EUROPEAN JOURNAL OF PHARMACOLOGY 12 (1970) 289–296. NORTH-HOLLAND PUBLISHING COMPANY

RELATIVE ACTIVITY OF PSYCHOTOXIC DRUGS ON THE AVIAN OPTIC LOBE * **

Norman W. SCHOLES *** and Michael J. GUTNICK
Department of Physiology and Pharmacology,
School of Veterinary Medicine, University of California,
Davis, California 95616, USA

Received 23 January 1970 Accepted 9 July 1970

Norman W. SCHOLES and Michael J. GUTNICK, *Relative activity of psychotoxic drugs on the avian optic lobe*, European J. Pharmacol. 12 (1970) 289–296.

Because of restrictions in the use of psychotoxic drugs in the human, a subhuman experimental tool suitable for the study of these drugs and their antagonists would be useful. Using standard electrophysiological techniques, the action of psychotoxic drugs on the electrical activity of the optic tectum of the young chick has been studied. The intravenous administration of lysergic acid diethylamide I(SD) to this animal produces a well defined and consistent change in tectal activity. A comparable change occurs following administration of other psychotoxic agents (psilocybin, mescaline and amphetamine). The relative potency of these agents on tectal activity compares favorably with their relative psychotoxic potency in man. These results favor the view that the mechanism of action of these psychotoxic agents on the chick tectum resembles, to some degree, their psychotoxic properties in man. It is suggested that the avian preparation may be useful for the study of the pharmacology of psychotoxic drugs and antagonists.

Psychotropic drugs Avian optic lobe Hallucinogens
Neuropharmacology Optic lobe, avian LSD

1. INTRODUCTION

Ultimately, the effect of psychotomimetic or antipsychotic drugs on the behavior of man must be obtained from direct studies in man. However, because of legal restrictions regarding such drugs, human experimentation is difficult.

Therefore, in order to obtain objective, quantitative data regarding sites and mechanisms of action and to conduct preliminary studies on these drugs, it would be convenient to have available reliable animal tests.

The present report is concerned with a study of the activity of psychotoxic drugs on the electrophysiology of avian tectum. The results suggest that this system may prove to be a useful tool for extended studies of the mechanisms of action of and potency of psychotomimetic and anti-hallucinogenic drugs.

2. METHODS

Experimental animals were New Hampshire strain chickens between 1 and 2 weeks old of either sex.

* Supported in part by U.S. Public Health Service Grant FR 05457–04, GRS 67–23.

** This work has been previously reported in part to the Western Pharmacology Society (Proc. West. Pharmacol. Soc. 8 (1965) 1 and the Second Congress Latino-Americano de Farmacologia, 1965.

*** Present address: Department of Physiology and Pharmacology, Creighton University, School of Medicine, Omaha, Nebraska 68131, USA.

They varied in weight between 70 and 90 g. A total of 100 birds, 10 each from separate hatches were used. The chicks were prepared for the recording of bioelectric potentials from the optic tectum, the electrocardiogram and blood pressure, as described in detail elsewhere (Scholes and Roberts, 1964; Scholes, 1966).

Briefly these methods are as follows: Surgical procedures were completed under ether anesthesia. The chicks were then immobilized with d-tubocurarine, and topically anesthetized with lidocaine at all operative sites. Artificial respiration was administered by the unidirectional air flow technique described by Burger and Lorenz (1960).

Monopolar recording of bioelectric activity from the exposed dorsal surface of the optic tectum was referred to an independent electrode embedded in the curarized neck musculature. Potentials were differentially coupled in the usual manner to an A.C. amplifying system with paper write-out. Recordings were obtained continuously before, during and after drug administration. The recordings for the traces shown in fig. 1 were obtained on a Sandborn Heat Recorder interfaced with Tectronix Type 122 Preamplifier. The traces shown in the remaining figures were recorded on a Dynograph Ink Stylus Instrument using a Grass P-511 high gain preamplifier. The voltage-gains in each case were as reported in the legends.

