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Independent Regulation of Alpha$_1$ and Alpha$_2$ Adrenergic Receptor–Mediated Vasoconstriction *in vivo*

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Abstract

Background—Vascular α_1- and α_2-adrenergic receptors (ARs) mediate vasoconstriction and are major determinants of peripheral vascular tone. There is wide variability in vasoconstrictor sensitivity to α_1- and α_2AR-agonists among individuals. In previous studies this variability was not explained by identified α_1- and α_2-AR genetic variants. Thus, we hypothesized that adrenergic vasoconstrictor sensitivity is determined by shared constrictor mechanisms downstream of the individual receptors and that α_1- and α_2-AR-mediated vasoconstrictor sensitivity would therefore be correlated.

Methods—Dorsal hand vein responses to increasing doses of the α_1-AR agonist phenylephrine (12 ng/min –12,000 ng/min) and the α_2-AR agonist dexmedetomidine (0.01 ng/min – 100 ng/min) were measured in healthy subjects using a linear variable differential transformer. From individual dose-response curves we calculated the dose of phenylephrine and dexmedetomidine that produced 50% (ED_{50}) of maximum venoconstriction (E_{max}) for each subject. We examined the correlation between phenylephrine and dexmedetomidine ED_{50} and E_{max} before and after adjustment for covariates (age, gender, ethnicity, BMI, blood pressure, heart rate, and baseline plasma norepinephrine concentrations).

Results—In 62 subjects (36 males, 34 African American, 28 Caucasians) the median ED_{50} for dexmedetomidine was 1.32 ng/min (IQR, 0.45–5.37 ng/min), and for phenylephrine 177.8 ng/min (IQR, 40.7– 436.5 ng/min). The E_{max} for phenylephrine was 90.8% (82.2–99.6%) and for dexmedetomidine 80.0% (64.7–95.2%). There was no correlation between individual sensitivities (ED_{50}) to phenylephrine and dexmedetomidine, before and after adjustment for covariates ($p>0.30$).

Conclusions—Phenylephrine and dexmedetomidine both produce strong venoconstriction in the dorsal hand vein; however, there is no significant correlation between vascular sensitivity to an α_1-

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AR and α_2-AR agonist. These findings suggest independent regulation of vascular α_1- and α_2-AR-mediated responses.

Keywords

α_1 adrenoceptors; α_2 adrenoceptors; vasoconstriction

INTRODUCTION

Post-synaptic α_1- and α_2-adrenergic receptors (AR) are widely distributed in the peripheral vasculature [1,2] and both mediate vasoconstriction [1,2]. In humans, direct infusion of the α_2-AR agonist, clonidine, into the brachial artery causes vasoconstriction [3,4], and in the forearm vasculature of young healthy men post-synaptic α_2-ARs contribute more than α_1-ARs to basal vascular tone [5]. In the hand vein, we and others have shown that both α_1-AR and α_2-AR agonists cause pronounced vasoconstriction, with sensitivity among individuals varying several fold [6–8].

However, the factors contributing to this interindividual variability in vascular sensitivity are poorly understood. Pharmacogenetic studies have not identified α_1- and α_2-AR variants that affect response to agonists substantially. For example, variants in the gene (*ADRA2B*) encoding the α_{2B}-AR, an important mediator of vasoconstriction [9], contribute only a small amount to variability in dorsal hand vein responses to the α_2-AR agonist, dexmedetomidine [10–12]. Similarly, genetic variants of the α_1-AR studied thus far do not explain the large interindividual variability in vascular response to the α_1-AR agonist phenylephrine [8].

Since genetic variants of the respective receptors studied to date do not explain variability in α-AR-mediated vascular response, this variability may be determined by factors that are not directly dependent on the receptor, and are shared by α_1- and α_2-ARs such as factors that determine the drug concentration at the site of action, or factors that determine the response of pathways downstream of the receptor. If such factors contribute to variability in α_1- and α_2-ARs responses, then one would expect the sensitivities to vasoconstriction mediated by α_1- and α_2-ARs to be correlated. However, the possibility that α_1-AR and α_2-AR vascular sensitivity are co-regulated, has not been studied.

Therefore, to examine the hypothesis that α_1- and α_2-AR-mediated vasoconstrictor sensitivity are correlated we measured responses to the α_1-AR agonist, phenylephrine, and to the highly selective α_2-AR agonist, dexmedetomidine, in healthy subjects *in vivo* using the dorsal hand vein model.

