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A PSYCHO-PHARMACOLOGICAL STUDY OF SOME INDOLE ALKALOIDS

BY

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INTRODUCTION

Yohimbine in fairly high doses in animals exerts adrenolytic effects and in still higher doses produces sympathetic nerve blockade (RAYMOND-HAMET, 24; BARRY, 1; YONKMAN *et al.*, 35; BOVET and BOVET-NITTI, 2; and NICKERSON, 22). The yohimbine blockade of cardiovascular responses to adrenaline is not altered by any of a considerable number of anaesthetic agents (HUTCHINSON *et al.*, 14; KOPPANYI *et al.*, 16). An antiserotonin activity of yohimbine has been demonstrated on isolated strips of carotid artery (SHAW and WOOLEY, 29). Yohimbine has been shown to suppress carotid cardiovascular reflexes in animals (NICKERSON, 22). Local anaesthetic properties have been shown for yohimbine and little direct action on smooth muscle is claimed (GOODMAN and GILMAN, 9). The central nervous system actions are reported to be less prominent than those of the ergot alkaloids and benzodioxanes. Yohimbine significantly prolonged the sleeping time produced by barbiturates (KILLIAM *et al.*, 15). Although long considered an " aphrodisiac ", present evidence provides no endocrine basis for this effect, the observed response appears to depend upon circulatory changes (RAYMOND-HAMET, 25).

Clinical studies have recently been reported by HOLMBERG and GERSHON (12) and the autonomic effects produced by yohimbine are stated to be both adrenergic and cholinergic in nature. Concomitant

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with these autonomic effects, psychic changes simulating an anxiety state were observed and the subjects displayed a tense expression, and became restless and irritable. The degree of these responses to yohimbine correlated well with the basic level of emotional activity. Yohimbine was found to activate the more or less latent psychotic process in some schizophrenic subjects.

These autonomic changes in man are not in keeping with reports on animal experiments. In particular the rise in both systolic and diastolic blood pressure in conscious man is contrary to the animal pharmacology reported (HUTCHINSON *et al.*, 14; YONKMAN *et al.*, 35).

To elucidate this problem it was decided to investigate the factors that may account for these discrepancies.

Ibogaine and harmine, two other indole alkaloids, have been reported by SCHNEIDER and SIGG (28) to have psychotomimetic effects with the production of excitement, inebriated states, mental confusion and hallucinations. TURNER *et al.* (32) challenged the reported hallucinogenic properties of these drugs. These authors state that " the situation with regard to harmine is extremely complicated " and claim that a careful review of the literature for the past 100 years reveals no record of pure harmine producing visual or auditory hallucinations. They claim the few statements to the contrary all seem to be on hearsay evidence and in any event do not exclude delirium. According to TURNER *et al.* (32) the natives of French West Africa do not ascribe any hallucinogenic properties to ibogaine, but insist it has an action identical with that of alcohol without impairing reason. LAMBERT and HECKEL (17) assume hallucinations in a dog from its behaviour after treatment with ibogaine.

MARINESCO *et al.* (19) have described harmine as having caused a fall in blood pressure and having a potentiating effect on the pressor response to adrenaline. Harmine has been described as a short acting inhibitor of monoamine oxidase by HORITA and MCGRATH (13). Ibogaine is reported by VINCENT and SERO (33) to produce hypotension and to potentiate the pressor response to adrenaline. The drug also is said to inhibit serum cholinesterase although not as strongly as do crude extracts of *Tabernanthe Iboga*.

These three indole alkaloids have central stimulatory actions but different pharmacological properties. Therefore it was decided to study the effects of these and other psycho-active drugs on behaviour and physiological effects in both conscious and anaesthetised animals.

Methods and Materials

Experiments were performed on dogs, sheep and cats.

1. *Conscious animal experiments.* See Figure 1.

Dogs and sheep were surgically prepared with an exteriorized carotid artery. To measure blood pressure, the artery was cannulated with polyethylene tubing of a fixed length, which was inserted through a 17 gauge needle while the animal was conscious and without medication. The cannula was connected to a Statham Transducer Model P 23 AA. Sterile normal saline was infused into the side arm of the transducer dome, from a Thorp constant injection device set at a speed of 1 inch in 320 minutes using a 20 ml syringe. In this way the cannula was kept patent, and the mean arterial pressure was read at 5 second intervals on a galvanometer calibrated for direct reading. Blood pressure was then plotted on a graph. Electrocardiographic recording was made using the standard Lead 2.

The dogs were trained by regular and frequent conditioning to remain in a Pavlov type stand and harness. The sheep were kept in small wire cages during the experiment.

Injections were given intravenously at a constant rate through a polyethylene cannula inserted into the external jugular vein. Behavioural changes were noted in all conscious animal experiments.

2. *Anaesthetised animal experiments.*

Anaesthetised preparations were set up in the normal way. Dogs and cats were anaesthetised with Pentobarbitone 50 mg/kg intraperitoneally and more was given if and when necessary. A tracheal cannula was inserted. Intravenous injections were given by a cannula into the saphenous vein at a constant rate. Blood pressure was recorded using a mercury manometer connected to the carotid artery or in some cases if this was non functional (failed carotid loop dogs), femoral artery was used. E.C.G. was recorded using standard Lead 2, from needle electrodes.

Sheep were anaesthetised with Cyclopropane or intravenous Amylobarbitone sodium. Endotracheal tubes were inserted. E.C.G. and blood pressure were recorded, and injections given as in the conscious animal.