Simultaneous recordings on an electronic tape recorder (ampex 400) for averaging were also obtained. Tape output was run through a second high-gain preamplifier to a computer of average transients (TMC Cat. 400B) was employed (see fig. 2). Evoked potentials were generated by stimulation of the dark adapted, intact eye with a Strobe Lamp (American Electronic Laboratories Model 127). Stimulation frequency of one stimulus every ten

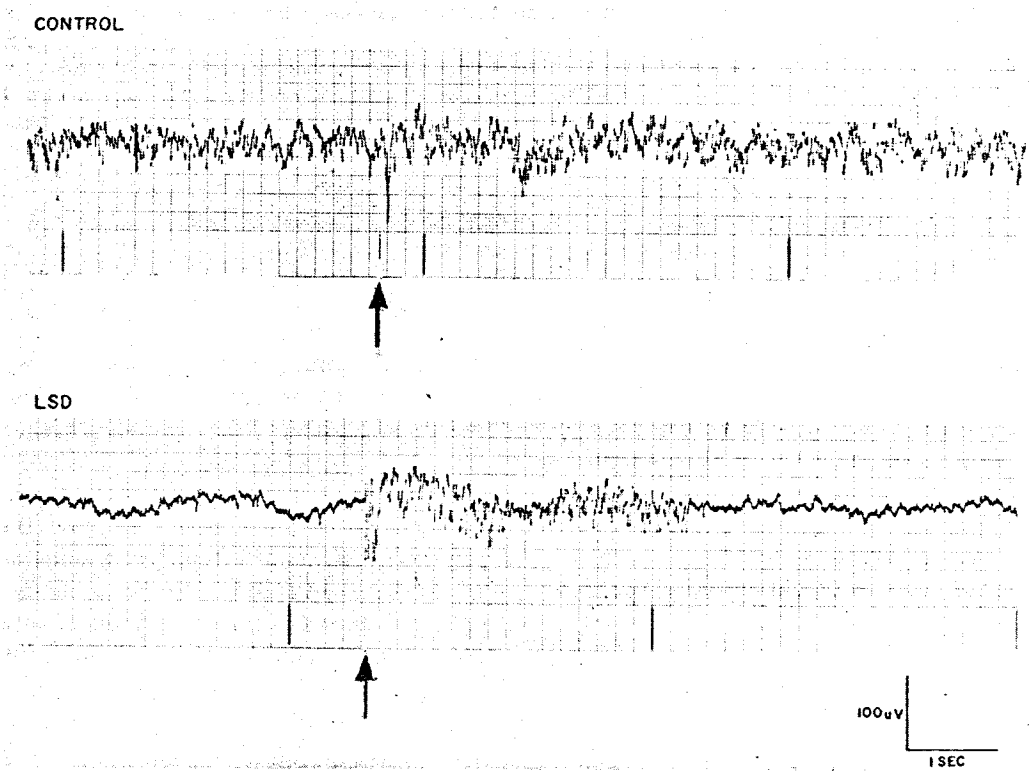

Fig. 1. Polygraph tracings of the spontaneous and photically evoked bioelectric activity recorded from the avian optic lobe. In this and the other figures, electrical negativity is recorded as a downward deflection. Time and amplitude scales are as indicated. Arrow denotes stimulus. *Upper trace*: control. *Bottom trace*: 16 min after beginning administration of 12.5 μg (total dose) of LSD-25.

