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COMPARATIVE ASPECTS OF SELECTED PSYCHOACTIVE COMPOUNDS: BIOGENIC AMINES, MONOAMINE OXIDASE INHIBITORS, AND LYSERGIC ACID DIETHYLAMIDE

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THREE related areas of biochemical and physiological investigations with biogenic amines and psychotropic drugs have produced enough information to permit some firm generalizations and important exceptions to be made across species, classes and phyla. These are: (1) the distribution of serotonin and norepinephrine in the central nervous system of vertebrates; (2) the effects of drugs directly affecting amine storage and metabolism: monoamine oxidase inhibitors and reserpine; and (3) the universality of action of LSD throughout the animal kingdom.

The reader is referred to more generalized reviews for the function and action of serotonin: Eichler & Farah (1965); norepinephrine: Glowinski & Baldessarini (1966); monoamine oxidase inhibitors: Pscheidt (1964a); reserpine: Carlsson (1965); and lysergic acid diethylamide: Evarts (1957).

BIOGENIC AMINES

The biogenic amines, serotonin and norepinephrine, derive from the amino acids tryptophan and phenylalanine respectively according to the metabolic schemes shown in Figs. 1 and 2. They are localized in the central nervous system of vertebrates in specific fiber tracts (Fuxe, 1965). Their exact function is controversial, but it is clear that they either participate directly in or modify synaptic transmission of nerve impulses. This portion of the review is concerned only with their regional distribution in anatomically distinct portions of the central nervous system and a discussion of deviations from the standard pattern of distribution in representative species.

It is important to realize that many different methods of analysis and preparation of tissue have been used by different investigators which tends to make absolute comparisons of levels of amines irrelevant. However, sufficient uniformity of amine distribution and drug response exists so that valid generalizations may be made.

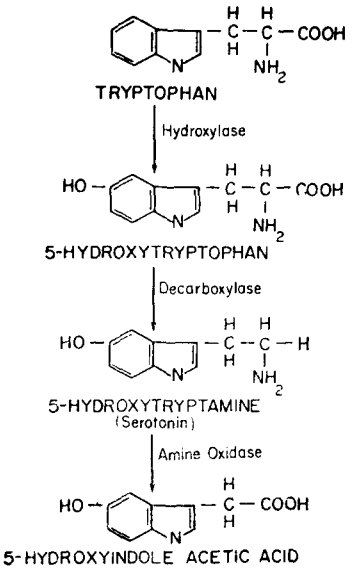

FIG. 1. Formation of serotonin and metabolites from tryptophan.

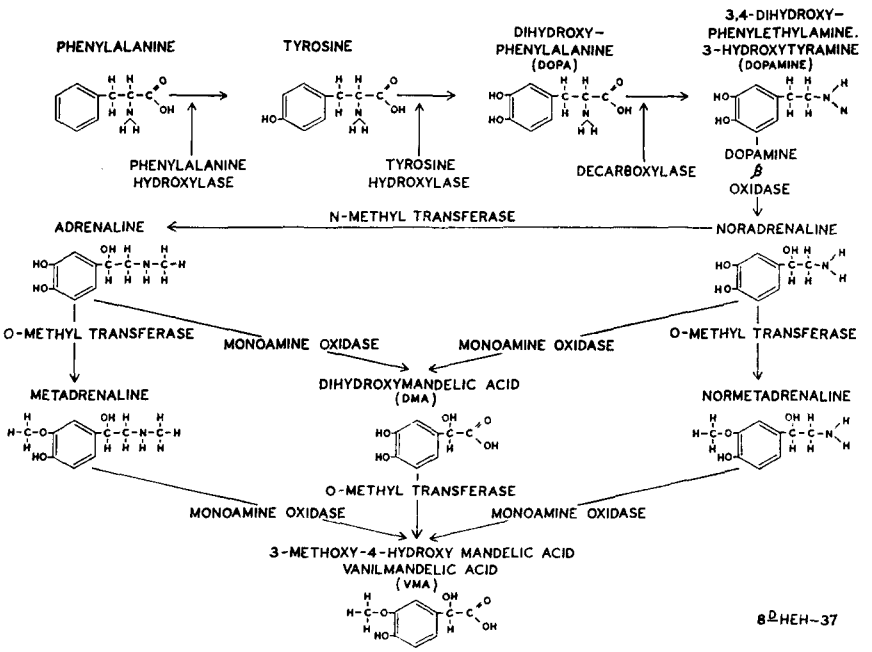

FIG. 2. Formation of catecholamines and metabolites from phenylalanine.