Anaesthesia was found to be difficult to control in sheep using Amylobarbitone sodium. The sheep showed a rapid recovery and continued injection of the barbiturate was needed throughout the experiment.

This resulted in rather large fluctuations in the level of anaesthesia obtained and fluctuations of blood pressure base line.

All drugs were given by intravenous injections as sterile solutions in normal saline. Adrenaline hydrochloride, noradrenaline bitartrate, acetyl chloride, histamine acid phosphate, serotonin creatinine sulphate were given at 10 minute intervals before the test drug and then repeated afterwards. The effects of carotid artery occlusion, vagus and cervical sympathetic chain stimulation were recorded before and after the test drug.

The test drugs were yohimbine hydrochloride 0.5 mg/kg, harmine hydrochloride 2 mg/kg, ibogaine hydrobromide 5 mg/kg, and phentolamine 0.5 mg/kg. Reserpine was given in various doses.

Results

It is proposed to present the data under the following headings, firstly the analysis of the responses to the administration of the five test standard substances (adrenaline, noradrenaline, acetylcholine, histamine and serotonin) in all the experimental animals. Secondly, the effect of each of the test compounds will be presented and thirdly, how these compounds modified the responses to the 5 standard substances.

The results of experiments with a total of 21 conscious animals (17 dogs, 4 sheep) are compared with those of a total of 18 anaesthetised preparations (11 dogs, 3 sheep, 4 cats).

I. In all animals whether conscious or anaesthetised adrenaline, noradrenaline, acetyl-choline and histamine produced typical responses on blood pressure.

The most significant difference in responses to the five standard humors as shown by parallel studies in conscious and anaesthetised animals were changes in the heart rates. With adrenaline and noradrenaline the marked reflex slowing accompanying the pressor response in conscious dogs was not seen in the barbiturised animals. The marked increases in heart rate of conscious dogs injected with acetyl choline and histamine were absent in anaesthetised animals.

This can be readily explained by the anaesthetic agent inhibiting the reflex regulatory processes. The secondary fall in blood pressure after pressor response to adrenaline seen in anaesthetised cats and dogs was not apparent in the conscious dogs, nor in sheep whether conscious or anaesthetised. This is again ascribed to the effect of the anaesthetic agent on the compensatory processes.

Table I

Average values of all experiments

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TABLE 1

Average values of all experiments

		Nor-Adren. 2 γ/kg		Adren. 2 γ/kg		A. Ch. 0.4 γ/kg		Hist. 0.6 γ/kg	
		B.P. mm Hg	H.R. beats/min	B.P. mm Hg	H.R. beats/min	B.P. mm Hg	H.R. beats/min	B.P. mm Hg	H.R. beats/min
Dog	Conscious	+52	+10, −70	+40	+5, −65	−45	+90	−30	+70
	Anaesthetised	+49	+10	+50, −5	+12	−45	+10	−40	0
Sheep	Conscious	+55		+70		−30		−30	
	Anaesthetised	+45		+65		−30		−50	
Cat	Anaesthetised	+45	+5	+35, −15	+15	−65	−15		

A table of mean values of changes in all animals studied. Where two numbers appear on same line, this indicates a biphasic response in either a positive or negative direction as indicated.

The serotonin responses in animals tested were more varied than the other standard drug results.

Serotonin produced variable blood pressure responses in sheep and anaesthetised cats and dogs but did produce consistent rises in blood pressure of conscious dogs.

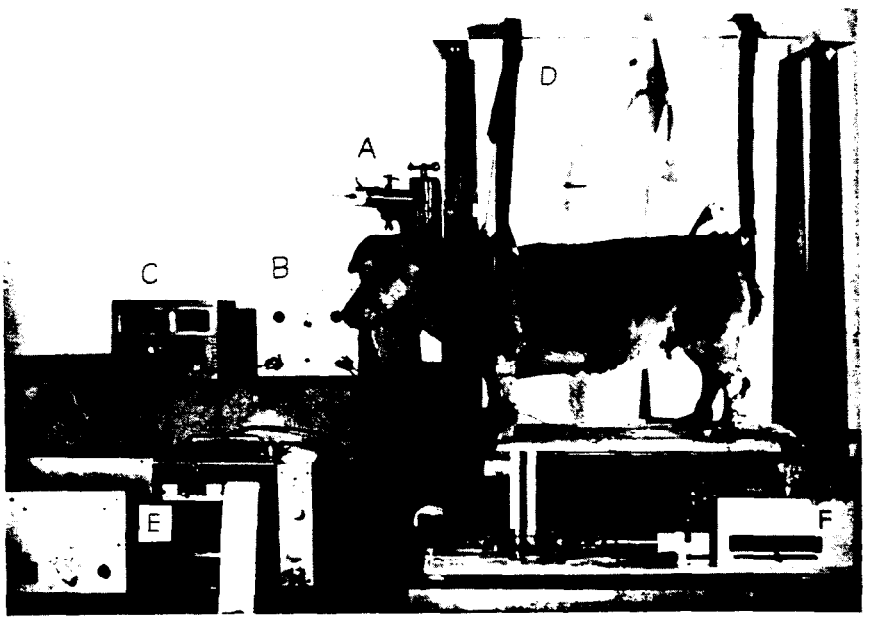

FIG. 1

Conscious dog experiment for observing changes in blood pressure, electrocardiograph and behaviour.