METHODS

Subjects

The Institutional Review Board of Vanderbilt University Medical Center approved the study protocol, and subjects gave written informed consent. Male and female Caucasians and African-Americans were eligible for the study if they were 18 to 45 years of age and had no clinically significant abnormalities according to medical history, physical examination, and laboratory testing.

Sixty-two subjects were studied. Ethnicity, family history of hypertension, and exercise history were determined by self-report, and body mass index (BMI) was calculated. Subjects took no medications for at least 2 weeks, and abstained from alcohol and caffeine for at least 5 days before the study. Each subject received a diet containing 150 mmol/day of sodium, 70 mmol/day of potassium, and 600 mmol/day of calcium for the 5 days prior to each study

day. Studies were performed in the morning after an overnight fast, in the same temperature-controlled room.

Measurement of Vascular Responses

Hand vein responses to the α_2-AR agonist dexmedetomidine HCl (Abbott Laboratories, Chicago, IL, USA) [6] and the α_1-AR agonist phenylephrine HCL (Elkins-Sinn, Cherry Hill, N.J., USA) [8] were measured on separate days. Venous responses were measured in a dorsal hand vein by use of a linear variable differential transformer (LVDT), (Schaevitz, model 100 MHR) as previously described [13,14]. This instrument, when mounted on the hand, measures and records changes in the diameter of the vein.

Subjects rested on a comfortable bed and remained supine throughout the study. The subject's arm was placed on a support sloping upward. A 23-gauge needle was inserted into a suitable dorsal hand vein, and an infusion of normal saline was administered for at least 30 minutes. Following three stable baseline measurements of hand vein diameter, drugs were infused into the vein over which the LVDT was mounted.

Phenylephrine (12 ng/min to 12,000 ng/min) or dexmedetomidine (0.01 ng/min to 100 ng/min) were administered in increasing doses with each dose infused for 7 minutes using a Harvard syringe pump and response recorded during the last 2 minutes of each infusion. The total flow rate into the vein was maintained constant by changing the rate of infusion of saline and drug. Heart rate was monitored continuously with a bedside cardiac monitor, and blood pressure was measured in the arm on the side opposite the side receiving the hand vein infusion using a semiautomated device (Dinamap MPS, Johnson and Johnson Medical, Tampa, Fla. USA). A blood sample for measurement of plasma norepinephrine concentration was obtained on the first study day at baseline before drug infusion.

Analysis of hand-vein response to dexmedetomidine and phenylephrine

Venoconstriction was expressed as the percentage reduction in vein diameter from maximal dilation, which was defined as the average of three stable baseline measurements of hand vein diameter. Measurements for the phenylephrine and dexmedetomidine hand vein responses were plotted as individual semi-logarithmic dose-response curves and analyzed using a sigmoid dose-response model (Prism 5.01 software). The dose that produced 50% (ED_{50}) of maximum venoconstriction (E_{max}) was determined for each subject, and these values were converted to molar concentrations to compare sensitivity (ED_{50}) to dexmedetomidine and phenylephrine for each subject.

Statistical analyses

Continuous parameters were expressed as median and interquartile range (IQR). ED_{50} values are presented in original units (ng/min), and in log transformed molar units [log femtomole/min (log fmol/min)] for the comparison of ED_{50} values for dexmedetomidine and phenylephrine.

ED_{50} values for dexmedetomidine and phenylephrine in the same individuals were compared using Wilcoxon signed rank test, as were the E_{max} values. The Kruskal-Wallis test was used to compare dexmedetomidine ED_{50} among quartiles of phenylephrine ED_{50} values.

Correlations between the ED_{50} for dexmedetomidine and phenylephrine, the E_{max} for dexmedetomidine and phenylephrine, and between plasma norepinephrine concentrations and the ED_{50} for dexmedetomidine and phenylephrine were calculated using Spearman's test.

To evaluate the effects of covariates on the relationship between dexmedetomidine and phenylephrine ED_{50} values, we performed multiple linear regression analyses using log transformed dexmedetomidine ED_{50} as outcome and log transformed phenylephrine ED_{50} as the independent variable, adjusting for the covariates age, gender, ethnicity, BMI, mean arterial pressure, heart rate, and plasma norepinephrine concentrations. Similarly, we used multiple linear regression analysis to evaluate the effect of these covariates on phenylephrine log transformed ED_{50}.