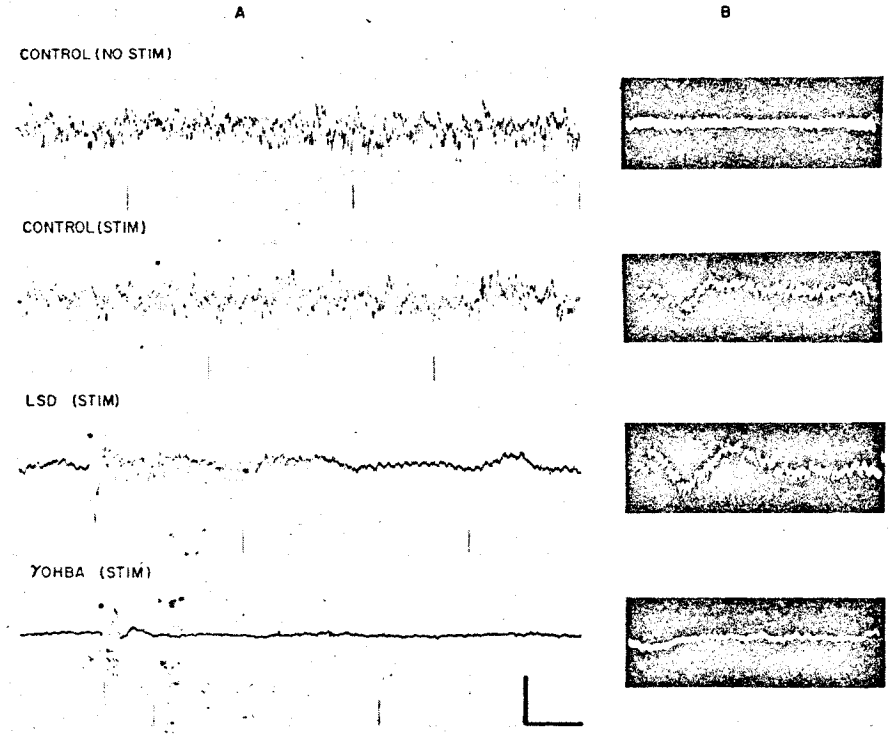

Fig. 2. A: Polygraph tracings of spontaneous and evoked tectal biopotentials. Top trace, control without stimulus. Second trace, control with stimulus. Third trace, 17 min after beginning administration of 12.5 μg (total dose of GOHBA, Scholes, 1966). Dot above each trace indicates stimulus.
B: Averages of 270 runs of tectal activity corresponding to conditions in (A). Sample duration is 4 sec beginning 1 sec post stimulus (see text). Bars in lower trace refer to time (horizontal) of 1 sec and amplitude (vertical of 100 μV for (A) and 40 μV for (B).

Table 1

	Tectal response		Halucinations in man
	Mean effective response[a] (±S.D.) (mg/kg)	Ratio of dose levels to produce	Ratio of dose levels to produce
LSD	0.17 ± 0.095	1	1[b]
Psilocybin	5.10 ± 0.40	30	40[b]
Mescaline	96.5 ± 3.7	565	3000[b] 2970[c] 1000[d]
Amphetamine	191 ± 10.3	1124	950–2500[e]

[a] $n = 20$.
[b] Values calculated from data reviewed by Downing, 1964.
[c] Wolbach et al., 1962.
[d] Jacobsen, 1963.
[e] Herman and Nagler, 1954.

seconds and stimulus intensity were controlled by an electronic stimulator (American Electronics Model 140A).

All drugs were administered intravenously by slow infusion (0.08 ml/min) through the femoral vein. In each case the infusion is continued until a maximal or characteristic response occurs. The average effective dose of LSD-25 * ** administered by this technique was 0.17 μg/g of body weight (see table 1). For an 80 g chick this amounted to 13.6 μg or 1.36 ml (see below). At an infusion rate of 0.08 ml/min the maximal response occurred after 17 min. On average, the change in tectal electrical activity occurred rapidly, usually within a minute or two of maximal response. The advantages and disadvantages of the slow infusion method when comparing these results with those of others have been discussed in detail elsewhere (Scholes and Roberts, 1964).

3. MATERIALS

LSD-25 and psilocybin used for this study were supplied in 100 μg (LSD) and 3 mg (psilocybin) vials of solutions. Mescaline hemisulfate and d-amphetamine were obtained in crystalline form from commercial sources. All drugs were prepared and administered as aqueous solutions in the following concentrations (mg/ml): 0.01 LSD; 1 psilocybin; 10 mescaline; 20 d-amphetamine. At these concentrations the total volume administered was usually less than 1.5 ml.

