Selective α2-adrenergic properties of dexmedetomidine over clonidine in the human forearm

Shizue Masuki, Frank A. Dinenno, Michael J. Joyner, and John H. Eisenach. Selective α2-adrenergic properties of dexmedetomidine over clonidine in the human forearm. J Appl Physiol 99: 587–592, 2005. First published March 31, 2005; doi:10.1152/japplphysiol.00147.2005.—We tested the hypothesis that dexmedetomidine (Dex) has greater α2- vs. α1 selectivity than clonidine and causes more α2-selective vasoconstriction in the human forearm. After local β-adrenergic blockade with propranolol, forearm blood flow (plethysmography) responses to brachial artery administration of Dex, clonidine, and phenylephrine (α1-agonist) were determined in healthy young adults before and after α2-blockade with yohimbine (n = 10) or α1-blockade with prazosin (n = 9). Yohimbine had no effect on phenylephrine-mediated vasoconstriction but blunted Dex-mediated vasoconstriction (mean ± SE: −41 ± 5 vs. −11 ± 2%; before vs. after yohimbine) more than clonidine-mediated vasoconstriction (−39 ± 5 vs. −28 ± 4%; before vs. after yohimbine) (P < 0.02). Prazosin blunted phenylephrine-mediated vasoconstriction (−39 ± 4 vs. −8 ± 2%; before vs. after prazosin) but had similar effects on both Dex− (−30 ± 4 vs. −39 ± 6%; before vs. after prazosin) and clonidine-mediated vasoconstriction (−29 ± 3 vs. −41 ± 7%; before vs. after prazosin) (P > 0.7).

Both Dex and clonidine reduced deep forearm venous norepinephrine concentrations to a similar extent (−59 ± 12 vs. −55 ± 10 pg/ml; Dex vs. clonidine, P > 0.6); this effect was abolished by yohimbine and blunted by prazosin. These results suggest that Dex causes more α2-selective vasoconstriction in the forearm than clonidine. The similar vasoconstrictor responses to both drugs after prazosin might be explained by the presynaptic effects on norepinephrine release.

forearm blood flow; sympathetic nervous system; vasoconstriction; resistance vessels

ONLY RECENTLY HAS THE CONTRIBUTION and importance of α2-adrenergic receptors (ARs) to resting vasomotor tone been described (6). Traditionally, the location of α2-ARs was generally considered to be limited to presynaptic nerve endings, inhibiting terminal release of norepinephrine, whereas α1-ARs were present on vascular smooth muscle cells, responsible for α1-AR-mediated vasoconstriction (23, 25). However, the additional presence of vasoconstricting postjunctional α2-ARs is now recognized and has become a major area of interest in the development and treatment of hypertension (17, 22) and in the role of the sympathetic nerves in regulating blood flow to leg (32) and forearm muscles during exercise (7, 24).

Activation of postsynaptic α2-ARs on vascular smooth muscle cells causes vasoconstriction, and, compared with α1-ARs, α2-ARs contribute to roughly 60% of basal sympathetic tone in the human forearm (6). Previously, to study α2-AR responsiveness, clonidine has been frequently used. However, it has been reported that clonidine-induced vasoconstriction is blunted (2, 12, 29) or abolished by α1-AR blockade (10, 11, 26), suggesting that clonidine is a partial α1-AR agonist as well as an α2-AR agonist. Therefore, vascular responses to clonidine might represent the sum of its effects on both α1- and α2-ARs. From a practical standpoint, more problems with clonidine exist in its pharmacokinetic properties, primarily a long duration of effect (6–10 h), a long elimination half-time (t1/2 = 6–23 h), and a prolonged dose-dependent duration of side effects, contributing to prolonged sedation. Thus clonidine has several limitations as a tool for studying α2-adrenergic vasoconstrictor responses and a more selective α2-AR agonist would clearly be useful.

