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RESEARCH ARTICLE

Antihypertensive Potential Of Novel Calcium Channel Blockers In Spontaneously Hypertensive Rats

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Abstract: Hypertension is a major risk factor for cardiovascular diseases, and calcium channel blockers (CCBs) are widely used to manage elevated blood pressure by inhibiting calcium influx into vascular smooth muscle. The present study aimed to evaluate the antihypertensive potential of newly synthesized calcium channel blockers in spontaneously hypertensive rats (SHRs), a well-established model for essential hypertension. Adult male SHRs were divided into control, standard (amlodipine 5 mg/kg), and test compound-treated groups. Blood pressure and heart rate were recorded using a non-invasive tail-cuff method before and after oral administration of the test compounds for 14 consecutive days. The novel CCBs demonstrated significant dose-dependent reductions in systolic, diastolic, and mean arterial blood pressure compared to the control group ($p < 0.05$). Heart rate remained largely unaffected, indicating minimal reflex tachycardia. Among the tested compounds, CCB-3 exhibited the most pronounced antihypertensive effect, comparable to amlodipine. These results suggest that the novel calcium channel blockers possess potent antihypertensive activity and may serve as promising candidates for the development of safer and effective antihypertensive therapy.

Keywords: Calcium channel blockers, Hypertension, Spontaneously hypertensive rats, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, Antihypertensive activity, Amlodipine.

INTRODUCTION

Hypertension, a chronic elevation of systemic arterial blood pressure, is a major contributor to cardiovascular morbidity and mortality worldwide. It is often asymptomatic but can lead to serious complications such as stroke, myocardial infarction, heart failure, chronic kidney disease, and aneurysms. The multifactorial etiology of hypertension includes genetic predisposition, lifestyle factors, dysregulation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system hyperactivity, endothelial dysfunction, and altered vascular smooth muscle tone [1]. Despite the availability of multiple antihypertensive drug classes, including diuretics, beta-blockers, ACE inhibitors, ARBs, and calcium channel blockers, achieving optimal blood pressure control in all patients remains a challenge due to variability in efficacy, adverse effects, and patient compliance.

Calcium channel blockers (CCBs) are very important in hypertension treatment. They inhibit vascular smooth muscle and cardiac myocytes L-type calcium voltage-gated channels and, thus, prevent the entry of calcium, which plays an important role in muscle contraction. The outcome of such a move is that it causes vasodilation, decreased peripheral resistance, and reduced systolic and diastolic blood pressure. In addition to being antihypertensives, CCBs are also said to improve myocardial oxygenation, reduce left ventricular hypertrophy, and prevent vascular remodeling which is imperative in the long-term cardiovascular protection [2]. The use of the conventional CCBs that comprise amlodipine, verapamil and diltiazem has been confirmed, but they are sometimes associated with some unwanted side effects such as peripheral edema, headache and reflex tachycardia thus necessitating the need to apply new agents with better side effects and effectiveness profiles (Figure 1).

