Some pharmacologic actions of yohimbine and chlorpromazine in man

Yohimbine was found to produce psychic and autonomic changes resembling anxiety in man. Chlorpromazine, reserpine, amobarbital and atropine modified the response to yohimbine. Both reserpine and amobarbital reduced the drug's psychic and autonomic effect, while atropine decreased the pressor response to yohimbine. Chlorpromazine acted paradoxically, potentiating both psychic and autonomic responses.

It is suggested that in the dose used in this study, yohimbine does not have its usual alpha-adrenergic blocking action but may produce these reactions by central stimulation of the autonomic nervous system.

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Yohimbine partially blocks the pressor response to sympathetic nerve stimulation and produces vasomotor reversal to injected epinephrine,[1, 17, 18, 20] and it is now classified as an alpha-adrenergic blocking agent largely on the basis of these pharmacologic effects in studies on animals. Recently, Holmberg and Gershon[7] reported that small doses had a stimulant action in man resulting in psychic and autonomic changes commonly associated with the subjective experience of anxiety. The degree of autonomic response was reported to correlate highly with the subject's initial anxiety level. On the basis of this report, it seemed that the yohimbine response could provide a useful method for testing the effectiveness of drugs used to control anxiety. The present study was therefore undertaken to determine the effect of several known psychoactive drugs upon the autonomic and psychic responses produced by yohimbine and to attempt a fuller understanding of its mechanism and site of action.

Method

The subjects were 25 patients, 13 schizophrenics, 8 alcoholics, and 4 sexual deviates, between the ages of 18 and 40 years. Five of the schizophrenics were diagnosed as paranoid and the other 8 were of the chronic undifferentiated type. All tests were carried out with the subjects lying supine in a polygraph test room. Blood pressure, electrocardiogram, respiration, skin resistance, skin temperature, and ballistocardiogram measurements were re-

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corded. A heparinized Heyman-Olafson needle was inserted into a suitable vein while electrodes were applied to the subject. The needle, having a rubber diaphragm, allows administration of repeated, accurately timed injections without disturbing the subject. A 5 minute baseline recording was taken after an acclimatization period, then 2 ml. of saline was injected over a 1 minute period. After a 5 minute recovery period, yohimbine hydrochloride in a dose of 0.1 mg. per kilogram of body weight per minute was administered intravenously over a 5 minute period. The dose was chosen because it had previously been shown to produce a stimulant action.[7] Recordings were continued for at least 20 minutes after the injection. A similar injection and recording routine was used in testing the subject's response to intravenous epinephrine and norepinephrine. L-Epinephrine bitartarate and L-norepinephrine bitartarate were infused in a dose of 0.2 μg per kilogram of body weight per minute over a period of 6 minutes.

After the initial test establishing the response to yohimbine, epinephrine, and norepinephrine, the subjects were given chlorpromazine, reserpine, sodium amytal, or atropine sulfate and then retested with yohimbine, epinephrine, and norepinephrine. Twenty of the subjects were given chlorpromazine (10 mg. per kilogram per day) orally for at least 4 weeks and then retested while still receiving it. Ten patients were retested with yohimbine, epinephrine, and norepinephrine after receiving oral doses of 0.05 mg. per kilogram per day of reserpine for 3 weeks. Amobarbital sodium (5 mg. per kilogram) was given intravenously to 8 subjects just prior to retesting. Six patients received atropine sulfate (0.04 mg. per kilogram) by intravenous injection immediately prior to retest with yohimbine.

Results

Saline injection. None of the patients showed either subjective or autonomic reaction to the intravenous injection of normal saline.

