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β_2-Adrenoceptor influences on the α_1- and α_2-mediated vasoconstriction induced by phenylpropanolamine and its two component enantiomers in the pithed rat

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Abstract—Phenylpropanolamine (PPA, (±)-norephedrine) is commonly found in appetite suppressants and nasal decongestants. Within the cardiovascular system of the pithed rat, the drug and its two component enantiomers ((−)- and (+)-norephedrine) are largely direct-acting agonists. The interaction between simultaneous α_1-, α_2- and β_2-adrenoceptor mediated effects of the drug and its two enantiomers have been examined using the cardiovascular system of the pithed rat. On all adrenoceptors tested the potency was (−)- >(±)-, >(+)-norphedrine. The α_1- and α_2-mediated pressor responses of each were enhanced in the presence of the β_2-adrenoceptor antagonist, ICI 118,551, and diminished in the presence of the selective β_2-adrenoceptor agonist salbutamol. It is concluded that each form of the drug possesses the intrinsic ability to interact with the α_1-, α_2- and β_2-adrenoceptors in the system used and that the interaction with those adrenoceptors determines the net increase in diastolic blood pressure that follows the intravenous administration of the compounds. These findings have a bearing on the recent controversy regarding the use of β-blocking agents in the treatment of overdosage of the drug.

Phenylpropanolamine ((±)-norephedrine HCl) is present in numerous cough, cold, antiallergy products and appetite suppressants (Hoebel & Hernandez 1978). It has been shown to act both directly and indirectly on adrenoceptors depending on the site and the dose administered (Trendelenburg et al 1962; Trendelenburg et al 1963). The drug binds to α_1-adrenoceptors, but with low affinity and low intrinsic activity (Minneman et al 1983). Those investigators concluded that it acts as a partial agonist at the α_1-adrenoceptor. Moya-Huff & Maher (1987) reported that the drug is largely a direct acting α_1- and α_2-agonist in the cardiovascular system of the pithed rat, and that its β_1- and β_2-mediated responses are significantly smaller when compared with the responses observed at the α-adrenoceptor subtypes. Moreover, Pentel et al (1985) were not able to show it had significant β_2-activity.

Hypertension due to large overdoses of products containing phenylpropanolamine may be accompanied by arrhythmias. Other concurrently consumed compounds, such as caffeine and ephedrine, may also contribute to the observed hypertension and arrhythmias (Saxena & Kingston 1981; Pentel et al 1985). Because the potential for arrhythmogenesis may result from excessive cardiac β_1-stimulation, subsequent treatment with a β-blocking drug such as propranolol has been suggested (Sawyer et al 1982; Pentel et al 1985). However, the safety of propranolol in that situation has been questioned because of the possibility that intensified α-mediated pressor responses could result (Weesner et al 1982), since non-selective β-blocking agents have been shown to exaggerate pressor responses induced by α-agonists such as noradrenaline (Reeves et al 1984). This phenomenon most likely results from the antagonism of β_2-mediated vasodilation, thus leaving α-mediated vasoconstriction unopposed.

In view of the widespread use of phenylpropanolamine we investigated whether the α_1- and α_2-adrenoceptor mediated increases in diastolic blood pressure effected by the drug and its enantiomers are altered by, or independent of β_2-mediated vasodilation, or β_2-adrenoceptor blockade.

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Methods

Normotensive male albino Sprague Dawley rats (N = 108), 200–300 g, (Charles River Breeding Laboratories, Wilmington, MA) were housed individually and acclimated for one week before use. On the day of the experiment, animals were anaesthetized with diethylether and the trachea, left carotid artery and right jugular vein cannulated with polyethylene tubing. The animals were then pithed by inserting a steel rod into the spinal canal through the orbit and down the foramen magnum. Immediately following pithing, the tracheal cannula was attached to a Harvard Apparatus dual phase control respirator pump (model 613) and the animal artificially ventilated at a frequency of 60 cycles min^{-1} with a volume of 2 mL/100 g weight. Systemic arterial blood pressure was then recorded from the left carotid artery with a Statham P23 pressure transducer and a Grass Model 7D polygraph. The venous cannula was used for intravenous (i.v.) administration of the test compounds and pharmacological agonists/antagonists in a volume of 0·5 mL kg^{-1} and 1 mL kg^{-1}, respectively. Rectal temperature was maintained at 37°C throughout the experiment.