4. RESULTS

When an electrode is placed upon the dorsomedial surface of the optic tectum of a one to two week old chick and suitably coupled to a recording device, an electrical signal (top trace, fig. 1) is obtained. This signal consists of spontaneous potentials. This activity is not unlike the usual electroencephalographic recording in mammals and consists of primarily negatively directed potentials having a frequency of 25–35 cps superimposed upon low voltage slow waves of 1–3 cps. The dominant or high frequency component has amplitudes of 40–70 μV while the slower frequencies rarely exceed 15 μV.

During a recording a brief flash of light applied to the intact eye contralateral to the tectum from which the recording is obtained causes an evoked potential of larger amplitude (200–300 μV) occurring 15 msec after the stimulus (fig. 1, arrow).

Previous studies have shown that both spontaneous and evoked activities can be altered in different ways by various centrally acting drugs: e.g. GABA (Scholes and Roberts, 1964), pentobarbital (Ibid), and GOHBA (Scholes, 1966).

A different effect in tectal electrical activity is observed following the administration of LSD-25 (fig. 1, 2, column A, and fig. 3). In this case the amplitude of the high-frequency spontaneous activity is depressed, and the evoked response is often enhanced both in amplitude and frequency but never depressed.

A prominent feature of the LSD-25-induced change is the occurrence of a prolonged discharge of negative potentials after the evoked response (hereafter referred to as after-discharge). This lasts for one to three seconds with amplitudes of the order of 40 to 60 μV (figs. 1, 2 and 3).

Because of the possible implications of the relationship between a decrease in amplitude of spontaneous potentials which may or may not be similar to activation, desynchronization or randomization and the occurrence of a high-frequency, prolonged after-discharge in central visual-sensory elements following administration of a potent hallucinogen, it was important to establish whether this response occurred as a consequency of drug action or is a normal feature of recordable activities which is here unmasked by LSD-25 through depression of background activity.

The computer of average transients was employed to test this possibility. Magnetically taped records of tectal activity were evaluated by averaging 270

* Abbreviations:
LSD-25: lysergic acid diethylamide
GABA: γ-aminobutyric acid
GOHBA: γ-hydroxybutyric acid
BOL 148: 2-brom-d-lysergic acid diethylamide

* The LSD-25 and psilocybin and 2-brom-d-lysergic acid were supplied by Sandoz Pharmaceutical Company through the U.S. Food and Drug Administration by application to the National Institute of Mental Health, Psychopharmacology Division (Ref: IND 4027).

