed and tested for the ability to inhibit cardiac β₁-ARs as well as lower blood pressure in spontaneously hypertensive rats (SHRs).

Methods and Results—Radioligand binding assay showed that a single intravenous injection of β₁-AS-ODN delivered in cationic liposomes significantly decreased cardiac β₁-AR density by 30% to 50% for 18 days (P<0.01), with no effect on β₂-ARs. This was accompanied by marked attenuation of β₁-AR-mediated positive inotropic response in isolated perfused hearts in vitro (P<0.02) and in conscious SHRs monitored by telemetry in vivo (P<0.02). Furthermore, the blood pressure of SHRs was reduced for 20 days, with a 38 mm Hg maximum drop. Heart rate was not significantly decreased. Quantitative autoradiography was performed to assess β₁-AS-ODN effects on the CNS, which demonstrated no changes in β₁-ARs in brain, in contrast to a significant reduction in heart and kidney (P<0.05). For comparison with β-blockers, the effects of atenolol on cardiovascular hemodynamics were examined, which lowered blood pressure for only 10 hours and elicited appreciable bradycardia in SHRs.

Conclusions—These results indicate that β₁-AS-ODN, a novel approach to specific β₁-blockade, has advantages over currently used β-blockers in providing a profound and prolonged reduction in blood pressure without affecting heart rate, β₁-ARs, and the CNS. Diminished cardiac contractility resulting from less β₁-AR expression contributes to the antihypertensive effect. (Circulation. 2000;101:682-688.)

Key Words: gene therapy ■ receptors, adrenergic, beta ■ hypertension ■ contractility

The sympathetic nervous system plays a crucial role in the regulation of blood pressure (BP), mainly through activating α- and β-adrenergic receptors (β₁-ARs) in the effector organs, including heart, kidney, and blood vessels. Adrenergic-blocking agents, especially β-blockers, are commonly used in the treatment of hypertension, ischemic heart disease, and arrhythmia (reviewed in Sproat and Lopez2). However, β-blockers cause several side effects, which are usually associated with their central nervous system (CNS) reaction (eg, sleep disturbance, depression, impotence, dizziness, and fatigue) and β₁-adrenergic antagonistic activity (eg, increase in peripheral vascular resistance, worsening of asthma symptoms). In addition, because of their short half-life (3 to 10 hours), β-blockers must be taken daily to be effective. Because a cardiovascular disease such as hypertension is a life-long disorder, longer-lasting treatment without side effects would be desirable.

Although the precise mechanism underlying the antihypertensive effects of β-blockers remains unclear, it is generally accepted that they antagonize the β₁-AR activity in heart and kidney, decreasing cardiac output and plasma renin activity.¹ We have designed a new approach to β₁-blockade that reduces the number of receptors. Antisense oligonucleotides (AS-ODN) or antisense DNA designed specifically against β₁-ARs might represent a new class of β-blockers. Antisense technique, through a number of mechanisms,² can effectively downregulate the expression of target proteins. Clinical trials using antisense in targeting AIDS,³ cancer,⁴ and other genetic and acquired diseases⁵ indicate their potential clinical usefulness. The antisense approach has several potential advantages over β-blockers. First, the specificity of AS-ODNs is based on DNA sequence. Second, AS-ODNs do not have direct CNS effects, because of the negligible transport of these highly polar molecules through the blood-brain barrier.⁶ Third, antisense elements tested in different systems produce long-term effects after single treatment.⁷ This prolonged effect can be attributed to 2 features of AS-ODN. One is the extended half-life of chemically modified ODN. The half-life

Received May 28, 1999; revision received August 5, 1999; accepted August 13, 1999.
From the Department of Physiology, School of Medicine, University of Florida, Gainesville.
Correspondence to Dr M. Ian Phillips, Department of Physiology, School of Medicine, University of Florida, Box 100274, Gainesville, FL 32610.
E-mail mip@phys.med.ufl.edu
© 2000 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

682
of 15- to 20-mer phosphorothioated ODN is 20 to 50 hours in rats and mice after intravenous injection.8,9 The other is associated with the nature of antisense inhibition, which provides a delayed yet prolonged blockade of target proteins distinct from the direct competitive antagonists currently available.

We hypothesize that β1-antisense, through specific inhibition of β1-AR expression, will decrease the functional sensitivity of β1-AR–mediated responses in the face of sympathetic activation and thereby achieve an antihypertensive effect. In this study, we designed an AS-ODN complementary to rat β1-AR mRNA and tested its ability to inhibit β1-AR density and function in the heart and to reduce BP in spontaneously hypertensive rats.