A. Statham transducer;
B. Constant voltage source;
C. Galvanometer;
D. Pavlov type stand and harness;
E. Electrocardiogram;
F. Thorp constant injector.

In conscious dogs the blood pressure rise was most consistent with in all cases an increase average value of 40 mm Hg, but in anaesthetised dogs the response was varied and included falls, rises and diphasic changes in blood pressure. Heart rate in conscious dogs was increased between 15–75 beats/min in all but one case with 5–7 μg/kg serotonin. Larger doses (10 μg kg) produced a diphasic change in heart rate with initially an increased rate and then a slowing. In all anaesthetised dogs the heart rate was slowed (5–60 beats/min at dose range 5–10 μg/kg

serotonin). In sheep under anaesthesia there was a fall in blood pressure of 10 mm Hg and very variable responses in conscious sheep. The blood pressure response of anaesthetised cats was also very variable.

Interpretation of blood pressure and heart rate responses to serotonin is therefore very difficult. In all anaesthetised preparations studied serotonin produced a " lightening of anaesthesia " with twitching and movement of the body and increase in respiratory rate and volume whether blood pressure rose or fell.

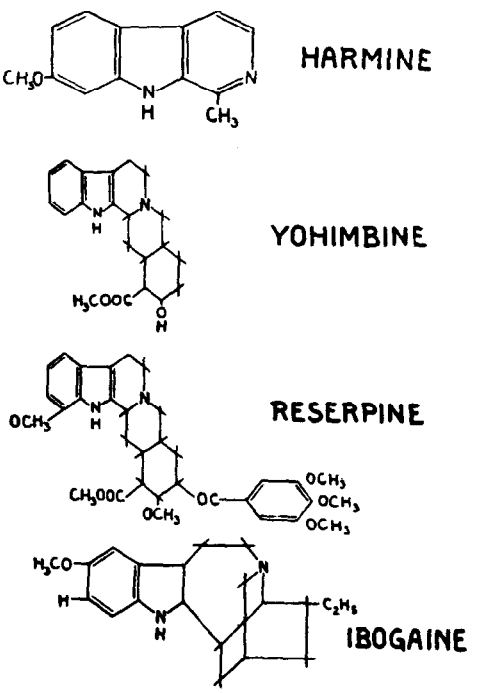

FIGURE II

Structural relationship of the indole alkaloids used in the study.

A.II. Yohimbine 0.5 mg/kg produced a rise in mean arterial blood pressure in conscious dogs and conscious sheep. In dogs the average blood pressure rise was 60 mm Hg, while in sheep the rise was smaller (20 mm Hg). In dogs the heart rate rose after yohimbine (80–190 beats/min) — see Table II. This agrees with findings in man (HOLMBERG and GERSHON, 12). The electrocardiogram changes in conscious dogs include tachycardia and an increase in T wave potential. This change is like that produced during exercise when it is claimed to be due to adrenaline/nor-adrenaline release. It is of significance that adrenaline

TABLE II

Stim. vag. indicates stimulation of vagus carried out at 10 volts, 10 pulses per second, for 2 seconds.
This table shows representative values obtained in some animals.

Yohimbine		Blood Press				Heart Rate			
		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Dog	0.5 mg/kg	155	−35						
		155	−55			95	+35		
		100	−32			95	+40		
Anaesthetised		130	−35			180	+20		
		Before Yohimbine		After Yohimbine		Before Yohimbine		After Yohimbine	
Nor adr.	2 γ/kg	160	+30	140	(+10) −40	90	+10	95	0
		160	+50	170	(+30) −30	110	+ 5	125	− 5
		145	+75	95	+30	120	−30	130	0
		145	+80	125	+45	200	+30	180	+20
Adr.	2 γ/kg	160	(+30) −30	140	−80	85	+10	100	0
		170	+60	160	−75	120	+20	130	+ 5
		140	(+80) −25	95	(+35) −20	120	−50	135	− 5
		140	+70	125	+45	200	+30	180	+20
Ach.	0.1 γ/kg	160	−20	140	−10	90	0	90	0
	0.4 γ/kg	160	−20	160	−60	110	+ 5	135	0
		155	−27	105	−20	140	+10	135	− 5
		145	−55	130	−45	[illegible]	[illegible]	[illegible]	[illegible]

TABLE II *(Continued)*

Yohimbine		Blood Press				Heart Rate			
		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.

			−25		−20				
		140	+70	125	+45	200	+30	180	+20
Ach.	0.1 γ/kg	160	−20	140	−10	90	0	90	0
	0.4 γ/kg	160	−20	160	−60	110	+ 5	135	0
		155	−27	105	−20	140	+10	135	− 5
		145	−55	130	−45	200	0	180	0

TABLE II *(Continued)*

Yohimbine		Blood Press				Heart Rate			
		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Hist.	0.1 γ/kg	160	−30	140	−25	90	0	95	− 5
	0.4 γ/kg	160	−45	165	−65	110	+ 5		
		150	−42	105	−30	120	− 5	130	+ 5
		140	−25	130	−20	200	−10	180	−20
Serotonin	5 γ/kg	160	+50	160	+70	110	− 5		
		145	−40	105	−30	125	−35	110	−25
	7 γ/kg	140	−10	140	−30	190	−40	160	−20
	10 γ/kg	135	+10	140	−15	180	−30	160	0
			(−15)		(+35)				
Occ. Carot.	10″	160	+40	135	+10				
		160	+55	165	+45				
		160	+30	105	+15				
		120	+15	110	+15				
Stim. Vag.		160	−50	140	−70				
		160	−85	160	−85				
		160	−50	105	−40				
		125	−30	120	−20				
Dog									
	0.5 mg/kg	125	+60			150	+80		
		140	+90			90	+190		
		115	+50			100	+160		
Conscious		115	(−30)						
			+45						

