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ACTION OF PSYCHOTOGENIC DRUGS ON SINGLE MIDBRAIN RAPHE NEURONS[1]

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ABSTRACT

AGHAJANIAN, G. K., W. E. FOOTE AND M. H. SHEARD: Action of psychotogenic drugs on single midbrain raphe neurons. J. Pharmacol. Exp. Ther. 171: 178–187, 1970. Because of the previous observation that D-lysergic acid diethylamide (LSD) inhibits raphe neurons, the possible effects on raphe units of other psychotogenic drugs were investigated. In addition to LSD, the following drugs were tested: 1) 2-brom-LSD; 2) N,N-dimethyltryptamine; 3) mescaline; 4) 2,5-dimethoxy-4-methylamphetamine; 5) scopolamine and atropine; 6) phencyclidine; and 7) various non-psychotogens (*e.g.*, chlorpromazine). There were marked differences in the way the various psychotogenic drugs affected the activity of raphe units. These effects differed according to the structural class of the compounds administered as follows. 1) The drugs containing a N-methylated indolethylamine moiety (*i.e.*, LSD, 2-brom-LSD and N,N-dimethyltryptamine) inhibited all raphe units, although 2-brom-LSD was usually not capable of producing total inhibition. 2) The derivatives of phenethylamine or α-methylphenethylamine (*i.e.*, mescaline and 2,5-dimethoxy-4-methylamphetamine) inhibited only those units located in the ventral portion of the dorsal raphe. 3) Atropine, scopolamine and phencyclidine had no effect on raphe unit activity. None of the nonpsychotogenic compounds tested inhibited raphe activity. These results indicate that the indole and phenethylamine psychotogens, which have similar effects on behavior, also have an overlapping although not identical effect on single units in the raphe nuclei. On the other hand, the psychotogenic drugs which differ from the indole and phenethylamine compounds both in chemical structure and behavioral effect do not affect raphe units.

D-Lysergic acid diethylamide (LSD) given in minute parenteral doses (~10 μg/kg) produces a reversible cessation of the firing of single neurons in the midbrain raphe nuclei (Aghajanian *et al.*, 1968). This inhibition is extremely selective, and neurons in other midbrain areas (*e.g.*, reticular formation and pontine nuclei) are either unaffected or accelerated by LSD. In contrast, amphetamine does not inhibit and actually accelerates the firing rate of some raphe units, and large doses of parenteral norepinephrine have no effect at all (Foote *et al.*, 1969). The raphe nuclei are notable in that they are composed of neurons containing 5-hydroxytryptamine (5-HT; Dahlström and Fuxe, 1965). The 5-HT-containing neurons are closely packed and appear to comprise most, if not all, of the neurons in these nuclei. This apparent histochemical homogeneity of the raphe neurons correlates well with their uniform response to LSD (Aghajanian *et al.*, 1968). This work represents the first instance of unit recordings from histochemically identified neurons in the brain.

The finding that LSD inhibits raphe neurons is of interest in relation to the long-standing hypothesis, first proposed by Gaddum (1953) and Woolley and Shaw (1954), that the central action of LSD might involve an interaction with 5-HT. LSD has been shown to increase the concentration and decrease the turnover of brain 5-HT (Freedman, 1961; Rosecrans *et al.*, 1967; Diaz *et al.*, 1968; Andén *et al.*, 1968; Freedman *et al.*, 1970). It has been speculated that this alteration in 5-HT metabolism may be explained by an LSD inhibition of the 5-HT neurons in the raphe nuclei (Aghajanian and Freedman, 1968; Aghajanian *et al.*, 1968; Andén *et al.*, 1968). LSD also blocks the release of tritiated 5-HT induced

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by electrical stimulation of brain slices (Chase *et al.*, 1967). However, the amounts of LSD required for this effect are much greater than for the inhibition of raphe units, and therefore the relationship between these two phenomena is unclear.