Methods

Antisense Design and Administration

Antisense ODN and inverted ODN control were 15-mer and targeted to the AUG start codon of rat β1-AR mRNA.10 The sequence of AS-ODN is 5’-CCCGCACCATTGGCGA-3’, and the inverted ODN is 5’-AGCGGCTCCGGCGCC-3’. This AS-ODN was chosen from 6 AS candidates targeted to different regions of β1-AR mRNA on the basis of the intensity of cardiac β1-AR inhibition and reduction of BP in SHRs. These oligonucleotides were modified by backbone phosphorothioation. ODNs delivered with cationic liposomes were injected into the tongue vein.

Preparation of Liposomes and ODN/Liposome Complex

The cationic lipid 1,2-bis(oleoyloxy)-3-(trimethylammonio)propene (DOTAP) was mixed with helper lipid l-α-dioleoyl phosphatidylethanolamine (DOPE, Avanti Polar Lipids) at a 1:1 molar ratio, briefly sonicated, and stored at 4°C until use. The average diameter of liposomes is 200 to 350 nm.11 ODN/liposome complex was prepared on the day of use by mixing the desired amounts of ODNs with DOTAP/DOPE to the final DNA concentration of 300 μg/mL in 5% (wt/vol) dextrose in water and incubating at room temperature for 60 minutes. Two DNA/lipid molar ratios, ie, 1.0, 1.5, and 1.25, were used in the experiments.

Animal Surgery

Adult male SHRs (250 to 350 g, Harlan, Indianapolis, Ind) were kept in cages in a room with a 12-hour light-dark cycle. Animals were fed standard laboratory rat chow and tap water ad libitum. All care and surgical conditions were approved by the University of Florida Animal Care Committee.

Telemetric Sensor Implantation

Before implantation, the zero of each radiotransmitter (TA11PA-C40, Data Sciences) was verified to be ≤5 mm Hg. SHRs were anesthetized with 100 mg/kg ketamine and 15 mg/kg xylazine, and a midline abdominal incision was made. A fluid-filled sensor catheter was then inserted into the right femoral artery, and the tip of the catheter was in the abdominal aorta caudal to the renal arteries. The rats with implants were allowed to recover for 1 week.

Jugular Vein Cannulation

One week after telemetric implantation, rats were anesthetized, and a curved catheter made of PE 50 and vinyl tubing was inserted into the jugular vein. The tubing was led under the skin of the neck and exposed on the back to allow for drug infusion. Rats were allowed to recover for 24 hours before experimentation. The catheters were flushed with 100 U heparin every day to prevent clogging.

Membrane Preparation and β-AR Binding Assay

Four days after intravenous injection of saline (n = 6) or 1 mg/kg inverted ODN (n = 6) or 2, 4, 10, or 18 days after injection of 1 mg/kg β1-AS-ODN (n = 24), animals were euthanized, and membranes were prepared from heart ventricles as previously described.12 For saturation experiments, 100 μg membrane protein was incubated in triplicate with 6 concentrations of [125I]–(–)-iodocyanopindolol (ICYP, NEN Life Science, 6.25 to 100 pmol/L) in a total volume of 250 μL containing 50 mM tris-HCl (pH 7.4), 5 mM MgCl₂ at 36°C for 60 minutes. The nonspecific and β1-AR–binding levels were determined in the presence of 1 μmol/L (±)-alprenolol and 150 μmol/L CGP20712A (RBI), respectively. Then the reaction mixture was passed through Whatman GF/B glass fiber filter using a Brandel harvester, and the bound radioactivity was counted for 1 minute.

