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Report

The Antiarrhythmic Activity of *N*-Alkyl-1,2-diphenylethanolamines

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The activity of *N*-alkyl-1,2-diphenylethanolamines against $CaCl_2$-induced cardiac arrhythmia was evaluated in the rat. The potencies of the compounds were compared with that of the established calcium ion-channel blocker, verapamil. The *N*-methyl, *N*-ethyl, and *N*-isobutyl derivatives as well as verapamil at doses of 2–8 μmol kg^{-1} protected the animals against the induced arrhythmia. The potency order was verapamil > *N* methyl > *N*-ethyl > *N*-isobutyl derivatives. The *N*-isopropyl and *N*-butyl derivatives were inactive. The antiarrhythmic activity of the compounds was not due to local anesthetic activity but may be caused by calcium-channel inhibition.

KEY WORDS: *N*-alkalyl-1,2-diphenylethanolamines, antiarrhythmic activity; phenethylamines; α-phenyl, β-hydroxy antiarrhythmic activity; verapamil.

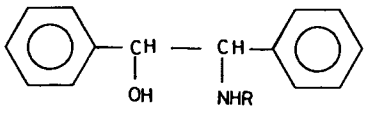
INTRODUCTION

We previously reported the synthesis and pharmacological properties of *N*-alkyl-1,2-diphenylethanolamines (Fig. 1) (1). The compounds depressed smooth and cardiac muscles, and the effects were reversed by exogenous $CaCl_2$, suggesting an inherent calcium-channel blocking activity. Conduction along the sinus and A–V nodes within the heart depends upon slow calcium ion currents (2,4), and calcium-channel blocking agents slow down sinoatrial node discharge (5,6) and depress ectopic pace makers (7,8). Further, the established calcium-channel blockers, such as verapamil and diltiazem, possess potent antiarrhythmic activities in various experimental models (9,10). These findings prompted us to investigate the antiarrhythmic action of the *N*-alkyl-1,2-diphenylethanolamines in experimentally induced arrhythmias in rats and to compare their activities with known antiarrhythmic agents such as verapamil and lidocaine.

METHODS

Induction of Arrhythmias. Male Wistar rats (200–250 g) were anesthetized with urethane, 1.25 g kg^{-1} ip (25%, w/v, aqueous solution) and left in spontaneous respiration. The electrocardiogram (ECG; Lead II) was recorded using subcutaneous steel needle electrodes connected to a Narco physiograph fitted with an ECG coupler No. 7176 (Narco Bio-Systems). The speed of the chart was adjusted to 25 or 50 mm sec^{-1}. Cardiac arrhythmias were induced with $CaCl_2$ (10% aqueous solution) at a dose of 50–60 mg kg^{-1} iv via the right external jugular vein. Heart rate was calculated from the QRS complexes per unit time. The times of onset and duration of persistent ventricular fibrillations were recorded.

Effects of the Test Compounds, Verapamil and Lidocaine. The influence of these compounds on $CaCl_2$-induced arrhythmias was examined by injecting the drugs, iv, 2 min before arrhythmia induction. In each animal only one single drug was tested at an interval of 30 min between the doses. All drugs were dissolved in saline to give a concentration of 1 or 2 mg ml^{-1}. The first dose of each drug was administered 30 min after complete recovery from the $CaCl_2$-induced arrhythmias. Before induction of the arrhythmias an appropriate volume of saline equivalent to the injected drug solution to be examined was administered iv into the experimental animal. A complete successful suppression of $CaCl_2$-induced arrhythmia by a particular dose of a drug was de-



Compound	R
1	CH_3
2	CH_3CH_2
3	$(CH_3)_2CH$
4	$CH_3CH_2CH_2CH_2$
5	$(CH_3)_2CHCH_2$

Fig. 1. The chemical structures of compounds 1–5.