In the present study, the effects on raphe unit activity of drugs representing different classes of psychotogens have been investigated. The purpose of this survey was to explore the limits of specificity of the LSD inhibition of raphe units. Of particular concern was the question whether psychotogenic drugs related to LSD in structure and/or activity would also inhibit raphe units. Psychotogens unrelated to LSD in structure or activity were also studied for possible effect on these neurons. In addition to LSD, the following drugs have been investigated: 1) 2-brom-LSD (BOL), an LSD congener of much reduced psychotogenic potency (Isbell *et al.*, 1959); 2) N,N-dimethyltryptamine (DMT), a tryptamine derivative with LSD-like psychotogenic activity (Szara, 1956); 3) mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM), derivatives of phenylethylamine and amphetamine, respectively, whose behavioral effects resemble those of LSD (Snyder *et al.*, 1967); 4) scopolamine and atropine, anticholinergic drugs that produce a psychosis of a different type than LSD, namely, a confusional or delirium state (Cerletti *et al.*, 1963; Crowell and Ketchum, 1967); and 5) phencyclidine, another psychotogenic drug producing effects unlike those of LSD (Chen *et al.*, 1959). In addition, certain nonpsychotogenic drugs were studied in terms of a possible action on raphe neurons.

METHODS. A total of over 200 male rats (Charles River Laboratories, Inc., Wilmington, Mass.; CD) 2 to 3 months of age and weighing 250 to 300 g were used for the single unit recordings. The animals were mounted in a stereotaxic instrument after being anesthetized with chloral hydrate (350 mg/kg). We found that this anesthesia did not interfere with the reported effect of LSD on brain 5-HT metabolism which consists of an increase in 5-HT and decrease in 5-hydroxyindoleacetic acid concentration (Rosecrans *et al.*, 1967). However, chloral hydrate has been reported to increase the concentration of 5-HT in brain (Bonnycastle *et al.*, 1962). Tungsten microelectrodes, with tip diameters of approximately 1 μ, were employed for recording unit activity. Microelectrodes were lowered with a hydraulic microdrive through a small burr hole into various regions of the midbrain. Signals from microelectrodes were passed through a high-impedance amplifier and displayed on an oscilloscope. Unit rates were followed with an electronic counter whose analog output was plotted on a potentiometric recorder. Electrical signs as well as stereotaxic coordinates were utilized for judging positions of electrode tip. When an electrode, as later determined by histologic examination, is accurately in the midline, a zone of electrical quiet approximately 1 mm in extent corresponding to the cerebral aqueduct is encountered. In the midline area of the caudal midbrain ventral to the aqueduct, units of the dorsal raphe nucleus are found. The raphe units were tentatively identified by their characteristic slow rate (~1–2 spikes/sec) and regular rhythm (Aghajanian *et al.*, 1968). Another zone of relative quiet, corresponding to the decussation of the superior cerebellar peduncle, lies ventral to the dorsal raphe nucleus. Ventral to this zone and in the midline is the median raphe nucleus. The cells in this region, as in the dorsal raphe, have a slow rate and regular rhythm. In contradistinction, units in other midbrain regions (*e.g.*, reticular formation, third and fourth nerve nuclei, tectum and pontine nuclei) usually fire at rates in excess of 1 to 2 spikes/sec and/or have an irregular rhythm.

Once a raphe or other unit was located, spontaneous activity was observed for a period of about 10 minutes. Extracellular spikes of raphe units under our conditions of recording were typically biphasic, with the positive preceding the negative component. Units exhibiting a stable base-line rate and constant spike amplitude and waveform were used for the drug experiments. Drugs solutions were given over a 10 second interval and in small volumes (*e.g.*, 0.1–0.2 ml) i.v. *via* the tail vein. Depending on the experimental protocol, a second drug was sometimes given at varying times after the first drug. However, because of possible residual drug effects, only one neuronal unit was studied in each animal. To mark tip location upon completion of an experiment, a small electrolytic lesion was made through the microelectrode. Animals were then perfused through the left ventricle with fixative (5% glutaraldehyde in 0.15 M sodium phosphate buffer, pH 7.4). Serial frozen sections (50 μ in thickness) were cut and stained with cresyl violet, and as illustrated in figure 1, the location of electrode tip was ascertained. The location of electrode tips was determined by this technique in all experimental animals.