The preparation was allowed to equilibrate for at least 30 min before drug administration. The increases in diastolic blood pressure mediated by α_1- or α_2-adrenoceptor subtypes were studied in the presence and absence of the selective β_2-adrenoceptor antagonist, ICI 118,551 or the selective β_2-adrenoceptor agonist, salbutamol. (−)-, (+)- or (±)-Norephedrine were administered i.v. in a cumulative-dose fashion 30 min after yohimbine (1 mg kg^{-1} i.v.) or prazosin (0·1 mg kg^{-1} i.v.) and 15 min after ICI 118,551 (5 mg kg^{-1} i.v.) or salbutamol (1 mg kg^{-1} i.v.; Wilffert et al 1983a,b).

All results were expressed as the net change in diastolic blood pressure (mmHg) ± s.e.m. (N = 6 per group). Cumulative dose-response curves were drawn by linear regression and tested, for deviations from linearity by analysis of variance in regression (Wallenstein et al 1980; Difazio 1984).

Drugs. Drugs were prepared daily in 0·9% NaCl, with the exception of prazosin which was prepared in distilled water. Yohimbine and diethylether were purchased from Sigma Chemical Co. (St. Louis, MO); prazosin HCl was a gift from Pfizer Inc. (New York, NY); ICI 118,551 (erythro-DL-1-(7-methylinden-4-yloxy)-3-isopropylaminobutan-2-ol) was a gift from Imperial Chemical Industries (Cheshire, UK); (+)-norephedrine HCl was from Aldrich Chemical Co. and (±)-norephedrine HCl (PPA) and (−)-norephedrine HCl were from Roehr Chemicals, Inc. (Long Island City, NY). The identity of the norephedrine compounds was confirmed by determining melting points and optical rotation.

Results

All responses are presented as changes in diastolic blood pressure, however the systolic and mean blood pressure changes were of similar magnitude and identical in significance with the diastolic blood pressure. The average starting diastolic blood pressure following pithing was 43 ± 2 mmHg. Pretreatment with yohimbine and either salbutamol or ICI 118,551 yielded new

baselines of 30 ± 2 and 59 ± 7 mmHg, respectively. Pretreatment with prazosin and either salbutamol or ICI 118,551 yielded new baselines of 27 ± 2 and 64 ± 3 mmHg, respectively.

The α_1-adrenoceptor-mediated vasoconstriction produced by all three compounds was studied in pithed rats subjected to β_2-adrenoceptor blockade or vasodilation with ICI 118,551 or salbutamol, respectively (Fig. 1). When administered cumulatively to rats pretreated with yohimbine all forms of the drug induced a significant increase in diastolic blood pressure ($P < 0.05$) in a cumulative dose-related fashion (from 6 ± 3 to 43 ± 5 (−)-, 8 ± 3 to 23 ± 6 (+)- and 6 ± 2 to 48 ± 4 mmHg (±)-norephedrine, respectively). Moreover, in the presence of ICI 118,551, the respective cumulative dose-response curves were displaced to the left of the control cumulative α_1-mediated dose-response curves. Additionally, the respective dose-response curves in the presence of salbutamol were displaced to the right of the control cumulative α_1-mediated dose-response curves. These results indicate that the α_1-mediated cumulative dose-response curves to each compound tested were enhanced and diminished by β_2-adrenoceptor blockade and activation, respectively.

