Influence of Yohimbine on Blood Pressure, Autonomic Reflexes, and Plasma Catecholamines in Humans

MICHAEL R. GOLDBERG, M.D., PH.D., ALAN S. HOLLISTER, M.D., PH.D., AND DAVID ROBERTSON, M.D.

SUMMARY  We studied the influence of the a 2-adrenoreceptor-blocking drug, yohimbine, on blood pressure, plasma norepinephrine, and other measures of autonomic function in normal male volunteers. These studies were designed to evaluate the role of a 2-receptors in the tonic regulation of sympathetic outflow in humans. In a dose-ranging study, we found that yohimbine HCl (0.016-0.125 mg/kg) elicited dose-related rises in mean, systolic, and diastolic pressures. At the maximal dose used (0.125 mg/kg), respective increments in mean, systolic, and diastolic pressures were 14 ± 1 torr; 28 ± 3 torr; and 8 ± 1 torr (p < 0.01) (mean ± SE). No significant changes in heart rate occurred. Associated with the rise in blood pressure were enhanced pressor and heart rate responses to the cold pressor, isometric handgrip, and Valsalva maneuvers. In a double-blind study, yohimbine (0.125 mg/kg bolus, 0.001 mg/kg/min infusion) induced a two-to-threefold rise in plasma norepinephrine (p < 0.01), without significantly altering plasma epinephrine or plasma renin activity. Ex vivo platelet aggregation in response to epinephrine was inhibited during yohimbine, showing that non-innervated a 2-adrenoreceptors were inhibited. Central effects of yohimbine were evaluated through use of linear analog mood rating scales which showed a shift from calm toward excited ends of these scales. If yohimbine is acting through blockade of a 2-receptors, then these receptors tonically suppress sympathetic outflow in humans. (Hypertension 5: 772-778, 1983)

KEY WORDS  • a 2 adrenoreceptors • sympathetic outflow • blood pressure regulation

SYMPATHETIC outflow can be inhibited in humans and in animals by drugs that stimulate central alpha adrenergic receptors. 1-3 Animal studies suggest that these actions are mediated by a subtype of alpha-adrenergic receptors, the a 2-receptor. 4-6 Pharmacologically similar receptors have been shown to mediate epinephrine-induced platelet aggregation 7 and catecholamine-induced inhibition of lipolysis. 8 The a 2-receptors located on adrenergic terminals also inhibit peripheral adrenergic neurotransmission, 4-6 although demonstration of this action in vivo in humans 9 and animals 10-11 has been difficult. Based on these data, we postulated that a 2-receptors tonically inhibit sympathetic outflow in humans and that the extent of this activity could be estimated through the study of a 2-antagonists. Although several relatively selective a 2-adrenoreceptor antagonists have been described, 4-6 we chose yohimbine for our studies because it has been studied in humans, and because its pharmacology has been extensively investigated. 12 Yohimbine (fig. 1) is a plant alkaloid derived from the bark of the Pausinystalia yohimbe tree and other sources. It has a long folk history as an aphrodisiac, and has been given to humans with apparent safety for over 100 years. 12 Yohimbine has high affinity for a 2-receptors in radioligand-binding studies, and recent studies in animals have shown yohimbine to be a relatively selective a 2-antagonist. 12 Thus, yohimbine antagonizes a-adrenergic inhibition of adrenergic transmission and reverses the effects of many centrally active antihypertensive agents. 12 Furthermore, it has been shown to raise blood pressure and heart rate and
AUTONOMIC EFFECTS OF YOHIMBINE IN HUMANS/Goldberg et al. 773

Fig. 1. Chemical structure of yohimbine (17α-hydroxyyohimban-16α-carboxylic acid methyl ester).

induce an anxiety-like state when given to humans in high doses (0.5 mg/kg i.v.). We studied the autonomic effects of several doses of yohimbine in humans and specifically determined its influence on baseline blood pressure and heart rate and on physiologic and biochemical indices of sympathetic outflow.

