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A Possible Correlation between Drug-Induced Hallucinations in Man and a Behavioural Response in Mice

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An animal test for presumptive hallucinogenic activity in man would be a valuable aid in the choice or rejection of psychoactive compounds for clinical trial. Since it is impossible to say whether an animal is experiencing hallucinations or not, an attempt to predict whether a drug, untested in humans, is likely to be hallucinogenic must be based on a correlation between the hallucinogenic activity of known drugs and a measurable specific effect of those drugs in animals. Such correlations have been reported by JACOB *et al.* (1962) and JACOB and LAFILLE (1963) for a variety of chemically different hallucinogens using hyperthermia in rabbits and anti-analgetic action in mice; by LIPMAN *et al.* (1963) for a series of piperidineglycolates using hyperactivity in rats; and by KNOLL *et al.* (1966) for derivatives of methylamphetamine using behavioural responses in cats and the hot-plate jumping test in rats. These correlations would have even stronger validity if it could also be shown that antagonists of the drug-induced hallucinations in humans were also antagonists of the drug-induced effect in animals. Various antagonists of drug-induced hallucinations have been reported—chlorpromazine and haloperidol for lysergide (LSD), mescaline and phencyclidine (DIVRY *et al.*, 1960; JACOBSEN, 1963; GOOL and CLARK, 1964), sodium succinate for mescaline and phencyclidine (SCHUELER, 1948; STEVENSON and SANCHEZ, 1957; GERSHON and OLARIU, 1960), tetrahydroaminacrine for JB329 (GERSHON *et al.*, 1960), monoamine oxidase inhibitors for N,N-dimethyltryptamine (DMT) and LSD (SAI-HALASZ, 1963; RESNICK *et al.*, 1964). Antagonism in the form of cross-tolerance has also been obtained in humans between LSD and mescaline (WOLBACH *et al.*, 1962) between LSD and psilocybin (ISBELL *et al.*, 1961) and a mild degree of cross-tolerance between LSD and DMT (ROSENBERG *et al.*, 1964).

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By chance, we have discovered a correlation between hallucinogenic activity in man and a behavioural response in mice, which is simple to determine, quantitative and applies to hallucinogens of a wide variety of chemical structure. Moreover, we have been able to parallel the antagonism studies in humans with antagonism experiments in mice.

CORNE *et al.* (1963) have shown that the administration of 5-hydroxytryptophan (5-HTP) to mice produces a characteristic head-twitch which is probably due to the formation of serotonin in the brain. This head-twitch resembles a strong pinna reflex involving the whole head of the animal but, unlike the pinna reflex, occurs without tactile stimulation. During the course of examining a large series of known compounds, we found that a number of them also produced head-twitches, similar to those elicited by 5-HTP. With few exceptions, these active compounds were all known hallucinogens.

Methods

Male albino mice (Schofield strain 12/1a) were kept in groups of 10 in boxes 18 × 18 × 12 cm and allowed to acclimatize to their cages for at least 1 hour before starting the experiment, so that they had quietened down and exploratory activity was reduced to a low level. The drugs, dissolved in normal saline, were administered subcutaneously and the mice observed for 2 min periods at the following times after injection: 2—4, 4—6, 9—11, 14—16, 19—21, 24—26, 29—31 min and so on if necessary.

Those mice which exhibited at least one head-twitch during an observation period, were removed from the box with a pair of forceps so as not to disturb the remaining mice, and were returned to their box at the end of each observation period. Whenever possible, an ED50 and 95% limits (that dose producing head-twitches in 50% of mice) at the time of peak effect, was calculated using logit analysis (FINNEY, 1964). The actual compilations were performed on the I.C.T. computer at Manchester. This is called Procedure 1.

In some cases, it was not possible to obtain an ED50 using a single observation period, as only a proportion of mice, rarely greater than 60%, exhibited head-twitches at any one 2 min period irrespective of the dose. To overcome this drawback, mice were individually marked and those that exhibited head-twitches during each successive observation period as above were noted. By this method it was found that, depending on the dose, it was possible to obtain 90—100% response, i.e. 9 or 10 out of 10 mice exhibited at least one head-twitch over the whole time course, though not at the same time. This is not the same as, say, the same 2 mice exhibiting head-twitches over 5 successive periods. The ED50 values and 95% limits were determined as before and the time-range from which

the values were calculated is also given. Thus a range given as 9—26 min means 4 observation periods of 2 min starting with the 9th min and ending 26 min after injection. This is called Procedure 2.