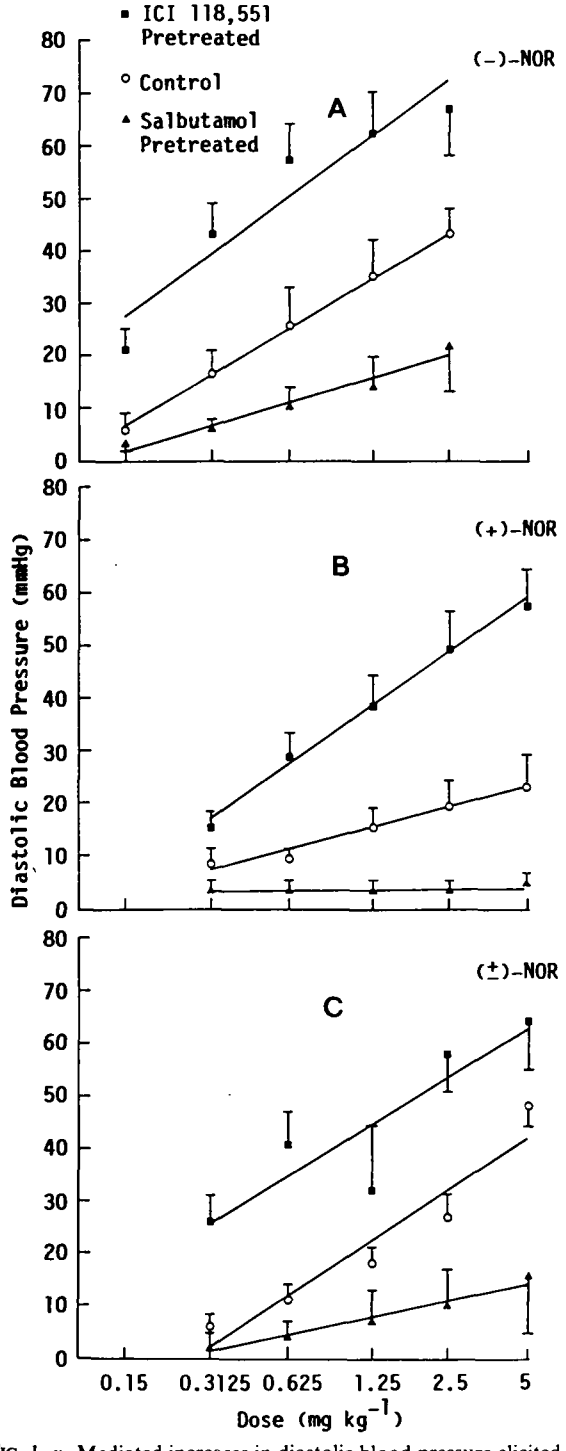

FIG. 1. α_1-Mediated increases in diastolic blood pressure elicited by (−)-norephedrine ((−); A), (+)-norephedrine ((+); B) and (±)-norephedrine ((±); C) administered i.v. to pithed rats. Pressor responses were obtained after i.v. pretreatment with yohimbine (1 mg kg^{-1}) alone or with either ICI 118,551 (5 mg kg^{-1}) or salbutamol (1 mg kg^{-1}). Data are presented as net increases in diastolic blood pressure ± s.e.m. (n = 6 per group).

The α_2-adrenoceptor-mediated vasoconstriction produced by all forms of the drug was studied in pithed rats subjected to β_2-adrenoceptor blockade or vasolidation with ICI 118,551 or salbutamol, respectively (Fig. 2). When (−)- and (±)-norephedrine were administered cumulatively to rats pretreated with prazosin the diastolic blood pressures increased significantly ($P < 0.05$) in a cumulative dose-related fashion (from 5 ± 2 to 22 ± 5 and 3 ± 1 to 19 ± 4, mmHg, respectively). However, (+)-norephedrine's α_2-mediated increases in diastolic blood pressure were not significant (from 3 ± 1 to 7 ± 1 mmHg). Pretreatment