TABLE II *(Continued)*

Yohimbine		Blood Press				Heart Rate			
		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Nor Adr.	2 γ/kg	120	+30	155	+ 5	130	(30) −70	120	−10
		150	+35	185	0	125	−75	145	+25
		115	+65	145	+13	100	(+40) −60	160	−40
		100	+55	110	(85) −55				
Adr.	2 γ/kg	120	+30	135	+ 5	150	−100	110	+90
		140	+45	180	−30	120	−70	140	+120
		115	+55	150	−15	100	(+40) −60	160	−40
		120	0	110	−55				
Ach.	0.4 γ/kg	125	−35	140	−30	160	+40	140	−20
		140	−40	185	−35	100	+110	130	+110
		110	−25	140	−20	100	+20	160	+80
	0.1 γ/kg	110	−20	115	−30				
Hist.	0.6 γ/kg	120	−30	135	−23	170	+60	120	+90
		150	−40	190	−30	110	+80	140	+120
		110	−20	140	−10	100	+80	140	+60
	0.1 γ/kg	100	−10	110	−20				
				short duration					
Serotonin	5 γ/kg	120	+34	140	+26	155	+15	130	+70
		150	+50	190	+45	110	+30	160	−10
	7 γ/kg	115	+35	140	+70				
				short duration					+80

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TABLE II*a*

Stim. vag. indicates stimulation of vagus carried out at 10 volts, 10 pulses per second, for 2 seconds.

This table shows representative values obtained in some animals.

Yohimbine Results		Blood Pressure			
		Cont.	Diff.	Cont.	Diff.
		138	(−12)		
Anaesthetised Sheep			+ 6		
Yohimbine 0.5 mg kg		96	−10		
		Before Yohimbine		After Yohimbine	
Nor Adr.	2 γ/kg	128	+46	136	−24
		85	+45	90	−26
Adr.	2 γ/kg	130	+55	136	+16
		100	+65	98	+30
A.Ch.	0.4 γ/kg	135	−15	140	−13
		108	−38	96	−48
Hist.	0.4 γ/kg	135	−65	136	−56
		110	−50	100	−48
Serot.	7 γ/kg	134	−10	138	− 8
		90	−10	95	−19
Conscious Sheep		70	+20		
Yohimbine 0.5 mg/kg		56	+22		
Nor Adr.	2 γ/kg	70	+70	85	+50
		66	+50	60	+28
Adr.	2 γ/kg	70	+95	90	+30
		82	+80	64	+14
Ach.	0.4 γ/kg	75	−30	90	−30
		60	−13	64	−24
Hist.	0.4 γ/kg	70	−35	85	−50
		64	−29	60	−36
Serotonin	7 γ/kg	75	+35	90	+15
		60	(−48)	68	(−30)
			+23		+22

alone produces tachycardia without much elevation of the T wave whereas nor-adrenaline produces less tachycardia but much more elevation of the T wave.

Behavioural changes in the dogs include general body tremors, increased anxiety, restlessness, hypersalivation, diarrhoea, hyperventilation and dilatation of conjunctival blood vessels. In sheep the behavioural changes were very much less; the sheep became more alert, with ears pricked and legs extended.

This behavioural response in conscious dogs may be interpreted as an anxiety like reaction, simulating very closely the response elicited in man (HOLMBERG and GERSHON, 12).

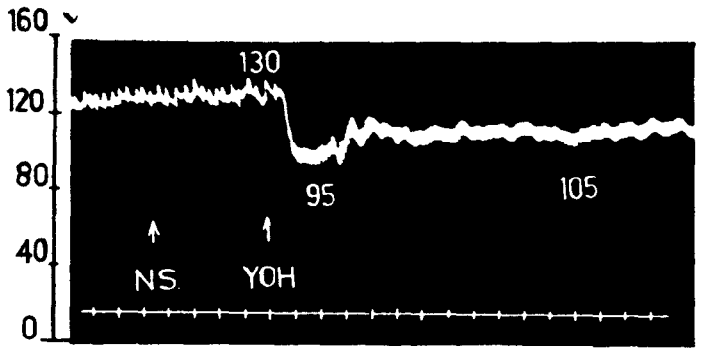

FIGURE III.

Blood pressure trace in an anaesthetised dog experiment.
Pressure in m.m.Hg; time scale units of 30 seconds;
N.S. intravenous injection of 2 cc normal saline;
YOH. injection of Yohimbine hydrochloride 0.5 mg/kg.

In all anaesthetised animals tested yohimbine produced a fall in blood pressure. In dogs, it produced an average fall in blood pressure of 35 mm Hg; again the effect was less in sheep under anaesthesia, the average fall being only 10 mm Hg. The heart rate of anaesthetised dogs rose by an average of 30 beats/min which was much less than in the conscious animals.

In anaesthetised dogs, sheep and cats yohimbine produced an apparent "lightening" of the anaesthesia with motor responses and an improvement in respiratory rate and volume.