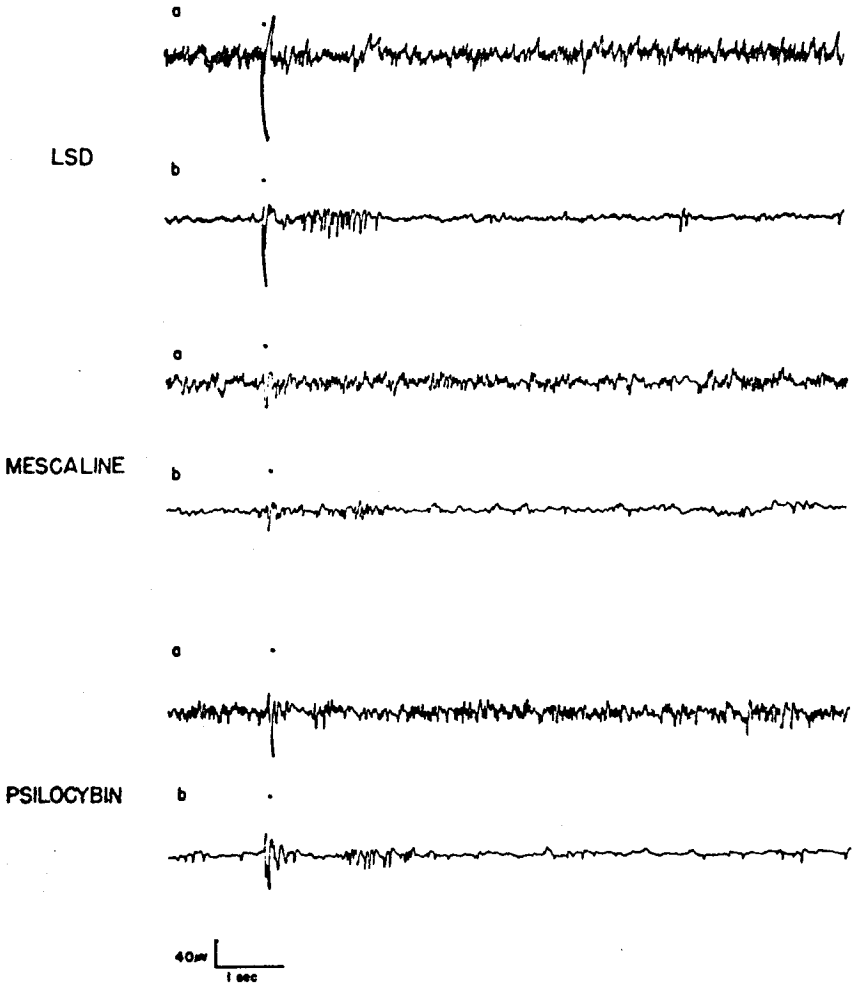

Fig. 3. Polygraph tracings of tectal activity for conditions indicated. (a) control record; (b) during maximal response change for each drug (see text). Time-voltage parameters as indicated. Dot indicates stimulus.

samples of normal activity coinciding in time with the after potentials observed following LSD. Individual parameters of the recordable spontaneous activity were then selectively depressed using the appropriate drug (see preceeding) and the averaging repeated. The averages obtained are shown in fig. 2, column B. In each case analysis time was four seconds at a frequency of once every ten seconds. The synchronizing pulse was obtained from the photostimulator, a preanalysis delay of one second was employed to remove the evoked response from the average.

The results (fig. 2, column B) show that in the absence of a synchronizing signal or an evoked response, a four-second run once every ten seconds resulted in an average characteristic of random activity (top trace, column B). When a stimulus was applied and the averaging repeated, coherent activity became evident (second trace, column B). When all the spontaneous activity except the after-discharge was depressed with LSD-25, a repeat of the averaging again showed coherent activity of a nature similar to the previous recording. Finally, when GOHBA was administered to inhibit after-discharge, coherent activity was virtually absent.

These data strongly suggest that the after-discharge observed following LSD-25 administration is a normal component of evoked activity in the tectum. The after-discharge is uncovered through the action of

LSD-25 on spontaneous background electrical activity, and may be enhanced in amplitude and prolonged in duration by the action of this drug.

4.1. *Comparative activity of other psychotoxic agents*

The tectal response to LSD-25 administration has been shown to be different from that obtained from several other centrally acting drugs (cp. Scholes, 1966). In order to evaluate the possibility that the LSD-25-induced response might be related to its psychotoxic properties in man, two other drugs, psilocybin and mescaline which are chemically different, but have pharmacologic properties similar to those of LSD-25 in man, were obtained for these studies.

Following i.v. administration both drugs altered the electrical activity of the tectum in a manner unmistakably similar to that caused by LSD-25 (fig. 3). In each case these drugs depressed the high-frequency component of the spontaneous activity, enhanced the evoked response and unmasked an after-discharge.