Antagonists of drug-induced head-twitches were given intraperitoneally and unless otherwise stated 30 min before a fixed dose of agonist which by itself induced head-twitches in 90—100% of mice. AD50 values for antagonists (that dose of antagonist which causes the agonist drug to produce head-twitches in only 50% of mice) and 95% limits were calculated using Procedure 2. This was a greater test of the efficacy of an antagonist as it had to act over a longer period of time than if a fixed observation period was used. It also standardized the method to include those cases in which a 90—100% response was unobtainable at a fixed observation period.

Mice were used once only and a total of about 3,000 were used in these experiments.

Drugs

Doses of drugs are in terms of active acid or base and the following were used: lysergide (LSD), l-acetyl-lysergide bitartrate (ALD), l-methyl-lysergide bitartrate (MLD), bromolysergide (BOL), ergometrine maleate, psilocin, psilocybin, bufotenine bioxalate, N,N-dimethyltryptamine hydrochloride (DMT), dl-α-methyltryptamine hydrochloride, dl-α-ethyltryptamine hydrochloride, 5-hydroxytryptamine creatinine sulphate (5-HT), 5-hydroxytryptophan (5-HTP), mescaline sulphate, dl-α-methylmescaline hydrochloride, dl-α-butylmescaline hydrochloride, 3,4-dimethoxyphenylethylamine (DMPE), hyoscine hydrobromide, atropine sulphate, benzhexol hydrochloride, phencyclidine hydrochloride, yohimbine hydrochloride, diphenhydramine hydrochloride, cyproheptadine, morphine sulphate, methysergide bimaleate, ergotamine tartrate, dl-amphetamine sulphate, adrenaline acid tartrate, pheniprazine hydrochloride, tranylcypromine sulphate, isocarboxazid, nalorphine hydrobromide, acetylcholine chloride, histamine acid phosphate, bradykinin, chlorpromazine hydrochloride, haloperidol, sodium succinate, tetrahydroaminacrine hydrochloride (THA) and a mixture of the hydrochloride salts of l-ethyl-3-piperidyl ester of α-cyclopentylmandelic acid and l-ethyl-2-pyrrolidinyl methylester of α-cyclopentylmandelic acid (JB329, Ditran).

Results

Production of Head-twitches

Generally, head-twitches were only observed in about 10% of saline-treated mice at any one observation period. Thus, using Procedure 1, the control animals usually gave low or no response. However, some batches of mice were more active than others and using Procedure 2, control ani-

mals gave a larger proportion of head-twitches than might have been expected, usually during the initial observation periods. When this occurred, either that batch was discarded or if the activity was limited to a few observation periods only, then those periods were not used when determining the final result in the test mice.

Table 1. *Compounds that produced head-twitches in mice*

Compound	ED50 and 95 % limits (mg base/kg s.c.)		Time of max. effect (min)[1]
LSD	0.045	0.025—0.080	9—11
MLD	0.074	0.058—0.11	4—6
Ergometrine	10	6.7—15	14—16
Psilocin	1.3	0.67—2.2	4—6
Psilocybin	1.1	0.55—2.0	4—6
DMT	2.8	0.74—8.0	2—4
Bufotenin	15	11—21	14—16
dl-α-Methyltryptamine	7.9	3.4—18	44—46
5-HTP	75	50—105	9—11
Mescaline	9.6	4.7—17	19—21
α-Methylmescaline	11	6.0—23	14—16
α-Ethylmescaline	20 approx.	—	14—16
DMPE	15	9.2—27	9—31
Hyoscine	4.2	1.8—7.2	9—11
Atropine	8.9	4.2—15	2—16
Benzhexol	7.6	4.5—16	14—16
JB329	11	6.9—16	4—6
Phencyclidine	0.36	0.17—0.62	4—21
Yohimbine	8.4	3.7—14	14—31

[1] Most of the compounds exhibited a definite peak of activity at a particular time after injection and in these cases the ED50 was calculated from the results at this time. In a few cases a definite peak was not obtained and the ED50 was calculated from the results obtained from a number of 2 min observation periods over the times given as described in the Methods section.

Table 1 lists all the drugs found to produce head-twitches with their ED50 values, 95 % limits and time of maximum effect or time-range over which the ED50 was calculated. With the exception of ergometrine, 5-HTP, α-ethylmescaline and DMPE, all these compounds are known hallucinogens in humans.