Dosage of drugs is given in terms of the weights of the following salts: D-lysergic acid diethylamide bitartrate; 2-brom-D-lysergic acid diethylamide

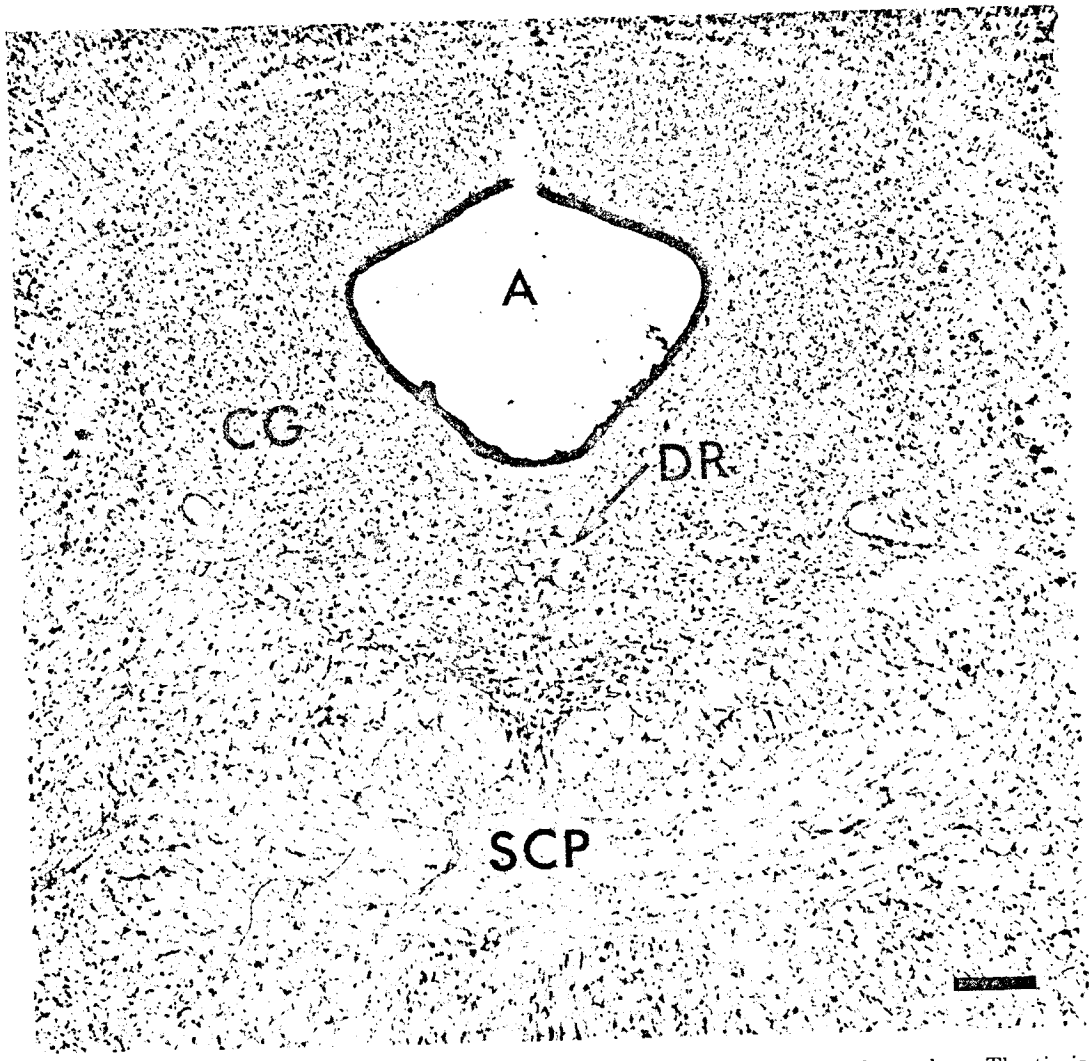

FIG. 1. Histologic section showing placement of a microelectrode in dorsal raphe nucleus. The tip is marked by a lesion produced by anodal current (2 μA, 30 seconds). The lesion (arrow) is situated in the dorsal portion of the dorsal raphe nucleus. The frontal plane of this section corresponds to A160 of König and Klippel (1963). A, cerebral aqueduct; CG, central gray; DR, dorsal raphe nucleus; SCP, decussation of superior cerebellar peduncle. Cresyl violet stain; scale, 0.25 mm.

bitartrate; N,N-dimethyltryptamine oxalate; mescaline hydrochloride; 2,5-methoxy-4-methylamphetamine hydrochloride; atropine sulfate; scopolamine hydrochloride; phencyclidine hydrochloride; chlorpromazine hydrochloride; and *p*-chlorophenylalanine (free acid). Except where noted, drugs were given i.v. in 0.9% saline solutions.

RESULTS. *LSD.* The response of units in various areas of the midbrain to LSD was, with one modification (see below), as previously reported (Aghajanian *et al.*, 1968). Units in the following areas of the midbrain were studied: 1) dorsal raphe nucleus (77 units); 2) median raphe (15 units); 3) neurons surrounding medial lemniscus (7 units); 4) reticular formation (26 units); 5) pontine nuclei (13 units); 6) central gray (11 units); 7) nuclei of nerve III and IV (3 units); 8) interpeduncular nucleus (2 units); and 9) ventral tegmental nucleus of Gudden (6 units).