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Table I. Influence of *N*-Methyl-1,2-diphenylethanolamine (Compound 1) and Verapamil on $CaCl_2$-Induced Arrhythmia in the Rat

Treatment	% decrease in heart rate		Onset time of fibrillation (sec)	Duration of fibrillation (sec)	Magnitude of arrhythmia suppression
	Control	After $CaCl_2$			
A. Saline	0	80 ± 2	4.1 ± 1.1	4 ± 0.2	0
Compound 1					
2 μmol kg^{-1}	9.2 ± 3.1	80 ± 2.5	5.5 ± 1	4 ± 1	0
4 μmol kg^{-1}	14.6 ± 2.1*	46.6 ± 4*	—[a]	—	Complete
8 μmol kg^{-1}	18.3 ± 2.2	6.6 ± 1.5**	—	—	Complete
B. Saline	0	76 ± 6.5	5 ± 0.5	6 ± 0.8	0
Verapamil					
1 μmol kg^{-1}	30.7 ± 3.4**	66.6 ± 5	11 ± 1.2	2.8 ± 0.4	Partial
2 μmol kg^{-1}	46.1 ± 4.5**	53.8 ± 5.9*	—	—	Complete

[a] No fibrillations were observed.
* $P < 0.05$ ($N = 6$) compared with the respective control.
** $P < 0.01$ ($N = 6$) compared with the respective control.

fined as complete prevention of the induced fibrillation. Partial suppression was defined as a 50% decrease in the duration of fibrillations, whereas poor suppression was defined as a delay in the onset of the induced arrhythmia without a decrease in the duration of the arrhythmia.

Local Anesthetic Activity. To examine the local anesthetic activity of the compounds, the frog limb withdrawal reflex (11) was used. Frogs weighing 70 g were used, and 3 ml of 8 m*M* solutions in saline was instilled into the empty abdominal cavity. The reflex was examined every 5 min for 30 min using a 0.1 *N* HCl solution.

Statistical Analysis. Statistically significant differences between the various treatments in the examined parameters were calculated using paired or unpaired Student's *t* tests or analysis of variance as appropriate.

All test compounds used in this study were in the form of racemates. However, studies using ^1H and ^{13}C NMR suggest that each of the compounds consists of only the erythro configuration as revealed by the coupling constants of the adjacent methine protons.

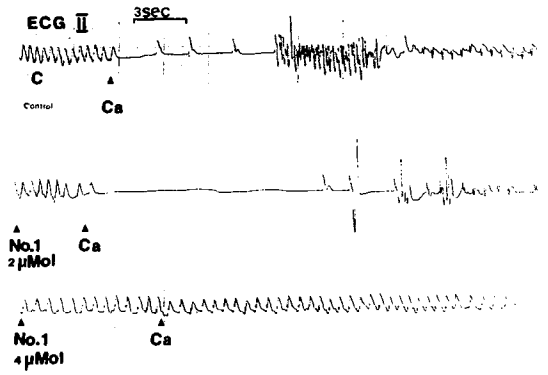

Fig. 2. Effect of compound 1 on $CaCl_2$-induced fibrillations in the rat. $CaCl_2$ (Ca) (50 mg kg^{-1} iv) converted the normal cardiac rhythm (C) to cardiac fibrillation. Pretreatment of the animal with compound 1, 2 μmol kg^{-1} (No. 1, 2 μmol), 2 min before the administration of $CaCl_2$ produced partial protection against $CaCl_2$-induced arrhythmias. However, pretreatment of the animal with 4 μmol kg^{-1} completely protected the animal against the induced arrhythmias.

RESULTS

Antiarrhythmic Properties

In eight animals the mean control heart rate was 232 ± 10 (SE) beats min^{-1}. In all animals intravenous administration of 50 mg $CaCl_2$ kg^{-1} produced initial bradycardia followed by ventricular fibrillations. Control ECG and heart rate returned to normal 15 min after the injection of $CaCl_2$. The mean duration of the initially induced bradycardia was 4.1 ± 1.1 sec, and the mean percentage decrease in the heart rate was 80 ± 2%. The mean duration of the fibrillations was 4 ± 0.2 sec. The mean onset time for the fibrillations was 4.1 ± 1.1 sec. The influence of compound 1, administered at doses of 2–8 μmol kg^{-1}, on the above parameters is shown in Table I. The administration of 1 decreased the control heart rate in a dose-dependent manner. The decreases induced by 4 and 8 μmol kg^{-1} were significant ($P < 0.05$, $N = 6$). At a dose of 2 μmol kg^{-1} the compound delayed the onset of $CaCl_2$-induced fibrillations but this delay was insignificant. At a dose of 4 or 8 μmol kg^{-1} the compound completely suppressed $CaCl_2$-induced arrhythmias including the initially induced bradycardia. Figure 2 shows the influence of compound 1 at doses of 2 and 4 μmol kg^{-1} on the induced arrhythmias. Similarly, pretreatment of the animals with compounds 2 and 5, albeit at a higher dose (8 μmol/kg), significantly reduced the basal heart rate and suppressed $CaCl_2$-induced arrhythmias ($P < 0.05$, $N = 6$). However, pretreatment of the animals with compounds 3 and 4 at doses of up to 16 μmol kg^{-1} did not affect the basal heart rate and did not protect against the induced arrhythmias.