Comparison of amine content is also rendered difficult by the decision of the various investigators to analyze different subdivisions of the central nervous systems. The commonest partitions in order of increasing localizations are: (1) whole brain, (2) whole brain less cerebellum, (3) telencephalon or hemispheres, which include all brain regions above the level of the thalamus, and brain stem, (4) telencephalon, diencephalon, mesencephalon, rhombencephalon, and (5) dissection of discrete anatomical structures as indicated in the text. It will be instructive to consider first the distribution of amines in the rodent and lagomorph brain inasmuch as they have received the most attention.

Rodents and lagomorphs

In the mouse the highest levels of norepinephrine are found in the diencephalon with the mesencephalon, rhombencephalon, cerebellum and telencephalon exhibiting lesser amounts of the amine (Izquierdo *et al.*, 1964). The rat shows a similar distribution of norepinephrine: diencephalon, rhombencephalon, mesencephalon, cortex and cerebellum (Izquierdo *et al.*, 1964). There do not appear to be any studies on the distribution of serotonin in rat or mouse brain. In the rabbit, however, the serotonin content of the di- and mesencephalon was 0·65 μg/g with the rhombencephalon 0·58 μg/g and the telencephalon 0·28 μg/g, cerebellum 0·12 μg/g (Costa & Rinaldi, 1958). A common division of the rodent brain is into telencephalon and brain stem comprising the remainder of the brain less cerebellum. In this division the stem content of both serotonin and norepinephrine is always found to be higher than that of the telencephalon (Pscheidt *et al.*, 1964; Costa & Rinaldi, 1958). In addition, the content of serotonin is usually higher than that of norepinephrine on a weight basis, in all of the regions tested.

Insectivores

The serotonin content of different brain parts of the hedgehog (*Erinaceus europaeus*) was determined by Uuspaa (1963) and the regions ranked as follows from highest to lowest: mesencephalon, diencephalon, pons-medulla, cerebral hemispheres, olfactory bulbs and cerebellum. In addition there were seasonal variations in the absolute content of the brain parts which appeared to be related to the state of activity of these hibernating mammals.

Carnivora

The carnivores (cats and dogs) have yielded the most detailed information regarding the distribution of amines in discrete portions of the brain (Vogt, 1954; Amin *et al.*, 1954; Himwich & Costa, 1960). The hypothalamus contains the highest concentration of both norepinephrine and serotonin in the brain of the cat (Kuntzman *et al.*, 1961). In the dog the colliculi and portions of the rhinencephalon were found to contain more serotonin than the hypothalamus although no structure had a higher level of norepinephrine (Himwich & Costa, 1960). The cerebral cortex of both species had the lowest concentration of amines; however,

appreciable amounts were found in the rhinencephalon and corpora striata. Other brain regions exhibited 30–80 per cent of the hypothalamic amine concentration. Again the concentration of serotonin was higher than that of norepinephrine. The pioneering studies of Vogt (1954) provide the most detailed examination of norepinephrine in dog brain.

Artiodactyla

Sheep and pigs follow the usual mammalian pattern of amine distribution in the brain (Bertler & Rosengren, 1959). The brain parts rank in descending order: hypothalamus, pons, mesencephalon, medulla, telencephalon and cerebellum.

Primates

The distribution of amines in both humans and monkeys has been studied. The monkey brain follows (Pscheidt & Himwich, 1963b) more closely the rodent and carnivoral pattern than does the human (Bertler, 1960). The Maccaus rhesus monkeys have the lowest levels of amine in the cortex and other telencephalic structures and no area was found with a higher amine level than the di- and mesencephalon (Fig. 3). However, two different groups have found that the substantia nigra in the human has a higher serotonin level than the hypothalamus (Costa & Aprison, 1958). Cortical levels of amines were quite low.