Methods

These studies were performed in 10 normal male volunteers (aged 21–39 years). All procedures and consent forms were approved by the Vanderbilt University Committee for the Protection of Human Subjects. Studies were performed in the Elliot V. Newman Clinical Research Center (CRC). Initially, a dose-ranging design was employed to determine the dose-response relationship for yohimbine's effects on both blood pressure and pressor reflexes. Subsequently, a double-blind study of yohimbine's effects on plasma catecholamines, plasma renin, and other autonomic functions was performed.

Dose-Ranging Study

Volunteers were admitted overnight to the CRC and kept supine and fasting from midnight through the time of the study. The morning of the study, an intravenous line was placed in the forearm for drug administration and blood sampling. A 20 g 1/2 inch Teflon catheter (Quik-Cath) was placed percutaneously in the radial artery for direct measurement of arterial blood pressure. The electrocardiogram was continuously recorded and used to trigger a rate computer for continuous readout of heart rate with EKG and blood pressure on a Hewlett-Packard 4-channel recorder. A 20- to 30-minute accommodation period was allowed before baseline determinations of responses to several pressor reflexes were made, including: cold pressor test (immersion of hand in ice water for 1 minute), isometric handgrip (30% maximum for 3 minutes), mental arithmetic (1 minute), and Valsalva maneuver (40 torr for 15 seconds). After baseline determinations, cumulatively increasing doses of yohimbine were given intravenously (0.016–0.125 mg/kg yohimbine HCl). Yohimbine was purchased from Sigma Chemical Company (F and D Division), St. Louis, Missouri, and prepared for human use by dissolving in sterile, bacteriostatic saline (0.5 mg/ml) followed by Millipore filter sterilization (0.22 μ). Yohimbine was prepared freshly each day. Small doses of yohimbine were given by rapid intravenous injection, and larger doses were administered over 2 to 5 minutes. Blood pressure was observed for 10 to 15 minutes after each dose. At that time, the reflexes were repeated in random order, before administration of the next dose of yohimbine. Ex vivo platelet aggregation in response to epinephrine and adenosine diphosphate (ADP) was determined in three supine volunteers, using a Payton aggrerometer (Payton Associates, Inc., Buffalo, New York) before yohimbine administration and after two doses of yohimbine.

In single-blinded fashion, three volunteers were given multiple saline injections rather than yohimbine, to assess the reproducibility of the various reflexes and platelet aggregation. In these individuals, we noted that responses to cold pressor, handgrip, and Valsalva maneuvers were reproducible while the response to mental arithmetic showed tachyphylaxis and could not, therefore, be accepted as a reproducible measure of stimulated sympathetic outflow. Platelet sensitivity to epinephrine- and ADP-induced aggregation was stable over time.

In evaluating the cold pressor and isometric handgrip tests, the peak change in mean arterial pressure or heart rate at the termination of the maneuver was used as a measure of the reflex response. The Valsalva maneuver is more complex and not subject to as simplified an interpretation as the other maneuvers. Noting the four phases of the maneuver, we used the change in mean arterial pressure from baseline to the peak mean pressure during Phase IV as an index of reflex sympathetic vasoconstriction. The increase in heart rate from baseline to peak heart rate during Phase III was used to measure the reflex tachycardia elicited by the maneuver.

Double-Blind Study

This portion of the study was performed in five previously dose-ranged volunteers, admitted as outpatients to the CRC on two mornings at least 1 week apart. On arrival at the CRC, after fasting from the night before, subjects had an intravenous line placed for drug administration and a heparin-lock placed in the opposite arm for blood sampling. Electrocardiogram, heart rate, respirations, and blood pressure (Dinamap automated sphygmomanometer) were continuously monitored. The subjects were allowed to rest undisturbed for 60 to 90 minutes. At that time, an initial blood sample was drawn for measurement of plasma catecholamines (radioenzymatic method) and plasma renin activity. A bolus injection followed...
by a continuous infusion of test substance was administered (yohimbine: 0.125 mg/kg and 0.001 mg/kg/min, or equivalent volumes of bacteriostatic saline). Neither the investigator nor the subject knew the treatment being administered. The subject was maintained supine for an additional 45 minutes, and blood samples were drawn for catecholamine and renin determinations 15, 30, and 45 minutes after the bolus injection. At the end of this 45-minute period, with the infusion being maintained, the subject stood motionless for an additional 30 minutes. Blood samples were taken at the end of 5, 15, and 30 minutes of upright posture. Following the last sample, an estimate was made of each subject's mood and mental state using linear analog rating scales.