It should be noted that the values for DMPE, atropine and phencyclidine were determined by Procedure 2, as it was impossible to obtain ED50 values at any one time. It is unlikely that this was due to differences in absorption of the compounds as a similar difficulty was encountered when using intravenous administration. It was also presumably not due to inadequate dosage either, as increasing the dose did not elicit a greater

response. On the contrary, increasing the doses above certain limits decreased the response resulting in a bell-shaped dose-response curve. This was also true for the other drugs in Table 1 except that for DMPE, atropine and phencyclidine, the point at which the dose-response curve reached a maximum and then decreased was obtained with doses which

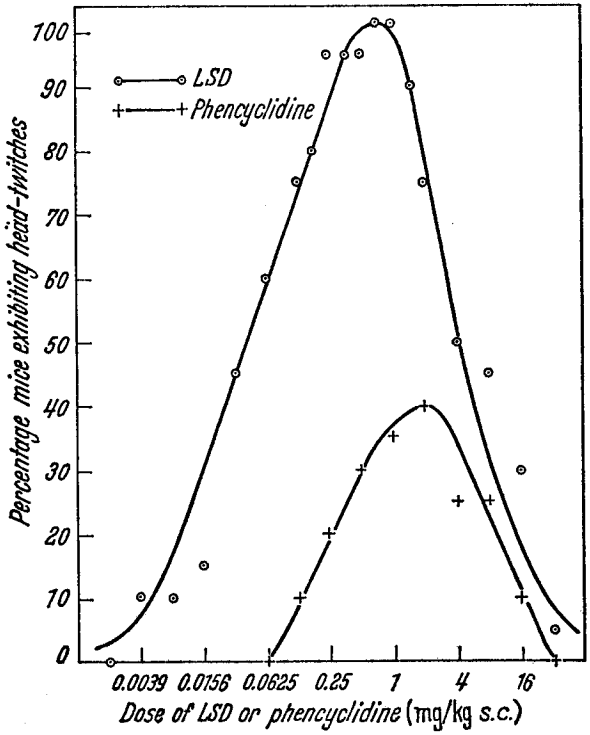

Fig. 1. Dose-response curves for head-twitches induced by LSD, 9—11 min and phencyclidine, 14—16 min after subcutaneous injection. Each point represents the mean result obtained from 20 mice in 2 experiments

gave less than 100% response. This is illustrated in Fig. 1 using LSD and phencyclidine as typical examples of the two types of drugs. Though the head-twitch response decreased after reaching a maximum, other effects did not. In the cases of LSD and phencyclidine excitement and autonomic stimulation increased with increasing dosage until at the highest doses the animals were ataxic and disco-ordinated.

In Table 2 are given some of the compounds which did not produce head-twitches in mice. Included are compounds that are structurally similar to those in Table 1 and which are known not to produce hallucinations in humans, for example, BOL, methysergide, α-propylmescaline

and α-ethyltryptamine. Also included are substances such as histamine, serotonin and bradykinin which might be expected to produce head-twitches from local irritation if given subcutaneously and thus provide misleading results. However, even though local irritation was observed, for example, writhing and scratching, head-twitches were not.

Table 2. *Compounds that did not produce head-twitches in mice*

ALD	Amphetamine
BOL	Adrenaline
Ergotamine	α-Propylmescaline
Methysergide	α-Butylmescaline
	Pheniprazine
	Tranylcypromine
α-Ethyltryptamine	
5-Hydroxytryptamine	Acetylcholine
	Histamine
Nalorphine	Bradykinin
Atropine methylnitrate	Hypertonic Saline

ALD, which is as active as LSD in producing hallucinations (ROTHLIN, 1957) did not induce head-twitches in mice by whatever route of administration. This compound was tested early on in these studies and further supplies were not obtainable to test it by Procedure 2 which was developed later. Nalorphine may also produce hallucinations in normal patients (GOODMAN and GILMAN, 1965) but did not induce head-twitches in mice. So far, these are the only two hallucinogens examined that have given negative results.

An attempt to show how these drug-induced hallucinations may be correlated in terms of dosage with drug-induced head-twitches in mice is illustrated in Fig. 2. Subcutaneous ED50 values for producing head-twitches have been plotted against the dosage usually employed or reported to produce hallucinations in man in mg/kg by mouth, whenever this was known. In those cases in which an oral route had not been used the parenteral dose is shown and appropriately marked. An arbitrary weight of 70 kg per patient has also been assumed in those references in which this information was lacking.