A.III. Yohimbine has been shown to produce the classical reversal of adrenaline pressor response in all anaesthetised dogs; the pressor response of nor-adrenaline was reversed in some anaesthetised dogs

and inhibited in others (YONKMAN *et al.*, 35; HUTCHINSON *et al.*, 14; DELGA *et al.*, 7). The reversal of adrenaline response was shown in conscious dogs also, but in these preparations there was only an inhibition of nor-adrenaline pressor response.

In conscious and anaesthetised sheep yohimbine produced an inhibition of pressor response to adrenaline and nor-adrenaline, and in no cases a reversal — see Table II*a*.

In conscious dogs the heart rate response to adrenaline and nor-adrenaline after yohimbine always appeared to be reflex depending on the state of the blood pressure change. In the anaesthetised preparations yohimbine did not significantly effect the heart rate changes after adrenaline and nor-adrenaline.

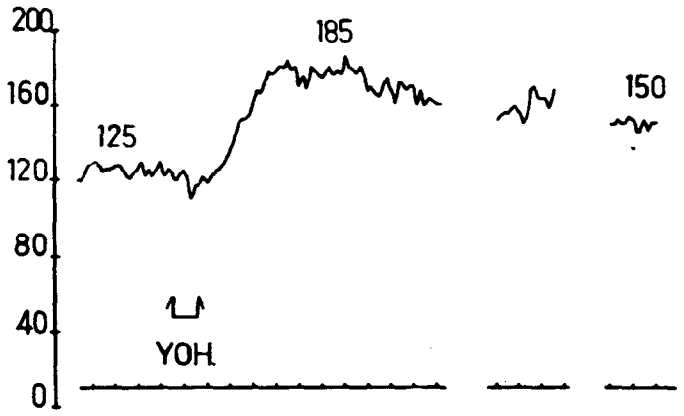

FIGURE IV

Blood pressure graph in a conscious dog experiment.
Pressure in m.m.Hg; time scale units of 30 seconds;
YOH. injection of Yohimbine hydrochloride 0.5 mg/kg.

Yohimbine has a slight potentiating action on the acetyl-choline depressor response, and no difference in this is apparent whether the animal is anaesthetised or conscious. Changes in heart rate do not appear significant.

Histamine responses on blood pressure are not significantly modified by yohimbine in any animals studied. In conscious dogs there was some indication that the heart rate rise after histamine was greater following yohimbine.

Yohimbine caused essentially a diminution of the pressor response to serotonin in conscious dogs and sheep. Of more significance was the effect on duration of the response to serotonin. This was much less

TABLE III

Stim. vag. indicates stimulation of vagus carried out at 10 volts, 10 pulses per second, for 2 seconds. This table shows representative values obtained in some animals.

Dog	Harmine	Blood Press				Heart Rate			
Conscious		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Harmine	2 mg/kg	100 145 Before Harmine	+50 +125	After Harmine		150 100 Before Harmine	− 0 +140	Variable H.R. Not recordable After Harmine	
Nor Adren.	2 γ/kg	140 90	+50 +75	160 100	+30 +50	150	−95	130 140	−80 −40
Adren.	2 γ/kg	140 90	+30 +55	140 105	+45 +75	100 135	−70 −80	120 175	−70 −105
Acetyl Choline	0.4 γ/kg	140 95	−50 −55	170 110	−50 −40	90 150	+150 +70	110 140	+90 +120
Histamine	0.4 γ/kg	140 95	−30 −35	140 105	−35 −25	110 160	+90 +40	120 155	+80 +40

95 | −35 | 105 | −25 | 160 | 40 | 155 | 40

TABLE III *(Continued)*

Harmine *Dog*		Blood Press				Heart Rate			
Anaesthetised		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Serotonin	5 γ/kg	140	0	140	0	120	−50	110	+20 (−10)
		95	+45	110	+35	130	+45	150	+70
Harmine	2 mg/kg	150	−30			95	−40		
Nor Adren.	2 γ/kg	140	+70	140	+60	90	+10	80	+25
Adren.	2 γ/kg	140	+100	130	+125	100	+40	65	+65
Acetyl Choline	0.1 γ/kg	140	−10	150	−20	90	+ 5	95	+ 5
Histamine	0.1 γ/kg	140	−10	150	−35	90	0	90	+10
Occl. Carotid	10″	140	+15	145	+15				
Stim. Vag.		140	−55	150	−60				

after yohimbine, and in fact became merely a very transient rise with restoration to the previous base line.

In anaesthetised dogs yohimbine inhibited the pressor response produced by occlusion of the carotid artery as reported by NICKERSON (22), but had no significant effect on the depressor response to electrical stimulation of the vagus nerve.

B.II. Phentolamine produced a fall of blood pressure in dogs whether conscious or anaesthetised. Their heart rate was increased after phentolamine but the increase in rate was greater in conscious than in anaesthetised dogs. No significant change in behaviour of conscious dogs was observed.