All tests were two-sided, and p-values < 0.05 were considered significant. Statistical analyses were performed with the statistical software SPSS v. 17 (SPSS Inc, Chicago, Il, USA).

RESULTS

Subjects

We studied 62 subjects [36 men (56.3%), 34 African Americans (53.1%), and 28 Caucasians (43.8%)] with a median age (IQR) of 25.0 years (22.0– 32.0), and BMI 25.3 kg/m^2 (22.7–28.3). Demographic and baseline characteristics are shown in Table 1.

Hand-vein responses dexmedetomidine and phenylephrine

The median ED_{50} for dexmedetomidine was 1.32 ng/min (0.45–5.37 ng/min) [3.75 log fmol/min (3.27–4.36 log fmol/min)], and the ED_{50} for phenylephrine was 177.8 ng/min (40.7–436.5 ng/min) [5.94 log fmol/min (5.31–6.34 log fmol/min)]. The ED_{50} in molar units was significantly smaller for dexmedetomidine than that for phenylephrine ($p<0.001$; Figure 1), suggesting greater vascular sensitivity to dexmedetomidine in the dorsal hand vein. The E_{max} for phenylephrine [90.8% (82.2–99.6%)] was significantly greater than that for dexmedetomidine [80.0% (64.7–95.2%)], ($p<0.001$; Table 2; Figure 2).

There was no correlation between individual sensitivities (ED_{50}) to phenylephrine and dexmedetomidine in all subjects [r= 0.12 (p=0.34)], or when African Americans [r= 0.06 (p=0.74)] and Caucasians [r= 0.21 (p=0.29)] were analyzed separately (Table 3; Figure 3). Dexmedetomidine ED_{50} did not differ significantly among subjects grouped by quartiles of phenylephrine ED_{50} (p=0.22) (Table 4).

Similarly, there was no correlation between individual E_{max} values for phenylephrine and dexmedetomidine in all subjects [r= 0.15 (p=0.23)], or when African Americans [r= 0.18 (p=0.32)] and Caucasians [r= 0.17 (p=0.39)] were analyzed separately (Table 3).

Determinants of hand-vein responses to dexmedetomidine and phenylephrine

In univariate analysis, plasma norepinephrine concentrations and phenylephrine ED_{50} were significantly correlated [r=0.28 (p=0.037)], suggesting that higher plasma norepinephrine concentrations are associated with reduced phenylephrine sensitivity. In contrast, there was no significant correlation between plasma norepinephrine concentrations and dexmedetomidine ED_{50} [r=−0.01 (p=0.96)].

In multiple linear regression analyses, phenylephrine ED_{50} was not associated with dexmedetomidine ED_{50} (β=0.25, p= 0.31), and neither was any of the other covariates (all p-values > 0.15). With phenylephrine ED_{50} as the dependent variable, the association between phenylephrine ED_{50} and plasma norepinephrine was weakened after adjustment for covariants, and of borderline statistical significance (p=0.063).

DISCUSSION

The major new finding of this study is the lack of correlation between the vascular sensitivities (ED_{50}) for dexmedetomidine and phenylephrine *in vivo* in humans. Therefore, our findings suggest that using the hand vein model with α_1- and α_2-AR-specific agonists provides independent information about α_2-AR and α_1-AR-mediated vasoconstrictor responses.

Interactions between the signaling pathways of α_1-, α_2- and β2-ARs were suggested by previous *in vitro* studies [15,16]. Simultaneous activation of α_{2B}-ARs and β_2-ARs decreased the threshold concentration of epinephrine required for α_{2B}-AR down-regulation, and this was associated with up-regulation of GRK3 expression [15]. Co-activation of α_{1a}-ARs and β_2-ARs resulted in a facilitatory interaction which led to increases in calcium influx from the extracellular compartment [16]. Thus, we tested the hypothesis that variability in downstream constrictor pathways or other factors that are shared by α_1- and α_2-ARs contribute to the interindividual differences in α_1- and α_2-AR-mediated vasoconstrictor responses in the human hand vein. Our findings suggest that the large variability among individuals in both α_1- and α_2-AR-mediated hand vein vasoconstrictor responses is not explained by interindividual differences in factors that are shared by both receptors.

We found that in the dose-range of agonists used in this study (selected previously to elicit maximal response in the hand vein without systemic hemodynamic effects [6,8]), the human dorsal hand vein is more sensitive to dexmedetomidine than to phenylephrine, since a lower molar concentration was required to produce half the maximal constriction. Also, although both agonists resulted in pronounced venoconstriction (E_{max} >80%), phenylephrine resulted in a larger median maximal venoconstrictor effect than dexmedetomidine.

