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Studies on the cardiovascular depressant effects of N-Ethyl- and N-Benzyl-1,2-diphenylethanolamines in the rat Elucidation of the mechanisms of action

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Abstract

The influence and mechanisms of action of N-ethyl- and N-benzyl-1,2-diphenylethanolamines (compounds E and B, respectively) on the arterial blood pressure and the heart rate of the rat together with their effects on $CaCl_2$-induced arrhythmias in the rat were investigated. Both E and B in doses of (1.5–12 μmol/kg IV) decreased the arterial blood pressure and the heart rate in a dose-dependent manner. Studies with various receptor blockers, enzyme inhibitors and $CaCl_2$ revealed that E-induced cardiovascular depressant effects were mainly due to $CaCl_2$ channel blocking action and activation of cyclic guanylyl cyclase or release of NO whereas the cardiovascular effects of B seemed to involve both blockade of Ca^{2+} channels and activation of parasympathetic ganglia. Both compounds (12–14.5 μmol/kg) completely protected the rat against $CaCl_2$ (60 mg kg^{-1})-induced tachyarrhythmias. The B compound seemed to be several times more potent than the E compound in its cardiovascular depressant actions. The results suggest the potential usefulness of both compounds in the treatment of hypertension and supraventricular arrhythmias.
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Keywords: N-ethyl 1,2-diphenylethanolamine; N-benzyl 1,2-diphenylethanolamine; Ca^{2+} channels; Heart; Blood vessels

Calcium ion (Ca^{2+}) influx across plasma membranes is known to occur mainly via special channels known as Ca^{2+} channels. These are further divided into voltage- or depolarization-operated channels and receptor-operated channels (Schwartz, 1992; Tsunoda, 1993). Other channels such as non-selective cation channels (Isenberg, 1993) and stretch-activated channels (Sigurdson et al., 1992) are also involved in such Ca^{2+} movements. Various voltage-operated channels are now known to exist in different organs and neurons. These are known as L, T, N, P, and Q types (Gaur et al., 1994; Schmitt et al., 1995; El Tahir and Bakheet, 1997). The most widely distributed and studied channels are the L-type which exist in the heart and smooth and skeletal muscles (McCleskey, 1994).

Although Ca^{2+} play important roles in various body functions such as cardiac and smooth muscle activity, secretion of hormones, release of neurotransmitters and autacoids, platelet aggregation, and many others (El Tahir and Bakheet, 1997), yet excessive Ca^{2+} influx has been implicated in various forms of cellular disturbances and diseases such as hypertension, arrhythmias, irritable bowel syndrome, premature deliveries, migraine, and many others (Resnick, 1990; Bailey et al., 1991; Lubbe et al., 1992; Fisher and Grotta, 1993). For these reasons many attempts have been made during the last three decades to discover drugs that block Ca^{2+} influx across plasma membranes. These attempts were crowned by the discovery of various drugs belonging to diverse chemical groups that found important clinical uses in the treatment of the above mentioned diseases, e.g., some phenylalkylamine, benzothiazepine, dihydropyridine derivatives, etc. Most of these clinical drugs were found to block mainly Ca^{2+} influx via the L-type. However, a clear disadvantage of some of these drugs is their non-selectivity towards the L-channels in the various organs, albeit with different potencies (Triggle, 1992; Materson, 1995). This non-selectivity resulted in various side effects in the non-diseased organs. For this

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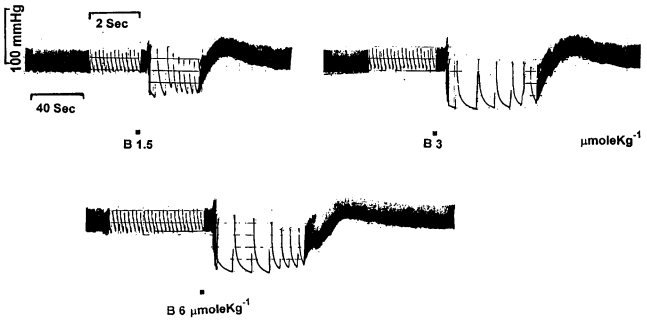