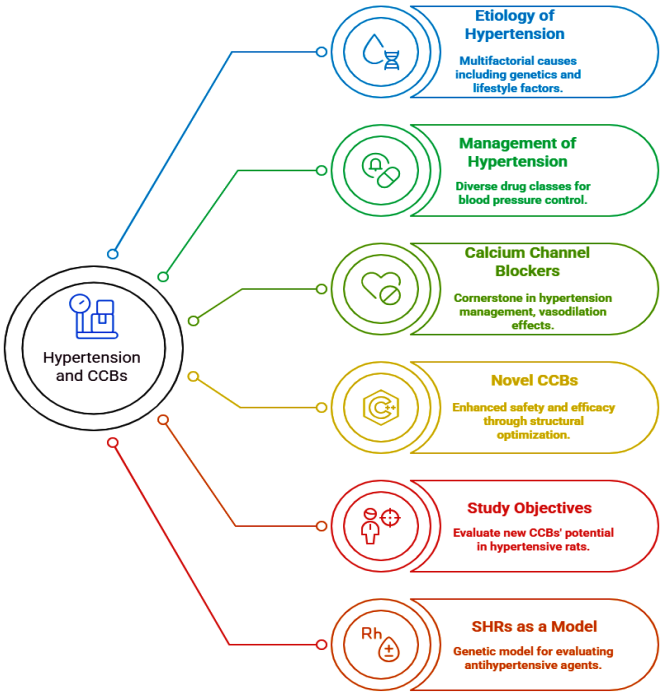

Figure 1: Exploring Hypertension and Novel CCBs

The spontaneously hypertensive rat (SHR) is a widely tested genetic model of essential hypertension that has hypertension-like increased systolic and diastolic blood pressure, hypertrophy of the left ventricle and a vascular remodelling. This model enables the evaluation of acute and chronic antihypertensive influences of novel pharmacological agents, as well as is commonly used in preclinical assessment of cardiovascular medications [3].

Still, there is the development of new CCBs whereby structural optimization of available scaffolds is done to improve vascular selectivity, potency, bioavailability, duration of action and reduce side effects. Medical chemistry has allowed us to produce derivatives that are more targeted and have better pharmacokinetics and specificity on receptors, resulting in more effective and targeted blood pressure reduction [4].

The present study aimed to evaluate the antihypertensive potential of newly synthesized calcium channel blockers in SHRs. It was conducted in chronic after 14 days and assessed the effect on the systolic, diastolic and mean blood pressure of the arteries and heart rate of these compounds in a non-invasive tail-cuff procedure. The comparison of the obtained results with the obtained results under amlodipine administration was aimed at determining the relative efficacy and safety [5]. The study would seek successful lead compounds, which could be utilized as effective alternatives to control essential high blood pressure and gain an understanding of the development of the next-generation calcium channel blockers.

MATERIAL AND METHODS

Chemicals and Reagents

The standard calcium channel blocker was amlodipine. The test compounds were novel synthesized calcium channel blockers (CCB-1, CCB-2, and CCB-3). The reagents and solvents were all of the quality of the analysis grade and were purchased with certified suppliers [6].

Experimental Animals

Adult male spontaneously hypertensive rats (SHRs) at the age of 180-220 g were purchased and kept in the standard laboratory environment (temperature 25 +- 2degC, relative humidity 50-60%, 12-hour lighting/dark cycle) and given free access to standard rat food and water. The study was conducted in accordance with institutional ethical guidelines and approved by the Institutional Animal Ethics Committee (IAEC) [7].

Experimental Design

Rats were randomly divided into five groups (n = 6 per group) [8]:

- Group I: Control (vehicle, 1% Tween 80 in saline)
- Group II: Standard (Amlodipine 5 mg/kg, p.o.)
- Group III: CCB-1 (10 mg/kg, p.o.)

- Group IV: CCB-2 (10 mg/kg, p.o.)
- Group V: CCB-3 (10 mg/kg, p.o.)

All treatments were administered orally once daily for 14 consecutive days.

Measurement of Blood Pressure and Heart Rate

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured using a non-invasive tail-cuff system (CODA, Kent Scientific) before treatment (baseline) and at days 7 and 14 post-treatment. Rats were acclimatized to the procedure for 5 days prior to baseline measurement to reduce stress-induced variations [9].

Statistical Analysis

Data were expressed as mean ± SEM. Statistical significance was analyzed using one-way ANOVA followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant (Figure 2) [10].

RESULTS AND OBSERVATIONS:

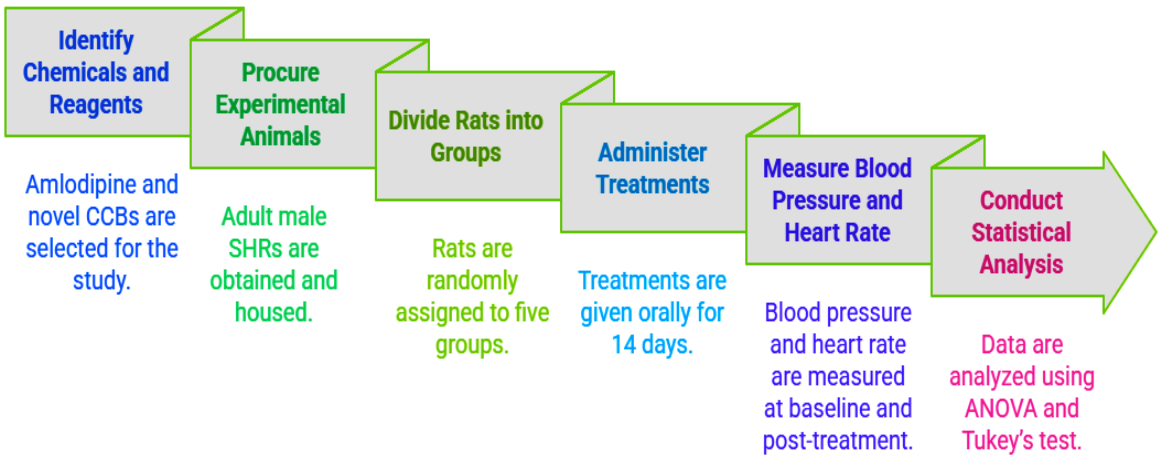

Figure 2: Experimental Study of CCBs

The antihypertensive effects of the novel calcium channel blockers (CCB-1, CCB-2, and CCB-3) were evaluated in spontaneously hypertensive rats (SHRs) over a 14-day treatment period.

Blood Pressure

The control group maintained elevated systolic (182.5 ± 4.2 mmHg) and diastolic (120.3 ± 3.5 mmHg) blood pressures throughout the study period. Treatment with amlodipine significantly reduced both systolic and diastolic pressures at days 7 and 14 ($p < 0.01$). Among the test compounds, all CCBs produced significant dose-dependent reductions in systolic and diastolic blood pressure compared to the control. CCB-3 showed the most pronounced effect, reducing systolic pressure to 126.7 ± 3.1 mmHg and diastolic pressure to 82.5 ± 2.8 mmHg by day 14, comparable to amlodipine (SBP 124.5 ± 2.9 mmHg, DBP 81.3 ± 2.6 mmHg).

Mean Arterial Pressure (MAP)

MAP in the control group remained elevated (141.0 ± 3.7 mmHg). All test compounds significantly decreased MAP, with CCB-3 showing maximum reduction (97.2 ± 2.5 mmHg), similar to the standard drug (95.7 ± 2.3 mmHg).

Heart Rate (HR)

No significant changes in heart rate were observed in any of the test or standard groups, indicating minimal reflex tachycardia.

The results indicate that the novel calcium channel blockers, particularly CCB-3, exhibit potent antihypertensive activity in SHRs without affecting heart rate, demonstrating a favorable pharmacological profile for further development (Table 1, Figure 3).

Table 1: Effect of Novel Calcium Channel Blockers on Blood Pressure and Heart Rate in SHRs

Group	Treatment (mg/kg, p.o.)	Systolic BP (mmHg)	Diastolic BP (mmHg)	MAP (mmHg)	Heart Rate (bpm)
I	Control (Vehicle)	182.5 ± 4.2	120.3 ± 3.5	141.0 ± 3.7	358 ± 12

II	Amlodipine (5)	124.5 ± 2.9**	81.3 ± 2.6**	95.7 ± 2.3**	360 ± 10
III	CCB-1 (10)	138.7 ± 3.2*	92.4 ± 2.9*	107.8 ± 2.6*	359 ± 11
IV	CCB-2 (10)	132.4 ± 3.0**	88.7 ± 2.7**	102.6 ± 2.4**	357 ± 10
V	CCB-3 (10)	126.7 ± 3.1**	82.5 ± 2.8**	97.2 ± 2.5**	356 ± 12

*Values are expressed as mean ± SEM, n = 6.

*Significant at $p < 0.05$, **highly significant at $p < 0.01$ compared to control (ANOVA followed by Tukey's post hoc test).