The spontaneous rates of the raphe units ranged from 0.2 to 2.5 spikes/sec (mean rate 1.1 spikes/sec). After an initial dose of 10 μg/kg, the LSD was given in increments of 5 μg/kg at inter-

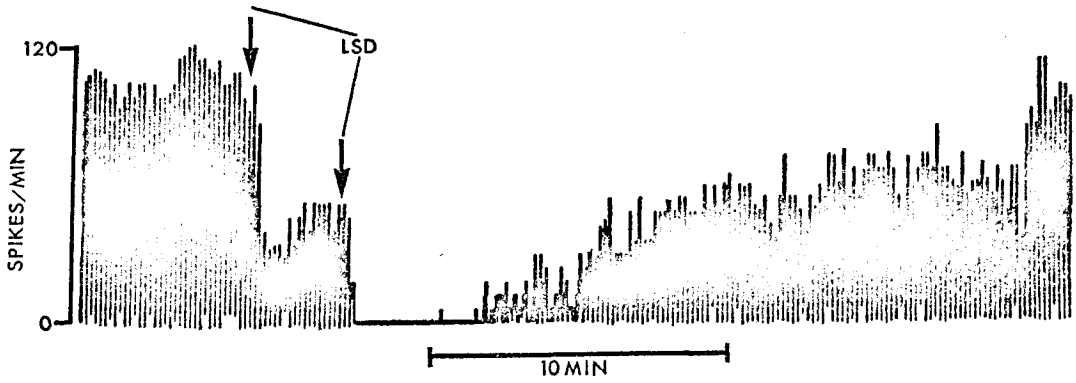

FIG. 2. Typical response of a raphe unit to LSD. This unit, which was situated in the dorsal raphe, had a spontaneous rate of about 120 spikes/min. Within 30 seconds after an i.v. injection of 10 μg/kg of LSD, this unit slowed; after a second dose of 5 μg/kg it ceased firing entirely. Recovery took place gradually over a period of about 20 minutes. The record consists of consecutive 10-second samples of the analog output of a counter triggered by the unit spikes.

vals of one to two minutes until activity ceased for at least one minute. All of the dorsal and median raphe units were completely inhibited according to this criterion by an i.v. dose of LSD ranging between 10 and 25 μg/kg with an ED50 of 12.5. The mean duration of total inhibition at this dose level was 6.5 minutes; larger doses produce a more prolonged inhibition (Aghajanian *et al.*, 1968) but this dose-response relationship has not been studied in detail. There was no correlation between the dose of LSD required for inhibition and the spontaneous rate (*i.e.*, the units with higher initial rates were as sensitive as those with lower rates). Recovery from inhibition took place gradually and required a period of 15 to 30 minutes for completion (fig. 2). The time course of recovery correlates well with the 20-minute biologic half-life of LSD in the rat (Freedman, 1966).