It will be seen that the compounds fall into 2 main groups, there being a good correlation between human and animal doses in each. One group contains the indole and mescaline-type compounds whereas the other comprises the anti-cholinergics and bufotenin, which chemically belongs to the first group. Phencyclidine is probably an example of yet a third group of which insufficient compounds have yet been tested in man to substantiate this point.

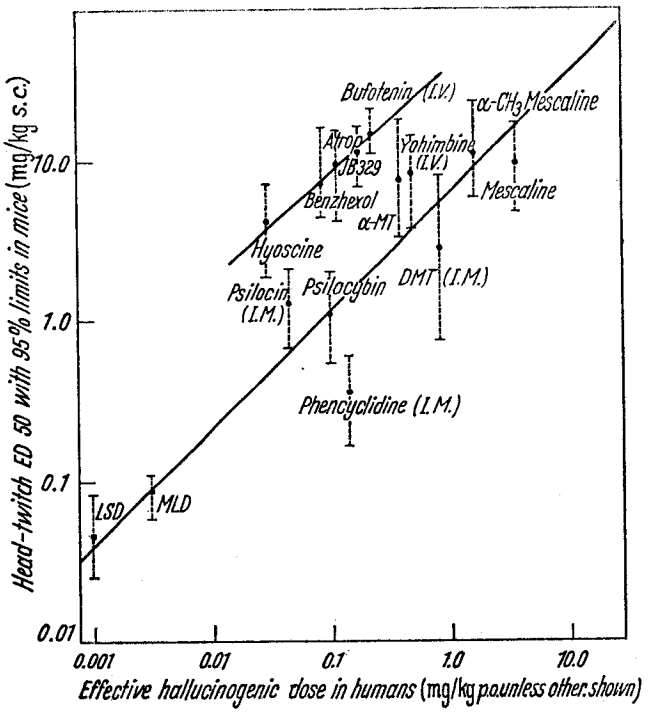

Fig. 2. Correlation between doses of drugs required to produce hallucinations in humans and their ED50 values for producing head-twitches in mice. The ED50 values were taken from Table 1 and the hallucinogenic doses from the following: — LSD, psilocybin, ISBELL, (1959); MLD, ISBELL *et al.* (1959); psilocin, WOLBACH *et al.* (1962); α-MT, MURPHREE *et al.* (1961); DMT, SAI-HALASZ (1962); mescaline, α-methylmescaline, SHULGIN (1964); hyoscine, SOLLMAN (1957); atropine, benzhexol, PFEIFFER *et al.* (1959); bufotenin, FABING, and HAWKINS (1956); yohimbine, HOLMBERG, and GERSHON (1961); JB 329, BROWN *et al.* (1966); phencyclidine, JOHNSTONE *et al.* (1959). The human dose was calculated on the basis of a weight of 70 kg unless given in the reference. The vertical broken lines are the 95 % limits

Antagonism of Head-twitches

Antagonists of drug-induced hallucinations in man were tested as possible antagonists of drug-induced head-twitches in mice. Using the appropriate combination of hallucinogen and antagonist, inhibition of head-twitches in mice was obtained and Table 3 gives the AD50 values and 95 % limits for these drugs. These experiments in mice paralleled the human experiments except for the antagonism of LSD by the monoamine oxidase inhibitor pheniprazine which was substituted for iproniazid, used in man (SAI-HALASZ, 1963). In all these experiments, with the exception of isocarboxazid, a single dose of antagonist, given intraperitoneally 30 min before the hallucinogen subcutaneously, was sufficient to antagonize head-twitches. In the case of isocarboxazid, this had to be given

Table 3. *The antagonism of drug-induced head-twitches in mice by compounds that antagonise drug-induced hallucinations in humans.*

With the exception of isocarboxazid the antagonists were injected 30 min before the hallucinogen. Isocarboxazid was injected daily for 5 days and LSD given 1 hour after the final dose. Head-twitches were noted over the observation periods shown