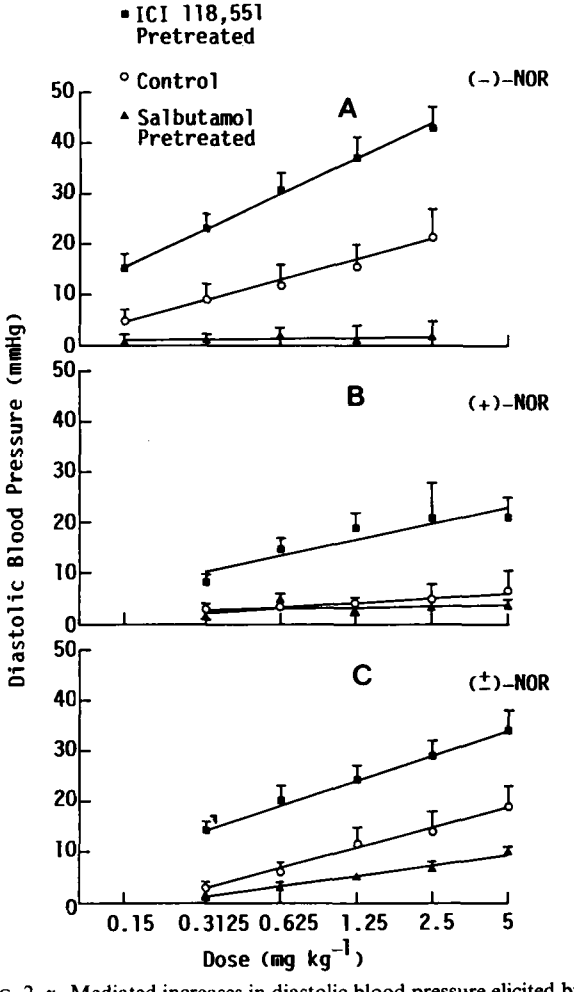

FIG. 2. α_2-Mediated increases in diastolic blood pressure elicited by (−)-norephedrine ((−); A), (+)-norephedrine ((+); B) and (±)-norephedrine ((±); C) administered i.v. to pithed rats. Pressor responses were obtained after i.v. pretreatment with prazosin (0·1 mg kg^{-1}) alone or with either ICI 118,551 (5 mg kg^{-1}) or salbutamol (1 mg kg^{-1}). Data are presented as net increases in diastolic blood pressure ± s.e.m. (n = 6 per group).

with prazosin and ICI 118,551 displaced each of the α_2-mediated cumulative dose-response curves to the left, while in the presence of prazosin and salbutamol the respective α_2-mediated cumulative dose-response curves for (−)- and (±)-norephedrine were displaced to the right. The α_2-mediated increases in diastolic blood pressure produced by (+)-norephedrine were significant ($P<0.05$) in the presence of ICI 118,551 (from 8 ± 2 to 21 ± 4 mmHg). These results indicate that (−)- and (+)-norephedrine induced increases in diastolic blood pressure mediated via α_2-receptors were enhanced and diminished by β_2-adrenoceptor blockade and activation, respectively. Additionally, in the presence of β_2-adrenoceptor blockade, the pressor activity of (+)-norephedrine was unmasked.

Discussion

The α_1- and α_2-mediated increases in diastolic blood pressure produced by the three forms of norephedrine were potentiated in the presence of the β_2-antagonist ICI 118,551 while partially attenuated in the presence of the β_2-agonist, salbutamol. In excessive doses, (±)-norephedrine has been reported to cause hypertension and arrhythmias (Frewing et al 1978; Horowitz et al 1979; King et al 1979). However, in most of these reports (±)-norephedrine has been described as 'Trimolets' a commercial product which, labelled as 'D-Phenylpropanolamine' (for norephedrine this corresponds to the optically active (−)-form), most likely contained only the vasopressor (−)-enantiomer (Frewing et al 1978; Horowitz et al 1979; King et al 1979). In addition, other authors have confused (±)-norephedrine with (+)-norpseudoephedrine (Zelger & Carlini, 1981).

(+)-Norpseudoephedrine, (±)- and (−)-norephedrine are pharmacologically distinct within the cardiovascular system of the anaesthetized and pithed rat with (−)-norephedrine being twice as potent as a pressor agent than the racemate (Moya-Huff et al 1987). (+)-Norpseudoephedrine is largely an indirect acting agonist in this preparation (Moya-Huff & Maher 1987; Moya-Huff et al 1987). Therefore, attention needs to be paid to the isomer causing reported effects.

Propranolol has been suggested as a possible treatment for patients overdosed with phenylpropanolamine. However, caution should be exercised when that non-selective β-blocking agent is administered to antagonize or decrease such an overdose-induced hypertension in man as suggested by Pentel et al (1985). As β_2-adrenoceptor blockade by ICI 118,551 increases the pressor responses induced by the racemate in the cardiovascular system of the pithed rat by blocking β_2-adrenoceptor-mediated vasodilation, propranolol could potentially produce a similar effect by leaving α_1- and α_2-mediated vasoconstriction unopposed.

We conclude that (−)-, (+)- and (±)-norephedrine possess the intrinsic ability of interacting with α_1-, α_2- and β_2-adrenoceptor subtypes. The net alterations in blood pressure following the administration or ingestion of those drugs will be determined largely by the interaction with the adrenoceptor subtypes, especially the α_1- and β_2-adrenoceptors. The selection of a specific α_1-adrenoceptor antagonist might constitute a more rational therapy in hypertension induced by overdosage with phenylpropanolamine since β_2-adrenoceptor blockade leads to an increase in vasoconstrictor responses following that drug's administration. A calcium channel antagonist could also be useful by interfering with both vasoconstriction and arrhythmogenesis at a location beyond the agonist recognition site.

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