Yohimbine response prior to drug treatment. The intravenous injection of yohimbine produced psychic and autonomic effects, as previously reported.[7] Most commonly, the initial signs were facial flush and increased heart rate. These were quickly followed by perspiration, lacrimation, salivation, dilation of the pupils, increased rate and depth of respiration, and elevation of blood pressure. The rise in blood pressure usually occurred 3 minutes after the beginning of the injection and remained elevated for 30 minutes or more after the injection was completed. The magnitude of the pressor response varied considerably from patient to patient but was present in all cases. The magnitude of this increase in blood pressure correlated positively, at a statistically significant level, with the baseline anxiety rating of the patient as rated by six independent raters. Both the systolic and diastolic blood pressures increased with the injection of yohimbine. The mean rise in systolic blood pressure for the 25 subjects in this study was 18.5 mm. Hg (S.E. ± 0.4). The mean rise in diastolic blood pressure was 6.1 mm. Hg (S.E. ± 1.2). Skin temperature always rose, and skin resistance dropped. Those subjects who reacted most strongly to yohimbine showed generalized tremors.

The psychic changes observed were restlessness, irritability, a tense facial expression, obvious anxiety, and a marked reluctance to repeat the drug test. It was not possible to have several observers rate the anxiety induced by the yohimbine, but it was always much more marked than that seen during the injection of other autonomic drugs. A few subjects complained of nausea and urgency of micturition and defecation. No differences in response to yohimbine were observed between the different diagnostic groups used in the study.

Response to epinephrine and norepinephrine. There was a pressor response to both epinephrine and norepinephrine in the dosage used (0.2 μg per kilogram). The mean rise in systolic blood pressure with epinephrine was 21.7 mm. Hg (S.E. ± 2.9)

and was 21.3 mm. Hg (S.E. ± 4.1) with norepinephrine. Apart from a slight throbbing in the neck no subjective sensations were reported after norepinephrine. During the injection of epinephrine, only 3 of the 20 patients reported feeling anxious and 15 said they noticed somatic sensations similar to those felt when they were excited or anxious, but that they did not feel anxious.

Responses to test drugs after chlorpromazine medication. The yohimbine response was found to be greatly exaggerated in patients who had received chlorpromazine for 4 weeks and were still taking the drug when tested. Whereas some patients responded to yohimbine with only a small increase in blood pressure or slight anxiety prior to chlorpromazine medication, all subjects now showed an obvious anxiety reaction and a marked potentiation of the autonomic effects after it. The pressor response to yohimbine especially was markedly increased. The mean systolic blood pressure rise in these 20 subjects was 17.1 mm. Hg before and 41.9 mm. Hg after chlorpromazine medication. Similarly, the increase in diastolic blood pressure with yohimbine was greater after chlorpromazine than before. Both increases are significant ($p < 0.001$). There was a slight but not statistically significant increase in heart rate with yohimbine after chlorpromazine. Table I summarizes the changes in vasomotor responses. All patients showed the potentiated response. The pressor response in a typical case is shown in Fig. 1.

The difference in response to epinephrine and norepinephrine infusions before chlorpromazine medication was less marked than during it. The data are summarized in Tables II and III. The systolic blood pressure response to epinephrine was consistently depressed, the rise being 21.7 mm. Hg before and 14.7 mm. Hg after chlorpromazine medication ($p < 0.005$). No significant changes in diastolic blood pressure or heart rate were observed. The pressor response to norepinephrine was potentiated and prolonged in some cases but very little increased in others. The mean rise in systolic blood pressure was from 21.3 to 25.2 mm. Hg, and the mean rise in diastolic blood pressure was from 3.9 to 6.5 mm. Hg. Both differences are statistically significant ($p < 0.05$). When potentiation of the norepinephrine pressor response by chlorpromazine did occur, it was always considerably less than that observed with yohimbine. During the infusion of epinephrine and norepinephrine no alterations in the subjective symptoms were observed by the patient as a consequence of chlorpromazine premedication.

