β-Receptor agonist activity of phenylephrine in the human forearm

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PHENYLEPHRINE IS GENERALLY regarded as a “pure” α1-agonist (17). However, after treatment of the forearm with the α-adrenergic-blocking drug phentolamine, brachial artery infusion of phenylephrine can cause transient forearm vasodilation (K. D. Torp, M. E. Tschakovsky, and M. J. Joyner, unpublished observations). This dilation is not seen when saline is infused at the same or higher rate (1–4 ml/min). In this context, there appear to be no published reports indicating that phenylephrine may possess β-adrenergic activity, but there have been some isolated observations in animal tissues (N. A. Flavahan, personal communication). In view of these observations, and because phenylephrine is commonly used to study the pharmacology and physiology of α1-mediated vasoconstrictor effects in humans, any β-adrenergic-dilating effects might confound the interpretation of studies conducted with phenylephrine (17). With this information as a background, we sought to determine systematically whether phenylephrine possesses β-mediated vasodilator properties in the human forearm.

MATERIALS AND METHODS

Subjects. Twelve healthy, normotensive, nonsmoking subjects (6 women, 6 men) between the ages of 20 and 40 yr (mean 29 ± 6 yr) participated in the study. Participants were not taking any medications. The study was approved by the institutional review board, and each subject gave written informed consent. All female subjects had a negative serum pregnancy test within 12 h before participation. Six of the subjects were part of a pilot study using α-blockade with phentolamine when we initially noted marked vasodilation when phenylephrine was given after phentolamine. Subsequently, six additional subjects (3 men and 3 women) were studied as a part of the formal protocol reported in this paper, which sought to “pharmacodissect” this unexpected response.

Subject monitoring. During the study, heart rate was monitored by using a five-lead electrocardiogram. Arterial pressure measurements and drug infusions were performed by using a 5-cm 20-gauge brachial artery catheter placed in the left arm using sterile technique after 1–2 ml of 1% lidocaine. A three-port connector was placed in series with a catheter-transducer system so that drugs could be infused and arterial pressure measured simultaneously (3).

Forearm blood flow. Forearm blood flow was measured using venous occlusion plethysmography with mercury-in-silastic strain gauges in both forearms (3, 7). During recordings, a wrist cuff was continuously inflated to suprasystolic pressure (250 mmHg) to occlude arterial blood flow to the hand while a venous occlusion cuff around the upper arm was inflated to 50 mmHg for 7.5 of every 15 s, providing one blood flow measurement every 15 s. Forearm blood flow values were expressed as milliliters per deciliter of forearm volume per minute. Each participant served as their own control, which allowed comparisons of blood flows during baseline conditions and drug infusions for each drug. To ensure that there were no systemic effects of the infused drugs, the forearm blood flow of the nontreated arm was also measured.

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Drug doses and protocol. Throughout the blood flow measurements, the rate of infusion of saline or drugs into the brachial artery was 1–2 ml/min at all times. After baseline blood flows were obtained, phenylephrine (0.5 μg/dl forearm volume) was infused over 1 min into the brachial artery (trial 1). After the blood flow measurements had returned to baseline, a phentolamine dose of 100 μg/min was infused into the brachial artery for 5 min (500 μg total) followed by a 50 μg/min infusion until the end of the study. This dose of phentolamine was selected on the basis of previous studies indicating that a lower dose blocks the forearm vasoconstrictor responses to intra-arterial tyramine, which causes local release of endogenous norepinephrine (6). We confirmed this observation during pilot studies. A second phenylephrine trial was then conducted. After forearm blood flow returned to baseline, propranolol (100 μg/dl forearm volume) was infused into the brachial artery over 5 min, followed by the third phenylephrine trial. This dose of propranolol was selected on the basis of previous studies demonstrating that it blocked the forearm vasodilator response to intra-arterial β-agonists (4, 10, 11).

Data analysis. Data were digitized at 200 Hz and stored on computer. Data were analyzed off-line with signal-processing software (WinDaq, Datq Instruments, Akron, OH). Heart rate was derived from the electrocardiogram waveform. Mean arterial pressure was derived from the arterial pressure waveform. To assess the impact of changes in forearm blood flow and arterial pressure on vascular tone, forearm vascular conductance (FVC) was calculated as 100 times blood flow (ml·dl−1·min−1) divided by mean arterial pressure (mmHg) and expressed as arbitrary units (units).