Tissue Preparation and Quantitative Autoradiography

Four days after injection of 1 mg/kg β1-AS-ODN (n = 6) or saline (n = 6), rats were killed, and tissues were removed and frozen in dry ice. Coronal sections of brain, horizontal sections of heart, and sagittal sections of kidney (20 μm) were cut on a cryostat (Microm) at −20°C and mounted on microscope slides. Every seventh slide was stained with hematoxylin and eosin for histology. Tissue sections were preincubated in Krebs buffer (mmol/L: NaCl 118.4, KCl 4.7, MgSO₄ 1.2, CaCl₂ 1.27, and NaHPO₄ 10.0, pH 7.1) containing 0.1 mM GTP, 0.1 mM ascorbic acid, and 10 mM PMSF for 30 minutes at 37°C. Sections were then incubated in Krebs buffer containing 0.1 mM ascorbic acid and 10 μmol/L PMSF with 100 μmol/L ICYP at 25°C for 150 minutes in the presence of 1 μmol/L (–)-propranolol, 100 nmol/L ICI 118,551 (β1-selective antagonist), or 100 nmol/L CGP20712A (β2-selective antagonist) to distinguish nonspecific, β1- , and β2- bindings. Labeled sections were rinsed in the same buffer, followed by two 15-minute washes at 37°C in the buffer, and rinsed in distilled water at 25°C.13 Dried sections were then exposed to x-ray films. The images were quantified with a computerized image analysis system (MCID, Imaging Research) and normalized with 125I standards. Nonspecific binding was <10% of total binding.

Determination of Effects of β1-AS and Atenolol on Cardiovascular Parameters in Response to β-Stimulation

Langendorff Heart Perfusion

Forty-eight hours after injection of 1 mg/kg β1-AS-ODN (n = 9) or inverted ODN (n = 6), SHRs were anesthetized and killed. Hearts were quickly removed and perfused via the aorta with oxygenated Krebs buffer (118 mM NaCl, 18.75 mM NaHCO₃, 1.2 mM KCl, 4.7 mM KH₂PO₄, 2.5 mM CaCl₂, 11.1 mM MgSO₄, and 0.01 mM MgCl₂) supplemented with 50 mM glucose at a constant flow of 7.0 mL/min at 36°C. Coronary perfusion pressure was measured via a catheter placed proximal to the aorta and connected to a pressure transducer (Gould Statham P23ID). A latex balloon filled with water and connected to the pressure transducer was inserted into the left ventricle through the left atrium to measure left ventricular end-diastolic pressure (LVEDP), left ventricular systolic pressure (LVSP), and developed left ventricular pressure (dLVP) (dLVP = LVSP − LVEDP). LVEDP was measured when coronary perfusion pressure, LVEDP, and LVSP were recorded continuously on a 4-channel recorder (AstroMed). After baseline values for dLVP and heart rate (HR) were stable for 5 minutes, isoproterenol (ISO, nonspecific β-agonist) was given at 0.01, 0.025, 0.05, and 0.12 μmol/L at 10-minute intervals so as to avoid the effect of tachyphylaxis.

Telemetric Monitoring of Live Animals

The effects of β1-AS-ODN and atenolol on cardiac dP/dt max, HR, and systolic blood pressure (SBP) were compared in the same group of SHRs (n = 4). Two days after catheterization of the jugular vein, control values were taken and 1 mg/kg β1-AS-ODN was injected.
Forty-eight hours later, rats were tested for the effect of β2-AS-ODN. The rats were allowed to recover until all the cardiovascular parameters returned to control values. Then 1 mg/kg atenolol (β1-selective antagonist) was injected, and rats were tested 30 minutes later. For β1-stimulation, SHRs were infused with dobutamine (β1-selective agonist) through a jugular vein catheter at 5, 10, 20, and 40 μg · kg⁻¹ · min⁻¹. Each dose was given for 5 minutes continuously and at 1-hour intervals until all the cardiovascular parameters returned to baseline values so as to avoid the effect of tachyphylaxis. BP and HR were sampled every 1 minute. dP/dtmax was calculated from the slope of the rising pulse-pressure curve and determined every 1 minute. The difference between values at each dose and baseline was denoted as Δ.

BP Monitoring

Telemetry
Each rat cage was placed on a receiver (RLA1020, Data Sciences) for measurement of cardiovascular parameters. Data were collected with a computer-based data acquisition program (Dataquest LabPRO3.0; Data Sciences). BP and HR were measured every 10 minutes and averaged every 1 to 24 hours. Before treatment, SHRs were monitored for a week to get a stable baseline.

Tail Cuff
Rats were warmed for 20 to 30 minutes in cages on heating pads. The temperature was controlled at 35°C to 37°C. Then the rats were placed in a plastic restrainer kept at 37°C. A pneumatic pulse sensor was attached to the tail. After cuff inflation, SBP was determined as the first pulsatile oscillation on the descending side of the pressure curve. HR was determined by manual counting of pulse numbers per unit time. BP and HR were recorded by a Narco physiograph. Data values of each rat were taken as an average of at least 4 stable readings. Baseline was determined by averaging 3 days of measurements before antisense administration.