Hallucinogen	Dose (mg/kg s.c.)	Antagonist	AD50 and 95 % limits (mg/kg i.p.)		Observation periods (min)
LSD	1.0	Chlorpromazine	0.76	(0.48—1.2)	2—11
LSD	1.0	Haloperidol	3.3	(2.1—5.0)	2—11
LSD	1.0	Pheniprazine	2.3	(0.42—5.8)	2—11
LSD	1.0	Isocarboxazid	93	(64—141)	2—11
Mescaline	40	Chlorpromazine	0.49	(0.29—0.72)	9—26
Mescaline	40	Haloperidol	0.56	(0.32—0.90)	9—26
Mescaline	40	Sodium Succinate	377	(250—957)	9—26
Phencyclidine	2.0	Sodium Succinate	177	(38—819)	4—21
Phencyclidine	2.0	Chlorpromazine	0.74	(0.42—1.1)	4—21
Phencyclidine	2.0	Haloperidol	0.16	(0.052—0.25)	4—21
JB 329	40	THA	4.5	(0.84—12)	4—6[1]

[1] Only one observation period used as the onset and offset of head-twitches with JB 329 were very rapid.

Table 4. *Antagonism of LSD-induced head-twitches by other hallucinogens.*

The antagonists were given 30 min before LSD and head-twitches noted during observation periods 2—11 min

Dose of LSD (mg/kg s.c.)	Antagonist	AD50 and 95 % limits (mg/kg i.p.)	
1.0	Mescaline	24	(11—42)
1.0	Psilocybin	2.9	(1.8—4.3)
1.0	DMT	12	(7.6—19)

for 5 days prior to challenge with LSD. A single dose of isocarboxazid was ineffective.

It was unnecessary to use chronic dosing when simulating the human cross-tolerance experiments. A single dose of hallucinogen was sufficient to antagonize a subsequent dose of another. Table 4 gives the AD50 values and 95 % limits for mescaline, psilocybin and DMT as antagonists of LSD-induced head-twitches in mice.

In a search for other antagonists of hallucinogen-induced head-twitches, we found that methysergide, BOL, cyproheptadine, diphenhydramine and morphine inhibited LSD-induced head-twitches. Since all these drugs have anti-serotonin properties, methysergide, being the most potent, was investigated in more detail and was found to inhibit the head-twitches induced by a wide variety of hallucinogens. These results are given in Tables 5 and 6.

Table 5. *The antagonism of various drug-induced head-twitches by methysergide. Methysergide was given 30 min before the hallucinogen and head-twitches noted over the times given*

Hallucinogen	Dose (mg/kg s.c.)	AD50 and 95 % limits Methysergide (mg/kg i.p.)		Observation periods (min)
LSD	1.0	3.0	(0.27–5.5)	2–11
Psilocybin	3.0	0.70	(0.4 –1.0)	2–11
DMT	5.0	0.38	(0.26–0.55)	2–11
Mescaline	40	2.3	(1.5 –3.4)	9–21
Hyoscine	15	8.6	(4.4 –22)	2–21
Benzhexol	40	5.0	(2.1 –12)	4–21
Phencyclidine	2.0	2.4	(1.4 –3.6)	4–21

Table 6. *Antagonism of LSD-induced head-twitches by drugs with anti-serotonin properties.*

The drugs were given 30 min before LSD (1.0 mg/kg s.c.) and the head-twitches observed during observation periods 2–11 min

Drug	AD50 and 95 % limits (mg/kg i.p.)	
BOL	3.0	(0.27–5.5)
Cyproheptadine	8.7	(6.1 –15)
Diphenhydramine	2.9	(2.0 –4.4)
Morphine	14	(9.8 –21)

Discussion

Previous attempts to obtain correlations between animal tests and hallucinogenic activity have either required more than one test to encompass the different chemical structures (JACOB *et al.*, 1963, 1966) or have been restricted to correlations within a specific chemical series (LIPMAN *et al.*, 1963; KNOLL *et al.*, 1966) and are thus of only limited application. Furthermore, none of these workers have attempted to confirm the value of the animal tests they used by examining the effects of known hallucinogenic antagonists. Production of head-twitches in mice however, by hallucinogens of widely differing chemical structure appears to provide a suitable laboratory model for prediction of hallucinogenic activity in man. Support for this contention is given by the correlation between production of head-twitches and hallucinogenic action and the antagonism experiments which parallel human findings with these drugs.