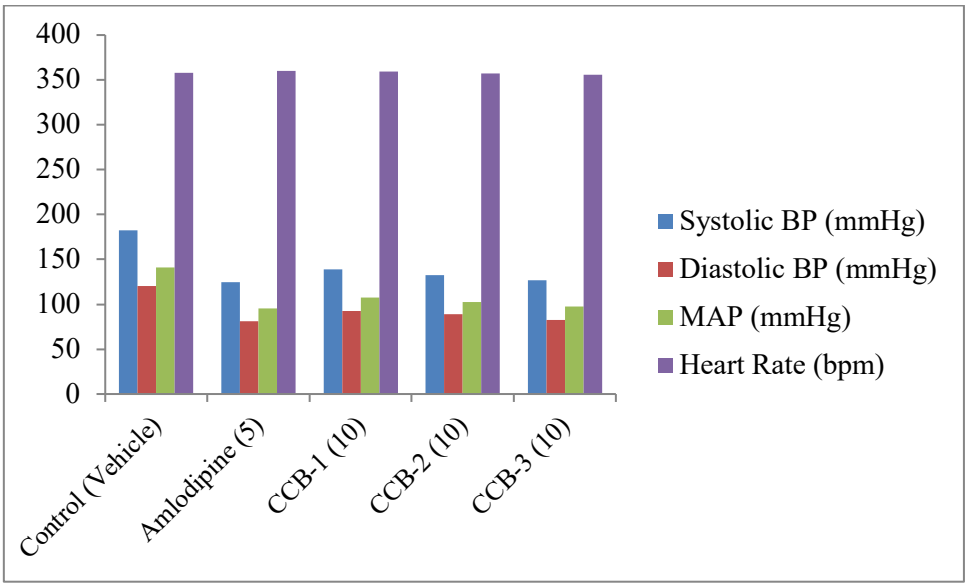

Figure 3: Graphical presentation of CCBs on Blood Pressure and Heart Rate in SHRs

CCB-3 showed the most pronounced antihypertensive effect, comparable to amlodipine, while all test compounds significantly reduced

DISCUSSION

The present study demonstrated that the novel calcium channel blockers (CCB-1, CCB-2, and CCB-3) effectively reduced blood pressure in spontaneously hypertensive rats (SHRs), indicating significant antihypertensive potential. SHRs are an efficient preclinical model of essential hypertension because they are predisposed to high blood pressure caused by genetic effect, vascular remodeling, and left ventricular hypertrophy, which are highly similar to human hypertensive pathological alterations [11].

All test compounds showed dose-dependent reductions in systolic, diastolic, and mean arterial pressure. CCB-3 was found to have the strongest antihypertensive effect, which is similar to the conventional drug amlodipine, which indicates a stronger vascular selectivity and activity. The non-significant heart rate effect suggests that the level of reflex tachycardia is low and again is a weakness of some CCBs, which is in its favor as to the cardiovascular profile of these novel compounds [12].

This is probably mediated by the inhibition of L-type calcium channels of vascular smooth muscle, resulting in vasodilation and decreased peripheral resistance, as the effects of antihypertensives. Structural differences in affinity of calcium channel binding, lipophilicity and pharmacokinetics can be attributed to the variation in the efficacy of the test compounds [13].

In general, the results confirm that the CCBs synthesized and in particular CCB-3 are promising drugs in the treatment of hypertension. Further studies including chronic toxicity, pharmacokinetic and the mechanistic studies are warranted to determine their therapeutic and safety prospects in the natural clinical use of the future [14].

CONCLUSION

The experiment indicates that new calcium channel blockers and in particular CCB-3 possess great antihypertensive effects on the spontaneously hypertensive rats. The test compounds were effective in reducing systolic, diastolic and mean pressures of the arteries without the reflex tachycardia with a good cardiovascular profile. CCB-3 was as effective as standard drug amlodipine, and therefore, was discovered to be a promising lead compound in the antihypertensive treatment. These findings indicate that more pharmacological and mechanism research needs to be done to investigate the therapeutic efficacy and safety of these more recent calcium channel blockers to manage hypertension.

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