Cardiovascular Pharmacology: Open Access

Hasan, Cardiovasc Pharmacol open access 2015, 4:5
DOI: 10.4172/2329-6607.1000164

Research Article Open Access

Comparative Study of Leptin and Phentolamine Effects on Cardiovascular System

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Abstract

Background: Various lines of evidence suggest that leptin participates not only in negative feedback control of body adiposity but also in cardiovascular and sympathetic regulations. The aim of this research is to study the acute effects of leptin on cardiovascular system. Rabbits were used as an experimental animal.

Materials and method: These experimental animals were divided into two groups: first group consists of 15 rabbits, given intravenous injection of leptin. Second group consists also of 15 rabbits, injected by phentolamine as α-adrenergic blocker before given them leptin. Heart rate and mean arterial blood pressure were recorded by using Fukuda Denshi Apparatus.

Results: In group one, mean arterial blood pressure, and heart rate have been significantly increased after intravenous injection of leptin ($p<0.0001$). In the second group which was injected by phentolamine, leptin did not cause significant increase in arterial blood pressure ($P>0.05$), but heart rate increased significantly ($p>0.001$).

Conclusion: These results suggest that intravenous injection of leptin causes increases in arterial blood pressure and heart rate in anesthetic rabbits, and these effects could be opposed by α -adrenergic blockade. This may be partially explained by the effect of leptin on cardiovascular system could be mediated by sympathetic pathway.

Keywords: Leptin; Phentolamine; Sympathetic pathway; Blood pressure; Heart rate

Introduction

LEPTIN is a 16-kDa protein monomer that has been identified as a blood-borne factor regulating appetite [1]. Various lines of evidence suggest that leptin participates not only in negative feedback control of body adiposity but in cardiovascular and sympathetic regulations [2]. Previous studies have been shown that leptin is increased in human and animals with overweight, and these increased levels of leptin were positively correlated with body mass index [3]. Leptin, which is peptide hormone, contributes in high blood pressure through activation of sympathetic system [4]. Moreover, it has been suggested that leptin binding sites in certain parts of the brain play important role in controlling blood pressure [5]. Leptin may play a role in cardiovascular function through its effects on central nervous system, Haynes and his colleagues demonstrated that infusion of leptin increased activity of sympathetic system in kidney, adipose tissue and adrenal in animals [6].

Sympathetic nervous system plays an important role in high blood pressure in overweight animals and humans [7,8]. Previous research studies elucidated that blocking of Sympathetic nervous system by medications decreased blood pressure which was associated with diet rich with fat in experimental animals [9,10].

Another study has been published by Shek EW and his colleagues demonstrated that chronic intravenous injection of leptin causes increases in blood pressure and heart rate in rats [11]. However, it has not known that if these effects are centrally or peripherally mediated. Dunbar and his colleagues observed increased blood pressure in anesthetized rats after injected large doses of leptin in ventricular brain [12].

The aim of this study is to examine the acute effects of leptin on blood pressure and heart rate, and changes of these effects by blocking of α-adrenergic receptors of sympathetic nervous system.

Materials and Method

Animals and drugs

The source of leptin was from Bio-Vendor Laboratory Medicine, Inc. (Czech Republic). Leptin, which is produced by *E. coli*, is derived by human recombinant DNA technology. The experiments were conducted on 30 white rabbits weighing 2.2-2.4 kg. Rabbits were anesthetized with intravenous injection of sodium thiopental (50 mg/kg) from Abbott Laboratories, and for sustainable of anesthesia inhalation ether has been used.

A 23-gauge stainless steel cannula was used into the marginal vein on the edge of the lateral posterior rabbit ear; this cannula has been used for IV injection drugs. Polyethylene catheter (PE-50) inserted into carotid artery, which is used to measure blood pressure by using ECG of Fukuda Denshi, Autocardiner FCP 2155 (Japan).

Blood pressure and heart rate have been recorded at basal and after injection of these medications. Intravenous bolus of 500 μg/kg of leptin has been injected into marginal vein in the first group of 15 rabbits, whereas the second group, which also consists of 15 rabbits, has been injected by phentolamine (0.01 mg/kg) to block α-adrenergic receptors.

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Received October 26, 2015; **Accepted** December 01, 2015; **Published** December 06, 2015

Citation: Hasan KM (2015) Comparative Study of Leptin and Phentolamine Effects on Cardiovascular System. Cardiovasc Pharm Open Access 4: 164. doi:10.4172/2329-6607.1000164

Statistical analysis

All results are given as means SEM. Data were processed by use of Stat View 5.0 software (SAS Institute, U.S.A). ANOVA was used to compare groups and when ANOVA yielded statistically significant differences between groups, comparison was done using Spearman test to study the relationship among variables (blood pressure and heart rate).

Results

Parameters before injection medications

Mean heart rate was 225 ± 3.04 beat/minute, and mean blood pressure 75.60 ± 0.61 mmHg. Characteristics of two groups have been shown in table 1, first group was for control and the second was for leptin injection. Whereas treatment with phentolamine before injection of leptin appears in table 2.

First group of animals (treated only with leptin)

In this group of animals which have been received IV leptin 500 microgram/kg, there was significant increase in mean arterial blood pressure from 75.60 ± 0.61 mmHg to 94.63 ± 0.51 mmHg (P value<0.001). Moreover, heart rate has been significantly increased after IV leptin, from 225 ± 3.04 beat/min to 291 ± 4.42 beat/min (P value <0.001), Table 1, Figure 1 and 2).

