The clinical pharmacology of the hallucinogens

Whereas, formerly, interest was mainly paramedical, in recent years medical interest in hallucinogenic drugs has greatly increased. Because of the large number of new drugs with unusual effects as well, there has been the hope that the drugs might lead to better understanding of abnormal mental processes. The history structure, and pharmacologic effects of these drugs in man is considered. In addition, differences between the effects in man and animals and differences in the actions of the several drugs are discussed.

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Certain agents cause in man distortion of perception, at times accompanied by vivid dream images or hallucinations. Several names are being used for these agents, but none of these terms is happily chosen: psychosomimetics, psycholytics, phantastica, or hallucinogens. Although most commonly used, the last-named term is just as inadequate as are the other names.

In general, these agents are characterized by the predominance of their effects on mental and psychic functions. In contradistinction to other centrally acting drugs, they exert few peripheral effects, mostly on the autonomic nervous system.

Many drugs, such as cocaine and hyoscine, are also able to induce hallucinations, but, as will be seen later, hallucinations are not their most typical effect. Nevertheless, the term "hallucinogens" is so extensively used that it would be difficult to substitute another, perhaps more satisfactory term. The terminologic confusion in this field is not greater than it is in other areas of psychopharmacology.

History and chemistry

The formulas and the relative strength of the typical hallucinogenic agents are given in Table I. Three rather widely chemically different groups are found: the mescaline group, the lysergic acid group, and the tryptamine group. Some of these drugs are found in nature, others are synthetic products.

The main representative of the *mescaline* group is mescaline itself. It is an alkaloid found in the Mexican cactus, peyotl (*Anhalonium lewinii* or *Lophophora williamsii*), which, according to the reports of Berhardino de Sahagun, was used by the Aztecs in their religious ceremonies. Heffter[86] isolated mescaline and a few other alkaloids from the cactus. Mescaline is the least active among the hallucinogens; about 500 mg. are required to provoke characteristic symptoms.

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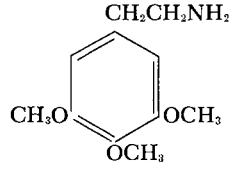
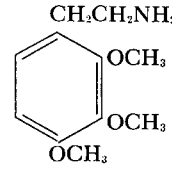
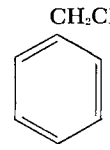
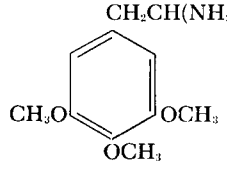
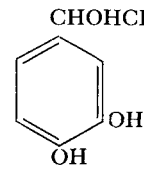
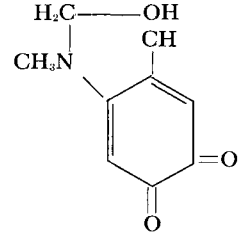
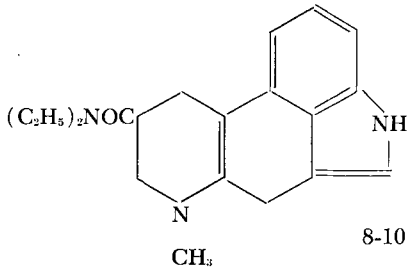
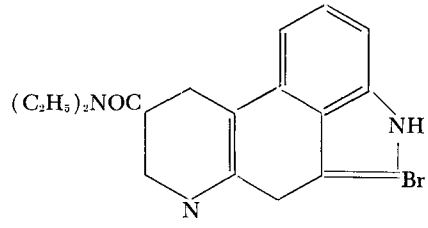
The hallucinogenic effect of the *lysergic acid* group was discovered accidentally less than 20 years ago. Lysergic acid is an essential molecular constituent of ergot alkaloids. In the laboratories of the Swiss pharmaceutical firm, Sandoz, in which also an important contribution to the knowledge of the constitution of the ergot alkaloids was made, synthesis of derivatives of lysergic acid was attempted presumably in order to develop agents with properties superior to those of natural ergot alkaloids. Albert Hofmann,[92, 93] one of the chemists of the team, accidentally tasted a minute amount of one of the derivatives, d-lysergic acid diethylamide, and experienced, to his great surprise, its hallucinogenic effects. This compound, also known under the name of lysergide, LSD or LSD-25, is the most patent of the presently known hallucinogenics. Ingestion of 100 μg or even less is sufficient to cause symptoms of the same intensity as elicited by 500 mg. mescaline. Some closely related compounds are also hallucinogenic but, with the exception of the acetyl derivative, they are all less potent than lysergide, although still considerably more potent than mescaline.[78, 136]

Certain fungi containing hallucinogenic agents of the *tryptamine* group have been used in rites by the Central American Indians from pre-Columbian times, but the nature of these fungi remained unknown and their use was forgotten in the Western literature until recently.[43, 54] In 1953 the American banker and ethnologist, R. G. Wasson, and his wife succeeded in a mission to find tribes in a remote valley in Mexico where the mushrooms still were used in nocturnal religious rites. The Wassons gained the confidence of the Indians, were allowed to take part in the rites and convince themselves of the hallucinogenic effect of the drink made of the mushrooms, and also learned about its ingredients. The director of Musée National d'Histoire Naturelle of Paris, the French mycologist, R. Heim, joined the Wassons in a subsequent expedition, collected the active fungi and identified them botanically. They were brought to Europe and grown on a synthetic medium. Several closely related species are also active, of which some were later found in Thailand and Cambodia.[87] The active components from *Psilocybe mexicana Heim* were isolated by Hofmann,[95] who also identified them chemically.[94] Two active substances were isolated: psilocybin and psilocin, the former being the phosphate ester of the latter.[96] Both are considerably weaker than lysergide; about 150 times the dose is required to obtain the same effect.

Other, synthetic tryptamine derivatives, such as N-dimethyl- and N-diethyltryptamine were discovered by Hungarian investigators to have typical hallucinogenic effects.[34, 159] The first-named is found in the seeds of *Piptadenia peregrina,* from which a snuff called cohoba is prepared.[165]

The psychotropic effect seems to be specifically linked to the chemical constitution within each group so that even slight changes in the molecule will abolish the hallucinogenic action completely. For example, 2,3,4-trimethoxyphenylethylamine has no hallucinogenic effect in contrast to mescaline, which is 3,4,5-trimethoxyphenylethylamine.[149] A corresponding specificity is found within the lysergic acid derivatives.[136] Lysergide is dextrorotatory. The corresponding levo form is inactive. Also, the introduction of a bromine atom in one of the nuclei, forming 2-bromo-lysergic acid diethylamide ("brom-LSD," brom-lysergide or BOL-148), yields a product deprived of hallucinogenic properties. The monoethyl derivative of lysergide has a qualitatively identical, although slightly weaker, effect than lysergide. Lysergic acid amide, without ethyl groups, has no hallucinogenic effect, but causes sleepiness, while the effects on autonomic functions are preserved.[150, 151] The same relative specificity of the central action is also seen with the agents of the tryptamine group. The change of the hydroxy group in psilocin from position 4 to 5 leads to bufotenine, which has different pharmacologic properties.