Pretreatment of the animals with verapamil at doses of 1–2 μmol kg^{-1} induced significant decreases in the basal heart rate and protected against the induced arrhythmias (Table I and Fig. 3).

Pretreatment of the animals with lidocaine up to 8 μmol kg^{-1} did not protect against the induced arrhythmias.

Local Anesthetic Activity

At a concentration of 8 m*M* none of the test compounds exhibited local anesthetic activity as evidenced by their inability to suppress the limb withdrawal reflex of the frog.

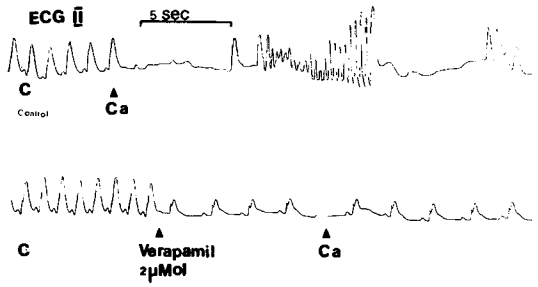

Fig. 3. Effect of verapamil on $CaCl_2$-induced fibrillations in the rat. Pretreatment of the animal with verapamil (2 μmol kg^{-1}) 2 min before the administration of $CaCl_2$ (Ca) (50 mg kg^{-1} iv) produced complete protection against $CaCl_2$- induced arrhythmia.

DISCUSSION

The results of the present study demonstrate the ability of compounds 1, 2, and 5 and verapamil to induce initial bradycardia and to protect against $CaCl_2$-induced initial bradycardia and fibrillations in the rat; the potency order was verapamil > 1 > 2 > 5. The effectiveness of compounds 1, 2, and 5 may result from blocking of the slow calcium channels across the sinus and A–V nodes. Conduction along these nodes is dependent upon slow calcium currents (2–4). Furthermore, the compounds may depress ectopic pacemakers as has been observed in the presence of the established calcium-channel blockers (7,8).

The antiarrhythmic action of the compounds did not seem to involve suppression of the fast movements of Na^+ and K^+ ions since none of the compounds possessed local anesthetic activity as shown in this study as well as in an earlier study (1). In fact, the local anesthetic agent lidocaine, which inhibits fast inward Na^+ currents and delays K^+ efflux, did not protect against $CaCl_2$-induced arrhythmia.

The negative chronotropic effect of compounds 1, 2, and 5 and varapamil was found to be in the following potency order: verapamil > 1 > 2 > 5. This effect may result, at least in part, from a direct action on sinus nodal cells leading to interference with normal influxes of the slow calcium currents.

The initially induced $CaCl_2$ bradycardia may result from disruption or occlusion of the specialized regions of low electrical resistance between adjacent atrial cells following the high concentrations of $CaCl_2$ administered. Indeed, such regions are found to be essential for the conduction of action potentials (12,13).

The results suggest that the potency of the test compounds is affected by the nature of the *N*-alkyl substituent. The general observation is that the smaller the alkyl group, the greater are the antiarrhythmic and the negative chronotropic effects.

The observation that the isobutyl derivative (compound 5) is active, whereas the isopropyl derivative (compound 3) is inactive may be due to differences in the intrinsic activities of the compounds at the slow calcium channels involved or, more likely, to differences in stereochemistry. This problem can be clarified by separation and pharmacological investigation of the pure isomers. This work is now in progress.

In conclusion, this study directs the attention to the possible calcium-channel blocking activity of compounds 1, 2, and 5 and their potential promise as antiarrhythmic agents.

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