The only nonraphe units that were inhibited by LSD were found, by histologic examination, to be situated in the vicinity of the medial lemniscus. Neurons in this area had not been studied at the time of the original report (Aghajanian *et al.*, 1968). These neurons would appear to correspond to the 5-HT-containing cells designated "B9" by Dahlström and Fuxe (1965). Unit rates in the reticular formation and other midbrain areas were either unaffected or accelerated by LSD. Spontaneous rates of the 26 reticular units studied ranged from 2 to 45 spikes/sec (mean, 17 spikes/sec). Sixteen of the reticular units showed little or no change in rate after a total dose of 50 μg/kg of LSD; the remainder accelerated to approximately twice their spontaneous rates. Usually acceleration was not seen except at doses greater than required for threshold inhibition of the raphe units. There was one notable exception to this pattern, namely, the response of units in the ventral tegmental nucleus. The six units in this area had a mean spontaneous rate of 2.3 spikes/sec. After 15 μg/kg of LSD the rates increased 5- to 10-fold.

BOL. The effects of this LSD congener on raphe units differed in some important respects from that of parent drug. Twelve raphe units were studied with BOL, and all were at least partially inhibited at a dose of 200 to 400 μg/kg. However, with the exception of two cells, total inhibition was not obtained even at doses of 1.2 to 2.0 mg/kg (*e.g.*, fig. 3). BOL was not given beyond a dose of 2 mg/kg because of respiratory depression. In all the BOL-resistant cells 10 μg/kg of LSD was effective in causing a prolonged total inhibition. In the two instances where complete inhibition was achieved with BOL, doses of 240 and 400 μg/kg were required (*e.g.*, fig. 4). The 10 BOL-resistant cells were scattered throughout the dorsal (7) and median (3) raphe nuclei. Of the sensitive units, one was in the dorsal and the other in the median raphe.

DMT. DMT was tested on 14 raphe units; 11 were in the dorsal and the remainder in the median raphe. In all the cells tested with DMT complete inhibition was attained at an i.v. dose of between 400 and 1500 μg/kg (mean dose, 700 μg/kg). Typically, the rate of recovery from

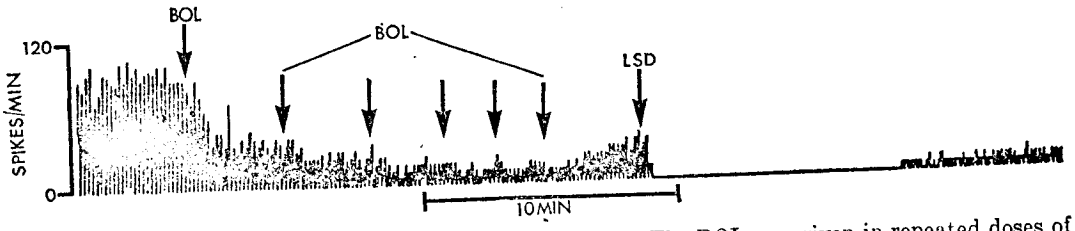

FIG. 3. Failure of BOL to completely inhibit a raphe unit. The BOL was given in repeated doses of 200 μg/kg i.v. totaling 1.2 mg/kg. Although rate was partially decreased after BOL, total inhibition was never achieved. After partial recovery from BOL, LSD given at a dose of 10 μg/kg induced a complete and prolonged inhibition.