It is also interesting that the compounds should fall into two well-defined groups (Fig. 2) which suggests that the compounds in each group might be acting in a like manner or on some common pathway. This adds support to the similar suggestion made by ISBELL *et al.* (1961) and WOLBACH *et al.* (1962) concerning LSD, psilocybin and mescaline. Our

results with LSD and DMT (Table 4) do not, however, support the conclusions of ROSENBERG *et al.* (1963) that the site or mechanism of action of these two drugs are probably different. Their own published figures indicate that the reduction in mental effects by the "mild degree" of cross-tolerance amounted to about 50%.

The apparent anomaly of bufotenin may be attributed to the human dose used in compiling Fig. 2 which was given intravenously. Oral administration would presumably require a larger dose to obtain the same effect and thus displace its position on the graph to the right, closer to its expected position with the indole derivatives. There is also some doubt about the hallucinogenic activity of bufotenin. TURNER and MERLIS (1959) using schizophrenic patients were unable to confirm FABING and HAWKINS (1956) original results with convict volunteers. However, TURNER and MERLIS quote from a letter from Dr. ISBELL whose subjects reported "elementary hallucinations" after an intramuscular dose of 10—12.5 mg (approx. 0.16 mg/kg) of bufotenin.

If it is accepted that the correlations shown in Fig. 2 are reasonable and that they might also apply to other hallucinogenic drugs then it is possible, knowing the head-twitch ED50, to interpolate on the appropriate graph and read off the approximate dosage likely to produce hallucinations in man. If this is done for three of the four anomalies in Table 1 — ergometrine, α-ethylmescaline and 5-HTP using the indole group line, it will be seen that the human dosages required are greater than have been given. In the case of ergometrine, the ED50 for the production of head-twitches is 10 mg/kg. This corresponds to a human dose of about 2 mg/kg, i.e. at least 150 times the therapeutic dose, so it is understandable why ergometrine has not been reported to be hallucinogenic. The highest dose of α-ethylmescaline given to man is 2.5 mg/kg (SHULGIN, 1963) but according to Fig. 1, the hallucinogenic dose should be about 5 mg/kg. According to the results reported in Table 1, 5-HTP should be hallucinogenic. It may well be that with increasing use of 5-HTP in humans, on its own or in conjunction with a monoamine oxidase inhibitor, some hallucinatory episodes may be reported. The dose required without monoamine oxidase inhibition, should be approximately 30 mg/kg, i.e. a great deal larger than has been given up to now.

The highest dose of DMPE we can discover that has been given to man is 1,000 mg i.e. approximately 14 mg/kg (FRIEDHOFF and HOLLISTER 1966a), but this did not have any discernible effect. However, according to the correlation figure, the human dose corresponding to a mouse ED 50 of 15 mg/kg should be about 3.5 mg/kg. FRIEDHOFF and HOLLISTER (1966b) found that DMPE is very largely and quickly converted to 3,4-dimethoxyphenylacetic acid, presumably by MAO and they suggest that this may account for its lack of effect in humans after oral adminis-

tration. If inactivation does not occur so quickly in mice then this might account for the discrepancy observed which might be resolved if it were given to humans parenterally. Because of the current interest in DMPE and its possible significance in schizophrenia, it would be interesting if this prediction were proved correct.

If the action of ALD in humans is due to its metabolism to LSD then the absence of effect in mice may be due to an inability of the mouse to de-acetylate this compound. Nalorphine appears to be qualitatively different from the other hallucinogens. JACOB and LAFILLE (1963) found that nalorphine did not produce hyperthermia in rabbits as did other hallucinogens.

The mechanism of action of the hallucinogens was attributed originally to their central antagonism of serotonin (GADDUM, 1954; WOOLLEY and SHAW, 1954). This hypothesis was based on the potency of LSD both as an anti-serotonin and as an hallucinogen. But since this relationship did not hold for other hallucinogens and other known anti-serotonins which were not hallucinogenic, this hypothesis has been discarded in favour of one proposing that hallucinogens may be mimicking, releasing or potentiating serotonin centrally (WOOLLEY, 1962; GYERMEK and SUMI, 1963). In this respect there is evidence that LSD, MLD, psilocin, bufotenin, mescaline and DMPE have a similar or closely related locus of action in rabbits (BRODEY *et al.*, 1963; SCHWEIGERDT and HIMWICH, 1964; TAKEO and HIMWICH, 1965; SCHWEIGERDT *et al.*, 1966). Added support for the serotoninergic hypothesis is now given by our finding that a number of drugs with anti-serotonin properties antagonized the head-twitches induced by LSD and in particular the antagonism exhibited by methysergide against a wide variety of hallucinogens.