Table I. *Formulas, names, effective human hallucinogenic doses (EHD), and approximate duration of effect of hitherto known hallucinogens**

Chemical formula and name	*Duration of effect (hours)*	*EHD (μg/Kg.)*	*Nonhallucinogenic chemically related compounds*
Group I	*Phenylamines (Mescaline group)*		
 *Mescaline* 3, 4, 5-trimethoxy-phenylethylamine	10-12	5,000-10,000	 2, 3, 4-trimethoxy-phenylethylamine
			 Amphetamine
 3, 4, 5-trimethoxy-phenylisopropylamine	10-12	5,000-10,000	 Epinephrine
			 Adrenochome
Group II	*Lysergic acid group*		
 Lysergide D-lysergic acid diethylamide LSD-25 LSD Delyside	8-10	1-2	 2-bromo-lysergic acid diethylamide 2-Brom lysergide Brom-lysergide BOL-148

*For the sake of comparison some related compounds without hallucinogenic properties are listed.

Table I *continued*

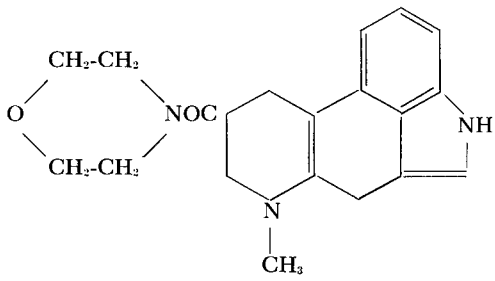
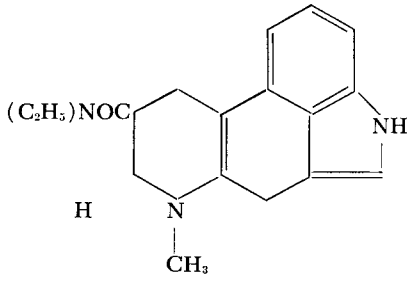
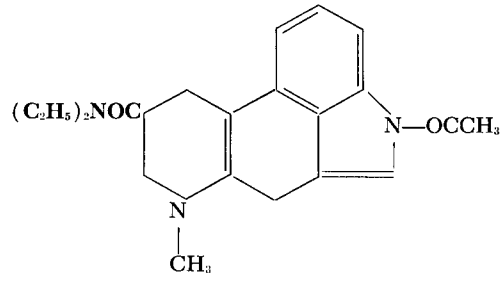
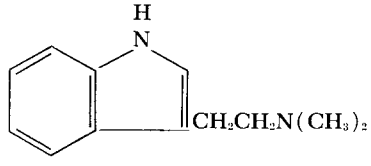
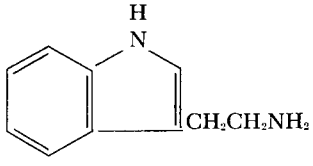
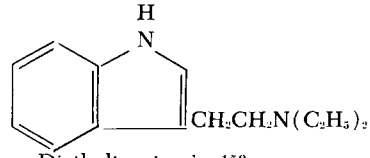
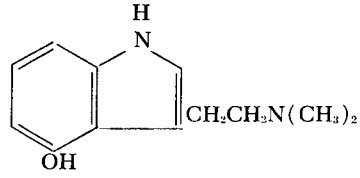
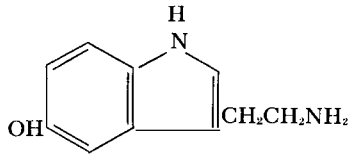
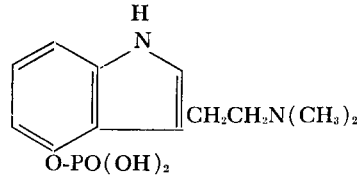
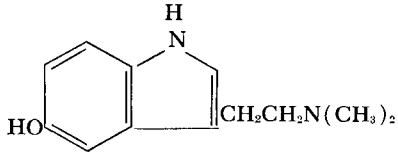
Chemical formula and name	*Duration of effect (hours)*	*EHD (μg/Kg.)*	*Nonhallucinogenic chemically related compounds*
 Lysergic acid morpholide (LSM)[78]	1-2	1.5-3	
 Lysergic acid monoethylamide (LAE)[150]	4-6	10-20	
 1 acetyl LSD[136]	?	1-2	
Group III			*Tryptamine Group*
 Dimethyltryptamine (DMT)[159]	1	1,000	 Tryptamine

Table I *continued*

Chemical formula and name	*Duration of effect (hours)*	*EHD (μg/Kg.)*	*Nonhallucinogenic chemically related compounds*
 Diethyltryptamine[159]	2-3	1,000 or a little less	
 Psilocin 4-Hydroxy-dimethyl-tryptamine	2-4	100-200	 Serotonin Enteramine 5-Hydroxytryptamine
 Psilocybin Phosphateester of psilocin	2-4	100-200	 Bufotenine 5-Hydroxy dimethyl-tryptamine

Absorption, distribution, elimination

All known hallucinogens are readily absorbed from the intestinal tract and no major difference is found between the effective oral, subcutaneous, or intravenous doses. After intraspinal injection a more rapid onset of the symptoms is claimed.

Mescaline is concentrated in the kidneys, liver, and spleen. The concentration in these organs is 3 to 6 times as high as in brain and in plasma.[31, 46] Some of the mescaline is bound to the proteins of the plasma or the liver.[31] In man, 60 to 90 per cent of a given dose is excreted unchanged with the urine, 9 to 39 per cent within the first 18 hours.[69, 134, 141] In the dog, only 28 to 46 per cent can be recovered from the urine.[46] A part is found deminated as trimethoxyphenyl acetic acid, which has no hallucinogenic effect.[31, 134, 152] Deamination of mescaline is attributed to an enzyme which is found in the liver and which is not an amine oxidase.[155]

The conventional methods for quantitative determination of lysergide are not sensitive enough to allow determination of its concentration in body fluids and tissues, particularly since the doses that can safely be administered are relatively small. For this reason, C^{14}-labeled lysergide has been used for such measurements. However, the long half-life of C^{14} precludes its administration to man; therefore, measurements of distribution of lysergide in the body with

this method have been carried out exclusively in laboratory animals. After intravenous injection, the radioactivity disappears rapidly from the blood into the organs, and an equilibrium is obtained after 10 to 15 minutes. The final distribution is independent of the route of administration. Twenty per cent of the blood lysergide is found in the red cells and 40 to 70 per cent is bound to plasma proteins. Corresponding to this, only about one fifth of the total blood concentration is found in the spinal fluid. The highest concentration is present in the liver and in the kidneys; in the central nervous system only low concentrations are found—in rats lower than in plasma, in dogs a little higher.[12, 15, 35, 156] Within the brain, the C^{14} activity is found in hippocampus, the basal ganglia, the thalamic nuclei, the cerebral cortex, and cerebellum, named in decreasing order. The radioactivity is concentrated on the surface of the cells.[12]