Aves

Complete information on brain amines is available for only one species of bird, the chicken (*Gallus domesticus*) which differs from mammals in two ways (Pscheidt & Himwich, 1963a, 1965). First the telencephalon contains more serotonin than lower brain regions. This has been ascribed to the distinctive features of the avian telencephalon, which is composed largely of structures related to the pallium of mammals and contains very little neocortex. In mammals the former structures contain more serotonin than the cortex, hence the avian telencephalon is comprised mainly of a structural analogue having a high serotonin content. Second, the cerebellum of the chicken contains relatively large amounts of norepinephrine in contrast to mammals.

Reptiles

In turtles, lizards and snakes the distribution of serotonin agrees only roughly with the usual mammalian pattern (Quay & Wilhoft, 1964). The lowest concentrations are found in the cerebellum and olfactory bulbs. The highest concentrations are found in regions of the brain stem. However, relatively high amounts of serotonin are encountered throughout the whole brain in contrast to mammals. In one distinct subclass, the alligator, the distribution of serotonin resembles very closely the mammalian pattern, and this species has significantly lower overall concentrations of serotonin than other reptiles.

In the alligator also, older or more primitive subdivisions of the cerebral hemispheres contained higher concentrations than those regions which are more fully developed in mammals. In a few species of reptiles high levels of serotonin are encountered (Brodie *et al.*, 1964).

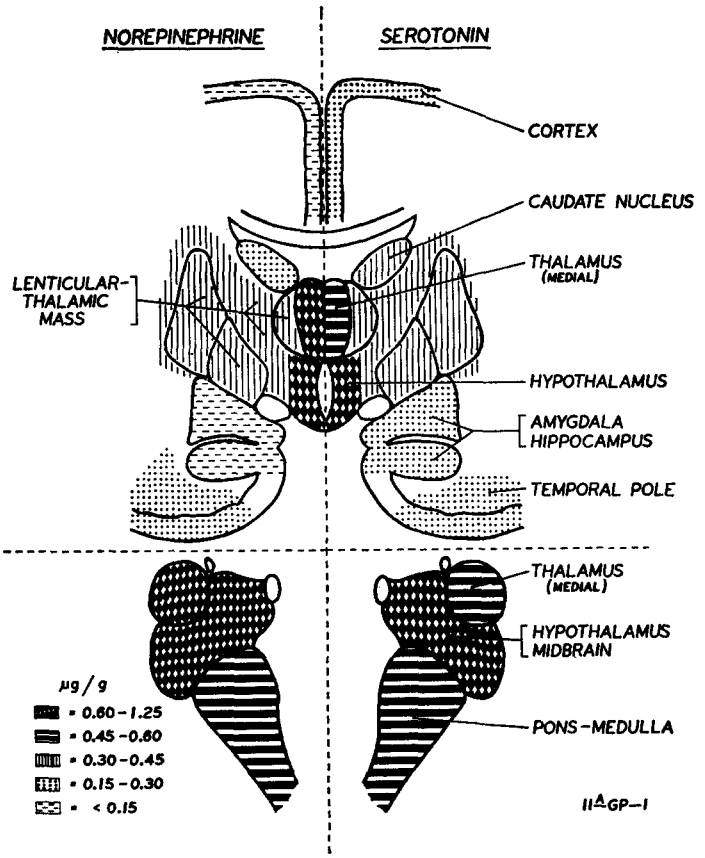

FIG. 3. Regional distribution of norepinephrine and serotonin in monkey brain.

Amphibia

In the amphibians a qualitative departure from previously considered species is encountered. The principal catecholamine found in the brain of members of this class is epinephrine in contrast to norepinephrine, which is the principal catecholamine in other vertebrate classes (Carlsson, 1959; Brodie *et al.*, 1964; Pscheidt, 1965). Normal levels of amines in brain and peripheral organs for several species of frogs, toads and salamanders were determined by Brodie *et al.* (1964), in addition to normal levels in other vertebrate classes. Serotonin concentrations were also determined and found to be higher in lizards and amphibia than in mammals or

fish. The highest amounts of epinephrine and serotonin in the frog are found in the di- and mesencephalon, intermediate in the rhombencephalon and lowest in the telencephalon (Pscheidt, 1964b).