Statistical Analysis
Values were expressed as mean±SEM. The difference was considered statistically significant at P<0.05. An unpaired t test was used to compare Bmax, dLVP, and BP in 2 groups. One-way repeated-measures ANOVA and Tukey test were used to compare Bmax, dLVP, and BP in 2 groups. Pearson product-moment correlation was used to assess the relationship between β1-AR Bmax and dLVP.

Results

Effect on Cardiac β-AR Density
Figure 1A shows that a single intravenous injection of 1 mg/kg β1-AS-ODN delivered with cationic liposomes at a 1:2.5 molar ratio significantly reduced the β1-AR density in the SHR hearts for 18 days (P<0.02). The drop was at its maximum of 47% on day 4, 33% on day 10, and maintained at 29% on day 18. In contrast, there was no significant change in the Bmax of β2-ARs. The K0 of both subtypes remained unaltered (Table). Consequently, the β1/β2 subtype ratio in the ventricles was diminished from ~70/30 to ~50/50 by β1-AS-ODN. Inverted ODN had no effect on either subtype (Figure 1B).

Effect on Cardiac Contractility and HR in Response to β-Stimulation
Forty-eight hours after injection of 1 mg/kg β1-AS-ODN, the cardiac inotropic and chronotropic responses to β-stimulation were determined in SHRs in vitro and in vivo.

First, isolated hearts were perfused with incrementing doses of ISO, which enhanced HR and contractility via activating β2-ARs. The dLVP-ISO dose-response curve, which reflected the positive inotropic effect of ISO, was significantly shifted downward by β1-AS-ODN (P<0.02). HR was not significantly decreased, except at 1 point, ie, 0.01 μmol/L ISO (P<0.05) (Figure 2).

An in vivo test was performed in conscious SHRs monitored by radiotelemetry. β1-AS-ODN significantly (P<0.02) dampened the increase in dP/dtmax in the face of dobutamine (β1-selective agonist) (Figure 3A). The change in HR was not significantly reduced (Figure 3B), which echoed the results in isolated perfused hearts. Conversely, the response of BP to dobutamine was biphasic (Figure 3C). Dobutamine elevated SBP by 5 to 8 mm Hg at low infusion speed and reduced SBP at higher speed, probably as a result of the partial β2-agonistic activity of dobutamine at high doses and the consequent vasodilatory effect on BP. Figure 3 also compares the results with β1-AS-ODN and atenolol (β1-selective antagonist). Relative to β1-AS-ODN, 1 mg/kg atenolol produced a more profound decline in ΔP/dtmax and ΔHR during a 5-hour period of time after injection. Moreover, it reduced basal dP/dtmax (2450±295 mm Hg/s versus control, 2937±277 mm Hg/s) and caused bradycardia (295±12 bpm versus control, 365±8 bpm).
(P<0.05), whereas β1-AS did not change basal contractility (2922±249 mm Hg/s) or HR (365±12 bpm). But the effects of atenolol on ΔdP/dt max and ΔHR were transient. Within 24 hours after atenolol administration, the inotropic and chronotropic effects of dobutamine had returned to control levels (data not shown).

**Effect on BP of SHRs**

Figure 4 shows the effects of a single injection of 1 mg/kg β1-AS-ODN on the BP of SHRs measured by the tail-cuff method. AS-ODN was delivered with cationic liposomes at different molar ratios of DNA/lipid, ie, 1:0.5 and 1:2.5. β1-AS-ODN delivered with liposomes at a 1:0.5 ratio diminished SBP for 8 days. The maximum drop was 38±5 mm Hg. When the molar ratio was increased to 1:2.5, this hypotensive effect was drastically prolonged to 20 days. No effect was seen with inverted ODN.

To compare the effects of β1-AS-ODN and atenolol, radiotelemetry was used to monitor BP and HR on a regular basis. β1-AS-ODN 1 mg/kg delivered with liposomes at a 1:0.5 ratio produced a maximum drop of 15 mm Hg in mean BP (Figure 5A). The antihypertensive effect lasted for 8 days, which was consistent with the results measured with the tail cuff. HR was not significantly altered (Figure 5B). In contrast to AS-ODN, although the onset of the hypotensive effect caused by 1 mg/kg atenolol occurred as early as 20 minutes after injection, it lasted for only 10 hours (Figure 6A). In addition, atenolol caused considerable bradycardia up to an average of −75 bpm (Figure 6B).