Dexmedetomidine (Dex) is a recently developed α2-AR agonist with high selectivity for the α2- vs. α1-AR, and in binding studies it is eight times more specific to α2-ARs than clonidine. This information stems from an experiment on rat brain membranes that reported that the α22/α11-AR selectivity ratio of Dex is 1,620:1, compared with 220:1 for clonidine (30). Furthermore, a rat aortic ring study showed that Dex has no agonistic activity toward α1-ARs in the concentration needed to stimulate α2-ARs (27). From a pharmacokinetic perspective, Dex has t1/2 of ~2 h, a duration of action of ~4 h, and a side effect profile that is shorter in duration than clonidine. To date in humans, there are no studies that have compared the α22-AR-selective vasoconstrictor properties of Dex with clonidine in resistance vessels of the human peripheral circulation. Utilizing brachial artery administration of these agents, the purpose of this study was to test the hypothesis that Dex has greater α2- vs. α1-selectivity than clonidine and causes more α2-selective vasoconstriction in the human forearm.

METHODS

Subjects. Ten healthy young adults (5 women, 5 men; age, 24 ± 1 yr; weight, 66 ± 3 kg; height, 173 ± 2 cm; body mass index, 22 ± 1 kg/m2; means ± SE) participated in protocol 1, and 9 young adults (5 women, 4 men; age, 25 ± 2 yr; weight, 67 ± 5 kg; height, 172 ± 3 cm; body mass index, 22 ± 1 kg/m2) participated in protocol 2. All subjects were nonsmokers, nonobese, normotensive, free of cardiovascular disease, and not taking medications other than oral contraceptives. Four of five female subjects in protocol 1 and two of five female subjects in protocol 2 were taking oral contraceptives. All female subjects had a negative serum pregnancy test the day of the study. All female subjects were studied in the early follicular phase of the menstrual cycle or in the low-hormone phase of oral contraceptives to minimize variability in autonomic control of cardiovascular...
function due to reproductive hormone status (8, 20). All subjects were fasting the morning of study. The studies were approved by the Institutional Review Board of the Mayo Clinic, and each subject gave written consent before participation.

**Arterial and venous catheterization and blood samples.** Under aseptic conditions, a 5-cm 20-gauge catheter was inserted into the brachial artery of the nondominant arm under local anesthesia (2% lidocaine; Abbott Laboratories, North Chicago, IL). The arterial catheter was connected to a pressure transducer for determination of arterial pressure and continuously flushed at 3 ml/h with heparinized saline (2 U/ml) (4). A 3-cm 18-gauge catheter was also inserted into an antecubital vein and directed toward the hand so that the tip was located in a deep vein that drained the forearm muscles (15). Forearm deep venous blood samples were obtained at selective time points for determination of plasma norepinephrine concentrations in blood draining the forearm (Fig. 1). These blood samples were centrifuged and stored at −70°C for later determination of plasma norepinephrine concentrations via high-performance liquid chromatography (HPLC) with electrochemical detection (5, 20). This assay involves extraction of plasma with alumina followed by HPLC. HPLC has been shown to be highly sensitive in detecting norepinephrine (detection limit = 1 pg) (21).

**Body mass index and forearm volume.** Body mass index was calculated as body weight (kg) divided by height (m) squared. Forearm volume was determined by water displacement for normalization of drug administration.

**Forearm blood flow.** Forearm blood flow (FBF) was measured using venous occlusion plethysmography with mercury-in-Silastic strain gauges (9). Briefly, a pediatric blood pressure cuff was placed around the wrist and inflated to suprasystolic levels (220 mmHg) to arrest the circulation of the hand, and a venous occlusion cuff was placed on the upper arm and rapidly inflated to 50 mmHg every 7.5 s, yielding one blood flow every 15 s. FBF was expressed as milliliters per 100 ml tissue per minute.