Fish

Biochemical data on vertebrate forms lower than amphibians are scarce. Moderate amounts of serotonin were found in the whole brain of *Carassius auratus* and *Amia calva* (Brodie *et al.*, 1964). In one study von Euler (1961) determined the brain content of epinephrine and norepinephrine in three representative species: a cyclostome, *Myxine glutinosa*; an elasmobranch, *Squalus acanthis*; and a teleost, *Gadus callarias*. The cyclostome had little or no epinephrine or norepinephrine, whereas the elasmobranch brain approximated that found in the whole brain of mammals.

The distribution of norepinephrine was determined in *S. acanthis* (von Euler, 1961). The regions ranked as follows: highest—pituitary gland, diencephalon, telencephalon, hypothalamus, optic lobes, medulla, down to the cerebellum where only a trace was present.

Invertebrates and acrania

Serotonin and catecholamines are present in the tissues of many lower forms (Welsh & Moorhead, 1960; von Euler, 1956; Sweeney, 1963) and in many instances shown to be concentrated in nervous tissue. However, the diversity of material precludes a discussion of topical organization.

Discussion

We may summarize the general amine distribution pattern as follows: Of the five major divisions of the brain, the diencephalon contains the highest amounts of the amines, serotonin and norepinephrine, intermediate levels are found in the diencephalon and rhombencephalon, whereas the telencephalon and cerebellum contain the least (Fig. 3). A rationale for exceptions to this rule is given below. Finer anatomical subdivision reveals that the hypothalamus usually contains the highest concentration of amines although there is evidence in the human to suggest that the intermediate nuclei have the highest levels and a few structures in other species exceed the hypothalamus in amine concentration. These are the substantia nigra and regions bordering the aqueduct and fourth ventricle. In the telencephalon, cortical values are low, whereas the rhinencephalon and corpora striata have appreciable amounts.

Roughly speaking the phyletically older portions of the brain contain higher concentrations of amines than the newer parts. And, as several authors have pointed out, the distributional data indicate that these amines are concentrated in those structures and brain regions concerned with autonomic or sympathetic functions and the emotional aspects of behavior.

The observation that the telencephalon in birds and fish contains higher levels of amines than lower regions can be accounted for by the fact that in other species the neocortex has developed extensively and comprises the major fraction of the mass of the telencephalon. Cortex has a low content of amine relative to the rhinencephalon and stratial structure which in the bird and fish constitute the major portion of the telencephalon.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (Fig. 4) block the conversion of amines to acidic metabolites (Fig. 1), and they elevate brain concentrations of serotonin and norepinephrine throughout the brain of most vertebrates.

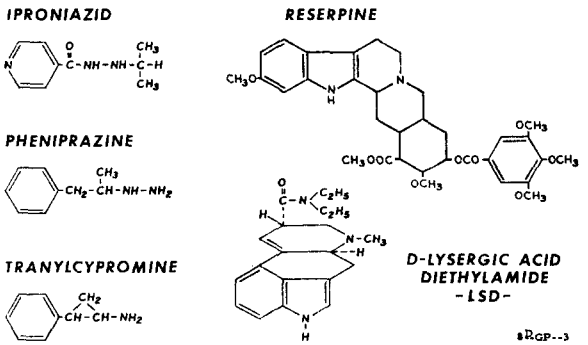

FIG. 4. Structural formulas of three monoamine oxidase inhibitors: iproniazid, pheniprazine, tranylcypromine, reserpine and D-lysergic acid diethylamide (LSD).

The reader is referred to Table 1 for particular inhibitors and species. Serotonin usually increases in concentration in the brain at a more rapid rate than norepinephrine and reaches higher levels (Fig. 5). It is difficult to generalize further than

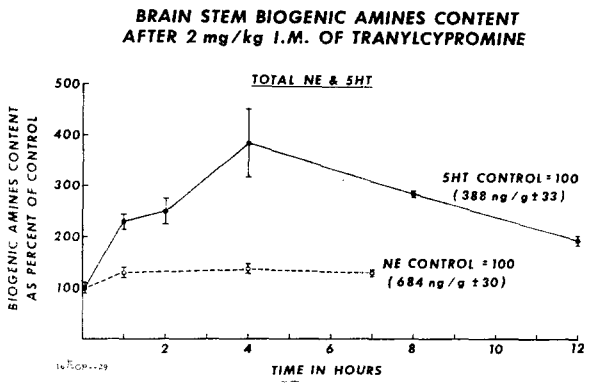

FIG. 5. Elevation of brain biogenic amines in rabbit brain after administration of tranylcypromine.