Responses to test drugs after medication with reserpine. Ten patients were tested with yohimbine, epinephrine, and norepinephrine before and after receiving reserpine (0.05 mg. per kilogram per day for 3

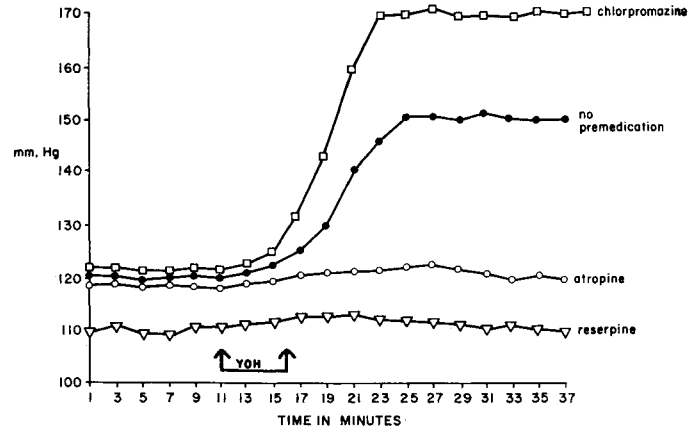

Fig. 1. Systolic blood pressure response to yohimbine before and during administration of other drugs.

Table I. *Mean systolic blood pressure, diastolic blood pressure, and heart rate response to yohimbine before and during chlorpromazine medication (20 subjects)*

Determination	*Before chlorpromazine*		*During chlorpromazine*		*Difference in change* ± S.E.	*p*
	Base line ± S.E.	*Change* ± S.E.	*Base line* ± S.E.	*Change* ± S.E.		
Systolic blood pressure (mm. Hg)	129.4 ± 2.6	17.1 ± 1.4	129.5 ± 3.4	41.9 ± 4.6	24.8 ± 4.6	0.001
Diastolic blood pressure (mm. Hg)	85.9 ± 2.2	4.7 ± 0.7	89.1 ± 2.2	11.1 ± 0.5	6.4 ± 0.5	0.001
Heart rate	79.0 ± 2.4	14.9 ± 1.2	83.1 ± 2.1	18.8 ± 1.3	3.9 ± 2.7	Not significant

Table II. *Mean systolic blood pressure, diastolic blood pressure, and heart rate response to epinephrine before and during chlorpromazine medication (20 subjects)*

Determination	*Before chlorpromazine*		*During chlorpromazine*		*Difference in change* ± S.E.	*p*
	Base line ± S.E.	*Change* ± S.E.	*Base line* ± S.E.	*Change* ± S.E.		
Systolic blood pressure (mm. Hg)	119.7 ± 2.5	21.7 ± 2.9	117.7 ± 2.7	14.7 ± 2.7	−7.0 ± 2.2	0.005
Diastolic blood pressure (mm. Hg)	90.1 ± 2.1	−4.1 ± 1.0	86.2 ± 2.5	−5.0 ± 0.9	0.9 ± 1.1	Not significant
Heart rate	77.3 ± 1.7	0.2 ± 1.6	81.5 ± 2.3	−0.3 ± 1.7	0.5 ± 4.8	Not significant

weeks). The psychic response to yohimbine was completely blocked by pretreatment with reserpine. The baseline systolic pressure was reduced by 13.6 mm. Hg after 3 weeks of treatment with reserpine; the systolic blood pressure rise induced by yohimbine was reduced from 20.1 to 12.3 mm. Hg ($p < 0.001$) (see Table IV).

The pressor response to epinephrine and norepinephrine was inconsistent from patient to patient among the 10 subjects tested, and no significant over-all change from their pressor responses before being given reserpine was observed.

Response to test drugs after intravenous injection of amobarbital sodium. Eight patients were tested with yohimbine and retested a few days later after an intravenous injection of sodium amytal (5 mg. per kilogram) just prior to retesting. After amobarbital, all the subjects went into a light sleep and 5 remained asleep during the subsequent injection of yohimbine. The baseline systolic blood pressure was somewhat reduced following the injection of sodium amytal. Yohimbine given 10 minutes later produced a mean pressor response of 7.8 mm. Hg, as compared with 16.2 mm. Hg before amobarbital($p < 0.05$). None of the other autonomic effects of yohimbine were observed. The usual increase in heart rate after the injection of yohimbine was abolished by amobarbital (Table V).