**Experimental protocol.** All measurements were performed with the subject supine, and all study drugs were administered via the brachial artery catheter at rates of <3 ml/min. The experimental protocols are shown in Fig. 1. After catheterization the subjects rested for 30 min. Propranolol (CURA Pharmaceutical, Oakhurst, NJ) was then given at 10 μg·100 ml forearm volume⁻¹·min⁻¹ for 5 min to control for any β-stimulating effects of phenylephrine (28). This dose has been documented to block forearm vasodilatation to isoproterenol (14). A “maintenance” dose of propranolol (5 μg/min) was then infused throughout the protocol. Phenylephrine (American Regent Laboratories, Shirley, NY) was administered at 0.031, 0.063, and 0.125 μg·100 ml forearm volume⁻¹·min⁻¹ for 2 min to stimulate α-ARs.

To compare α₂-AR selectivity for clonidine vs. Dex, clonidine (Roxane Laboratories, Columbus, OH) was administered at 0.15, 0.30, and 0.60 μg·100 ml forearm volume⁻¹·min⁻¹ for 2 min, and Dex (Abbott Laboratories) was administered at 6.25, 12.5, and 25.0 ng·100 ml forearm volume⁻¹·min⁻¹ for 2 min. Because this is the first study to use Dex in the human forearm, we chose these doses based on the systemic loading dose of Dex (1 μg /kg administered over 10 min) and extrapolated this dose for use in the isolated forearm. α-Agonist infusion trials were separated by 30 min of quiet rest, and at the middle of the rest sodium nitroprusside (Abbott Laboratories) was administered at 1.0 μg·100 ml forearm volume⁻¹·min⁻¹ for 2 min to wash out α-agonist effects and to regain baseline FBF level. The order of clonidine and Dex administration was randomized across all subjects. In protocol 1, yohimbine (Sigma, St. Louis, MO) was then given at 3.3 μg·100 ml forearm volume⁻¹·min⁻¹ to block β-ARs. The infusion of yohimbine was started 3 min before the administration of α-agonist. The administrations of α-agonists (phenylephrine, clonidine, and Dex) were then repeated in the presence of a constant infusion of yohimbine (13) with same order as before yohimbine infusion.

All procedures in protocol 2 were identical to protocol 1 except the process of prazosin infusion. In protocol 2, to block α₁-ARs, prazosin (Sigma) was administered at 1.0 μg·100 ml forearm volume⁻¹·min⁻¹ for 10 min before phenylephrine trial (6), and a low maintenance dose of prazosin (1.0 μg/min) was then infused throughout the remaining protocol. Additional prazosin was also administered at 1.0 μg·100 ml forearm volume⁻¹·min⁻¹ for 5 min before clonidine and Dex trials. Because prazosin has longer plasma half-life (~3 h) than yohimbine (~30 min), administration of prazosin was completed just before α-agonist infusion was started.

Because the ability of Dex to bind presynaptic α₂-ARs and inhibit norepinephrine release is unknown, we determined venous plasma norepinephrine concentrations at baseline and at the end of clonidine and Dex administration. Given that we were unable to obtain deep venous blood samples from all subjects, the present venous norepi-

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**Fig. 1.** Experimental protocols. PE, phenylephrine; Dex, dexmedetomidine; NE, norepinephrine. The order of clonidine and Dex was randomized before administration of α-adrenergic blockade, and the order was repeated after α-adrenergic blockade. α-Agonist infusion trials were separated by 30 min of quiet rest (see text for further details). Venous plasma NE concentrations were determined before PE administration (baseline) and at the end of 0.60 μg·100 ml forearm volume⁻¹·min⁻¹ of clonidine and 25.0 ng·100 ml forearm volume⁻¹·min⁻¹ of Dex administration.

**A**

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**Dexmedetomidine vs. Clonidine in the Forearm**

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venous norepinephrine responses to clonidine and Dex represent the values in six subjects for protocol 1 and six subjects for protocol 2.