Statistical analysis of the data was performed using Student's $t$ test for paired experiments and analysis of variance with Dunnett's procedure. The criterion for statistical significance was $p < 0.05$. Values are means ± SE.

**Results**

**Influence of Yohimbine on Blood Pressure and Heart Rate**

**Dose-Ranging Study**

Cumulative administration of yohimbine (0.016–0.125 mg/kg, i.v., total dose = 0.25 mg/kg) to the normal volunteers resulted in a dose-related increase in systolic, diastolic, and mean intraarterial blood pressure (fig. 2). The rise in blood pressure following each dose of yohimbine occurred gradually, beginning within 5 minutes of drug administration and reaching a plateau 10 to 15 minutes after each dose. This plateau of blood pressure persisted through the time of administration of the next yohimbine dose, usually 45 minutes. After termination of the study, blood pressure returned to baseline within 1 to 2 hours. At the maximal dose used (0.125 mg/kg), the respective increases in mean, systolic, and diastolic pressures were 14 ± 1 torr, 28 ± 3 torr, and 8 ± 1 torr ($p < 0.01$). At the doses studied, yohimbine did not alter heart rate (fig. 2).

**Double-Blind Study**

During double-blind administration of yohimbine, rises in blood pressure were noted, as during the dose-ranging study. Similarly, heart rate was unaltered by yohimbine (table 1). The blood pressure and heart rate changes in response to 30 minutes of quiet standing were not significantly altered following administration of yohimbine (table 1). There was a reduction in respiratory rate from 14.1 ± 0.4 to 12.5 ± 0.6 breaths/min ($p < 0.05$), during the first 10 minutes following double-blind administration of yohimbine.

**Influence of Yohimbine on Pressor Reflexes**

Three different reflexes were studied as reproducible measures of sympathetic responses initiated through somatic (cold pressor, isometric handgrip), and baroreceptor (Valsalva's maneuver) input to the vasomotor centers. As summarized in figure 3, cold

---

**Table 1. Hemodynamic Changes During Double-Blind Administration of Yohimbine**

<table>
<thead>
<tr>
<th>Hemodynamic response</th>
<th>Treatment</th>
<th>Supine 0 min</th>
<th>Supine 15 min</th>
<th>Supine 45 min</th>
<th>Standing 5 min</th>
<th>Standing 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (torr)</td>
<td>Saline</td>
<td>79±4</td>
<td>78±4</td>
<td>82±5</td>
<td>87±6</td>
<td>84±3</td>
</tr>
<tr>
<td></td>
<td>Yohimbine</td>
<td>83±4</td>
<td>93±4*</td>
<td>92±5*</td>
<td>96±5</td>
<td>94±6</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>Saline</td>
<td>58±5</td>
<td>60±5</td>
<td>60±4</td>
<td>78±5</td>
<td>83±6</td>
</tr>
<tr>
<td></td>
<td>Yohimbine</td>
<td>55±4</td>
<td>55±5</td>
<td>56±3</td>
<td>69±4</td>
<td>83±6</td>
</tr>
</tbody>
</table>

Treatments were yohimbine (0.125 mg/kg bolus and 0.001 mg/kg/min infusion) or equivalent volume of bacteriostatic saline.

*p < 0.01, saline vs yohimbine, indicating statistical significance.
AUTONOMIC EFFECTS OF YOHIMBINE IN HUMANS/Goldberg et al.

Influence of Yohimbine on Mean Arterial Pressure and Mean Peak Pressor Responses

Pressor, handgrip, and Valsalva maneuver pressor responses were enhanced in a dose-related fashion following yohimbine. The heart rate response to these reflexes was also increased following yohimbine (fig. 4). Responses to mental arithmetic showed tachyphylaxis after yohimbine, as after placebo.