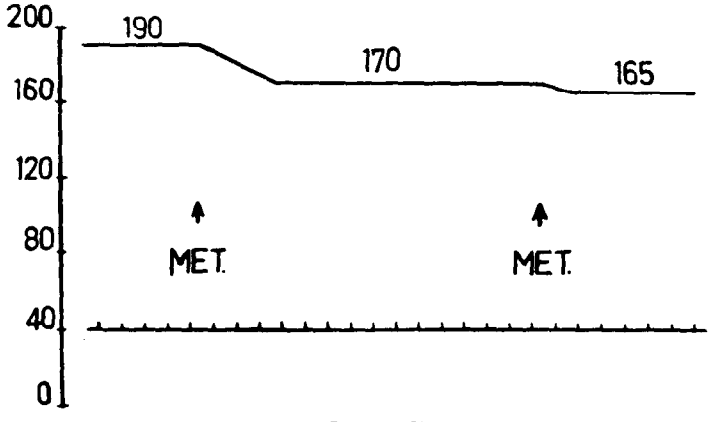

FIGURE V.

Diagrammatic representation of blood pressure graph in conscious dog. Blood pressure at 190 m.m.Hg after Yohimbine hydrochloride 0.5 mg/kg. MET. injections of methaminodiazepoxide " Librium " 10 mg showing fall in blood pressure produced at the same time as a decrease in anxiety.

B.III. The pressor response to nor-adrenaline was diminished in conscious and anaesthetised dogs after phentolamine, while the response to adrenaline was reversed in both cases. Heart rate changes were not significantly affected by phentolamine except in anaesthetised dogs when a diminished acceleration of heart rate was produced by adrenaline after the test drug. Acetyl-choline and histamine responses on blood pressure and heart rate were not modified in any animals tested. Phentolamine antagonised serotonin responses on blood pressure in conscious and anaesthetised animals. The pressor responses to occlusion of the carotid artery and electrical stimulation of the cervical sympathetic were diminished after phentolamine.

C.II. Harmine produced a rise in mean arterial blood pressure in conscious dogs and sheep with an increase in heart rate — see Table III. In conscious dogs, the electrocardiogram showed a variable tachycardia alternating with bradycardia and a slight increase in potential indicating a possible axis shift.

Anaesthetised dogs, sheep and cats showed different cardiovascular responses, after harmine. The blood pressure and heart rate fell in all anaesthetised animals tested.

The modifications of the standard drug responses by harmine were as follows : the action of nor-adrenaline was not significantly affected by harmine. The pressor response to adrenaline was however potentiated by harmine in all animals. This agrees with the findings of MARINESCO *et al.* (19) in man. There was no significant modification of the responses to acetyl-choline, and histamine.

The blood pressure changes due to serotonin were inhibited. This is of interest in view of the report that harmine is an inhibitor of monoamine oxidase (HORITA and MCGRATH, 13). Harmine caused an increase in the heart rate after serotonin.

Harmine did not significantly modify the blood pressure changes due to occlusion of the carotid artery or electrical stimulations of the vagus nerve.

D.II. Ibogaine produced a rise in blood pressure and an increased heart rate in conscious dogs — see Table IV. The changes in the electrocardiograms of conscious dogs indicated that ibogaine accentuates sinus arrhythmia by potentiating vagus effects. The electro-potential variations were greater, probably due to alteration of the axis of the heart by increased respiration. In anaesthetised dogs, the blood pressure fell and the heart rate was reduced. This is in agreement with report of SCHNEIDER and RINEHART (27), and is similar to the harmine and yohimbine responses except that yohimbine slightly increased the heart rate in anaesthetised dogs.

D.III. Ibogaine inhibited the acetyl-choline hypotensive response in the anaesthetised preparation as has also been shown by SCHNEIDER and RINEHART (27).

In anaesthetised dogs ibogaine potentiated the pressor response to both adrenaline and nor-adrenaline. In the conscious animals the changes were qualitatively similar.

The serotonin pressor response was potentiated in conscious and anaesthetised dogs.

TABLE IV

Stim. vag. indicates stimulation of vagus carried out at 10 volts, 10 pulses per second, for 2 seconds. This table shows representative values obtained in some animals.

Ibogaine *Dogs*		Blood Press				Heart Rate			
Conscious		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Ibogaine	5 mg/kg	120 140 Before Ibogaine	+45 + 5	After Ibogaine		135 90 Before Ibogaine	+75 +50	After Ibogaine	
Noradren.	2 γ/kg	105 110	+55 +80	135 140	+65 +70	140 70	−90 −30	155	−60
Adren.	2 γ/kg	115 105	+45 +45	140	+75	160 80	−80 −40		
Acetyl Chol.	0.4 γ/kg	115 110	−40 −40	140 140	−60 −50	130 70	+130 +70	150	+110
Histamine	0.4 γ/kg	115 120	−10 −15	140	−15	130 80	+100 +65		
Serotonin	7 γ/kg 11 γ/kg	100 120	+50 +50	125 140	+50 +70	130 70	+55 +75 (−15)	150	+70

TABLE IV *(Continued)*

Ibogaine *Dogs*		Blood Press				Heart Rate			
Conscious		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.

TABLE IV *(Continued)*

Ibogaine *Dogs*		Blood Press				Heart Rate			
Conscious		Cont.	Diff.	Cont.	Diff.	Cont.	Diff.	Cont.	Diff.
Anaesthetised									
Ibogaine	5 mg/kg	170 135	−45 −25			150	−50		
Noradre.	2 γ/kg	170 170	+30 +25	165 120	+45 +85	170	+15	115	+35
Adren.	2 γ/kg	170	+20 (−20)	165	+45				
	3 γ/kg	170 165	+10 +35	130 150	+70 +95	170	+15	120	+35
Acetyl Choline	0.4 γ/kg	180 180	−70 −85	155 125	−45 −45	180	+15	120	0
Histamine	0.6 γ/kg	160 150	−25 −30	160 145	−40 −45	155	0	130	−20
Serotonin	7 γ/kg	170 160	+30 −25	160 140	+50 (−25) +20	165	−25	130	−10
Occl. Carotid	10″	140	+20	120	+ 5				
Stim. Vag.		140	−20	115	− 5				

No significant effects of ibogaine could be seen on the heart rate changes induced by acetyl-choline, histamine and serotonin.