Statistics. One-way repeated-measures ANOVA was used to determine the effects of phenylephrine infusion within each of control, α-receptor blockade, and α + β-receptor blockade, and to compare baselines between control, α-receptor blockade, and α + β-receptor blockade. Significance was set at the P < 0.05 level. Significant differences were further analyzed with Student-Newman-Keuls post hoc testing. All values are reported as means ± SE.

RESULTS

Heart rate, mean arterial pressure, and forearm blood flow in the control arm were not different over time within experimental conditions or between experimental conditions (Figs. 1 and 2). During the first phenylephrine infusion, forearm blood flow decreased from 3.1 ± 0.7 to 0.8 ± 0.2 ml·dl−1·min−1 (P < 0.05 vs. baseline; Fig. 2) and FVC decreased (P < 0.05) from 3.5 ± 0.7 to 0.9 ± 0.2 units. Infusion of the α-blocker phentolamine increased forearm blood flow to 5.0 ± 1.2 ml·dl−1·min−1 (P < 0.05 vs. baseline; Fig. 2), and FVC increased (P < 0.05) to 5.7 ± 1.3 units. During α-blockade, infusion of phenylephrine caused forearm blood flow to rise considerably (P < 0.05) from 5.0 ± 1.2 to 11.2 ± 1.5 ml·dl−1·min−1 (Fig. 2) and FVC increased (P < 0.05) from 5.7 ± 1.3 to 13.1 ± 1.8 units. However, this dilation was transient, rarely lasting more than ~1 min and the duration of the dilation was shorter than the constriction seen during trial 1. β-Blockade with propranolol, given before the third trial with phentolamine, had no effect on baseline BFB or FVC (Fig. 2). When phenylephrine was given after both α and β-blockade (trial 3), there was a small, sustained decrease in forearm blood flow from 4.5 ± 1.0 to 3.2 ± 0.7 ml·dl−1·min−1 (P < 0.05) (Fig. 2) and FVC decreased (P < 0.05) from 5.1 ± 1.0 to 3.6 ± 0.8 units.

DISCUSSION

The major new finding of this study is that the α1-agonist phenylephrine can evoke forearm vasodilation in humans after administration of the nonselective α-blocker phentolamine. Because this vasodilation is blocked completely by local administration of the nonselective β-blocker propranolol, our observations suggest that phenylephrine can stimulate β-receptors and evoke transient vasodilation in the human forearm. It should also be noted that we performed an extensive review of the literature dating to some of the classic studies from the 1950s and 1960s on related topics and were able to find no information concerning potential β-agonist properties of phenylephrine in the human forearm (6, 9, 10, 15, 17). With this information as a background, the potential implications of this study in the design of pharmacological studies in human health and disease will be discussed.

Distribution of adrenoceptors in human muscle. Human skeletal muscle possesses vasoconstricting postsynaptic α1- and α2-receptors and presynaptic α2-receptors that can inhibit norepinephrine release from sympathetic nerves (17). There are also vasodilating β2-receptors (2, 4, 11, 15). These receptors are thought to be both located at the vascular neuromuscular junction and distributed throughout the blood vessels. In the case of α-receptors, animal studies suggest that “fast-twitch” muscles are especially rich in vasoconstricting postsynaptic α2 receptors, but no data on this topic are available in human muscle (5, 16). In this context, a variety of selective agonists and antagonists have been used to explore adrenergic control of the human forearm. Approaches include infusion of “selective” agonists, infusion of selective antagonists during concurrent administration of norepinephrine, and infusion of selective antagonists during sympathoexcitatory maneuvers or tyramine administration (which causes the sympathetic nerves to release their norepinephrine). These various approaches and some of the specific drugs used to study these issues are described in detail in a variety of references (4, 6, 9, 10, 17).