We found a negative correlation between resting plasma norepinephrine concentrations and vascular sensitivity to phenylephrine. This finding is consistent with down-regulation of vascular α_1-ARs by norepinephrine. The modulating effect of endogenous non-selective adrenergic agonists such as norepinephrine, which activates both α_1-ARs and α_2-ARs *in vivo*, on hand vein responses has not been defined. We have previously shown that hand vein response to α_1-AR -mediated venoconstriction is stable over time (and is thus used to produce background vasoconstriction in studies of hand vein vasodilation) [17]. These two observations - the previously reported lack of desensitization with short-term exposure to an exogenous agonist such as phenylephrine, and our current finding of a negative correlation between resting plasma norepinephrine concentrations and vascular α_1-AR sensitivity - would be most consistent with near maximal α_1-AR desensitization at baseline conditions *in vivo*.

However, plasma norepinephrine concentrations are affected by several factors, including BMI, gender and ethnicity [18], and after adjustment for these and other covariates, the association between resting plasma norepinephrine concentrations and vascular sensitivity to phenylephrine was weakned and of borderline significance. Thus, it is unclear if there is a direct relationship between phenylephrine sensitivity and norepinephrine concentrations, or if it is due to factors that affect norepinephrine concentrations. To determine the specific relationship between endogenous sympathetic tone and α_1-AR-mediated local vascular response would require a study designed specifically for that purpose.

There are several methodological considerations regarding the measurement of vascular α_1-AR and α_2-AR responses to agonist *in vivo*. Systemic administration of either α_1-AR or α_2-AR agonists increases and decreases blood pressure, respectively, and thus results in the activation of homeostatic cardiovascular reflexes that would confound the measures of local vascular response. In particular, activation of central α_2-ARs results in a decrease in

sympathetic tone, a factor that would mask the direct vasoconstriction mediated by peripheral α_2-ARs [4,19]. Thus, although vascular α_2-ARs are functional, it has been difficult to establish their importance in the vasculature relative to α_1-ARs.

Accordingly, in order to define α_1-AR and α_2-AR vascular sensitivity it is necessary to minimize the effects on blood pressure and sympathetic activity that occur after systemic administration of agonist. Thus, we used the dorsal hand vein model [13,14], that allows the direct infusion into the vessel studied of low doses of drugs that act on α_1- and α_2-ARs locally minimizing systemic effects [6,13] and thus avoiding reflex cardiovascular responses that occur after systemic administration.

We defined α_1-and α_2-AR sensitivity using highly selective agonists, but cannot rule out the possibility of some non-selective α-AR activation. However, this is unlikely. First, phenylephrine and dexmedetomidine are both highly selective for their respective α-ARs, as compared to other α-ARs agonists for *in vivo* use [20,21]. Second, non-selective α-AR activation by either agonist would be expected to increase the correlation between responses to dexmedetomidine and phenylephrine, whereas our study showed lack of correlation between responses.

The clinical implications of the current study are speculative. Since our findings suggest independent regulation of α_1- and α_2-AR- mediated vasoconstriction, dual blockade of both receptors peripherally could theoretically be used clinically to achieve an antihypertensive or vasodilating effect. However, while α_1-AR antagonists are extensively used in the treatment of hypertension, α_2-AR antagonists such as yohimbine cause an increase in blood pressure, [22] presumably because of the blockade of central pre-synaptic α_2-ARs, resulting in increased sympathetic outflow. Currently, no selective, peripherally acting post-synaptic α_2-AR antagonist is available for use in humans, precluding the use of α_2-AR antagonists as potential antihypertensive agent [23].

In summary, we found that phenylephrine and dexmedetomidine both produce powerful venoconstriction in the dorsal hand vein *in vivo*, but that there was no correlation between α_1- and α_2-AR vascular sensitivity. The large variability among individuals in α_1- and α_2-AR vascular sensitivity is not explained by differences in shared pre- or post-receptor factors.