**Effect on β-AR Distribution in Brain, Heart, and Kidney**

Quantitative autoradiography of 6 to 18 tissue slices in brain, heart, and kidney was analyzed 4 days after intravenous β1-AS-ODN administration (Figure 7). No changes in the distribution of β-ARs in the forebrain and brain-stem regions were detected. This indicated the absence of antisense effect on the β-AR expression in CNS. However, β1-AS-ODN significantly (P<0.05) reduced β2-AR density in cardiac ventricles (from 30.2±2.1 to 20.6±2.5 fmol/mg) and renal cortex (from 26.4±3.1 to 17.4±3.3 fmol/mg). This was consistent with the binding results. β2-ARs were not affected in any tissues (data not shown).

**Discussion**

This study was designed to compare the effects of a novel β1-AS-ODN on high BP in a model of hypertension with a currently used β-blocker. β1-AS-ODN knocked down β1-adrenergic activity, resulting in long-term attenuation of BP. The results indicated that β1-AS-ODN reduced β1-AR density and cardiac contractility after β1-stimulation in vitro and in vivo and lowered high BP of SHRs. These findings are consistent with our hypothesis that β1-AS, through the inhibition of β1-AR expression, is able to render heart, kidney, and other tissues less sensitive to sympathetic activation, which is a major contributing factor in high BP. A single injection of β1-AS-ODN effectively decreased the cardiac β1-AR density, which was accompanied by diminished ven-
tricular contractility and cardiac output in response to β-stimulation. The antihypertensive effect in SHRs was up to a 38 mm Hg reduction lasting as long as 20 days.

Treatment of β₁-AS-ODN reduced cardiac β₁-AR density by about 50% in 4 days. Considerable variation is reported in the literature on the half-life of β-ARs. From our results with the AS-ODN inhibition, we deduce that the half-life of cardiac β₁-ARs is about 2 to 4 days to allow for 50% reduction of β-AR density within 4 days.

We noted that both tail-cuff and telemetry measures of BP showed a significant drop after antisense treatment. SHRs responded to β₁-AS-ODN to a greater degree of hypotension when subjected to tail cuff versus telemetry. In addition, the baseline measured with the tail cuff was consistently higher than that with telemetry by 20 to 30 mm Hg in the same rats. Bazil et al reported a similar phenomenon. They compared the cardiovascular parameters recorded by telemetry, tail cuff, and arterial catheter and observed a more sensitive hypotensive effect of captopril with tail cuff. Tail-cuff measurement of BP involves warming and restraint of rats. It is conceivable that β₁-AS, through the suppression of sympathetic activity, can decrease the BP of animals under stress more effectively.

Cationic liposomes are effective vehicles for gene delivery. It has been shown that liposome entrapment not only improves the cellular uptake of DNA but also protects DNA from degradation and extends its circulation time. Numerous factors influence the efficiency of cationic liposome-mediated intravenous gene delivery, such as DNA/lipid ratio, selection of lipids, and preparation procedure. We chose a widely used lipid formula, DOTAP/DOPE, to deliver β₁-AS-ODN at 4 molar ratios (data for ratios 1:1.5 and 1:3.5 are not shown). The optimal ratio of 1:2.5 was determined on the basis of the duration and magnitude of the antihypertensive effects. A profound and prolonged fall in BP of 38 mm Hg up to 20 days was achieved at this ratio, which followed the reduction in β₁-AR binding to a maximum of 47% at day 4, 33% at day 10, and 29% at day 18. This implies that β₁-AS-ODN effectively inhibits the functionally active receptors involved in the BP.

The blood-brain barrier formed by capillary endothelia is permeable only to small lipophilic molecules with a molecular weight of <600 Da (reviewed by Partridge). Owing to their high hydrophilicity, ODNs undergo negligible transport through blood-brain barrier and have very limited access to CNS. The cellular and organ distributions of DNA/liposome
complexes with fluorescent labeling were previously studied in mice after intravenous injection, and the results indicated that the complexes were taken up primarily by capillary endothelial cells in most of the peripheral organs, including lung, heart, kidney, and spleen, but were absent in the brain. In our study, autoradiography in brain revealed no detectable changes in the expression and distribution of \( \beta_1 \)-ARs after intravenous \( \beta_1 \)-AS-ODN injection. This provided further evidence that our antisense approach did not have CNS effects.