The concentration of lysergide in the organs, measured as the radioactivity, decreases rapidly, the rate varying from species to species. In plasma, the half-time is 100 minutes for monkeys, 130 minutes for cats, and 7 minutes for mice.[15] The rate of elimination from brain is also high in mice. There is no correlation between the brain concentration of lysergide and the observed behavior changes at different times after drug administration.[82]

Lysergide is transformed into some hitherto unknown metabolites and excreted as such. These metabolites are presumably formed in the liver. When incubated with liver tissue in vitro, lysergide is hydroxylated in the 2 position. In vivo most of the lysergide is metabolized to 3 or 4 or perhaps more different compounds, none of which is identical with 2-hydroxy lysergide. None of the metabolites is hallucinogenic. The metabolites are excreted with the bile to the extent that 60 to 80 per cent of the radioactivity of the injected lysergide is found in the intestinal tract.[12, 15, 35, 156] Presumably some of the radioactive material is reabsorbed, but most is excreted with feces.

In the organism, psilocybin is rapidly dephosphorylated, perhaps even in the intestine.[99] The dephosphorylated product, psilocin, appears to be the psychoactive compound. After distribution in the body the highest concentration is found in liver and kidney. No accumulation is found in the brain.[109] Of a dose of psilocybin and psilocin, 11 per cent is excreted in the urine unchanged, and 20 per cent as a glucuronic acid derivative; 3.5 per cent is demethylated and degraded to indole acid derivatives. Some 15 to 20 per cent of the dose is found in the bile.[109] Pretreatment with monoamine oxidase inhibitors has no effect on the metabolism of psilocybin.[75]

The alkylated tryptamines seem to be oxidized to 3-indolylacetic acid, which is excreted in the urine partly in free form, partly conjugated with glycine.[159]

Clinical effect of the hallucinogens

Vegetative phase. After a latency period, depending largely on the route of administration, a series of disagreeable symptoms are felt: nausea, sometimes combined with vomiting, dizziness, headache, and palpitations.[27, 47, 90, 107] Most subjects feel extremely chilly, shiver and develop goose flesh. This feeling may alternate with periods of heat flushes. Among other symptoms, polyuria, and hunger, increasing to stomach cramps, may occur. All these symptoms are generally accompanied by a feeling of restlessness. To quote Beringer[27]: "the hang-over precedes the ebriety." The discomfort is diminished if the agents are given in consecutive small single doses, spaced over some time, e.g., in two portions 30 to 60 minutes apart.

Slight pupil dilatation is found. The systolic and the diastolic arterial pressure is increased about 10 to 20 mm. Hg. As a rule, the heart rate is increased 10 to 20 beats per minute, but sometimes a slight bradycardia is found instead, as a reflex compensation of the hypertension. Generally also, a small increase of 10 to 20 mg. per cent blood sugar is found. This syndrome is a result of a stimulation of the

sympathetic nerve system. Little or no effect on parasympathetic functions is found. Sometimes a fine tremor of the fingers and the hands is present. The most prevalent neurological sign, besides the stimulation of the sympathetic system, is an increase of spinal reflexes.

While the subjective vegetative symptoms, such as nausea, vomiting, and chilliness, subside, as a rule, before the development of the psychic symptoms, the objective vegetative signs, such as pupil dilatation and increased pulse rate, generally follow the time course of the psychic effects.

Psychic phase. A comprehensive description of the psychic symptoms is beyond the scope of this review. The reader is referred to the copious psychiatric literature where all symptoms and their possible variants are described and analyzed. Descriptions of the effects of mescaline are given by Beringer[27] and Mayer-Gross,[120] of lysergide by Delay and Benda[49] of psylocybin by Delay and associates[53, 54, 55, 58] and Malitz and co-workers[115] and of diethyltryptamine by Böszörményi.[33, 34] The principal symptoms are (1) the distortion of sense perception; (2) the visions, pseudohallucinations, and hallucinations; and (3) the images and the thought-flow dreams.

The distortion of the sense perception is most specific in that it first and with a relatively small dose. It involves all senses. In the visual system, one color quality, especially the red, green, or blue, seems unusually bright. Cracks and irregularities in surfaces are perceived as cuttings in a deep relief, and folds in a curtain may seem like hill ridges in an archaic geological landscape. Persons and furniture and other objects seem sometimes large or very near, sometimes far away. The picture is constantly shifting; objects which appeared brilliant and shining may suddenly be dull and uninteresting. The perception of the proprioceptive senses is distorted almost to the same extent as is that of the vision. Characteristic is that the subject at times finds his feet far away or his arms so short that his hands seem to be fixed to his shoulders. The whole body may be felt changing from the size of a dwarf to that of a giant. In psychiatric terms these effects are described as a distortion of the body image. The function of the other senses does not seem to be distorted to the same extent, although a clear influence is also felt. In fact, the occurrence of sudden changes of a perceived quality is also observed with sense modalities other than those of the visual and somatosensory system. A wine may, for example, have an extreme sour taste at one moment and be extraordinarily sweet and tasty at the next. A certain sound, such as dripping from a tap, may be perceived as a pounding noise, and so on. Apart from perception, more complex subjective experiences are affected. Especially the sense of time is distorted; short periods, lasting only a few seconds, may in extreme cases be experienced as several minutes.[13, 24]

Visions, pseudohallucinations, and hallucinations appear after larger doses than those causing the distortion of sense perception. The visual system is practically the only one involved in these manifestations. Constantly moving brightly colored spots, sparks, zigzags, squares, circles, or others, are seen, especially with closed eyes. To begin with, these phenomena do not take the shape of known objects, but at a later stage they may be visualized as human or animal figures, landscapes, interiors, etc. The subject is frequently still aware that these visions are formed within his brain, and consequently are unreal pseudohallucinations. True hallucinations may also appear. They are almost exclusively visual; auditory, olfactory, or gustatory hallucinations are rarely reported.

The thought-flow dreams may best be described as dreamlike thoughts and associations appearing as streaming film strips coming from the sides, from above, from below, and presenting themselves as vivid dream images. Their speed or content cannot be varied at will. They vary much from person to person and from time

to time, and are colored by the accompanying mood changes: they may be pleasant, emotionally neutral, or disquieting. Frequently, these dreams remind one of early childhood.

Except for severe intoxication, consciousness and judgment remain preserved. Accordingly, the experimental subjects are fully aware of the fact that their perception is distorted. Experimental subjects often describe this situation in terms of being split into two persons: one registering the peculiar and unusual experiences, the other knowing that the unusual experiences do not depict events in the physical environment. Some psychiatrists call this phenomenon "depersonalization."