Fig. 1. Effect of compound B on the arterial blood pressure and heart rate of a urethane anesthetized rat. Intravenous administration of B (1.5, 3, and 6 $\mu m/kg^{-1}$) decreased the arterial blood pressure by 45, 72, and 82 mm Hg, respectively. The corresponding decreases in the heart rate were 42, 70, and 74%.

reason, many recent investigators directed their attention toward synthesizing new compounds with the hope that organ selective blockers may be discovered, with the ultimate goal of decreasing the wide spectrum of Ca^{2+}-channel blockade-induced side effects. Such hopes stimulated El Obeid et al. (1987) to synthesize and examine the pharmacological activity of a series of N-alkyl-1,2-diphenyl ethanolamines. Some of these compounds behaved as Ca^{2+} antagonists (El Obeid et al., 1987; El Tahir et al., 1989, 1990). Two of these compounds, namely the N-ethyl- and N-benzyl-1,2-diphenylethanolamines (hereafter known as compounds E and B, respectively) are selected for detailed mechanismatic studies with regard to their actions on the cardiovascular system in the rat.

1. Methods and materials

1.1. Preparation of rats for measurement of the arterial blood pressure and heart rate

Male Wistar rats (250 g) were anesthetized using 25% (w/v) aqueous urethane at a dose of (1.25 g/kg IP) The procedure used for preparation of the rats for measurement of the arterial blood pressure and heart rate was essentially that described by El Tahir et al. (1993a). The right external jugular vein and the left carotid artery were exposed and cannulated for administration of drugs and recording of the arterial blood pressure, respectively. Changes in the arterial blood pressure were quantified in mm Hg using the calibration system built in the Narco Physiograph coupler (Narco Biosystems, Houston, USA). Changes in the heart rate were calculated by increasing the speed of recording from 0.05 cm/sec to 1 cm/sec for 5–10 seconds and then counting the beats per unit time. All changes in the heart rate were calculated as percentage change compared with the predrug level. The compounds were administered at 20 min intervals.

1.2. Effect of receptor blockers, enzyme inhibitors and $CaCl_2$

To examine the influence of receptor blockers and enzyme inhibitors on E- and B-induced changes in the cardiovascular parameters, each was administered 5 min (in case of the receptor blockers) or 30 min (in case of enzyme inhibitors) prior to the administration of the submaximal dose of the test compound. The doses used have been shown to antagonize or inhibit the effects of their respective agonists (El Tahir et al., 1991, 1993a, 1993b) and reconfirmed.

To examine the influence of $CaCl_2$ on compound-induced cardiovascular changes during the test the following procedure was used: after determining the submaximal dose of the test compound, the selected dose of 10% aqueous $CaCl_2$ was administered (IV) in 3 increments at 1-min intervals. Three minutes later, the submaximal dose of the test compound was administered (IV). The percent effectiveness of $CaCl_2$ in antagonizing the test compound-induced changes was then calculated.

1.3. Preparation of rats for induction of arrhythmias

Male Wistar rats (250 g) were prepared for recording of ECG and induction of $CaCl_2$-induced arrhythmias by the same procedure described by El Tahir et al. (1989). A Narco coupler no. 7176 that fits into a Narco Physiograph (Narco Biosystems, Houston, USA) was used to record the ECG from Lead II at a speed of 2.5 cm/sec. To induce tachyarrhythmias $CaCl_2$ (60 mg/kg) was injected (IV) into the cannulated jugular vein as a bolus injection. Following the injection of $CaCl_2$ the following parameters were noted and quantified:

Table 1
Effect of compound E and B on the cardiovascular system of the rat

Dose (μmol/kg)	Decrease in arterial pressure (mm Hg)		Percentage decrease in heart rate	
	Compound E	Compound B	Compound E	Compound B
1.5	8.1 ± 1.7*	30.3 ± 9.8*	6.01 ± 2.3*	39.2 ± 7.3*
3	13.3 ± 3.1*	54.1 ± 10.8*	8.2 ± 2.4*	65.1 ± 3.4
6	19.5 ± 2.4*	61.9 ± 11.5*	7.7 ± 2.7*	69.3 ± 2.7*
12	31.7 ± 4.1*	—	11.4 ± 4.9*	—

* $p < 0.05$, n = 4–8.