High specificity based on gene sequence has made antisense an increasingly useful tool in numerous studies and clinical trials. Its success is manifested by the recent approval of the first antisense drug, Vitravene, by the Food and Drug Administration. However, sequence-independent interactions have also been reported with AS-ODNs. High doses are usually responsible for the nonspecific effects, but another possible reason is that currently available databases do not cover every gene; thus, homology comparison by BLAST search may not guarantee sequence specificity of AS-ODNs. In our study, \( \beta_1 \)-AS-ODN inhibited \( \beta_1 \)-AR expression without changing \( \beta_2 \)-ARs. Although we hypothesize that this is due to the specificity of the \( \beta_1 \)-AS-ODN sequence, we recognize that other possibilities remain, such as indirect effects on regulatory mechanisms.

In patients with chronic heart failure, the severity of the disease closely relates to the decrease in cardiac \( \beta_1 \)-AR density and functional responsiveness. In SHRs treated with \( \beta_1 \)-AS-ODN, we observed a marked attenuation of the \( \beta_1 \)-AR–mediated positive inotropic response in vitro and in vivo, concurrent with the diminished cardiac \( \beta_1 \)-AR level. Therefore, our results indicated a positive correlation between cardiac \( \beta_1 \)-AR number and functional sensitivity (correlation coefficient \( r = 0.90, P < 0.01 \)).

Despite the large decrease in BP, no reflex tachycardia was observed after antisense treatment. However, the suppressive effect of \( \beta_1 \)-AS-ODN on HR was less significant than its negative inotropic response. The reason for this is still under investigation. Several possibilities can be considered. First, \( \beta_1 \)-AS-ODN did not affect \( \beta_2 \)-ARs, which played an important role in the regulation of HR, although it was not involved in the cardiac contraction. Second, antisense inhibition of \( \beta_1 \)-AR expression is gradual and less extensive than with \( \beta \)-blockers. It is also possible that \( \beta_1 \)-ARs may have a larger reserve for controlling HR than contractility. Finally, preliminary evidence in our laboratory suggests that cardio-

---

**Figure 5.** Effect of \( \beta_1 \)-AS-ODN on mean BP (A) and HR (B) of SHRs monitored by telemetry. Dose of 1 mg/kg inverted ODN (\( \beta_2 \)-AS-ODN) was injected with liposomes at molar ratio of 1:0.5. BP and HR were recorded every 10 minutes and averaged every 24 hours. Data represent mean ± SEM of each group (n=6). *P<0.05 vs inverted ODN.

**Figure 6.** Effect of atenolol on mean BP (A) and HR (B) of SHRs monitored by telemetry. Saline or 1 mg/kg atenolol was injected intravenously. BP and HR were taken every 10 minutes and averaged every 1 hour. Data represent mean ± SEM of each group (n=6). *P<0.05 vs saline.
myocytes preferentially take up AS-ODN, whereas pace-makers are less efficient (unpublished data).

The cardiovascular effects of β1-AS-ODN were compared with those of a hydrophilic β1-selective antagonist, atenolol. β1-AS-ODN showed advantages over atenolol in reducing BP and maintaining normal HR. Although the onset of β1-AS-ODN action was slower than with atenolol, it lasted much longer, 20 days compared with <1 day with atenolol. Furthermore, β1-AS-ODN did not affect HR, whereas atenolol caused appreciable bradycardia. Bradycardia is a common complaint by patients taking this drug. Atenolol also reduced basal ventricular contractility and HR and thereby reduced resting cardiac output. β1-AS-ODN is unlikely to alter resting cardiac performance. The results presented here suggest that β1-AS-ODN may offer a significant improvement over currently used β-blockers in both prolonged BP reduction and absence of effects on β2-ARs and CNS.

Acknowledgments

This study was supported by NIH Merit Award HL-27344 and American Heart Association Fellowships 9850002FL and 9704009. The authors thank Debbie Otero for technical assistance in binding assay and Fuxing Tang for liposome preparation.

References

Antisense Inhibition of $\beta_1$-Adrenergic Receptor mRNA in a Single Dose Produces a Profound and Prolonged Reduction in High Blood Pressure in Spontaneously Hypertensive Rats
Yuan Clare Zhang, Jonathan D. Bui, Leping Shen and M. Ian Phillips

Circulation. 2000;101:682-688
doi: 10.1161/01.CIR.101.6.682
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/6/682

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/