Response to yohimbine after atropine sulfate. Six subjects were given atropine sulfate (0.04 mg. per kilogram) by intravenous injection. This treatment also considerably reduced the pressor response to yohimbine from a rise of 23.4 to one of 5.4

mm. Hg ($p < 0.005$) (Table IV). However, other autonomic responses were not significantly altered, and the psychic effects seemed only partially depressed.

Discussion

The literature on yohimbine is limited to studies in animals and has dealt only with its action in blocking the effects of epinephrine and sympathetic stimulation. The dose required to ensure block of sympathetic stimulation is reported to be 2 to 5 times as great as that required to block responses to injected epinephrine. This dosage range is much greater than that used in the present study in man. Jang[8] describes the use of low concentrations of yohimbine in experiments with the perfused rabbit's ear to sensitize the ear to epinephrine, but there appears to be no report in the literature of small doses causing psychic stimulation or sympathomimetic effects. Koppanyi[11] states that yohimbine does not have an initial pressor effect like ergotamine when administered to dogs. He was, however, using large doses.

In his review of adrenergic blocking agents, Nickerson[17] lists some central, but mainly depressant, actions of yohimbine.

One possibly significant factor is that all the animal investigations reported with this drug have been carried out under general anesthesia. The present study demonstrates that amobarbital blocks the psychic and autonomic stimulant effects of yohimbine, and it is likely therefore that the failure to observe a pressor response has been due to the use of anesthetized preparations.

In his studies of the subjective effects produced by the injection of autonomic drugs in psychotic and psychoneurotic patients, Lindemann[12, 13] first demonstrated that the epinephrine and methacholine effects were not related to the type of the disease but to the adjustment prevailing in the patient. As previously stated, no correlation was found in this study between either the degree of induced anxiety or the magnitude of the pressor response and the diagnostic category. The intensity of anxiety induced by yohimbine did correlate positively with the preinjection anxiety level, as did the magnitude of the pressor response. Lindemann[12] also demonstrated the variability of subjective responses on repeated testing of the same subject. In the few patients who were subjected to repeated tests with yohimbine, no great variability was observed. Certainly, no change in response seen on repeated testing was ever as great as the change induced by prior medication with the drugs used in this study.

The administration of reserpine for 3 weeks markedly inhibits pressor responses to yohimbine, which may indicate that only a small part of the normal pressor response is due to direct stimulation of peripheral adrenergic receptors and that the normal pressor response is mediated by catechol-

Table III. *Mean systolic blood pressure, diastolic blood pressure, and heart rate response to norepinephrine before and during chlorpromazine medication (20 subjects)*

	Before chlorpromazine		*During chlorpromazine*		*Difference in change*	
Determination	*Base line* ± S.E.	*Change* ± S.E.	*Base line* ± S.E.	*Change* ± S.E.	± S.E.	*p*
Systolic blood pressure (mm. Hg)	121.4 ± 2.3	21.3 ± 4.1	119.7 ± 2.1	25.2 ± 4.2	3.9 ± 2.0	0.05
Diastolic blood pressure (mm. Hg)	90.4 ± 2.2	3.9 ± 0.4	88.3 ± 2.5	−6.5 ± 0.8	2.6 ± 1.1	0.05
Heart rate	71.1 ± 1.4	−19.1 ± 1.8	78.8 ± 2.5	−20.9 ± 1.6	−1.8 ± 2.0	Not significant

Table IV. *Mean systolic blood pressure response to yohimbine before and after reserpine and atropine*

Drug	Number of subjects	Before drug: Base line ± S.E. (mm. Hg)	Before drug: Change ± S.E. (mm. Hg)	After drug: Base line ± S.E. (mm. Hg)	After drug: Change ± S.E. (mm. Hg)	Difference in change ± S.E. (mm. Hg)	p
Reserpine 0.05 mg. per Kg. per day for 3 weeks	10	124.7 ± 6.0	20.1 ± 2.4	111.1 ± 6.4	7.8 ± 2.1	−12.3 ± 1.6	0.001
Atropine sulfate	6	133.1 ± 4.3	23.4 ± 6.9	120.2 ± 4.7	5.4 ± 4.7	−18.0 ± 3.9	0.005

amines which are depleted after reserpine premedication.