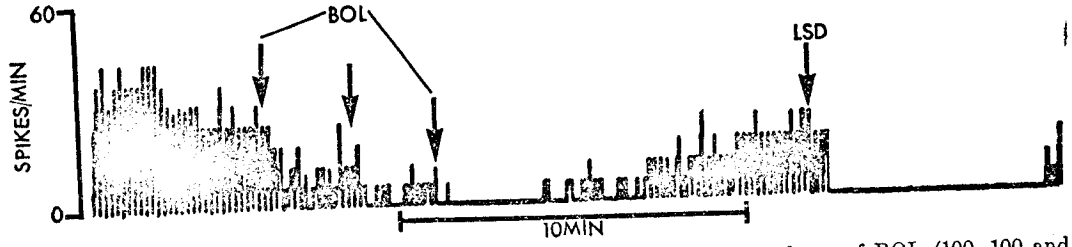

FIG. 4. Complete inhibition of a raphe unit by BOL. Three successive doses of BOL (100, 100 and 200 μg/kg) produced a slowing, then, atypically, a total inhibition lasting three minutes. Initial recovery from BOL was rapid. LSD (10 μg/kg) produced complete inhibition in this unit.

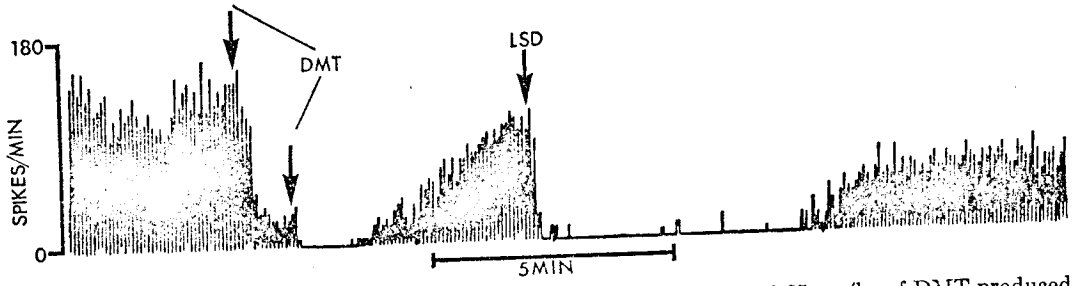

FIG. 5. Inhibition of a raphe unit by DMT. In this typical experiment, 0.25 mg/kg of DMT produced partial inhibition, and another 0.25 mg/kg, complete inhibition. Recovery from the DMT was rapid in comparison to that seen after LSD (10 μg/kg).

DMT in comparison to LSD was quite rapid (fig. 5).

Mescaline and DOM. A total of 53 raphe units were tested with mescaline; of these, 47 were in the dorsal raphe and 6 in the median raphe. Only 21 of the 53 units were inhibited by mescaline (*e.g.*, fig. 6); the remainder were either unaffected or showed a slight acceleration in rate (*e.g.*, fig. 7). The 32 raphe units that were not inhibited by mescaline were inhibited by LSD (mean dose, 17 μg/kg). The threshold dose of mescaline required for complete cessation of firing was usually between 2 and 4 mg/kg. As summarized in figure 8, 18 of the 21 units inhibited by mescaline were in the ventral portion of the dorsal raphe or the dorsal aspect of the median raphe. The mean spontaneous rate was 0.75 spikes/sec and 1.3 spikes/sec respectively for the inhibited and resistant cells. The pattern of response of raphe units to DOM was similar to that of mescaline: 7 of 15 units were inhibited (*e.g.*, fig. 9); 6 of the 7 inhibited units were in the ventral portion of the dorsal raphe. Elsewhere in the dorsal raphe DOM either had no effect (3 units) or produced a slight (3 units) or marked (2 units) acceleration in rate to 5 times the spontaneous rate. As in the case of mescaline, the mean of the spontaneous rates of the units inhibited by DOM was less than that