Ibogaine in anaesthetised dogs blocked the blood pressure responses to occlusion of the carotid, and electrical stimulation of the vagus nerve.

E.II. Differences in response of conscious and anaesthetised dogs were also apparent with reserpine. In both cases a slowly developing slight fall in blood pressure occurred, but this was preceded by an initial rise in blood pressure in the conscious dogs. An initial phase of restlessness preceded the slow development of sedation in the conscious dogs. Heart rate increased in the conscious dogs during the initial stage of excitement.

In the anaesthetised dogs the reflex rise in blood pressure in response to occlusion of the carotid artery was abolished, but the response to electrical stimulation of the vagus nerve was not affected (PLUMMER *et al.*, 23).

DISCUSSION

From this study it is obvious that the responses to centrally acting drugs in conscious animals are at variance with those in anaesthetised preparations. The assessment of the pharmacological and haemodynamic effects of psycho active compounds has in the past always been carried out in anaesthetised or curarised animals (MAXWELL *et al.*, 20; MOYER *et al.*, 21; SPURR *et al.*, 31).

Furthermore since the action of these centrally acting drugs may modify or be modified by the effect of the anaesthetic or the neuro muscular blocking agent it would therefore be difficult to delineate clearly the actions attributed to the psycho active drug itself.

In fact the results obtained with the various indole alkaloids studied indicate a very distinct difference between the pharmacological and haemodynamic responses induced by these compounds in anaesthetised and conscious animals. There is a good deal of evidence for central activity of yohimbine, harmine, ibogaine and reserpine. Behavioural changes in conscious dogs were evident after injection of all the indole alkaloids investigated. Yohimbine, harmine and ibogaine all produced increased anxiety, with the dogs becoming more tense and alert. Extreme agitation and nervousness followed the use of harmine and these animals became less tractable and easy to handle. After ibogaine and harmine the dogs showed lack of recognition of their regular handlers and of their environment. Body tremor and shaking was apparent in all dogs

and sheep after the three alkaloids and in the case of ibogaine the dogs adopted a peculiar stance with legs apart and back arched. The use of reserpine in dogs produced an initial stage of excitation shown by increased restlessness and anxiety, followed by a slowly developing sedation. A similar biphasic response in man has also been observed by BRUNE and HIMWICH (3).

In anaesthetised cats, dogs and sheep yohimbine, ibogaine and harmine all produced an analeptic effect with " lightening of anaesthesia ", body twitching and movements, as well as increased depth and rate of respiration. This effect was of interest because of the reported yohimbine potentiation of barbiturate sleeping time in mice (KILLIAM *et al.*, 15).

The increased anxiety and the blood pressure rise produced by yohimbine in conscious dogs were counteracted by central nervous system depressants as was seen with the two compounds tried namely amylobarbitone and methaminodiazepoxide " Librium ". (FIG. 5).

Cats under pentobarbitone anaesthesia were prepared with denervation of both carotid sinuses. In this preparation the harmine potentiation of the pressor responses to adrenaline and nor-adrenaline is very obvious. Here also ganglion blockade with Tetraethylammonium iodide prevents this potentiation, suggesting that this effect is not due to action on the effector cell itself or through carotid sinus innervation. In a cat preparation with physiological decerebration produced by removing the blood supply to the cerebral cortex, no hypertensive effect was produced (CAIRNCROSS, LANG and GERSHON, 4).

Behavioural changes, presumably due to central effects of the indole alkaloids studied are widely reported in the literature.

Yohimbine has been reported to produce a psychic effect in man resulting in an anxiety type state (HOLMBERG and GERSHON, 12). The anxiety response to yohimbine is said to be much greater than with adrenaline and to be of central origin. The central nervous system depressants and stimulants studied inhibited and potentiated, respectively, both the autonomic and the psychic effects of yohimbine which is interpreted as further support for the view that the yohimbine effects are to a great extent centrally mediated. The potentiation of anxiety responses both behaviourally and physiologically was most marked when yohimbine was superimposed on a course of imipramine. It is of interest here that the central actions of imipramine are postulated to be adrenergic (SIGG, 30). Yohimbine was also shown to activate the more or less latent psychotic processes of some schizophrenic patients. There followed an increase in general reactivity, active hallucinations, ex-

pression of delusions and demonstrations of disturbance in behaviour. However yohimbine is not psychotogenic in normals (HOLMBERG and GERSHON, 12).