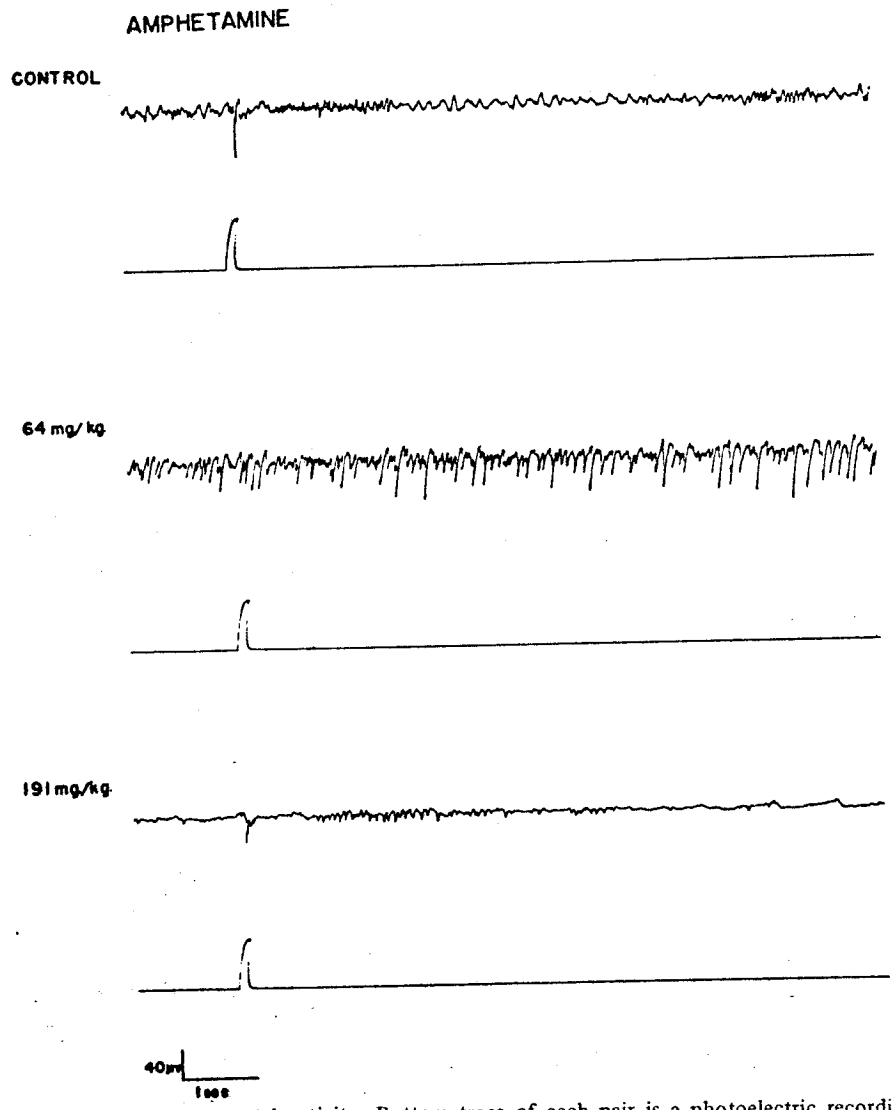

Fig. 4. Effect of d-amphetamine on tectal activity. Bottom trace of each pair is a photoelectric recording of the stimulus. Time-voltage parameters as indicated.

In order to evaluate further the concept that the psychotoxic properties of these drugs and the pharmacological activities on the avian tectum are related, two additional drugs were tested.

The 2-brom derivative of LSD-25, 2-BOL 148, which is known to have little or no hallucinatory activity in man, was administered under identical conditions. Dosages of 2-BOL 148 ten times in excess of the active dose of LSD-25 produced no marked change in the tectal activity.

D-Amphetamine, when taken for extended periods or in high doses, is well known to be psychotoxic in man (Bell, 1965). The results obtained from the administration of d-amphetamine to the chick are shown in fig. 4. At a dose of 64 mg/kg the dominant response consisted of high voltage negative spikes of a generalized seizure type, similar to activity obtained from the same system in response to other central nervous system stimulants (e.g. picrotoxin). As the dosage was increased to 190 mg/kg, however, the recorded activity abruptly changed to a pattern very similar to that produced by the other psychotoxic drugs.

A comparison of the potency of each of the active drugs studied lends further credence to the suggested similarity between the psychotoxic properties of these agents in man and their pharmacological activities on the avian tectum. The relative potencies of the drugs in man and in the avian preparation are compared in table 1.

Although there is considerable variability in the reported psychotoxic dose for the major hallucinogens in man, the range listed in table 1 seems to be generally accepted. The relative potencies of these drugs in the avian preparation are a little more precise. In any case the potency ratios for their respective activities in the bird and man are remarkably close.

5. DISCUSSION AND CONCLUSIONS

The avian tectal response to centrally acting drugs, measured by electrophysiological changes, varies between total suppression caused by anesthetic drugs (Scholes and Roberts, 1964) to specific independent inhibition of spontaneous activity (Scholes, 1966) or evoked potentials (Scholes and Roberts, 1964; Scholes, 1966). LSD-25 induces an intermediate response wherein the spontaneous activity is suppressed (activated?), the evoked response is enhanced and after potentials are revealed.