The other psychic symptoms vary considerably from person to person. Emotional responses are almost always present. While euphoria predominates in some subjects, anxiety and depression do in others. The type of this reaction appears largely influenced by the personality structure of the subject. Mood changes may also be found in the same person from time to time during the intoxication. High spirits, accompanied by bursts of uncontrolled laughter,[23] may alternate with feelings of deep depression or anxiety. The sensory and emotional manifestations preoccupy the individual to an extent that engenders a certain degree of autism with a corresponding decline in the results of mental tests, such as memory tests, computation tests, or the like. However, if the experimental subjects can be persuaded to concentrate on their task, little difference is found from normal scores. Large doses, causing violent psychic symptoms, lead to a delay in reaction time or to deterioration of precision in psychometric tests. At this stage, ataxia and other manifestations of muscular incoordination may appear, but the degree of these symptoms is much slighter than that seen during a moderate alcohol intoxication.

At times, the psychic experiences may make a deep impression on the individuals. For this reason hallucinogens are used as a tool in psychiatry to disclose forgotten experiences of importance for the diagnosis, or to help the patients to abreact. Severe reactions may follow after testing far beyond the direct pharmacodynamic effects of the drug.

It would be of great interest to know whether the different kinds of psychic effects of hallucinogens (i.e., distortion of perception; pseudohallucinations, hallucinations, emotional reactions) reflect a common site and mechanism of action in the central nervous system or whether these different effects correspond to different mechanisms of action.

There has been some discussion as to whether or not the various chemically different groups of hallucinogens have the same principal effect.[89] Qualitative differences have been claimed, e.g., that the vegetative symptoms are less pronounced after mescaline[90] or psilocybin[97] than they are after lysergide; or that lysergide causes more anxiety, while euphoria predominates after psilocybin.[130] Others described the reaction to lysergide as resembling a hebephrenia while the reaction to mescaline was believed to resemble a catatonia.[70, 119] However, the effect of two hallucinogens varies from time to time and depends on the dose. Therefore, all claims of a qualitative different effect must be evaluated with scepticism. In fact most authors who have directly compared two or more hallucinogens agree that their effects are essentially identical.[88, 109, 139, 148]

The effect of the hallucinogens is characteristic and easy to distinguish from other agents eliciting mental symptoms. Some highly active N-substituted piperidyl derivatives developed by Abood and his coworkers[1] result in complete loss of contact with the environment and dramatic visual and auditory hallucinations, an effect reminiscent of that of scopolamine, but clearly different from that of the hallucinogenics.[98, 112] The mental symptoms of phenylcyclidine (1-(1-phenylcyclohexyl) piperidine HCl, Sernyl are described as body-image changes, estrangement, disorganization of thought, negativism, hostility, and

terror. Patients who were tested with lysergide, mescaline, and phenylcyclidine were able to distinguish between the subjective experiences caused by these agents.[21, 130] Authors who compared hallucinogens with phenylcyclidine found the effect of the latter essential different from that of the hallucinogens.

According to the very experienced Lexington group,[175] the effect of hallucinogens is distinguishable from the effect of amphetamine, scopolamine, and marihuana.

Bufotenine is of a special interest not only because it is a tryptamine derivative, closely related to serotonin, dimethyltryptamine, and psilocybin, but also because it has some neurophysiologic effects in common with lysergide.[64, 65] Subjects tested with bufotenine reported seeing red spots and figures, but illusions, hallucinations, or major distortions of sense perception were not experienced.[66, 165]

Tolerance and cross-tolerance

When hallucinogens are given in individual doses repeated at not too long intervals, for example, 24 hours, tolerance develops rapidly. The tolerance is most pronounced for lysergide, less for psilocybin and mescaline. The tolerance for the vegetative phase is not developed to the same degree as for the psychic phase.[136]

The tolerance regresses rapidly, and initial responsiveness is attained after a pause in drug administration of 3 days' duration.

A marked mutual cross-tolerance is found between the hallucinogens, not only for closely related compounds,[3, 19] but is also between the groups, e.g., between lysergide, mescaline, and psilocybin.[106, 175] Agents which cause psychic symptoms of a clinical appearance different from that of the hallucinogens, do not develop cross-tolerance with the hallucinogens. Accordingly, the N-substituted piperidyl compounds developed by Abood and his coworkers[1] do not develop cross-tolerance with lysergide.[19, 20, 175] This phenomenon strongly suggests that the entire group of hallucinogens, in spite of the chemical differences, may be considered to possess some fundamental property in common. On the other hand, it is possible to develop a tolerance to lysergide by administering large doses of either brom-lysergide or 1 methyl-d-lysergic acid butylamide, both compounds devoid of hallucinogenic effects.[19, 175]

Influence of the hallucinogens on animal behavior

The effects on animals vary considerably with the type of hallucinogen and the species tested. Moreover, the doses necessary to cause changes in animal behavior are much larger than those giving symptoms in man. (The approximate effective doses in man are 1-2 μg per kilogram for lysergide, 100-200 μg per kilogram for psilocybin, and 5,000-10,000 μg per kilogram for mescaline. For the sake of comparison, this will subsequently be called the effective human dose [EHD]).

In monkeys, 5-10 μg per kilogram lysergide (5 EHD) causes some decrease of accuracy of a trained performance, but there is little influence on the working speed.[108] Animals trained to discriminate between differently shaped objects increase their reaction time.[72] At this stage no changes in gross behavior are seen. After a slightly larger dose (15 μg per kilogram = 7-8 EHD) the animals show a tendency to withdraw. After still larger doses (200 μg per kilogram = 200 EHD) the animals seem more sensitive to noise.[28] Considerably larger doses (1,000 μg per kilogram = 1,000-2,000 EHD) result in ataxia. The animals take a prone position, can easily be handled, and do not respond to visual or noxious stimuli. The animals die after 5 mg. per kilogram (5,000 EHD).

Dogs and cats are excited after 10-100 μg per kilogram lysergide (= 5-100 EHD). Ten effective human doses of lysergide lead to excitation and increased aggressiveness, and some traits in the cats' behavior suggest that they are hallucinating: the animals peer into their cages, act as they

are startled by some objects, and grasp at the air in front of them with their paws.[9] Excitation and aggressiveness are also seen after mescaline,[127] but the result apparently depends on the dose and the details of the observational procedure. Other observers have found dogs and cats much more docile after mescaline.[158] Lysergide has no influence on the conflict-induced behavior of cats ("experimental neurosis").[118]

In rats 200 μg per kilogram lysergide (100-200 EHD) elicits motor hyperactivity followed by quietness. The animals are confused in the rope-climbing test.[173] The reaction time in conditioned avoidance tests increases,[160] while the relative performance of conditioned responses remains uninfluenced.[114] A decrease of appetite is seen as after amphetamine.[83] Normally, two rats kept in the same cage and simultaneously given an electric shock will fight for a certain time. This time of "emotional aggressivity" is prolonged, as after cocaine, amphetamine, and pipradrol.[39] Mescaline seems to cause less hyperactivity but induces a characteristic catatonia in which the rats stiffen in bizarre positions, standing on their hind legs.