TABLE 1a—EFFECT OF MONOAMINE OXIDASE INHIBITORS ON ELEVATING BRAIN AMINES IN VARIOUS MAMMALIAN SPECIES

Species / Inhibitor	Man		Monkey		Rabbit		Guinea pig		Rat		Mouse	
	NE	5HT	NE	5HT	NE	5HT	NE	5HT	NE	5HT	NE	5HT
Nialamide			<[3]	<[3]			<[12]	<[12]	<[7]	<[7]		
Iso-carboxazid			<[3]	<[3]			<[12]	<[12]	<[12]	<[12]	<[12]	<[12, 13]
Iproniazid	<[1]	<[1]			<[4, 5, 11, 14]	[4, 5, 11, 14, 15]			<[8]	<[8]		
Pheniprazine					<[4, 5]	<[4, 5]					<[12]	<[12]
Tranylcypromine					<[4, 6]	<[4, 6]	<[12]	<[12]	<[9]	<[9]		
Pargyline					<[6]	<[6]					<[10]	<[10]

The sign < indicates increase of amine level in brain over control values and the numbers are for references.

TABLE 1b—ANOMALOUS RESPONSES TO INHIBITION IN CARNIVORES AND RESPONSE IN NON-MAMMALIAN SPECIES

Species inhibitor	Cat		Dog		Chicken		Frog	
	NE	5HT	NE	5HT	NE	5HT	E*	5HT
Nialamide	e[7]	<[7]	<[19]	<[19]	<[17]	<[17]		
Iso-carboxazid	e[7]	<[7]			<[17]	<[17]	e[16]	<[16]
Iproniazid	e[7]	<[7]						
Pheniprazine	e[5, 18]	<[5, 18]	e[5, 11]	<[5, 11]				
Tranylcypromine	e[7]	<[7]	e[12]	<[12]				
Pargyline							e[2]	<[2]

e: indicates no increase of catecholamine in brain.
* The predominant catecholamine in frog brain is epinephrine (E) not norepinephrine (NE).
The sign < indicates increase of amine level in brain over control values and the numbers are for references.

[1] Ganrot *et al.*, 1962. [2] Brodie & Bogdanski, 1964. [3] Pscheidt & Himwich, 1963b. [4] Costa *et al.*, 1960. [5] Brodie *et al.*, 1959. [6] Spector *et al.*, 1960. [7] Funderburk *et al.*, 1962. [8] Gey & Pletscher, 1961. [9] Costa & Pscheidt, 1961. [10] Wiegand & Perry, 1961. [11] Spector *et al.*, 1960. [12] Pscheidt *et al.*, 1964. [13] Bartlet, 1960. [14] Ehringer *et al.*, 1960. [15] Pletscher & Gey, 1962. [16] Pscheidt, 1964a. [17] Pscheidt & Himwich, 1965. [18] Brodie *et al.*, 1959a. [19] Schneider *et al.*, 1959.

this since considerable differences exist in the magnitude of the response to particular monoamine oxidase inhibitors by various species. For example, Pletscher *et al.* (1961) and Göschke (1961) determined the dose of five different inhibitors needed to produce a 50 per cent rise in the serotonin content of the brain in rabbits, rats, mice and guinea pigs. They found no correlation of the dose required with either species or particular inhibitor.