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Abbreviations and symbols

E_{max}	Maximal venoconstriction, expressed as the percentage reduction in vein diameter from maximal dilation
ED_{50}	The dose of agonist that produced 50% of maximum venoconstriction (E_{max}) for each subject
AR	adrenergic receptors
LVDT	linear variable differential transformer
IQR	interquartile range

fmol/min	femtomole/minute
BMI	body mass index

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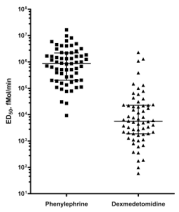

Figure 1. Hand vein sensitivity to dexmedetomidine and phenylephrine

The horizontal line represents the median, the error bars represent the IQR

Data are presented in log fmole/min.

P<0.001 comparing the sensitivities to phenylephrine and dexmedetomidine

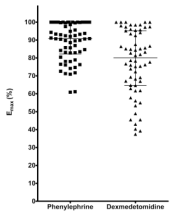

Figure 2. Maximal effect (E_{max}) for dexmedetomidine and phenylephrine

E_{max} – Maximal venoconstriction, expressed as the percentage reduction in vein diameter from maximal dilation

The horizontal line represents the median and the bars represent the IQR;

$P<0.001$ comparing E_{max} for dexmedetomidine and phenylephrine

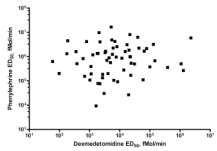

Figure 3. Relationship between log ED_{50} for phenylephrine and dexmedetomidine

ED_{50} - The dose of phenylephrine and dexmedetomidine that produced 50% of maximum venoconstriction (E_{max}) for each subject

ED_{50} is expressed in fmol/min

Spearman rho for the correlation: r= 0.12 (p=0.34)

Table 1

Subject characteristics and baseline measurements [Number (percentage); Median (IQR)]

Characteristic	Value
Men	36 (56.3%)
Race: African Americans: Caucasians	34 (53.1%): 28 (43.8%)
Family history of hypertension	23 (35.9%)
Regular exercise, >4 times/week	23 (35.9%)
Age (years)	25.0 (22.0– 32.0)
BMI (kg/m^2)	25.3 (22.7– 28.3)
Systolic blood pressure (mm Hg)	109.5 (102.8– 116.3)
Diastolic blood pressure (mm Hg)	61.0 (56.0– 67.0)
Mean arterial pressure (mm Hg)	78.3 (72.6–82.3)
Heart rate (beats per minute)	60.0 (53.0– 66.0)
Plasma norepinephrine (pg/mL)	156.0 (127.0– 202.0)

Table 2

Hand vein responses to phenylephrine and dexmedetomidine

	Phenylephrine	Dexmedetomidine	P-value
ED_{50} (ng/min)	177.8 ng/min (40.7– 436.5)	1.3 ng/min (0.45–5.37)	<0.001*
E_{max} (%)	90.8 (82.2–99.6)	80.0 (64.7–95.2)	<0.001

Data are expressed as median (IQR)

E_{max} – Maximal venoconstriction, expressed as the percentage reduction in vein diameter from maximal dilation

ED_{50} - The dose of phenylephrine and dexmedetomidine that produced 50% of maximum venoconstriction (E_{max}) for each subject

*P-value for the comparison of ED_{50} of phenylephrine and dexmedetomidine in fmole/min (see also Figure 1)

Table 3

Correlation between measures of phenylephrine and dexmedetomidine vascular response

	ED_{50} Rho (p-value)	**E_{max} Rho (p-value)**
All subjects (n=62)	0.12 (p=0.38)	0.15 (p=0.23)
African Americans (n= 34)	0.06 (p=0.74)	0.18 (p=0.32)
Caucasians (n=28)	0.21 (p=0.29)	0.17 (p=0.39)

E_{max} – Maximal venoconstriction, expressed as the percentage reduction in vein diameter from maximal dilation

ED_{50} - The dose of phenylephrine and dexmedetomidine that produced 50% of maximum venoconstriction (E_{max}) for each subject

Table 4

Comparison of dexmedetomidine ED_{50} in quartiles of phenylephrine ED_{50}

Phenylephrine ED_{50} quartile	**1st quartile (lowest quartile)**	**2nd quartile**	**3rd quartile**	**4th quartile (highest quartile)**	**P-value**
Dexmedetomidine ED_{50} (ng/min, median, IQR)	0.64 (0.30–1.89)	3.23 (0.26–34.57)	1.20 (0.43–5.08)	1.63 (0.52–9.48)	0.22

ED_{50} - The dose of phenylephrine and dexmedetomidine that produced 50% of maximum venoconstriction (E_{max}) for each subject