Lysergide administration to mice (50-100 EHD) causes hyperexcitability and hypersensitivity to sound and touch. The mice may walk backward with spread legs like animals placed on a sloping, slippery plane.[176] Piloerection[82] and a fine tremor[5] are seen as signs of sympathetic overactivity. In some strains, scratching episodes are seen after mescaline (50-100 mg. per kilogram) which are antagonized by serotonin, morphine, and the major tranquilizers, but not by barbiturates and meprobamate.[48, 68]

Elephants seem to be extremely susceptible to lysergide. A male elephant developed status epilepticus and died 100 minutes after an injection of 100 mg. per kilogram.[171a]

Pigeons develop catatonia.[22] In the salamander equilibrium disturbances and statuelike postures are seen after administration of lysergide.[129]

The effect of hallucinogens on fish differs from species to species. Siamese fighting fish *(Betta splendens)* placed in water with 0.2 μg per milliliter lysergide show a preliminary short excitation and then place themselves vertically near the surface of the water[11, 63, 164] as they do in asphyxia.[171] The guppy *(Lebistes reticulatis)* responds with rapid swimming toward the wall of the aquarium, where it continues to perform swimming movements, apparently unaware of the hindrance to locomotion. Goldfish fluctuate between a state of agitation, in which they occasionally swim backward, and short periods of quietness. Cave fish do not move at all. No effect can be seen after mescaline.[63, 164] Apparently, some lysergide effects are entirely of peripheral origin. The pigmentation of guppies is caused by an action directly on the melanophores and can be evoked in vitro on excised parts of the fish skin.[25, 26] Mescaline is devoid of this effect.

Lysergide effect can also be demonstrated on insects. Under the influence of lysergide, ants do not recognize their nest mates, but treat them as enemies and attack them.[153] Spiders spin their webs in a disorganized pattern, but their is such a great difference between the effect of lysergide and that of mescaline that it is doubtful whether this action is indicative of the hallucinogenic potency.[174]

Lysergide has also a prominent effect on low animals. The movements of the mystery snail become completely disorganized when it is kept in water containing as little as 0.01 μg per milliliter. This effect can be used for biologic determinations of lysergide.[2] The liver fluke is stimulated to rhythmic movements by lysergide.[116]

Pharmacodynamic effects of the hallucinogens

Peripheral effects. In higher animals the direct action of the hallucinogens on the peripheral cells is of little or no importance. Lysergide, mescaline, and psilocybin have all a slight contracting effect on certain smooth muscles, generally either mimicking

epinephrine or serotonin, or enhancing their effect.[144] The umbilical vessels of the human placenta respond with a constriction to lysergide and mescaline. In this effector system, lysergide is about 10 times more effective than is epinephrine, but 1 to 5 times weaker than serotonin.[14]

Central effects. The hallucinogens cause a facilitation of certain reflexes within the central nervous system. In the decerebrated cat, lysergide[169] and psilocybin[170] facilitate the knee-jerk reflex. Other reflexes are inhibited. Lysergide abolishes the carotid sinus reflex, but this effect is not specific for the hallucinogens as such, since it is not found after mescaline or acetyl lysergide.[76, 77]

The stimulation of the sympathetic centers is characteristic and is easily demonstrated in animal and human experiments. The slight increase in blood pressure, the pulse acceleration, and the moderate pupil dilatation in humans have already been described. When larger doses are administered to animals, sympathomimetic effects become still more pronounced as they result in protrusion of the eyes, piloerection, and hyperglycemia.[137] The intensity of these effects have been compared with the effects of reserpine in animals pretreated with monoamine oxidase inhibitors.[147] Curiously enough, mescaline given to rats causes hypoglycemia and not hyperglycemia.[69] The sympathetic effect is of central origin. Accordingly, pretreatment with ganglionic blockers abolishes the effect.[136]

The increase of body temperature, which in human experiments only occasionally exceeds 0.5°-1.0° C., may be very pronounced in animals. This effect is probably also a sign of sympathetic stimulation. Rabbits are especially sensitive, the medium effective dose of lysergide being 0.5 μg per kilogram.[137] The hyperthermic effect of lysergide is related to the hyperthermic effect of the amphetamines and different from that of pyrogens.[154] It is potentiated by methamphetamine and, like amphetamine hyperthermia, it is antagonized by chlorpromazine and reserpine.[59] The increase of body temperature can be provoked in decorticated animals, but not in decerebrated animals or animals with the midbrain removed.[126] Mescaline in rabbits is much less effective than is lysergide; 50 mg. per kilogram (5-10 EHD) raises the body temperature by as little as 0.3°. However, pretreatment with a monoamine oxidase inhibitor enhances the effect so that the same dose elevates the temperature by about 3.0°.[16] During treatment with lysergide, the food intake of rats is diminished.[83] The same appetite-decreasing effect is seen with the amphetamines. Only under exceptional circumstances (e.g., in hypophysectomized animals[142]) does the general sympathetic stimulation result in sham rage; this also applies to intracerebral administration of lysergide.[81]

The effect on the adrenocortical centers varies apparently with the species. An increased excretion of 17-ketosteroids[168] after administration of lysergide was found in man, but not in guinea pigs.[125]

In mice in which "waltzing" was induced by means of iminodipropionitrile, the circular movements could be abolished by means of hallucinogens, and the effective doses seemed to follow the rank order of the clinically effective doses[55]; but this action is not specific for hallucinogens.[161]

The hallucinogens affect the function of the ascending reticular system. In rabbits and cats, after 20 to 40 μg per kilogram lysergide, a consistent desynchronization is found in the neocortex, similar to that found after peripheral sensory stimuli, electrical stimulation of the reticular formation, and after stimulants like the amphetamines.[36, 37, 51] This effect is generally known under the name of electroencephalographic arousal. With lysergide, however, the appearance of the arousal pattern is abolished if the connections between the brain and the spinal cord are interrupted, but this does not occur with the desynchronization caused by amphetamine.[36] This is an important difference between the effect of lysergide and the amphetamines. In the

hippocampal region, in contrast to the desynchronizing effect on the neocortex, sensory stimuli and electric stimulation of the reticular formation cause a synchronization here with an electric activity of waves of about 0.5 mv. with 5 to 6 cycles per second, increasing with the intensity of the stimulation. Large doses of amphetamines release the same pattern. While lysergide gives an electroencephalographic arousal reaction on the neocortex like that after stimulation or amphetamines, the reaction on the hippocampal area is very different. Lysergide causes an activity with waves lower in voltage and much more irregular than in the normal stage.[38] Thus, in spite of certain apparent similarities between the effect of the amphetamines and the effect of lysergide on the electric activity of the neocortex, they differ so much in other respects that it is doubtful whether the cortical effect of lysergide should be called an arousal reaction at all.[38] With psilocybin, Monnier[123] finds that the appearance of an "arousal" electroencephalogram is due to a depression of the mediothalamic recruiting system, rather than to a direct activation of the reticular system.