In contrast to other mammalian species the carnivores, cat and dog, fail to accumulate increased amounts of norepinephrine in their brain after administration of a dose of monoamine oxidase inhibitor sufficient to produce large increases in the serotonin content (Brodie *et al.*, 1959; Bartlet, 1960; Costa *et al.*, 1960; Wiegand & Perry, 1961; Pscheidt *et al.*, 1964). The biochemical basis for the failure of

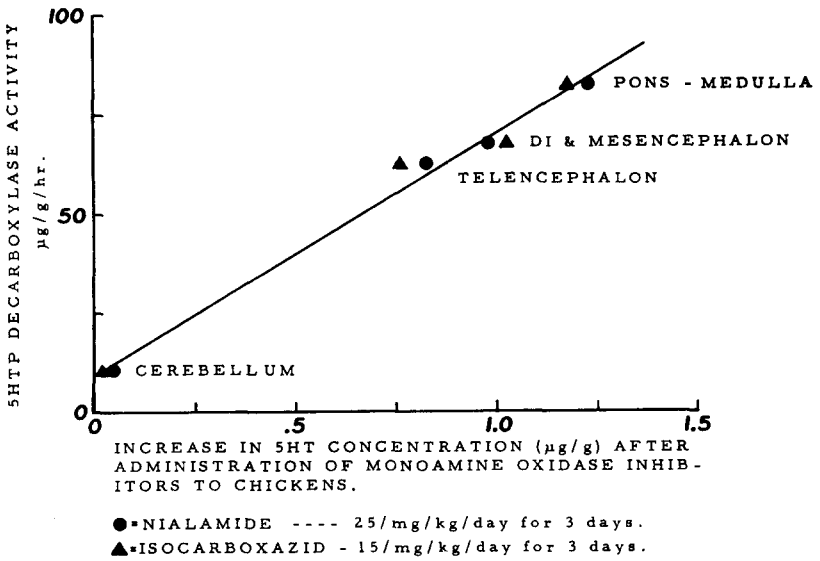

FIG. 6. Correlation between serotonin increases in various chicken brain regions after administration of MAO inhibitors with decarboxylase activity in the same regions.

monoamine oxidase inhibitors to elevate norepinephrine in cats and dogs is not known. However, it may be related to the fact that one specific brain region, the caudate nucleus, possesses both the precursor for norepinephrine—dopamine—and the necessary enzyme for converting dopamine to epinephrine—dopamine beta oxidase—yet this region does not contain appreciable amounts of norepinephrine (Udenfriend & Creveling, 1959).

The dog is one of the few animals in which discrete regional increases in serotonin have been measured after administration of a monoamine oxidase inhibitor (Himwich & Costa, 1960). After injection of tranylcypromine, the greatest

elevations of serotonin were found in the superior and inferior colliculi, the midbrain tegmentum and the hypothalamus.

In an avian species, the chicken (*Gallus domesticus*), the inhibitors elevated amines markedly throughout the brain with the exception of the cerebellum (Pscheidt & Himwich, 1965). It is also interesting that in this species, the increase in serotonin occurring in distinct brain regions after MAO injection was proportional to the amount of decarboxylase activity in the particular region (Fig. 6).

In one amphibian, the frog, epinephrine supplants norepinephrine as the predominant catecholamine as previously mentioned. In this species also, neither of the MAO inhibitors, pargylene or isocarboxazid, in relatively high doses, was able to increase the amount of epinephrine in the brain even though the serotonin content was elevated (Pscheidt, 1964b; Brodie & Bogdanski, 1964).

RESERPINE

The physiological and biochemical actions of reserpine (Fig. 4) are almost universal throughout the vertebrates. Therefore the salient actions of this compound may be described in general and the pertinent exceptions noted. Sedation or tranquilization follows administration of reserpine in all species studied with the exception of the frog. Both serotonin and norepinephrine are depleted in the brain, again in all species except the frog where serotonin is selectively released (Pscheidt, 1964a). A single large dose of reserpine is sufficient to cause almost complete release of brain amines within a few hours. The amine levels remain low for a day or two and require 2 weeks or longer to return to normal values. Depletion may also be accomplished by the continued administration of successive small daily doses. In the rat reserpine in sufficiently large doses produces the following autonomic effects: ptosis, miosis, hypothermia, stomach ulcers, diarrhea, bradycardia and parasympathetic stimulation (Metysova *et al.*, 1964).

When both reserpine and a monoamine oxidase inhibitor are administered to animals, the usual result is that the concentration of serotonin or norepinephrine found in the brain is intermediate between that expected from either drug given alone (Canal & Maffei-Faccioli, 1959; Green & Erickson, 1962). With appropriate doses the amine depleting effect of reserpine can be balanced by the augmenting effect of the inhibitors and normal values obtained. However, in the monkey (Pscheidt & Himwich, 1963b) and rabbit (Green & Erickson, 1962) it has been observed that a combination of drugs may result in higher levels of serotonin than would be expected to be obtained by the inhibitor alone.