Analyses. Data were digitized and stored on a computer at 200 Hz and analyzed offline with signal-processing software (Windaq, Dataq Instruments, Akron, OH). FBF was determined from the slope of the plethysmographic recording during venous occlusion (31). Heart rate (HR) was determined from the ECG signal (3-lead ECG), and mean arterial pressure (MAP) was derived from the arterial pressure waveform. For phenylephrine, Dex, and clonidine, the data reported represent an average of the last minute of each dose of drug infusion (5), since steady-state vasoconstriction was observed during this minute. Because MAP did not change during local infusions of the α-agonists, forearm vasoconstrictor responses were expressed as changes in FBF.

Statistics. Analyses were performed by repeated-measures ANOVA models. Dependent variables included FBF, HR, MAP, and venous norepinephrine responses measured across resting conditions and during the administration of study drugs. The overall repeated-measures ANOVA model included two main effects (pre- vs. post- and during the administration of study drugs: phenylephrine, Dex, and clonidine), followed by pairwise analyses to supplement the repeated-measures ANOVA models. These models were also run for each of the time points for the three vasoconstrictors (phenylephrine, Dex, or clonidine), one nested effect (dose within drug), and interactions. To investigate the specific effect of the α-blockers yohimbine and prazosin, repeated-measures ANOVA models were also run for each of the time points for the three drugs phenylephrine, Dex, and clonidine, followed by pairwise analysis to supplement the repeated-measures ANOVA models. These three models consisted of two main effects (pre- vs. post-α-blockade and dose) and an interaction. Values are expressed as means ± SE. All P values < 0.05 were considered statistically significant.

RESULTS

There were no differences in HR, MAP, age, height, body weight, and body mass index between the subjects in protocols 1 and 2 (P > 0.3 for all). Before drug administration, baseline MAP and HR were 90 ± 3 mmHg and 53 ± 2 beats/min in protocol 1 and 87 ± 2 mmHg and 55 ± 3 beats/min in protocol 2 and were not affected by forearm administration of all study drugs throughout the study (P > 0.3 in the yohimbine trial; P > 0.2 in the prazosin trial). No subjects reported side effects related to the infusion of α2-AR agonists, including sedation.

Protocol 1: α2-selectivity of clonidine vs. Dex assessed by α2-AR blockade with yohimbine. Figure 2 shows the forearm vasoconstrictor response to phenylephrine (A), clonidine (B), and Dex (C) before and after administration of α2-AR blockade with yohimbine. Before yohimbine, all three vasoconstrictors produced a significant dose-dependent decrease in FBF (P < 0.01, main effect of drug). Importantly, the degree of vasoconstriction (decrease in FBF from baseline) was similar between all three vasoconstrictors (P > 0.1). As expected, by blocking α2-AR tone, yohimbine administration produced a vasodilator effect, as baseline FBF increased significantly (P < 0.05, main effect of yohimbine). Importantly, the degree of vasodilation at baseline was similar before subsequent administration of all three vasoconstrictors (P = 0.13, yohimbine effect across all drug infusions).

Despite the baseline shift caused by yohimbine, it did not affect the absolute decrease in FBF to phenylephrine (P = 0.13). Thus α2-AR blockade had no effect on phenylephrine-mediated vasoconstriction. Similarly, yohimbine did not affect the absolute decrease in FBF to clonidine (P = 0.08). In contrast, after yohimbine, Dex-mediated vasoconstriction (absolute decrease in FBF to Dex) was nearly abolished (P < 0.001). Additionally, when the forearm vasoconstrictor responses to highest dose were expressed as a percent change from baseline, yohimbine blunted Dex-mediated vasoconstriction (−41 ± 5 vs. −11 ± 2%; before vs. after yohimbine) more than clonidine-mediated vasoconstriction (−39 ± 5 vs. −28 ± 4%; before vs. after yohimbine). There was no evidence to suggest that the effect of yohimbine on α-agonist mediated-vasoconstriction was influenced by gender.