In man, the α-activity of the electroencephalogram is generally suppressed when under the influence of hallucinogens, especially in periods when the experimental subjects report hallucinations or show symptoms of anxiety.[172] When present, the α-frequencies are accelerated by 20 to 30 per cent[6] and the β-waves appear accentuated. The latter effect is seen after administration of lysergide,[74] as well as of mescaline and psilocybin.[115]

The effect of the hallucinogens on the activity of neurons and neuron systems not related to the diffuse projection systems is rather complex. A variety of effects have been described. These comprise initiation of spontaneous activity as well as facilitation and block of evoked activity depending on the site where the effects are measured and the dose used. In retinal ganglion cells of cats and monkeys, hallucinogens cause discharges in the absence of light stimuli.[8, 9] Placed topically on the cortex, mescaline, but not lysergide, changes the responses to adequate stimuli in the same way as does strychnine, but the effect is weaker.[138] Purpura showed facilitation of the evoked auditory and visual cortical responses in unanesthetized cats under the influence of 2-30 μg per kilogram (1-15 EHD) lysergide given systemically.[131] But large doses of hallucinogens decrease the post synaptic response to photic stimulation of the retina in the lateral geniculate nucleus.[28, 29, 64, 65] The effect is not specific for the hallucinogens as it also occurs with bufotenine, brom-lysergide, and serotonin.[28, 29] Complete blindness is found in the cat and monkey after large doses of lysergide (350 μg per kilogram).[29, 64, 65] It has been suggested that lysergide blocks the synapses in the lateral geniculate nucleus by competitive antagonism with the natural transmitter substance. Whether or not a similar blocking causes the increase of visual threshold found in pigeons after relatively large doses (100 μg per kilogram),[32] or in man after moderate doses,[42] is an open question.

The postsynaptic component of the transcallosal response is also inhibited by lysergide.[117] This effect is, however, not specific for the hallucinogens, as it follows administration of most sympathomimetic agents. The simultaneous presence of inhibitory and facilitatory effects has been further studied by Purpura.[132] He proposes that lysergide inhibits axodendritic, and facilitates axosomatic, synapses, but it is still an open question whether this effect is characteristic for all hallucinogens or specific for lysergide.

Possible site of action

At present, however, no definite conclusion can be reached concerning the site of action of hallucinogens. Also, it is not certain whether the distortion of perception, the hallucinations, and the thought-flow dreams can all be attributed to a common, primary action of the hallucinogens, or whether these different manifestations of

drug action involve several different sites and mechanisms of action. Presumably, the perceptual dysfunction originates at a high level in the nervous system; it is not associated with impairment of skilled motor performance: an experimental person is able to unlace his shoes with normal precision even if he is feeling that his feet are "miles away."

The occurrence of spontaneous discharge in the retinal ganglia of cats under the influence of hallucinogens suggests that some of the sensory impressions may be formed in the perceptual organs itself, at least in cats. It is also possible that some of the perceived colored spots or zigzags are partly of peripheral origin. But the peripheral effect is insufficient to explain completely the hallucinogenic effect since visual hallucinations can be experienced by patients who have had their eyeballs enucleated.[8, 9] Nor can the hallucinations be fully explained as an enhancement of responses to peripheral stimuli: sensory deprivation has no influence on the hallucinations or pseudohallucinations[128]; in fact, the hallucinations seem to be more intense.

It, therefore, appears that the hallucinations are predominantly of central origin, although very little is known about the exact site. Experiments with topically applied hallucinogens have contributed little to this question. In mice, effects of lysergide administered by the intraventricular route do not differ from those obtained on intravenous administration.[82] In cats, however, intraventricular injection of lysergide results in sedation, sometimes after initial restlessness[37, 146, 157, 177]; but the vegetative symptoms consisting of micturition, sweating, salivation, and mydriasis are equally pronounced.[81] Sedation is seen when lysergide is injected in the ventromedial nucleus of hypothalamus.[177] The sedation after intraventricular application cannot be considered specific for hallucinogenics. Most agents with a sympathomimetic effect cause sedation when injected intraventricularly, and the same effect is elicited by brom-lysergide. More likely, this effect could be related to an unspecific antiserotonin action.

Olds and associates[128] found that lysergide was able to inhibit the rate of self-stimulation when the stimulating electrodes were placed in the anterior or posterior hypothalamus and in the subseptal region. A similar effect could be obtained with brom-lysergide, especially if the electrodes were implanted in the posterior hypothalamus and in the septal region. The effect seems to be unspecific and not connected with the hallucinogenic action.

Baldwin and co-workers[17] administered lysergide to chimpanzees in doses of 60 μg per kilogram orally (60-120 EHD). This large dose caused a characteristic behavior resembling panic. Ablation of the frontal lobes did not result in any changes of the reaction to lysergide, although some behavioral changes were observed after the operation. Bilateral removal of mesial temporal structures resulted in transient behavioral changes, but the animal operated upon in this way reacted to lysergide as did normal animals. On the other hand, bilateral ablation of the lateral temporal structures or complete temporal lobectomy gave no changes of the behavior as such, but the psychic effects of lysergide were completely abolished, although the vegetative symptoms remained. However, it is very doubtful if these experiments allow the general conclusion that the psychic effect of lysergide, or of the other hallucinogens, can be attributed to an action on the temporal lobes: in the first place, the necessary doses were extremely high compared with the effective doses in man; furthermore, no control experiments on specificity of action were made.

In patients with implanted cortical and subcortical electrodes, Monroe and associates[124] found changes after administration of lysergide and mescaline, mainly consisting of paroxysmal electric activity in the hippocampal gyri, nucleus amygdalae, and septum. These changes went parallel to the behavioral changes. No effect was seen

after L-lysergide in doses up to 1 mg., suggesting that this effect is rather specific.

Discussion

Taken as a whole, all hallucinogens have a central sympathomimetic effect. The increase of the body temperature is an example of this effect. Apart from this, there are other pharmacodynamic effects on the central nervous system, presumably consisting in a blocking of certain centers and pathways, and an enhancement of others. Which parts of the central nervous system are blocked and which parts facilitated depend apparently on the specific properties of the drug and on the applied doses. Few, if any, of the described behavioral or physiologic effects in animals are common to all hallucinogens. Some effects are characteristic for one type of hallucinogens, such as the posture of rats that received mescaline, an effect not obtained with lysergide. Other reactions are seen with all hallucinogens but can also be elicited by substances without hallucinogenic effect. It is impossible with our present knowledge to conclude from animal experiments alone whether a given substance has hallucinogenic properties. Moreover, in spite of the many investigations published on the subject, no results are available which reveal the mode or site of the hallucinogenic effect in the human brain. Some experiments indicate that the site of action can be located in the basal ganglia and the limbic system; however, this suggestion is preliminary and awaits further experimental tests.