Many of the behavioral and autonomic effects of reserpine can be overcome or reversed by administration of monoamine oxidase inhibitors either after reserpine or concomitantly with it (Costa *et al.*, 1960; Pscheidt & Himwich, 1963b).

The simple explanation that monoamine oxidase inhibitors restore amine concentrations to normal levels in the nervous system and thus return function to normal, while adequate in many instances, fails to explain many anomalous effects due to direct drug action or to distinguish the functional role played by each amine. In addition the frog behaves abnormally; reserpine fails to elicit

sedation when given alone but if the animals are pretreated with pargylene sedation is produced by reserpine (Brodie *et al.*, 1964).

EFFECTS OF LSD THROUGHOUT THE ANIMAL KINGDOM

Lysergic acid diethylamide (LSD) (Fig. 4) is a remarkable compound in that it affects all representative species throughout the animal kingdom. From the highest thought processes of man to the rhythmic contraction of parasitic worms LSD exerts a disruptive effect of the integration of physiological processes. This universality of action speaks strongly for its affecting a vital or basic controlling mechanism of the nervous system. It is active in man in amounts of 1 μg/kg or less and in lower classes it is effective in modest concentrations. The underlying chemical and physiological mechanisms of action are obscure, but LSD is known to be effective as a serotonin antagonist in various organ preparations (Goddum *et al.*, 1953; Welsh, 1954) and to alter the functional state of control centers in the central nervous system of vertebrates (Schweigerdt *et al.*, 1966). In order to emphasize the diverse and universal potency of LSD, descriptions of its actions are given below. From the large amount of mammalian literature only representative material has been drawn, whereas that relating to lower species is presented in more detail.

Vertebrates

Mammals. Man: In humans the effects of LSD were studied in normal adult volunteers after the oral administration of 1 μg/kg of the drug (Rinkel *et al.*, 1952). Prominent psychological changes were observed in thinking and speech patterns. The subjects experienced difficulty of power of expression and the flow of speech became increasingly diminished and blocked. Mood and affect were blunted and they developed feelings of suspiciousness, hostility and resentment. Visual distortions and imagery were prevalent, merging at times into frank hallucinations and delusions. Behaviorally the subjects became underactive and lacked spontaneity. Subjective reports of nausea, giddiness, faintness, etc. were received and objective signs of autonomic nervous system dysfunction were observed such as flushing, sweating and shivering.

Cat: LSD was injected intraperitoneally into cats in the dose range of 25–100 μg/kg and the following effects observed (Adey *et al.*, 1962). After 30 min the animals adopted a wide-based posture in the hind limbs with the tail extending curved upwards. Walking was intermittent and they would often strike out with claws extended or lie languidly with claws extended. Sometimes after walking short distances the cats would stop suddenly, remain arrested in a rigid posture, stare straight ahead or violently shake their heads from side to side. They purred incessantly but there was a loss of normal affective behavior. Pupillary dilatation was invariable and mild piloerection common.

Goat: Stereotyped walking patterns were found to develop in female goats given 15 μg/kg of LSD (Koella *et al.*, 1964). Prior to injection of the compound

the animals exhibited little or no walking activity but afterwards stereotyped patterns of activity specific for each individual animal occurred. The majority of the goats followed the walls of the test enclosure and produced a rectangular pattern but other patterns were observed.

Rats: The test animals were rats trained to climb a rope for a food reward (Winter & Flataker, 1956). After intraperitoneal injection of 250–500 μg/kg the following effects were noted: a short period of heightened exploratory activity, followed by violent shaking of the head which occasionally spread to involve the whole body. In 5 min the legs became flexed so that the abdomen touched the cage floor. Hyperactivity ceased, and the animals became unusually quiet and withdrew to the back of the cage and remained motionless for prolonged periods of time. At the height of the drug effect the rats might appear normal, but when placed in the test situation they appeared to be confused. They would receive, without attempting to escape, shocks applied to their feet before starting up the rope. Treated animals climbed more slowly and laboriously than normal rats and they would interrupt the climb and remain motionless. Often they circled around the rope or reversed direction.