To examine the α2-AR dependent component of vasoconstriction and compensate for the effect of the baseline shift caused by yohimbine, we also compared the pre- vs. post-yohimbine responses by subtracting the pre-yohimbine from the post-yohimbine response, or “delta” FBF response at each dose of vasoconstrictor, as shown in Fig. 3. Using Tukey-Kramer analysis for pairwise comparisons of the delta FBF and drugs, the delta FBF was greater for Dex vs. phenylephrine (P = 0.012) and greater for Dex vs. clonidine (P = 0.013) before and after yohimbine.

Protocol 2: α2-selectivity of clonidine vs. Dex assessed by α1-AR blockade with prazosin. Figure 4 shows forearm vasoconstrictor response to phenylephrine (A), clonidine (B), and Dex (C) before and after administration of α1-AR blockade with prazosin. Before prazosin, all three vasoconstrictors pro-
duced a significant dose-dependent decrease in FBF ($P < 0.05$, main effect of drug). Importantly, the degree of vasoconstriction (decrease in FBF from baseline) was similar between all three vasoconstrictors ($P = 0.3$). As expected, by blocking $\alpha_1$-AR tone, prazosin administration produced a vasodilator effect, as baseline FBF increased significantly ($P < 0.001$, main effect of prazosin). The degree of vasodilation caused by prazosin at baseline was similar before subsequent administration of Dex and clonidine, but the degree of vasodilation caused by prazosin was less (baseline FBF was lower) before phenylephrine ($P = 0.03$, prazosin effect on baseline vs. Dex or clonidine).

Confirming $\alpha_1$-AR blockade, prazosin nearly abolished the absolute decrease in FBF to phenylephrine ($P < 0.01$). For example, when forearm vasoconstrictor responses to the highest dose were expressed as a percent change from baseline, prazosin markedly blunted the response to phenylephrine ($-39 \pm 4\% \text{ vs. } -8 \pm 2\%$; before vs. after prazosin). There were no differences in the effect of prazosin on the vasoconstrictor responses between clonidine and Dex ($P = 0.08$ and $P = 0.11$, respectively). For example, when the forearm vasoconstrictor responses to highest dose were expressed as a percent change from baseline, prazosin had comparable effects on both Dex ($-30 \pm 4\% \text{ vs. } -39 \pm 6\%$; before vs. after prazosin) and clonidine-mediated vasoconstriction ($-29 \pm 3\% \text{ vs. } -41 \pm 7\%$; before vs. after prazosin). There was no evidence to suggest that the effect of prazosin on $\alpha$-agonist-mediated vasoconstriction was influenced by gender.

To examine the $\alpha_1$-AR-dependent component of vasoconstriction and compensate for the effect of the baseline shift caused by prazosin, we also compared the pre- vs. postprazosin responses by subtracting the preprazosin from the postprazosin response, or delta FBF response at each dose of vasoconstrictor, as shown in Fig. 5. Using Tukey-Kramer analysis for pairwise comparisons of the delta FBF and drugs, the delta FBF was greater for phenylephrine vs. Dex ($P = 0.001$) and greater for phenylephrine vs. clonidine ($P = 0.01$) before and after yohimbine. The delta FBF for Dex vs. clonidine was not significant ($P = 0.78$).

Effects of clonidine and Dex on venous norepinephrine. Deep venous norepinephrine concentrations at baseline were $141 \pm 24 \text{ pg/ml in protocol 1}$ and $138 \pm 25 \text{ pg/ml in protocol 2}$ with no difference between protocols 1 and 2 ($P > 0.8$).

In protocol 1, both Dex and clonidine reduced deep forearm venous norepinephrine concentrations from baseline to a similar extent ($-55 \pm 21 \text{ vs. } -46 \pm 17 \text{ pg/ml; Dex vs. clonidine, } P > 0.4$). For both Dex and clonidine, this effect was abolished by yohimbine, and the change in norepinephrine concentrations from baseline were $-2 \pm 26$ and $-1 \pm 27\text{ pg/ml}$ for Dex and clonidine after yohimbine, respectively.