The observation that amobarbital blocks the pressor response to yohimbine suggests a central mechanism. The view is strengthened by the fact that psychic effects induced by this drug do not seem to be due to its peripheral autonomic effects. Some patients who had a moderate pressor response after yohimbine showed marked anxiety but after an epinephrine-induced pressor response of similar magnitude gave no indication of anxiety.

Other adrenergic blocking agents are known to have central stimulating effects in low dosage, and the production of hypertension by benzodioxanes has been reported in unanesthetized animals by Bing and Thomas[2] and in man by Goldenberg, Snyder, and Aranow.[4] Handowsky[6] proposes that this pressor response to the benzodioxanes is mediated through central stimulation.

Atropine depression of the pressor response to yohimbine would seem to support the view that muscarinic synapses exist in the descending vasomotor pathways from the mesencephalon.[14] The finding that muscarinic responses to yohimbine such as sweating and salivation were not significantly altered suggests that the dose of atropine was too small.

In every subject, chlorpromazine potentiated yohimbine's autonomic and psychic effect ($p < 0.001$). Potentiation of the pressor response of both norepinephrine and yohimbine is somewhat surprising in view of the evidence for the alpha-adrenergic blocking action of chlorpromazine initially described by Kopera and Armitage,[10] who demonstrated that it blocked the local vasoconstrictor effects of L-epinephrine. Courvoisier and colleagues[3] and Jourdan, Duchêne-Marullaz, and Boissier[9] showed that it reduced or reversed the pressor responses to epinephrine. Martin and Riehl,[15] however, demonstrated that chlorpromazine could enhance and prolong

Table V. *Mean systolic blood pressure, diastolic blood pressure, and heart rate before and after amobarbital sodium*

Determination	Before drug: Base line ± S.E.	Before drug: Change ± S.E.	After drug: Base line ± S.E.	After drug: Change ± S.E.	Difference in change ± S.E.	p
Systolic blood pressure (mm. Hg)	120.1 ± 4.6	16.2 ± 3.8	116.1 ± 4.4	7.8 ± 3.7	−8.2 ± 3.2	0.05
Diastolic blood pressure (mm. Hg)	89.1 ± 1.9	5.1 ± 0.9	86.3 ± 2.3	3.7 ± 0.5	−1.4 ± 0.7	0.05
Heart rate	72.4 ± 1.7	12.9 ± 2.0	76.7 ± 1.7	2.1 ± 2.1	−10.8 ± 2.2	0.001

the pressor response evoked by levarterenol in cats which had undergone spinal vagotomy. After further investigation of this finding, Martin, Riehl, and Unna[16] proposed that chlorpromazine had two dissociated actions: (1) block of the adrenergic receptors and (2) depression of some deactivating process.

Among the possible mechanisms of this potentiation are the depression of normal cardiovascular buffer mechanisms and sensitization of the central autonomic system. It is interesting to note that imipramine, a structural analogue of chlorpromazine, also potentiates the psychic and autonomic effects of yohimbine.[7] Although the mode of action of imipramine is still uncertain, Sigg[19] proposed sensitization of central adrenergic receptors as one of its actions.

On the basis of (1) the depression of the yohimbine response by the previous administration of amobarbital and (2) by analogy with the central action of the benzodioxanes, it is suggested that yohimbine may produce its pressor and anxiety response by action through the central autonomic system.

Conclusion

In a dose of 0.1 mg. per kilogram per minute for 5 minutes, yohimbine was found to produce psychic and autonomic changes resembling anxiety.

Chlorpromazine, reserpine, amobarbital, and atropine modified the response to yohimbine. Both reserpine and amobarbital reduced the drug's psychic and autonomic effects, while atropine decreased the pressor response to yohimbine. Chlorpromazine acted paradoxically, potentiating both psychic and autonomic responses.

The results of this study and those of other workers suggest that in the dose used in this study, yohimbine does not exert its usual alpha-adrenergic blocking action but produces the reactions reported by central stimulation of the autonomic system.

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