Summary

The production of head-twitches in mice appears to be a suitable laboratory test for predicting whether a compound is likely to be hallucinogenic in man. This is based on the following findings:

1. With the exception of acetyl-lysergic acid diethylamide and nalorphine, hallucinogenic drugs induced head-twitches in mice.

2. Chemically related compounds which are not hallucinogenic did not induce head-twitches with the exception of 5-HTP, ergometrine, α-ethylmescaline and DMPE. It is suggested that these 4 drugs might produce hallucinations if they were given in high enough doses.

3. There is a good correlation between drug-induced hallucinations in man and drug-induced head-twitches in mice in terms of dose/kg.

4. Chlorpromazine, haloperidol, tetrahydroaminacrine and monoamine-oxidase inhibitors can antagonize hallucinations in man. These same

compounds antagonised head-twitches induced in mice by the appropriate hallucinogens.

5. Cross-tolerance has been demonstrated between LSD and mescaline LSD and psilocybin and LSD and DMT in man. Mescaline, psilocybin and DMT also antagonised LSD-induced head-twitches in mice.

A potent antiserotonin, methysergide, antagonised the head-twitches induced by a wide variety of chemically different hallucinogens. This gives support to the idea that hallucinogens may act by mimicking, releasing or potentiating serotonin centrally.

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References

BRODEY, J. F., W. G. STEINER, and H. E. HIMWICH: An electrographic study of psilocin and 4-methyl-α-methyl tryptamine (MP-809), J. Pharmacol. exp. Ther. **140**, 8—18 (1963).

BROWN, M. L., S. GERSHON, W. J. LANG, and B. KOROL: The effects of psychoactive drugs on the behavioural response to Ditran in dogs. Arch. int. Pharmacodyn. **160**, 407—423 (1966).

CORNE, S. J., R. W. PICKERING, and B. T. WARNER: A method for assessing the effects of drugs on the central actions of 5-hydroxytryptamine. Brit. J. Pharmacol. **20**, 106—120 (1963).

DIVRY, P., J. BOBON et J. COLLARD: Rapport sur l'activé neuro-psychopharmacologique du halopéridol (R 1625). Acta neurol. belg. **60**, 7—19 (1960).

FABING, H. D., and R. J. HAWKINS: Intravenous bufotenine injection in the human being. Science **123**, 886—887 (1956).

FINNEY, D. J.: Statistical method in biological assay, 2nd edition. London: C. Griffin & Co. Ltd. 1964.

FRIEDHOFF, A. J., and L. E. HOLLISTER: Effects of 3,4-dimethoxyphenylethylamine in man. Nature (Lond.) **210**, 1377—1378 (1966a).

— — Comparison of the metabolism of 3,4-dimethyloxphenylethylamine and mescaline in humans. Biochem. Pharmacol. **15**, 269—273 (1966b).

GADDUM, J. H.: Ciba Foundation Symposium on Hypotension. London: J. & A. Churchill Ltd. 1954.

GERSHON, S., and J. OLARIU: JB 329—a new psychotomimetic. Its antagonism by tetrahydroaminacrine and its comparison with LSD, mescaline and Sernyl. J. Neuropsychiat. **1**, 283—292 (1960).

GOODMAN, L. S., and A. GILMAN: The pharmacological basis of therapeutics, 3rd edition. New York: Macmillan 1965.

GOOL, R. Y., and H. L. CLARKE: Anaesthesia for under doctored areas. Anaesthesia **19**, 265—270 (1964).

GYERMEK, L., and T. SUMI: Potentiating actions of indolealkylamines and lysergic acid diethylamide on reflexes elicited by 5-hydroxytryptophan. Proc. Soc. exp. Biol. (N.Y.) **114**, 436—439 (1963).

HOLMBERG, G., and S. GERSHON: Autonomic and psychic effects of yohimbine hydrochloride. Psychopharmacologia (Berl.) **2**, 93–106 (1961).

ISBELL, H.: Comparison of the reactions induced by psilocybin and LSD-25 in man. Psychopharmacologia (Berl.) **1**, 29–38 (1959).

— A. B. WOLBACH jr., A. WICKLER, and E. J. MILNER: Cross tolerance between LSD and psilocybin. Psychopharmacologia (Berl.) **2**, 147–159 (1961).