In protocol 2, both Dex and clonidine reduced deep forearm venous norepinephrine concentrations from baseline to a similar extent ($-61 \pm 15 \text{ vs. } -63 \pm 10 \text{ pg/ml; Dex vs. clonidine,}$ $P < 0.001$).
P > 0.7). For both Dex and clonidine, this effect was blunted by prazosin, and the change in norepinephrine concentrations from baseline was −29 ± 22 and −30 ± 18 pg/ml for Dex and clonidine after prazosin, respectively. There were no differences in the change in norepinephrine concentration between protocol 1 with yohimbine and protocol 2 with prazosin (P > 0.6).

**DISCUSSION**

To our knowledge, this is the first report of intra-arterial administration of the selective α2-AR agonist Dex in the human forearm, including doses that were pharmacologically equipotent to clonidine and phenylephrine. The major findings are that α2-AR blockade with yohimbine blunted Dex-medi- ated vasoconstriction more than clonidine-medi- ated vasoconstriction without any effect on phenylephrine-mediated vasoconstriction. Thus it appears that Dex has greater α2- vs. α1-selectivity than clonidine in the forearm. However, α1-AR blockade with prazosin was unable to differentiate the vaso- constrictor responses, because both clonidine and Dex retained their ability to cause α2-AR-mediated vasoconstriction at the doses administered. The implications of these findings and the limitations associated with our experimental design will now be discussed in detail.

A growing number of studies are examining the role of α2-ARs in intermediate physiological characteristics relevant to blood pressure regulation, the pathogenesis and patho- nomics of hypertension, and ultimately the pharmacotherapy of hypertension. The seven-transmembrane, G protein-coupled α2-AR has three subtypes, α2A, α2B, and α2C (3). Despite structural similarity and general conservation among mamma- lian species, the α2-AR subtypes are differentially distributed in cells and tissues, with different pharmacological and phys- iological profiles (19). For this reason, we first felt it was important to develop and characterize FBF dose responses to Dex that were similar in efficacy to commonly utilized α-AR agonists. We chose this agent because we were seeking a readily available α2-AR agonist to replace clonidine and be- cause clonidine also has partial affinity for α1-ARs (2, 10–13, 26, 29). Several investigators have used clonidine to study human α2-AR responses, but the relatively low α2/α1-selectivity ratio of clonidine makes it difficult to isolate measurements of the α2-AR response. Furthermore, compared with Dex, clonidine has a longer systemic duration of action and a longer elimination half-life, potentiating the duration of central nervous system side effects and thereby limiting its practicality in human cardiovascular studies. Importantly, neither α2-AR agonist evoked a change in systemic cardiovascular variables or caused noticeable side effect in our subjects.

We employed two experimental approaches to demonstrate the greater α2/α1-AR selectivity of Dex vs. clonidine. In protocol 1, we reasoned that the predominance of α2-AR activity with Dex would be delineated from the relative defi- ciency of α2-AR activity and from relative presence of α1-AR activity, with clonidine. After α2-AR blockade with yohim- bine, Dex-mediated vasoconstriction was nearly abolished compared with clonidine-mediated vasoconstriction (Figs. 2, B and C, and 3). In addition, yohimbine had no effect on phenylephrine-mediated vasoconstriction (Fig. 2A), indicating that we gave a dose of yohimbine that only blocked α2-ARs and minimized Dex-mediated vasoconstriction. For clonidine, our findings are in support of a FBF study by Jie et al. (13), who reported that clonidine-mediated vasoconstriction was not blocked by yohimbine. Also, it is consistent with a forearm study by van Brummelen et al. (29), who showed that clonidine was only partly blocked by either yohimbine or the α1-AR antagonist doxazosin. For Dex, our data are consistent with in vitro receptor binding experiments that have calculated the α2/α1-selectivity ratio to be eightfold higher for Dex than for clonidine (30). Furthermore, a rat aortic ring study reported that Dex had no α1-AR agonist properties in this tissue, although high concentrations of Dex (100-fold higher than that needed for α2-receptor stimulation) antagonized α1-agonist induced contraction (27). Lastly, another ring study using human gastroepiploic arteries showed Dex enhanced the K+ induced contraction, and this effect was reversed by yohimbine but unaffected by prazosin (11). Consistent with these models, our findings also demonstrate that Dex has greater α2- vs. α1-selectivity than clonidine in human limb vessels.