Amphibia and fish. Salamander: Male salamanders (*Triturus viridescens*) injected with 700 μg/kg of LSD exhibited within 5 to 15 min disturbances of posture and reflex activity (Peters & Vonerahe, 1956). They would writhe or rest on their backs or belly and assume statue-like postures representing some component stages of standing or walking. Their limbs became wax-like in response to external manipulation. Retraction of the eyeball to touch did not disappear, but swimming, walking and visual reflexes were depressed. In this same species LSD was found to modify an established social order (Evans & Abramson, 1958). The salamanders were observed at feeding time and ranked individually by the occurrence of biting or fighting instigated by a particular animal. The number of times an animal attacked another was the basis for scoring "aggressiveness". After receiving LSD, salamanders low in the social order attacked animals higher up more often. The authors claimed that more than transient changes were observed and that an animal could move up the social scale.

Fish: The modification of aggressive behavior in salamanders was only partially confirmed in fish (McDonald & Heimstra, 1964). Green sunfish (*Lepomis cyanellus*) were placed by groups in aquaria and the order of social dominance determined. The fish not attacking others was termed the submissive fish and was administered LSD which greatly increased the frequency of attack behavior. However, the effects were transitory and no reversal of social dominance occurred in these fish.

Extensive modification of body movements takes place in Siamese fighting fish *Betta splendens* after they are exposed to concentrations of LSD varying between 1 and 50 μg/ml (Abramson & Evans, 1954; Turner, 1956). They normally exhibit graceful well-coordinated movements. After LSD, rolling and kinking of the body takes place, they may exhibit an alternate sinking and rising in the water, remain motionless, and spread their fins in a lateral display even though they are

immobile. A darkening of the basic body color also is evident, particularly in juvenile specimens.

Invertebrates

Molluscs. In the snail *Abularia cuprina* 1 μg of LSD per ml of bathing fluid causes the animal to open its operculum and extrude its tentacles, proboscis and gastropod (Abramson & Jarvik, 1955). The gastropod exhibits a wild, undulating movement which prevents the snail from adhering to any surface. The normal closing response to gentle tactile stimulation is not present but more vigorous stimulation results in closure, but shortly thereafter the snail reopens again. The mechanisms of action of LSD in numerous molluscus were studied in more detail by Mirolli & Welsh (1964). The postural behavior of all species was altered by LSD by its action on the tonus of the muscular meshwork of the haemoskeleton and disruption of the osmotic equilibrium of the visceral cavities. In general the molluscs lost their capacity of integrating the normal movements in proper sequence. In several species the appendages acquired an abnormal position and exhibited rippling movements.

Trematode. In the parasitic fluke *Fasciola hepatica*, LSD in appropriate concentrations stimulates rhythmic contractions of the muscle and alterations in the normal rate and amplitude occur (Mansour, 1957). The stimulation can occur in the absence of the central ganglion in this species.

Arthopods. LSD also affects the behavior of ants (Kostowski, 1966). Groups of ants, *Formica rufa*, were fed LSD in honey and allowed access to a beetle. The number of ants attacking the beetle during specified time intervals was scored as aggressiveness. Two to 3 hr after administration of LSD the number of attacking ants was decreased but between 18 and 24 hours after feeding the number increased. The web-spinning ability of spiders is also affected by LSD treatment (Witt, 1956).

Discussion

The fact that LSD is effective throughout the animal kingdom is impressive by itself although other substances such as narcotics have an equally wide spectrum of activity. What is striking is that LSD disrupts the normal integration of motor programs by the nervous system in all animals tested and produces abnormal or ineffective behavior patterns peculiar to the particular species. Spontaneous patterns of activity are modified, reflexes become altered, and the tonus of muscle groups is changed; subunits of motor programs are recombined under the influence of LSD to produce ineffective activity. In humans full expression of the disintegrating action of LSD on central co-ordination of motor activity is not pronounced, presumably because of the small doses employed.

LSD affects not only whole organisms but individual organ systems and specialized cell groupings in the nervous system as well. Thus, LSD is capable of exerting an influence of a fundamental process common to all animals which possess excitable cells.

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