Interaction with other agents

Chlorpromazine antagonizes the vegetative and the psychic effect of all hallucinogens. The effect of rauwolfia alkaloids is variable; barbiturates have little effect, and amphetamine enhances some symptoms and antagonizes others.

Hallucinogens as antagonists or synergists. Lysergide is a strong antagonist to serotonin. This can be shown in both in vitro and in vivo experiments.[44, 73, 79, 80, 169] When this fact was demonstrated it aroused considerable interest since serotonin had been found present in the basal ganglia of the central nervous system, although its function here was, and still remains, unclear. These points will be discussed in detail in a later paragraph. However, psilocybin is a weaker antagonist, and mescaline has no antiserotonin action.[163] The antiserotonin effect is not specific for the hallucinogenic effect and within the lysergic acid derivative series. This is also seen from the fact that the nonhallucinogenic brom-lysergide has a pronounced antiserotonin effect, similar to that of lysergide, at least in vitro.

The slight potentiation of epinephrine and norepinephrine by mescaline has already been mentioned. On the other hand, lysergide is slightly antagonistic to sympathomimetics when tested in vitro or on isolated organs.[144] This phenomenon explains why lysergide in large doses is able to antagonize lethal doses of epinephrine.[113]

The effect of substance P is enhanced by lysergide. Moreover, lysergide specifically inhibits the brain enzyme inactivating substance P. Mescaline lacks this effect.[110]

Even in high concentrations, the hallucinogens have no or only little antagonistic effect on other amines such as acetylcholine or histamine.[163] No effect is seen on the monoamine oxidase activity.[150]

Most hallucinogens have analeptic properties, i.e., they antagonize sedatives and morphine, but it requires large doses to demonstrate this effect. The hallucinogens share this effect with the amphetamines, of which methylamphetamine is almost as active as lysergide.[10, 40, 60]

Synergists and antagonists to hallucinogens. Chorpromazine is the strongest and most effective antagonist to the hallucinogens.[45, 57, 58, 89, 100, 101, 102, 167] The effect is not only observed on the dreams, visions, and hallucinations, but can also be demonstrated objectively on the electroencephalographic changes[57, 124] and the vegetative symptoms, provided that a proper dose relation between chlorpromazine and the hallucinogen is chosen.[58, 101]

The antagonistic effect of chlorpromazine can also be demonstrated in animal experiments.[158] As in man, the effect depends on the relation between the doses of agent and antagonist. Ray and Marazzi[133] found an inhibiting effect of lysergide on the rate of lever pressing of rats conditioned for a reward. The lysergide-inhibiting effect was antagonized by chlorpromazine in small doses, but if chlorpromazine was given in larger doses, the specific inhibiting effect of this drug on the conditioned responses became apparent so that a renewed inhibition of the rate of lever pressing appeared, this time caused by the overdose of chlorpromazine. An antagonism can also be demonstrated in cats when the effect is measured electroencephalographically, with the hallucinogen administered systemically[37] or intraventricularly.[157] The effect of lysergide on the body temperature of rabbits is antagonized by chlorpromazine and by reserpine.[59] The same is the case with the scratch response in mice.[68] Other phenothiazine derivatives or compounds with psychotropic action similar to that of chlorpromazine have the same antagonistic action on the hallucinogens.

As chlorpromazine itself is a strong antiadrenergic agent, it is not surprising that the various sympathomimetic effects of the hallucinogens are also antagonized by chlorpromazine. Other antiadrenergics also antagonize some of the effects of the hallucinogens. Thus, dibenzylene prevents the hallucinogen-induced aggressiveness in mice.[62]

While chlorpromazine indisputably antagonizes the effects of hallucinogens, the hallucinogens do not antagonize the chlorpromazine actions. If lysergide is administered after chlorpromazine, the action of the latter persists unaltered.[37]

In contrast to chlorpromazine, the other type of major tranquilizers, of which reserpine is a prototype, seems to have little or no antagonistic effect against the hallucinogens.[40, 89, 101, 124] According to several investigators, reserpine can actually enhance the effect of lysergide.[124, 167] However, some of the vegetative effects in rabbits, such as hyperthermia, hyperglycemia, and mydriasis, cannot be provoked in reserpine-pretreated animals; this can be accounted for by the fact that reserpine depletes the peripheral cells of catecholamines, the natural sympathetic transmitter.[137] Therefore, the suppressive effect of reserpine depends on the time interval between the administration of reserpine and lysergide: in rabbits, reserpine antagonizes the hyperthermia if given 2-4 hours before lysergide; if given immediately before, the hyperthermia is enhanced.[61] Isbell[100, 101] reports that, although pretreatment with reserpine is able to prevent the hallucinations, the simultaneous administration of reserpine and hallucinogen causes an intense sensation of unreality and an inadequate effectivity without self-criticism, a state which by the authors is interpreted as real schizophrenia.

Barbiturates are claimed to have some antagonistic effect.[74, 89] Perhaps this effect is not really specific, but only due to the general sedative effect which reduces the impressions of the thought-flow and the hallucinations. In animal experiments neither barbiturates nor meprobamate have any major antagonistic action.

Fabing[66] described an antagonistic effect of azacyclonol on the subjective symptoms of lysergide given to humans. This observation led to the introduction of azacyclonol as a tranquilizing agent. An antagonistic effect of the mescaline-induced electroencephalographic changes in the rabbit was also demonstrated,[135] but the attempts to reproduce the antagonistic effect of azacyclonol in humans have generally failed.[100, 101, 124]

Brom-lysergide with its antiserotonin effect has been regarded as an antagonist to lysergide. The obtained effect depends on the dose and on the way of administration. No effect is found even if 2-4 mg. is given simultaneously with, or some times after, lysergide; but if 1 mg. is given three times a day for 5 days, the response to a dose of lysergide given on the sixth day is signifi-

cantly reduced. It seems as if no direct competitive antagonism between bromlysergide and lysergide takes place, but rather that the administration of bromlysergide results in building up a tolerance to lysergide in spite of the fact that bromlysergide is not a hallucinogen.[105]

The effect of the amphetamines is not quite clear. It presumably depends on the symptoms selected for study whether an antagonism or a synergism is found. In psychiatric patients the amphetamines enhance the emotional changes induced by the hallucinogens.[18, 41] On the other hand, the amphetamines seem to improve the power for concentration in normal subjects under the influence of hallucinogens.[73, 162]

Other antagonists of different types have also been mentioned in the literature. The possible antagonizing effect of succinate will be discussed in a subsequent paragraph. Prednisone is claimed to diminish the anxiety after lysergic acid diethylamide.[4]

Hypotheses on the mode of action of hallucinogens

The hallucinogenic effect has been regarded as a "model psychosis." This fact has stimulated the research on the mode of action of the hallucinogenics, starting with the assumption that an "explanation" of the effect of the hallucinogens could serve as a clue to the understanding of the origin of the clinical psychoses. The interest has mainly been focused on three properties of the hallucinogenics: their effect on the cellular metabolism; their sympathomimetic effect; and their antiserotonin effect.

