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Original research article

The effects of celiprolol on serum concentrations of proinflammatory cytokines in hypertensive (SHR) and normotensive (WKY) rats

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ABSTRACT

Background: A growing body of evidence suggests that some cardiovascular drugs could modulate the level of proinflammatory cytokines. Therefore, the aim of the present study was to investigate whether celiprolol, a third generation β-adrenoceptor blocker, affects lipopolysaccharide (LPS)-induced serum concentrations of TNF-α, IL-1β, IL-6 in normotensive (WKY) and spontaneously hypertensive (SHR) rats.
Methods: Celiprolol (150 mg kg^{-1}) or vehicle was administered by gavage once daily for 21 days. Arterial blood pressure was measured in conscious rats, using the tail-cuff method. Serum concentrations of proinflammatory cytokines were measured with enzyme-linked immunosorbent assay kits. Additionally, plasma concentrations of total cholesterol, HDL-cholesterol and triglycerides were evaluated.
Results: In normotensive WKY rats celiprolol did not affect heart rate, blood pressure, or the serum concentrations of triglycerides, total cholesterol or HDL-cholesterol. In hypertensive animals the drug decreased lipid parameters, increased diastolic and mean blood pressure after the first week of administration, and produced a small but significant decrease in heart rate after the first two weeks of the treatment. In both groups of animals, celiprolol decreased LPS-stimulated serum concentration of IL-6 but did not affect levels of TNF-α and IL-1β.
Conclusions: It is suggested that the IL-6-modulating properties of celiprolol could provide additional value to the therapeutic effectiveness of the drug in the treatment of hypertension.

Introduction

Increased airway resistance, peripheral and coronary vasoconstriction, proatherosclerotic action, and increased insulin resistance are the most important side effects of conventional β-blockers, limiting their therapeutical usefulness [23,26]. A large body of clinical data has demonstrated that the contraindications of celiprolol, a selective β_1-blocker endowed with β_2-adrenomimetic activity, are markedly lower than those displayed by the first generation of β-adrenolytic drugs. For example, celiprolol is safer than conventional β-blockers in the treatment of asthmatic patients because of lower influence on the airway function [8,32]. Moreover, celiprolol does not produce venodilatation, and has negligible vasoconstricting effects on stenotic and normal coronary arteries. The vascular action of the drug is associated with the activation of β_2-adrenoceptors, NO release from the endothelium, and weak blockade of α_1-adrenoceptors [32,43]. Other desirable effects of celiprolol include an increase in insulin sensitivity in healthy volunteers and patients with an insulin-resistance state, and improvement of the serum lipid profile, i.e. a decrease in concentrations of triglycerides and LDL-cholesterol, and an increase in HDL-cholesterol [43].

Accumulating experimental evidence indicates the functional importance of an interplay between the autonomic nervous system and the immune system [15]. β-Adrenoceptors are expressed by various immune cells, such as lymphocytes, macrophages, neutrophils, eosinophils, and basophils. Stimulation of these receptors can lead to changes in the production of proinflammatory cytokines [42,52]. We have previously demonstrated that propranolol and atenolol, non-selective and cardioselective antagonists of β-adrenergic receptors, respectively, are endowed with immunomodulating properties [2,3]. This study analyzes the effects of celiprolol on lipopolysaccharide (LPS)-stimulated levels of proinflammatory cytokines, namely tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-6, in normotensive (Wistar-Kyoto; WKY) and spontaneously hypertensive (SHR) rats. In addition, the effects of celiprolol on heart rate, arterial blood pressure, and serum lipid profile were examined.

Abbreviations: IL, interleukin; LPS, lipopolysaccharide; SHR, spontaneously hypertensive rats; TNF-α, tumor necrosis factor alpha; WKY, Wistar-Kyoto rats.

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Materials and methods

Animals and treatment

The study was conducted on 12–14 weeks old spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto (WKY) male rats. The rats were housed in standard plastic cages, 10 animals per cage, at a constant temperature of 21 ± 1 °C, and under an illumination cycle of 12 h light–dark (lights on between 7.00 and 19.00). The animals, with an initial body weight 280–310 g, had free access to standard food and tap water. In order to select the rats for experimentation, preliminary examinations were carried out at the end of the second and third weeks of their adaptation. The animals with high blood pressure fluctuations were excluded from the study. Experiments were conducted between 8 a.m. and 4 p.m. All experimental procedures were performed in accordance with the Polish governmental regulations concerning experiments on animals (Dz.U.05.33.289) and were approved by the Local Ethics Committee for Experimentation on Animals.

Celiprolol (Celipres, Ranbaxy Laboratories Ltd., India; 150 mg kg^{-1} body weight) was suspended in 1% solution of methylcellulose (Sigma–Aldrich, Poznan, Poland) and administered by gavage at a volume of 2 ml kg^{-1} b.w. once daily for 3 weeks. Control rats received a 1% solution of methylcellulose (2 ml kg^{-1} b.w.). Measurements of arterial blood pressure were carried out after 7, 14, and 21 days of administration of celiprolol or vehicle.