Evidence that the vasodilation was β-receptor mediated. The observation that the vasodilation seen during phenylephrine administration after phentolamine was blocked almost completely by propranolol provides strong evidence that this vasodilator response was mediated by β-receptors. In this context, it is well known that brachial artery infusions of β-agonists can evoke marked forearm vasodilation that can be eliminated by administration of propranolol (2, 4, 11). The dose of propranolol we administered can also eliminate vasodilator responses to intra-arterial administration of norepinephrine or tyramine (which causes norepinephrine release) after α-blockade (6). In this context, the interpretation of our findings appears to be straightforward and consistent with β2-mediated vaso-
dilation stimulated by intra-arterial phenylephrine. Since skeletal muscle (including human) is rich in vasodilating \( \beta_2 \)-receptors, it seems reasonable to suggest that much of the response that we saw occurred in the forearm skeletal muscle (2, 15).

One interesting observation depicted in Fig. 2 is that the timing of the vasoconstriction seen with phenylephrine alone in the first trial was delayed compared with the dilation seen in the second trial when phenylephrine was given after phentolamine. It is also interesting that the constrictor responses to phenylephrine alone lasted longer. Although it is unclear how to interpret these observations, perhaps the delayed vasoconstriction after phenylephrine alone represents an initial competition between this drug’s transient \( \beta_2 \)-mediated vasodilating properties and its more sustained \( \alpha \)-mediated vasoconstricting properties.

**Pharmacological and physiological relevance of the present findings.** In humans, a variety of diseases and conditions such as aging and heart failure are associated with chronic changes in sympathetic tone directed toward the limbs (1, 12, 13). In this context, phenylephrine can be an important drug used to pharmacodissect the contribution of altered \( \alpha_1 \)-receptor tone and responsiveness in these conditions. However, the findings of the present study raise the possibility that any changes in the responses to phenylephrine would have to be viewed in the context of possible competing changes in \( \beta \)-mediated vasodilator influences. If augmented vasoconstrictor responses to phenylephrine were observed in a particular disease state or condition, it would be uncertain whether these differences were due solely to changes in \( \alpha \)-mediated constrictor responses or were due to concurrent changes in \( \beta \)-mediated dilator responses. For example, if aging blunted...
the vasodilator responses to β₂ stimulation in the forearm, it would be impossible to know whether enhanced vasoconstrictor responses to phenylephrine were due to a gain in α₁ constrictor “function” or due to a loss of β₂ mediated dilator function. Similarly, if there were blunted vasoconstrictor responses to phenylephrine, could augmented β₂-dilator responses have contributed? Therefore, concurrent use of β-adrenergic-receptor blockade when phenylephrine is used to evaluate α₁-mediated vasoconstriction in human limbs appears warranted. By contrast, systemic doses of phenylephrine (1–200 μg iv) are used both clinically and experimentally to raise blood pressure, and we are unaware of any reports of transient whole body vasodilation with the use of this drug. These systemic doses are ~25–50% of the dose we gave in the forearm when normalized for tissue volume (8, 14).

Limitations. There are several potential limitations of the study. First, it is possible that the vasodilation seen during infusion of phenylephrine after phentolamine was due to some sort of nonspecific effect of the infusion per se on the forearm vasculature that was seen only after α-blockade. Although this is theoretically possible, it would seem unlikely in the present study because the rate of infusion of saline or drugs was similar (1–2 ml/min) whenever blood flow was being measured. Also, given that the dilation could be abolished by propranolol, it was probably not due to the infusion alone. Second, it is theoretically possible that the absent dilator responses to phenylephrine might have been due to a reduction in the completeness of the α-receptor blockade by the time of the third trial. However, we gave a substantial loading dose of phentolamine followed by a maintenance dose. In this context, it should be noted that the dose of phentolamine we gave has previously been shown to block the local vasoconstrictor responses to intra-arterial tyramine, a drug that evokes presynaptic release of norepinephrine.
from sympathetic nerve terminals (6, 10). Therefore, we are confident that our level of β-blockade was both complete and stable over time.

In summary, we have demonstrated that after β-blockade with phentolamine phenylephrine possesses transient vasodilating β-agonist properties. These findings may have important implications for the design and interpretation of experiments on α-mediated vascular control in humans and perhaps in other species.

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