Influence of Yohimbine on Plasma Catecholamines and Renin

During the double-blind study, yohimbine (0.125 mg/kg bolus; 0.001 mg/kg/min infusion) elicited a two- to threefold increase in plasma norepinephrine (fig. 5, p < 0.01), without significantly altering plasma epinephrine. During upright posture, differences in plasma catecholamines were not observed when comparing control to yohimbine, although the expected postural rise in norepinephrine and epinephrine occurred in each subject.

Changes in mean plasma renin activity in the supine position were not significant during the double-blind administration of yohimbine, and the postural rise in plasma renin activity was not altered (fig. 6). Four of the five volunteers had baseline plasma renin activities less than 0.5 ng Al/ml/hr. One volunteer on each occasion had a basal renin of 1.5 ng Al/ml/hr. This indi-
individual doubled his renin to 3.4 ng Al/ml/hr during yohimbine, suggesting that yohimbine might, under appropriate conditions, cause an elevation in plasma renin. This individual was otherwise indistinguishable from the other volunteers in terms of blood pressure, heart rate, baseline or stimulated plasma catecholamines, or urinary Na⁺ excretion during the period of the study.

Influence of Yohimbine on Ex Vivo Platelet Aggregation

Epinephrine- and ADP-induced platelet aggregation was studied in three individuals following yohimbine infusions of 0.032, and 0.125 mg/kg. In each, as shown in figure 7, there was a dose-related inhibition of the platelet response to epinephrine, manifested by a reduction in the slope of the first phase of epinephrine-induced aggregation. The change in the dose-response curve following 0.032 mg/kg is similar to that induced by 100 nM yohimbine in vitro (data not shown). The threshold for ADP-induced biphasic aggregation was not altered following yohimbine.

Influence of Yohimbine on Subjective Rating Scale

At the conclusion of each segment of the double-blind study, volunteers were asked to complete linear analog rating scales of their subjective feelings (fig. 8). These scales showed the subjects to be more alert and less sedated on the day of yohimbine administration.

Side Effects

Investigator-observed, or subject-volunteered, effects of yohimbine during dose-ranging and double-blind phases are listed in table 2. During the double-blind studies, three of five subjects correctly guessed the yohimbine day in retrospect. Two were unable to differentiate yohimbine from saline, even in retrospect. The most prominent observation volunteered by the subjects was a feeling of restlessness. The more experienced volunteers stated that they were unable to relax as they had been able to during previous investigations involving unrelated agents. Three subjects noted an unusual taste or smell immediately following the yohimbine injections. Prominent autonomic effects observed directly were a fine rest tremor, which persisted for about 1 hour after the last dose of yohimbine, and transient piloerection. Three subjects admitted to a vague feeling of sexual arousal. One of these had an erection about 10 minutes following the rapid administration of yohimbine at 0.016, 0.032, and 0.125 mg/kg; it was of modest intensity and resolved spontaneously after 3 to 5 minutes.

Two individuals showed effects of yohimbine beyond the immediate period of drug administration. One reported the day following yohimbine administration that he felt uneasy and irritable. He also noted easy fatigability. These sensations had completely resolved within 36 hours of drug administration. The other voiced no symptoms following yohimbine, but his heart rate increased from 86 to 130 and blood pressure increased from 134/80 to 162/96 on assump-
tion of upright posture. This unusual postural response was noted 3 hours following the last dose of yohimbine and persisted for 8 hours. No hemodynamic abnormalities were noted either at 18 hours after yohimbine administration or during follow-up visits.

**Subjective Effects of Yohimbine (N = 7)**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restless</td>
<td>7</td>
</tr>
<tr>
<td>Cold sweaty hands</td>
<td>5</td>
</tr>
<tr>
<td>Urge to void</td>
<td>4</td>
</tr>
<tr>
<td>Fine tremor</td>
<td>3</td>
</tr>
<tr>
<td>Sexual arousal</td>
<td>3</td>
</tr>
<tr>
<td>Erection</td>
<td>1</td>
</tr>
<tr>
<td>Nervous</td>
<td>2</td>
</tr>
<tr>
<td>Piloerection</td>
<td>2</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>2</td>
</tr>
<tr>
<td>Unusual taste or smell</td>
<td>3</td>
</tr>
</tbody>
</table>

A key issue that is not resolved by these studies is whether yohimbine’s primary site of action is the peripheral or central nervous system. Pressor effects and increases in plasma norepinephrine and sympathetic reflexes could be explained either by a peripheral action to enhance sympathetic transmission or by a central effect on vasomotor relay nuclei to facilitate sympathetic outflow. Several observations are more suggestive of a central site of action. Earlier studies with yohimbine in humans and animals suggest that pressor effects are mediated in the central nervous system.