JACOB, J., and C. LAFILLE: Pharmacological characterization and detection of hallucinogenic substances (1) Hyperthermic activity in rabbits. Arch. int. Pharmacodyn. **145**, 528–545 (1963).

— — G. LOISEAU, P. ECHINARD-GARIN et C. BARTHELEMY: Recherche d'équivalents expérimentaux au pouvoir hallucinogène. Med. exp. (Basel) **7**, 296–304 (1962).

JACOBSEN, E.: The clinical pharmacology of the hallucinogens. Clin. Pharmacol. Ther. **4**, 480–503 (1963).

JOHNSTONE, M., V. EVANS, and S. BAIGEL: Sernyl (Cl-395) in clinical anaesthesia. Brit. J. Anaesth. **31**, 433–439 (1959).

KNOLL, J., E. S. VIZI, and Z. ECSERI: Psychomimetic methylamphetamine derivatives. Arch. int. Pharmacodyn. **159**, 442–451 (1966).

LIPMAN, V. C., P. S. SHURRAGER, and L. G. ABOOD: Effect of anticholinergic psychotomimetics on motor activity and body temperature. Arch. int. Pharmacodyn. **146**, 174–191 (1963).

MURPHREE, H. B., R. H. DIPPY, E. H. JENNEY, and C. E. PFEIFFER: Effects in normal man of α-methyltryptamine and α-ethyltryptamine. Clin. Pharmacol. Ther. **2**, 722–726 (1961).

PFEIFFER, C. C., H. B. MURPHREE, E. H. JENNEY, M. G. ROBERTSON, and A. H. RANDALL: Hallucinatory effect in man of acetylcholine inhibitors. Neurology (Minneap.) **9**, 249–250 (1959).

RESNICK, O., D. M. KRUS, and M. RASKIN: LSD-25 action in normal subjects treated with a monoamine oxidase inhibitor. Life Sci. **3**, 1207–1214 (1964).

ROSENBERG, D. E., H. ISBELL, E. J. MINER, and C. R. LOGAN: The effect of N,N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. Psychopharmacologia (Berl.) **5**, 217–227 (1964).

ROTHLIN, E.: Pharmacology of lysergic acid diethylamide and some of its related compounds J. Pharm. Pharmacol. **9**, 569–587 (1957).

SAI-HALASZ, A.: The effect of MAO inhibition on the experimental psychoses induced by dimethyltryptamine. Psychopharmacologia (Berl.) **4**, 385–388 (1963).

SCHUELER, F. W.: The effects of succinate in mescaline hallucinations. J. Lab. clin. Med. **33**, 1297–1303 (1948).

SCHWEIGERDT, A. K., and H. E. HIMWICH: An electrographic study of hypotension and 5-hydroxytryptophan. J. Pharmacol. exp. Ther. **144**, 253–259 (1964).

— A. H. STEWART, and H. E. HIMWICH: An electrographic study of d-lysergic acid diethylamide and nine congeners. J. Pharmacol. exp. Ther. **151**, 353–359 (1966).

SHULGIN, A. T.: Psychotomimetic agents related to mescaline. Experientia (Basel) **19**, 127–128 (1963).

— Psychotomimetic amphetamines: methoxy 3,4-dialkoxyamphetamines. Experientia (Basel) **20**, 366–367 (1964).

SOLLMAN, T.: A manual of pharmacology, 8th edition. Philadelphia: W. B. Saunders & Co. 1957.

STEVENSON, I., and A. J. SANCHEZ: The antidotal action of sodium succinate in the mescaline psychosis. Amer. J. Psychiat. **114**, 328–332 (1957).

TAKEO, Y., and H. E. HIMWICH: Mescaline, 3,4-dimethoxyphenylethylamine and adrenaline: sites of electroencephalographic arousal. Science **150**, 1309—1310 (1965).

TURNER, W. J., and S. MERLIS: Effect of some indolealkylamines on man. Arch. Neurol. Psychiat. (Chic.) **81**, 121—129 (1959).

WOLBACH, A. B., jr., H. ISBELL, and E. J. MINER: Cross tolerance between mescaline and LSD-25. Psychopharmacologia (Berl.) **3**, 1—14 (1962).

WOOLLEY, D. W.: The biochemical bases of psychoses. New York: John Wiley & Sons, Inc. 1962.

—, and E. SHAW: A biochemical and pharmacological suggestion about certain mental disorders. Proc. nat. Acad. Sci. (Wash.) **40**, 228—231 (1954).

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