The LSD-25 response in the avian tectum in this respect is somewhat unique. We have not observed it with other centrally acting drugs except those which like LSD-25 are psychotoxic in man – i.e. psilocybin, mescaline, amphetamine. Moreover, Katori (1962) observed a similar response with bufotenine in the same preparation. Bufotenine is similar to LSD-25 in its psychotoxic properties. The hallucinogenic properties of the d-amphetamine in man have received less attention than those of the other hallucinogenic drugs, but this property has been well documented (Carr, 1954; Greenwood and Peachy, 1957; Wallis et al., 1949; Herman and Nagler, 1954).

In view of the differences in chemical configuration of the various hallucinogens or psychotoxins, our findings suggest that the pharmacologically active moiety responsible for their psychotoxic properties in man may well be the same as that which induces the electrophysiological change in the avian tectum. This supposition is further strengthened by the fact that the 2-brom derivative of LSD-25, BOL 148, which is non-hallucinogenic in man, is ineffective in the bird. Moreover, a comparison of the dose-response ratios for the hallucinogens studied in bird and man shows that they not only fall in the same order but are closer in magnitude than in any other subhuman species yet compared with man (cf. Appel and Freedman, 1965; Callaway, 1955).

While it is not intended to imply that one can extrapolate quantitative findings on hallucinogenic drugs directly from bird to man, the present data support the view that the avian preparation might well be useful as a pharmacological tool for the initial investigation of chemical agents which are potentially hallucinogenic in man. It is our hope that further studies will confirm our view that drugs with psychotoxic properties like hallucinogens may be detected with our procedure. Of more potential importance, however, is the suggested value of the avian preparation as a tool for screening drugs with antipsychotoxic and/or antihallucinatory properties.

REFERENCES

Appel, J.B. and D.X. Freedman, 1965, The relative potencies of psychotomimetic drugs, Life Sci. 4, 2181–2186.

Bell, D.S., 1965, Comparison of amphetamine psychosis and schizophrenia, Brit. J. Psychiat. 111, 2.

Burger, R.E. and F.W. Lorenz, 1960, Artificial respiration in birds by unidirectional air flow, Poultry Sci. 39, 236–237.

Callaway, E., 1955, On the production of hallucinated and psychosis-like states, Ann. Intern. Med. 42, 721–728.

Carr, R.B., 1954, Acute psychotic reaction after inhaling methylamphetamine, Brit. Med. J. 1, 1476.

Downing, D.F., 1964, Psychopharmacological agents, ed. M. Gorden (Academic Press, New York).

Greenwood, R. and R.S. Peachy, 1957, Acute amphetamine poisoning, Brit. Med. J. 1, 742.

Herman, M. and S.H. Nagler, 1954, Psychosis due to amphetamine, J. Nervous Mental Disorders 120, 268–272.

Jacobsen, E., 1963, The clinical pharmacology of the hallucinogens, Clin. Pharmacol. Therap. 4, 480–503.

Katori, M., 1962, The development of spontaneous electrical activity in the brain of a chick embryo and the effects of several drugs on it, Japan. J. Pharmacol. 12, 9–25.

Scholes, N.W. and E. Roberts, 1964, Pharmacological studies of the optic system of the chick; effect of γ-aminobutyric acid and pentobarbital, Biochem. Pharmacol. 13, 1319–1329.

Scholes, N.W., 1966, Pharmacologic definition of neuronal components generating spontaneous and evoked potentials in the tectum of the chick: effect of γ-hydroxybutyrate, J. Pharmacol. Exptl. Therap. 153, 128–144.

Wallis, G.G., J.F. McHarg and O.C.A. Scott, 1949, Acute psychosis caused by dextroamphetamine, Brit. Med. J. 2, 1394.

Wolbach, A.B., E.J. Miner and H.Isbell, 1962, Comparison of psilocin, mescaline and LSD-25, Clin. Pharmacol. Therap. 3, 219–223.