In protocol 2, we reasoned that the α1-AR antagonist prazosin would partially block the vasoconstrictor response to the partial α1-agonist clonidine and have no effect on the vaso- constrictor response to the predominant α2 effect of Dex. After prazosin, clonidine-medi-ated vasoconstrictor responses were preserved as well as Dex-medi-ated responses (Fig. 4, B and C). On the other hand, prazosin minimized the reduction in FBF in response to phenylephrine (Fig. 4A, Fig. 5), documenting that prazosin blocked α1-ARs. Thus we did not detect a difference in α2/α1-AR selectivity between Dex and clonidine in this approach, as we did in protocol 1.

There are two potential explanations for this discrepancy. First, in spite of the lower α2-AR affinity of clonidine com- pared with Dex (19), during complete α1-AR blockade clonidine was still able to maintain α2-AR constrictor capability similar to Dex in the narrow dose ranges chosen for this study. This finding is consistent with another forearm study by Kiowski et al. (16) that showed α2-AR-mediated vasoconstric- tion by clonidine was abolished by nonselective α-blockade with phentolamine but present after prazosin. Second, the discrepancy may be partially caused by the difference in the blocked receptor sites. With yohimbine, the pre- and postsyn- aptic α2-AR effects would be eliminated, and only the α1-AR-dependent component to cause vasoconstriction would be seen. By contrast, with prazosin α1-ARs would be blocked, but the vasoconstrictor responses to α2-AR stimulation represent the net effect of contraction of smooth muscle cells (6) and presynaptic inhibition of norepinephrine release (18). Moreover, data from an animal study suggests that stimulation of endothelial α2-AR evoke a nitric oxide-mediated vasodilation (1), which also may affect the vasoconstrictor response to α2-AR stimulation in the present study. Thus the different effects of α2-AR activation might make it difficult to see the α2-AR selectivity of Dex in the approach using α1-AR blockade.

In the present study, Dex and clonidine reduced deep venous norepinephrine concentrations, and this effect was abolished by yohimbine, suggesting that presynaptic effect of α2-adrenergic receptors to inhibit norepinephrine release was effec- tively blocked by α2-adrenergic blockade with yohimbine. On the other hand, after administration of prazosin the reduction in deep venous norepinephrine concentrations by Dex and
clonidine was also blunted. The precise mechanism for this phenomenon is not clear. One explanation is that the dose of prazosin required to abolish phenylephrine-mediated vasoconstriction also influenced or blocked presynaptic α2-ARs. This is supported by the notion that prazosin has partial affinity for α2-receptors (19). Moreover, in contrast to the other three drugs in this study (Dex, clonidine, yohimbine), prazosin does possess differences in affinity among the α2-AR subtype, such that the affinity of prazosin is low for α2A- but high for α2B- and α2C-subtypes (19). The precise pre- and postsynaptic distribution and mechanistic relevance of these subtypes in human peripheral arterial beds remain to be elucidated.

In summary, our data suggest that Dex has greater α2- vs. α1-selectivity than clonidine in the human forearm. When the constrictor effect of the drugs was isolated by yohimbine it was possible to see a clear difference in α2-selectivity between Dex and clonidine. Thus we present Dex as an advantageous tool for examining α2-adrenergic vascular response in human resistance vessels.

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