Second group of animals (treated with phentolamine before leptin)

Phentolamine significantly decreased response of cardiovascular action of leptin. Leptin increased blood pressure non-significantly. Mean arterial blood pressure was before treatment 74.70 ± 0.51 mmHg and became after treatment with phentolamine and leptin in sequences 77.63 ± 0.41 mmHg (P value >0.05). However, phentolamine did not impair effects of leptin on heart rate. Heart rate was 229 ± 2.41 beat/min and significantly increased after treated with phentolamine and leptin in respectively 344 ± 3.52 beat/min (P value <0.001), Table 2, Figure 2).

Relationship between blood pressure and heart rate

This study elucidated significant positive relationship between blood pressure and heart rate in group one which was treated with leptin (p<0.001), but this relationship was inversely significant related in group two which was treated with phentolamine and leptin consequently (p<0.001).

Discussion

Previous studies have shown an association between serum leptin concentrations and various cardiovascular risks, including stroke [13], chronic heart failure [14], acute myocardial infarction [13], coronary heart disease [15], and left cardiac hypertrophy [16].

In humans, there is no direct evidence for a role of leptin in the regulation of the sympathetic nervous system because results from leptin infusions in humans are lacking. In experimental study, however, leptin has been shown to activate the sympathetic nervous system, as assessed by an increase in circulating norepinephrine levels after a single cerebroventricular administration of leptin [17]. Therefore, this study has been investigated the acute effects leptin on cardiovascular system and attempt to examine the role of sympathetic system mediated thee effects.

Variables	Heart rate (bpm)	Mean arterial blood pres s ure (mmHg)
Bas eline (N=15)	225 ± 3.04	75.60 ± 0.61
After leptin injection (N=15)	291 ± 4.42	94.63 ± 0.51
P value	<0.001	<0.001

Table 1: Characteristics of group of rabbits before and after injection of leptin treatment .

Variables	Heart rate (bpm)	Mean arterial blood pres s ure (mmHg)
Bas eline (N=15)	229 ± 2.41	74.70 ± 0.51
After phentolamine then followed by leptin injection (N=15)	344 ± 3.52	77.63 ± 0.41
P value	<0.001	>0.05

Table 2: Characteristics of group of rabbits treated with phentolamine before leptin injection .

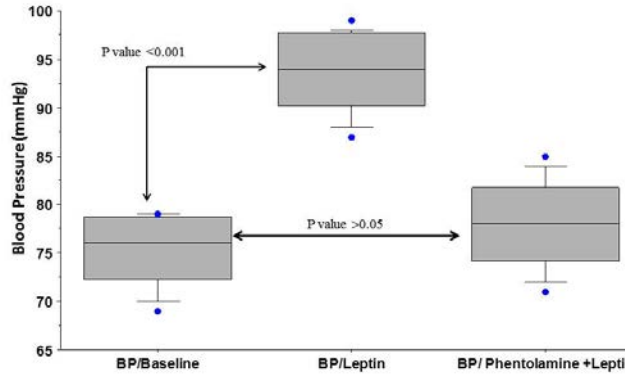

Figure 1: Box plot showing mean arterial blood pressure (MAP) before and after injection leptin alone, and injection of phentolamine then leptin consequently. BP: Blood Pressure.

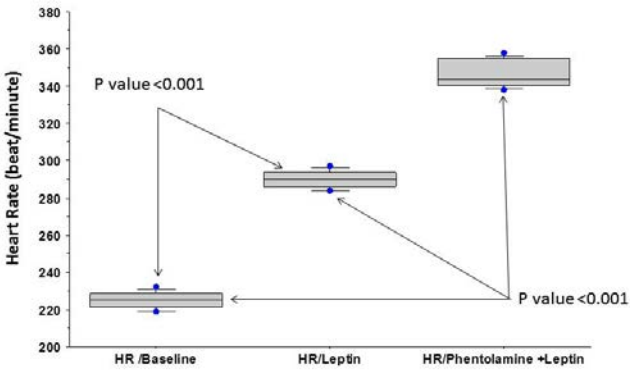

Figure 2: Box plot showing heart rate before and after injection leptin alone and injection of phentolamine then leptin consequently. HR: Heart Rate.

Intravenous leptin increases sympathetic nerve activity to adipose tissue [6]. In addition, injection of leptin into the third cerebral ventricle activates sympathetic nerves [18]. Intravenous leptin also increases sympathetic nerve activity to the kidneys, hind limbs, and adrenal glands in anesthetized rats.

These studies consist with our present study, which is demonstrated that IV injection of leptin increases blood pressure and heart rate significantly after single dose of leptin.

Phentolamine is a reversible nonselective alpha-adrenergic antagonist [19]. Its primary action is vasodilation due to α_1 blockade [20]. It also can lead to reflex tachycardia because of hypotension and α_2 inhibition, which increases sympathetic tone [21].

It has been shown that in the present study leptin intravenous injection increases significantly blood pressure and heart rate, and block of α-adrenergic system by using phentolamine results in decreasing effects of leptin effect on blood pressure without affecting heart rate. These reversible effects of phentolamine could be mediated by blocking alpha-adrenergic receptors.

In Conclusion, intravenous injection of leptin augments arterial blood pressure and heart rate in anesthetic rabbits, and these actions could be counteracting by α- adrenergic blocker. This may be partially explained by the effect of leptin on cardiovascular system could be mediated by sympathetic pathway. These data suggest that more future studies are needed to detect the relationship between leptin and cardiovascular risk factors.

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