Preliminary studies showed no detectable levels of cytokines in the serum of SHR rats. Thus, in order to achieve a measurable cytokine level, 24 h after the last administration of celiprolol or vehicle, the rats received *ip* a small dose of LPS from Escherichia coli serotype 055:B5 (Sigma–Aldrich, Poznan, Poland; 0.1 mg kg^{-1} b.w. in 1 ml of saline kg^{-1} b.w.). After 2 h, the animals were anesthetized with ethyl ether, and the blood samples were collected by heart puncture. The time of blood sample collection after LPS administration was chosen according to Dredge et al. [13]. The blood was allowed to clot overnight at 4 °C, and then the samples were centrifuged for 20 min at 2000 × *g*. The serum was removed and stored at −20 °C until used for biochemical measurements.

Arterial blood pressure and heart beat measurements

Arterial blood pressure was measured in conscious rats by a manometer manufactured by LETICA (Panlab S.L., Spain), using a tail-cuff method as described in details by Górska and Andrzejczak [17]. Before the measurements, in order to calm the animals and dilate the tail blood vessels, the rats were placed inside a warming chamber (about 34 °C) for 30 min. The measurements of arterial blood pressure (systolic, diastolic and mean) were carried out at least three times for each animal, and the mean values of several successive measurements were used for further analysis. Changes in blood pressure were expressed as the percentage of baseline values. The heart rate was measured by the same apparatus automatically and was registered as beats per minute.

Lipid profile determination

Total serum cholesterol concentration was determined by the cholesterol oxidase method using a commercially available kit (Cholesterol CHOD PAP, Biolabo, Maizy, France) according to the manufacturer's instructions. To measure HDL-cholesterol, low density lipoproteins, very low density lipoproteins, and chylomicrons were precipitated from serum samples by phosphotungstic acid and magnesium chloride. Following that, HDL-cholesterol was measured with the aid of commercially available kit (HDL-cholesterol-PTA, Biolabo, Maizy, France). Triglycerides were measured using a commercially available kit (Triglycerides GPO Method, Biolabo, Maizy, France) according to the manufacturer's instructions.

Table 1
Effects of the repeated administration of celiprolol (150 mg kg^{-1}) on systolic (A), diastolic (B) and mean blood pressure (C) in normotensive (WKY) and hypertensive (SHR) rats.

Time after drug administration (week)	Mean changes in systolic blood pressure (% of initial values)			
	WKY		SHR	
	Vehicle (n = 10)	Celiprolol (n = 15)	Vehicle (n = 10)	Celiprolol (n = 15)
(A)				
1	99.4 ± 1.6	96.9 ± 2.0	99.8 ± 2.3	97.0 ± 2.6
2	96.9 ± 1.9	98.9 ± 2.2	95.6 ± 2.6	97.2 ± 3.7
3	101.5 ± 1.1	98.4 ± 2.6	98.9 ± 3.9	101.7 ± 2.1
Time after drug administration (week)	Mean changes in diastolic blood pressure (% of initial values)			
	WKY		SHR	
	Vehicle (n = 10)	Celiprolol (n = 15)	Vehicle (n = 10)	Celiprolol (n = 15)
(B)				
1	97.8 ± 4.4	105.5 ± 4.4	97.1 ± 3.7	110.6 ± 3.9*
2	103.1 ± 1.4	108.8 ± 3.6	102.6 ± 3.6	112.0 ± 2.3*
3	101.6 ± 3.6	109.2 ± 5.7	98.3 ± 3.7	102.6 ± 2.3
Time after drug administration (week)	Mean changes in mean blood pressure (% of initial values)			
	WKY		SHR	
	Vehicle (n = 10)	Celiprolol (n = 15)	Vehicle (n = 10)	Celiprolol (n = 15)
(C)				
1	98.3 ± 3.0	101.9 ± 3.2	100.3 ± 2.8	107.3 ± 1.3*
2	101.1 ± 1.3	105.7 ± 2.6	99.2 ± 3.1	105.4 ± 2.1
3	101.0 ± 2.3	104.3 ± 4.0	99.3 ± 3.5	102.3 ± 1.1

Values are means ± SEM.
* $p < 0.05$ in comparison with vehicle-treated control animals.
Baseline values of blood pressure (mmHg) for WKY rats in vehicle-treated group: systolic 117.0 ± 2.0; diastolic 84.6 ± 1.7; mean 95.8 ± 1.5.
Baseline values of blood pressure (mmHg) for WKY rats in celiprolol-treated group: systolic 118.1 ± 2.2; diastolic 85.1 ± 1.8; mean 96.8 ± 1.8.
Baseline values of blood pressure (mmHg) for SHR in vehicle-treated group: systolic 237.3 ± 3.2; diastolic 128.2 ± 2.7; mean 165.2 ± 3.0.
Baseline values of blood pressure (mmHg) for SHR in celiprolol-treated group: systolic 235.6 ± 2.4; diastolic 129.2 ± 1.9; mean 164.3 ± 2.0.