The onset time, duration, and magnitude of the initially-induced bradycardia.

The onset time, incidence, and duration of the tachyarrhythmias, i.e., the *chaotic* cardiac contractions.

To examine the influence of the test compound on the induced arrhythmias pilot experiments were performed to find an effective dose for each compound. The selected dose was used to investigate the influence of the test compound on the above named parameters. The test compound was administered 3 min before the re-administration of the arrhythmogenic dose of $CaCl_2$.

1.4. Sources of the chemicals used

The E and B compounds were synthesized and characterized at the Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University (El Obeid et al., 1987). Urethane and $CaCl_2$ (BDH, Poole, UK); methylene blue and atropine sulphate (E. Merck, Darmstadt, Germany); Cyproheptadine hydrochloride (MS&D, West Point, PA, USA), propranolol hydrochloride (ICI, Leatherhead, Surrey, UK), mepyramine maleate (Drug Pharmaceutical Trading B.U., Holland); ranitidine hydrochloride (Glaxo, Greenford, UK) indomethacin (Dumex Ltd., Copenhagen, Denmark); mepacrine hydrochloride (Sigma Chemical Co., St. Louis, MO, USA); Hexamethonium bromide (Koch-Light Laboratories Ltd., Coinbrook Bucks, UK).

All chemicals were solubilized in distilled water. Solubilization of indomethacin was enhanced by addition of an equivalent weight of Na_2CO_3.

1.5. Statistical analysis

Significant differences between the different treatments were calculated using student's t-test (paired or nonpaired, as appropriate). All values were reported as mean ± SEM with n = number of animals used). Microsoft Excel software program was used to perform the statistical tests.

2. Results

2.1. Effect of compounds E and B on the arterial blood pressure and heart rate of the rat

Intravenous administration of compounds E and B (1.5–12 μmol/kg) into the urethane anesthetized rats induced dose-dependent decreases in the arterial blood pressure. However, clear dose-dependent decreases in the heart rate were observed only following compound B. Fig. 1 shows a typical experiment following administration of compound B. The cumulative findings from 4–7 such experiments are shown in Table 1. Both of the heart rate and the arterial blood pressure returned to the normal values within 5 min. Compound B seemed to be 3–4 times more potent than E in decreasing the arterial blood pressure and 8–10 times more potent in decreasing the heart rate (Table 1). Furthermore, although compound E seemed to be more potent in decreasing the arterial blood pressure than decreasing the heart rate, compound B seemed to be equipotent in decreasing both parameters.

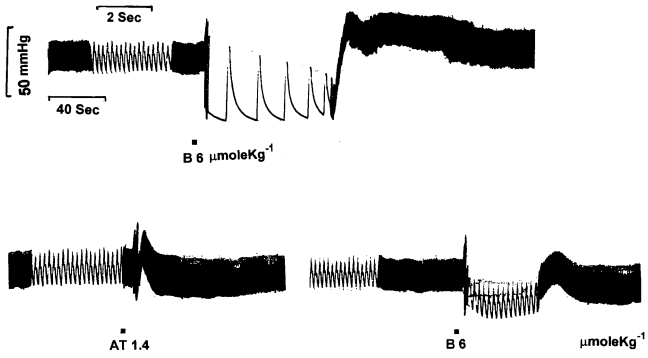

Fig. 2. Effect of atropine (AT) on compound B-induced cardiovascular depression in a urethane anesthetized rat. Intravenous administration of B (6 μmol/kg) decreased the arterial blood pressure and the heart rate by 35 mm Hg and 83% respectively. Treatment of the animal with atropine (1.4 μmol/kg) suppressed B-induced actions.