The effect on cellular metabolism is incompletely explored. In vitro tests have shown that mescaline, in a concentration of 0.1 per cent inhibits the oxidation of glucose, lactate, and pyruvate, but not that of succinate.[145] For this reason succinate was tested as an antidote for mescaline. Some authors have claimed an antagonistic effect[50, 145] but others did not confirm this effect, at least not when succinate was used to antagonize the effects of lysergide. Lysergide was found to increase the metabolism of brain cells in vitro,[121] but no effect was found on the uptake of P^{32} in brain lipids.[7] These effects are, however, not specific and are found with many other nonhallucinogenic agents. More interesting is an observation of Melander and Martens[122]: cats pretreated with lysergide presented behavioral changes subsequent to administration of substances which in themselves were without effect on normal cats in the given doses. The agents tested were: acetylcholine, epinephrine, adrenolutin, atropine, histamine, serotonin, and mescaline. The Swedish authors[122] suggest that lysergide facilitates the access of agents to brain structures otherwise inaccessible.

As already mentioned, all hallucinogens have a more or less pronounced sympathomimetic effect. It is not very likely that the hallucinogenic effect is directly connected with the sympathomimetic effect. Many other agents, such as the amphetamines, have a similar sympathomimetic action, also on central nervous system structures, but are not hallucinogenic. The psychotic symptoms seen after a prolonged overdosage of amphetamine differ in many respects from the hallucinogenic effects described here. Rabbits pretreated with a monoamine oxidase inhibitor and given reserpine exhibit symptoms that resemble those provoked with lysergide.[147] But in experiments with humans, the combined administration of lysergide and a monoamine oxidase inhibitor (iproniazid) does not mimic the hallucinogenic effect of lysergide.[56]

The discovery that lysergide was a strong antagonist to serotonin suggested a certain relation between the antiserotonin and the hallucinogenic action, perhaps in the way that the hallucinogens block some serotonin-regulated inhibiting pathways in the central nervous system. As mentioned earlier, serotonin is found in the central nervous system, especially in the basal ganglia, its distribution mainly following that of the catecholamines. It has been sug-

gested, therefore, by Gaddum and Vogt[73] that the hallucinogenic effect might be linked to an antagonism of lysergide to the effect of serotonin in the central nervous system. Many experiments have been done in order to throw light on this hypothesis. It could be shown that the actions of serotonin in a variety of test situations are directly contrary to those of hallucinogens: for example, in spinal cats serotonin blocks, while psilocybin and lysergide enhance, the knee-jerk reflex.[170] However, no relationship can be found between the hallucinogenic effect and the antiserotonin potency measured in vitro.[104] Brom-lysergide, for example, has the same antiserotonin effect as has lysergide, but has no hallucinogenic effect.[30, 136] On the other hand, Gaddum and Vogt[73] found the depressant action of serotonin on the brain of cats antagonized by lysergide, but not by brom-lysergide; and Sanker and his co-workers[143] found a definite difference between the effects of brom-lysergide and lysergide on the brain serotonin level. The latter increases the serotonin level in parts of the brain where it is decreased by brom-lysergide. At the same time Sai-Halász demonstrated that 1-methyl-d-lysergic acid amide, which is a strong antiserotonin agent but in itself not hallucinogenic, potentiates the effect of dimethyltryptamine.[140]

These observations seem to indicate that some relation between hallucinogens and serotonin seems to exist in the central nervous system, but many more experiments are necessary to decide if this connection is of significance for the hallucinogen effect. So far, the experiments have only been performed in animals, and we are still completely ignorant of the significance of serotonin for the effect of hallucinogens in humans.

Relation of hallucinogens to various psychotic states

Two such substances have been claimed, but, if they have an effect at all, it differs from that of the hallucinogens. Nevertheless, a compound closely related to mescaline has been isolated from the urine of schizophrenics.

The "model psychosis" provoked by the hallucinogens differ decisively from the illusions and hallucinations found in the clinical psychoses. Intelligent schizophrenics have been able to distinguish between the symptoms provoked by a hallucinogen and "their private hallucinations." Nevertheless, the work with hallucinogens has inspired the hypothsis that mental diseases, especially schizophrenia, are caused by abnormal hallucinogen-like agents occurring within the brain as a result of a metabolic disturbance. Some attempts have been made to isolate substances from schizophrenics which were able to provoke mental symptoms when given to normals.

In 1952 Osmond and Smythies stressed the chemical similarity between mescaline and epinephrine and suggested on this basis that a substance, or some substances, related to epinephrine might form an etiological factor in schizophrenia. Using this as a working hypothesis, Hoffer in collaboration with Osmond and Smythies[91] made an attempt to isolate such a compound which presumably could account for "the group of illness called schizophrenia."

These authors incidentally learned that asthmatics who had used epinephrine now and again had noticed a psychic effect which might be interpreted as hallucinogenic; this occurred if the preparation used was old and discolored due to oxidation products of the epinephrine. It was suggested, therefore, that epinephrine is incompletely oxidized in the central nervous system of schizophrenics, and that the accumulation of abnormal epinephrine metabolites causes the mental disturbances. Consequently, they administered adrenochrome to normal persons and claimed to have observed psychic effects. Their results are still disputed and many authors have been unable to repeat them. In any case, the symptoms observed by Hoffer and his co-workers[91] after adrenochrome are definitely different from those seen after the hallucinogens. Although a slight

distortion of sense perception was reported, neither the distortion of the ego-image nor the dreamlike images characteristic of the hallucinogens have been described.

Heath and his co-workers[85] have found taraxein, which differs from the epinephrine metabolites. This is a protein fraction isolated from the serum of schizophrenics, which is claimed to give psychic symptoms when injected in normals.[85] Many have been unable to confirm these results, but the original authors, by direct comparison, found the effect of taraxein quite different from that of lysergide, mescaline, and psilocybin.[122, 148] Taraxein does not elicit vegetative symptoms, nor does it evoke hallucinations; association defects and delusions are the only effects described.[148] Moreover, the effect on the electroencephalogram in monkeys differs decidedly from that caused by the hallucinogens.[84]

Taken as a whole, there does not exist any evidence that schizophrenia could be caused by the formation of a hallucinogen or a hallucinogenic agent in the diseased organism. Yet a recent observation suggests some connection. Friedhoff and Van Winkle[71] have isolated and identified 3, 4-dimethoxyphenylethylamine from the urine of 13 out of 15 schizophrenics; this compound was not found in the urine of an unstated number of normal persons. This compound is chemically closely related to mescaline, but not hallucinogenic in itself. It is still far too early to evaluate the significance of this finding.

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