Discussion

In these experiments, the increase in blood pressure following yohimbine administration in normal humans is shown to be dose-related and associated with two- to threefold elevation in plasma norepinephrine, suggesting that the pressor response to yohimbine is mediated by the sympathetic nervous system. An additional observation is that the rise in blood pressure and heart rate elicited by a variety of sympathetic reflexes is greater following yohimbine. If the effects of yohimbine are due to blockade of \( \alpha_2 \)-receptors, then the data suggest that these receptors tonically inhibit sympathetic outflow in man.

The key assumption in interpreting these results is that \( \alpha_2 \)-receptor blockade is the mechanism of action of yohimbine. Since platelet responses to epinephrine were attenuated in dose-related fashion, while the aggregatory response to ADP was unaltered, yohimbine was present in sufficient levels to block noninnervated \( \alpha_2 \)-receptors. Substantial evidence for the \( \alpha_2 \)-selectivity of yohimbine is apparent from radioligand-binding as well as in vitro and in vivo studies in experimental animals. Also, in vitro studies in human subcutaneous fat and platelets show the potency of the alkaloid at human \( \alpha_2 \)-receptors.

Although most effects of yohimbine observed in the present study can be attributed to blockade of \( \alpha_2 \)-receptors, yohimbine may have other pharmacologic actions, including blockade of \( \alpha_1 \) and dopamine receptors and stimulation or blockade of serotonin receptors. Other non-\( \alpha \) effects of yohimbine include local anesthetic actions, and inhibition of monoamine oxidase. These actions are not consistently demonstrable and are observed at higher doses or concentrations of yohimbine, and therefore do not explain our observations nearly as well as selective \( \alpha_2 \)-blockade.
to the pressor effects of yohimbine. 3) Local anesthetic actions of initially high levels of yohimbine may have prevented the baroreceptor from responding to changes in blood pressure. 4) A more intriguing possibility is that yohimbine acted in the central nervous system to attenuate vagally mediated bradycardia or reflex sympathetic withdrawal in response to the rise in blood pressure. This latter action is complemented by observations that clonidine, an α2-agonist, facilitates and yohimbine and phentolamine both depress, vagal bradycardia in the cat and dog. 24–26

Yohimbine enhanced the pressor and heart rate responses to the cold pressor and handgrip tests and Valsalva maneuver. Since these responses were highly variable, somewhat effort-dependent and involved multiple neuronal pathways, they must be interpreted with caution, even though multiple reflexes in placebo-treated control subjects did not change. It is not known whether the enhanced pressor responses were due to an increase in the amount of norepinephrine released by each reflex, or to the superimposition of normal reflex increments in norepinephrine on increased basal release or increased vascular tone. The change in heart rate responses could be due to an increase in sympathetic activity or to inhibition of the vagus. 24–26

In summary, we have shown that intravenous administration of yohimbine raises blood pressure, enhances sympathetic reflexes, and increases plasma norepinephrine. Furthermore, yohimbine antagonizes ex vivo platelet aggregation in response to epinephrine and causes changes in mood. We conclude from these findings that α2-adrenoceptors are important regulators of sympathetic outflow in humans.

Acknowledgments
The authors acknowledge the assistance of Dawn Wade, R. N., in the clinical aspects of these studies, and the technical assistance of Loreta Speier and Pamela Hoover. Bolton Smith assisted in improving the grammar and fluency of the manuscript. Dr. Robert Workman is acknowledged for the determinations of plasma renin activity.

References
Influence of yohimbine on blood pressure, autonomic reflexes, and plasma catecholamines in humans.

M R Goldberg, A S Hollister and D Robertson

Hypertension. 1983;5:772-778
doi: 10.1161/01.HYP.5.5.772

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/5/772

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/