2.2. Effect of receptor blockers and enzyme inhibitors on E- and B-induced cardiovascular depressant effects

Treatment of the animals with mepyramine (2.5 μmol/kg), ranitidine (28.5 μmol/kg), indomethacin (52.6 μmol/kg), and mepacrine (8.5 μmol/kg) did not affect E- and B-induced cardiovascular depressant effects

Table 2
Effect of some receptor blockers on compound B- (6 μm/kg^{-1}) induced cardiovascular depressant effects (mean ± SEM, n = 4)

	% Effectiveness against	
Blocker dose (μmol/kg)	Decrease in blood pressure	Decrease in heart rate
Atropine (1.4)	46.5 ± 8.1*	82.7 ± 4.1**
Hexamethonium (6.9)	48.7 ± 9.9*	75.31 ± 2.3**
Cyproheptadine (3.1)	24.7 ± 12.4*	64.8 ± 7.6*

* $p < 0.05$; ** $p < 0.01$.

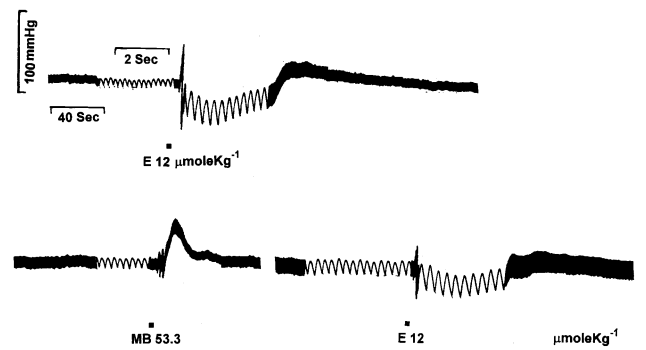

Fig. 3. Effect of methylene blue (MB) on compound E-induced cardiovascular effects in a urethane-anesthetized rat. Intravenous administration of E (12 μmol/kg) decreased the arterial blood pressure and the heart rate. Treatment of the animal with MB (53.3 μmol/kg) for 30 min suppressed E-induced cardiovascular depression.

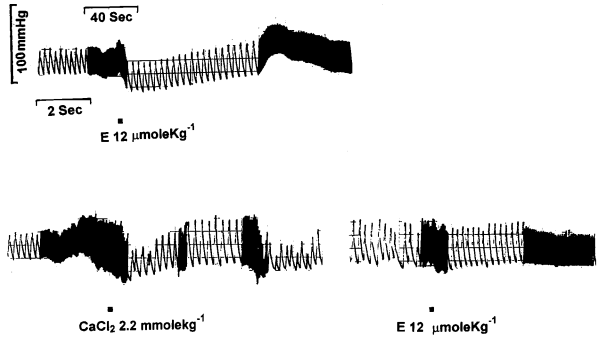

Fig. 4. Effect of $CaCl_2$ on compound E-induced cardiovascular changes in a rat. Treatment of the animal with $CaCl_2$ (2.2 mmol/kg) for 3 minutes prior to readministration of E (12 μmol/kg) suppressed E-induced cardiovascular effects.

to any significant level (n = 3). However, although treatment of the rats with atropine (1–4 μmol/kg), Hexamethonium (6.9 μmol/kg), and cyproheptadine (3.1 μmol/kg) did not affect E-induced cardiovascular depressant effects; these drugs induced significant antagonisms—albeit not to the 100% level—to B-induced cardiovascular depressant actions (Table 2). Fig. 2 shows the effect of atropine on B-induced cardiovascular depressant effects. On the other hand, although treatment of the rats with methylene blue (53.3 μmol/kg) did not affect B-induced effects, this treatment significantly antagonized E-induced decreases in the arterial blood pressure and heart rate by 57.04 ± 15.4%, and 50.37 ± 8.8%, respectively ($p < 0.05$, n = 4). Fig. 3 shows such antagonism.

2.3. Effects of $CaCl_2$ on E and B induced cardiovascular depressant actions

Treatment of rats with $CaCl_2$ (2.2 mmol/kg) for 3 min suppressed E- (12 μmol/kg) and B- (6 μmol/kg) induced cardiovascular effects. However, significant antagonisms were observed only in case of the E compound. Fig. 4 shows the effect of $CaCl_2$ on E-induced cardiovascular depressant effects. In eight such experiments $CaCl_2$ antagonized E-induced decreases in the arterial blood pressure and the heart rate by 75.59 ± 12.9% and 70.1 ± 6.8%, respectively ($p < 0.01$, n = 8). The corresponding values in case of compound B were 51.2 ± 17.9% and 27.5 ± 10.4% ($p > 0.05$).