Harmine was reported to have been used by American Indians during feasts and festivities to produce hallucinations (CHEN and CHEN, 5). These authors claimed monkeys treated with harmine demonstrated a trembling of the body, unsteady gait and tendency to stay in one corner of their cage. In larger doses the monkeys showed arching of their back, stiffening of their legs, shaking all over and clonic convulsions. HOFFER *et al.* (11) described harmine as an hallucinogen but this claim was disputed by TURNER *et al.* (32). This latter view is supported by HALPEN (10). Here it is stated that harmine in non psychotic man produced increased anxiety, tremor, pressing restlessness and aggressive acts without evidence of hallucinations or euphoria. This description for harmine is closely identical with that reported for yohimbine by HOLMBERG and GERSHON (12). We found with harmine that conscious dogs became restless and anxious with apparent hallucinations as was reported by VON FERDINAND (34). Motor paralysis and clonic convulsions of a central nature produced by harmine were described by CHIKASOLO (6). This action on the central nervous system was firstly stimulant and then depressant, and the convulsions were suppressed by ether inhalation.

Ibogaine was also described as an hallucinogen. It was claimed to enhance the potentiation of barbiturate sleeping time by serotonin and reserpine in mice (SALMOIRAGHI and PAGE, 26). SCHNEIDER and RINEHART (27) showed ibogaine had a hypotensive effect in anaesthetised dogs whereas in the unanaesthetised dog it caused a rise in blood pressure. This was considered to be due to a central stimulatory component in its action. SCHNEIDER and SIGG (28) reported that the alkaloid of Tabernanth Iboga (Ibogaine) had an unusual type of excitatory effect on various experimental animals. Conscious cats became markedly excited with dilated pupils and developed tremors that gradually merged into an actual picture of rage. Electroencephalographic studies showed that the pattern obtained after ibogaine resembled that after direct stimulation of the reticular formation in cats. The compound produced an alerting or analeptic effect under barbiturate anaesthesia. Ibogaine failed to produce any arousal syndrome after premedication with atropine (SCHNEIDER and SIGG, 28). SCHNEIDER and RINEHART (27) claimed that atropine prevented the rise in blood pressure produced in conscious dogs by ibogaine. We have confirmed this effect on blood pressure in conscious dogs but the behavioural changes in the dogs were not affected.

From our own experiments in man and animals and reports in the literature it would now appear that the chief central effects of these alkaloids are an anxiety type response in normal man and an activation of psychotic processes in schizophrenic subjects. This distinction is of the utmost theoretical importance in that these compounds may fall into a very special group of psychotominietic agents.

The behavioural effects of yohimbine in dogs resemble those seen in man. In man the behavioural changes have been correlated with anxiety while in dog the changes can be correlated with physiological responses. Therefore yohimbine can be considered to produce a " model anxiety " state in dogs and man which lends itself to use as a screening test for anti-anxiety drugs.

All three alkaloids produced a rise in blood pressure in the conscious and a fall in the anaesthetised preparations. The heart rate increased in all conscious animals whereas it was decreased in all anaesthetised animals with the exception of yohimbine where there was a slight rise. This smaller increase in heart rate in the anaesthetised preparation after yohimbine may be a result of:

(1) the anaesthetic agent dampening the central effect of the drug on anxiety and this having a resultant smaller increase in heart rate,

(2) or the rise in heart rate may be only due to reflex mechanism following the fall in blood pressure.

This latter explanation is not likely to be an important factor as the heart rate slows with the hypotensive effect of harmine and ibogaine in anaesthetised animals.

These rises in blood pressure and increase in heart rate in all conscious animals are understandable only if stimulation of central alerting systems is postulated. It has been adequately demonstrated that the reactivity of the reticular activating system is diminished in the anaesthetised state (FRENCH *et al.*, 8).

The hypotensive effect of yohimbine in dogs was shown with the following anaesthetics; pentobarbitone, chloralose and urethane and ether. This agreed with the findings in cats reported by HUTCHINSON *et al.* (14) that the result did not depend on the type of anaesthetic used. Thus the cardiovascular responses to these indole alkaloids in the non-anaesthetised preparations may well be in part or whole the resultant of the central stimulatory actions of these compounds.

It has been postulated by SCHNEIDER and SIGG (28) that the central stimulant effect of ibogaine is through cholinergic mechanisms of the ascending reticulating formation. This is certainly not the explanation of the mode of stimulation of yohimbine and harmine where the

pressor effect in the conscious preparation is not blocked by premedication with atropine (LANG and GERSHON, 18).

These several alkaloids studied however did not differ in their effects on the five neuro humors in the anaesthetised and non anaesthetised preparations. Although different pharmacological effects are manifested by each individual alkaloid, yet the overall effect on blood pressure was the same with all alkaloids. It is interesting in this context to compare especially the effects of yohimbine with those of another adrenolytic agent phentolamine. This compound produced a fall in blood pressure in both the conscious and anaesthetised animal. Further no behavioural effects were observed on our dogs with the drug. GOODMAN and GILLMAN (9) report that phentolamine has no central nervous system effects and this may be the explanation for the similarity in the blood pressure response in our conscious and anaesthetised animals.

This study demonstrates the factors that modify cardiovascular responses and illustrate the limitations that are inherent in the standard anaesthetised preparation. It is felt that central actions of drugs are modified or even distorted in this standard type anaesthetised preparation. Therefore one might propose that comparative studies should always be carried out but especially when psychoactive drugs are being investigated.

SUMMARY

1. The indole alkaloids yohimbine, harmine and ibogaine produce different cardiovascular responses in conscious as compared to anaesthetised animals.

2. These alkaloids produce behavioural changes in conscious animals and man indicating central stimulatory actions.

3. Different pharmacological properties of the individual alkaloids have been confirmed.

4. Utilisation of the " model anxiety state " produced by one of these compounds is proposed as a screening test for anti-anxiety agents.

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