2.4. Effect of E and B compounds on $CaCl_2$-induced arrhythmias in rats

Intravenous administration of $CaCl_2$ (60 mg/kg) into the urethane-anesthetized rat induced an initial bradycardia (36–60%) followed in a few seconds by chaotic tachyarrhythmias with varying incidences that continued for 5–20 sec with return to the normal ECG rhythm within 5 min (Fig. 5).

Treatment of rats with compounds E and B (12–14.5 μmol/kg) for 3 min prior to re-administration of $CaCl_2$ completely protected the animals against $CaCl_2$-induced tachyarrhythmias (n = 4) without any significant antagonism to the initially-induced bradycardia. Fig. 5 depicts one of the experiments showing the effect of compound B on $CaCl_2$-induced arrhythmias. The cumulative findings showing the effects of both E and B on the various arrhythmogenic parameters are shown in Table 3.

3. Discussion

The results of these experiments revealed clear differences in the cardiovascular depressant effects of compound E and B.

Generally, compound B seemed to be more potent as cardiodepressant. B seemed to be equipotent in depressing both the cardiac and the blood vessels whereas

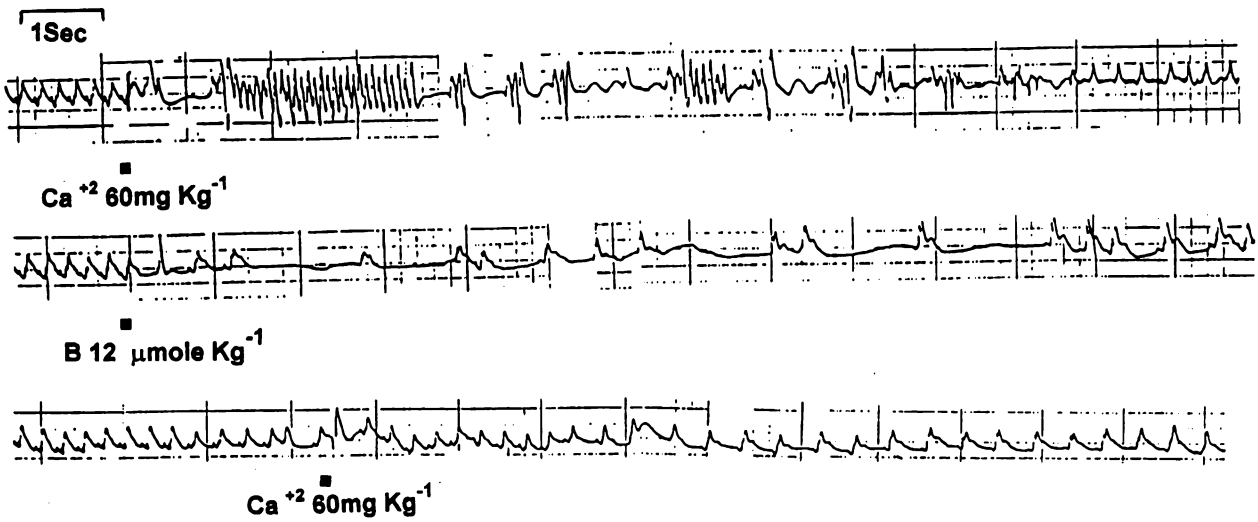

Fig. 5. Effect of compound B on $CaCl_2$-induced arrhythmias in a urethane-anesthetized rat. Intravenous administration of $CaCl_2$ (60 mg/kg) (Ca^{2+}) induced an initial bradycardia followed by waves of tachyarrhythmias. Treatment of the animal with compound B (12 μmol/kg) for 3 min prior to readministration of Ca^{2+} completely prevented the tachyarrhythmias. The speed of recording was 2.5 cm/sec.

Table 3
Effects of E and B compounds on $CaCl_2$-induced arrhythmias in the rat (mean ± SEM, n = 4)

Treatment	Percentage initial bradycardia	Onset tachyarrhythmias (sec)	Incidence of tachyarrhythmias (sec)	Duration of tachyarrhythmias (min)	% Protection against	
					Bradycardia	Tachyarrhythmias
$CaCl_2$	48.1 ± 8.3	5.8 ± 1.1	4.9 ± 0.05	10.6 ± 5.5	35.27 ± 14.2	100
E + $CaCl_2$	31.1 ± 10.7	0	0	0	17.3 ± 15.1	100
B + $CaCl_2$	39.8 ± 8.5	0	0	0		

E seemed to be more potent as vasodepressant than cardiodepressant. The failures of the histamine H_1 and H_2 blockers (mepyramine and ranitidine), the prostaglandin cyclo-oxygenase-inhibitor indomethacin and the phospholipase A_2-inhibitor mepacrine (Conricode and Ochs, 1989) to affect E- and B-induced cardiovascular depressant effects point to the lack of involvement of histaminergic, PAF, and eicosanoid mechanisms in the observed effects. Similarly, the failure of the muscarinic blocker atropine, the ganglionic blocker hexamethonium, and the nonselective 5-HT receptor blocker cyproheptadine to affect E-induced cardiovascular depressant effects rules out the involvement of muscarinic, nicotinic, and serotoninergic mechanisms in E-induced actions.

However, E-induced actions were significantly antagonized by $CaCl_2$ and the nitric oxide and cyclic GMP formation-inhibitor methylene blue (Ignarrow et al., 1986; Michel and Smith, 1993). Collectively these results suggest that E-induced cardiovascular depressant effects may be related to dual blockade of both cardiac and vascular L Ca^{2+} channels and release of nitric oxide or activation of guanylyl cyclase enzyme. Previous studies revealed the ability of Ca^{2+} to reverse the cardiovascular depressant effects of various Ca^{2+} channel blockers (Refsum and Landmark, 1977; Matsuo et al., 1989). Furthermore, elevation in cyclic GMP is shown to decrease the intracellular Ca^{2+} level in both the blood vessels and the heart (Sperelakis, 1994).

Unlike compound E, the actions of compound B seemed to involve a dual mechanism that blocked Ca^{2+} channels and activated parasympathetic ganglia with concomitant release of ACh at the SA node. The apparent effectiveness of cyproheptadine in antagonizing B-induced cardiovascular depressant effects and especially the cardiac depressant effect may be explained by the ability of this serotonin blocker to block the muscarninic receptors (Niemegeers et al., 1982). Further evidence for the involvement of Ca^{2+} channel blockade in the actions of both E and the B compounds comes from the significant effectiveness of both compounds to protect rats against $CaCl_2$-induced tachyarrhythmias. The compounds may have prevented the Ca^{2+}-dependent depolarizations and action potentials of the SA and AV nodes (Katz et al., 1984; Akhtar et al., 1989). Both B and E compounds failed to prevent the initial paradoxical Ca^{2+}-induced bradycardia. This is probably due to the various mechanisms involved in this bradycardia which are believed to involve high Ca^{2+}-induced release of NO (Lopez-Jaramillo et al., 1990; Kruse et al., 1994), uncoupling and suppression of conduction (Lubbe et al., 1992) and/or temporary inhibition of release of intracellular Ca^{2+} (Lino, 1990; Henzi and MacDermott, 1992).

The results of this study direct the attention to the potential antihypertensive and antiarrhythmic effects of both E and B compounds. However, the differences in the potencies of both compounds with regard to their actions on the blood vessels and cardiac muscles and their equipotency in preventing Ca^{2+}-induced tachyarrhythmias suggest that the E compound may be the most promising in its potential for treatment of supraventricular arrhythmias. This is based on its effectiveness against Ca^{2+}-induced tachyarrhythmias, its mild negative chronotropic effect, and its lower hypotensive activity compared with the B compound. On the other hand, the potent cardiovascular depressant effects of the B compound point to its promising potential as an antihypertensive agent.

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