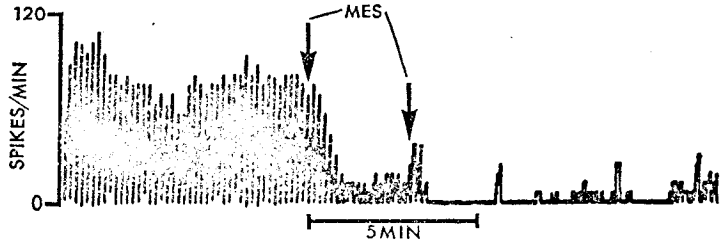

FIG. 6. Inhibition of a raphe unit by mescaline. Two successive doses of mescaline (2 mg/kg each) induced first a slowing, then total inhibition. This unit was situated in the ventral portion of the dorsal raphe nucleus.

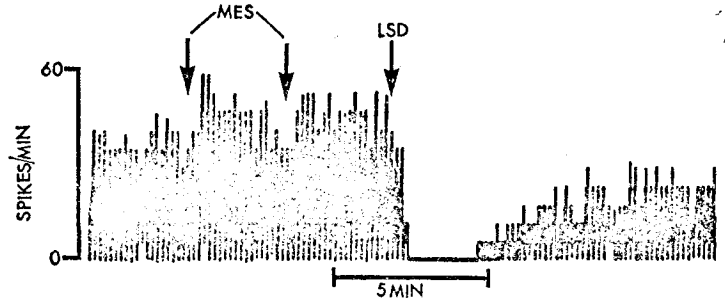

FIG. 7. Failure of mescaline to inhibit a raphe unit. Two doses of mescaline (5 mg/kg each) induced, if anything, a slight increase in rate. LSD (10 μg/kg) had its typical inhibitory effect. This unit was in the dorsal portion of the dorsal raphe.

of the resistant cells (0.57 *vs.* 1.2 spikes/sec). The response of midbrain units outside the raphe to mescaline or DOM was similar to that seen with LSD (*i.e.*, no effect or acceleration).

Other psychotogenics. Four animals were given 10 mg/kg of atropine and another four animals were given 5 mg/kg of scopolamine. Recording of the firing rate of raphe units was continued for 30 to 45 minutes after administration of the drugs. No change from spontaneous rate was found in this period. Phencyclidine was given to four animals at a dose of 1 mg/kg. During a 30- to 45-minute period of observation it also had no effect on raphe activity. Pretreatment with atropine, scopolamine and phencyclidine did not prevent raphe unit inhibition by LSD.

Miscellaneous. Chlorpromazine was given i.v. to six animals in increments of 0.5 mg/kg at intervals of one minute until a total dose of 2.5 mg/kg was reached. No effect of chlorpromazine on raphe unit activity was seen during a 45- to 60-minute period of observation after injection. Larger doses of chlorpromazine were not used because of respiratory depression. LSD was then given and was effective in inhibiting all the units at a mean dose of 14 μg/kg.

p-Chlorophenylalanine (300 mg/kg i.p.) was given to six rats 24 to 72 hours prior to observation of unit activity in the raphe nuclei. The mean spontaneous rate of raphe units in the pretreated rats was 1.4 spikes/sec as compared with 1.1 spikes/sec in nonpretreated rats (see above). LSD was given to the *p*-chlorophenylalanine-pretreated rats after a 5- to 10-minute period of base-line observation of the units. In all six pretreated rats LSD at a dose of 10 to 25 μg/kg (mean, 15 μg/kg) induced a complete but reversible inhibition.

DISCUSSION. The response of single units in the midbrain raphe nuclei to psychotogenic drugs differed according to the structural class of the compounds administered. In general, three different patterns could be discerned. 1) An inhibitory response was seen in all units tested after LSD, DMT and BOL, although in the case of the latter drug complete cessation of firing usually could not be obtained. 2) An inhibitory effect limited to a subgroup of raphe cells (principally located in ventral portion of dorsal raphe) was observed after mescaline and DOM. 3) No effect on raphe units was found after scopolamine, atropine and phencyclidine. The drugs that had in

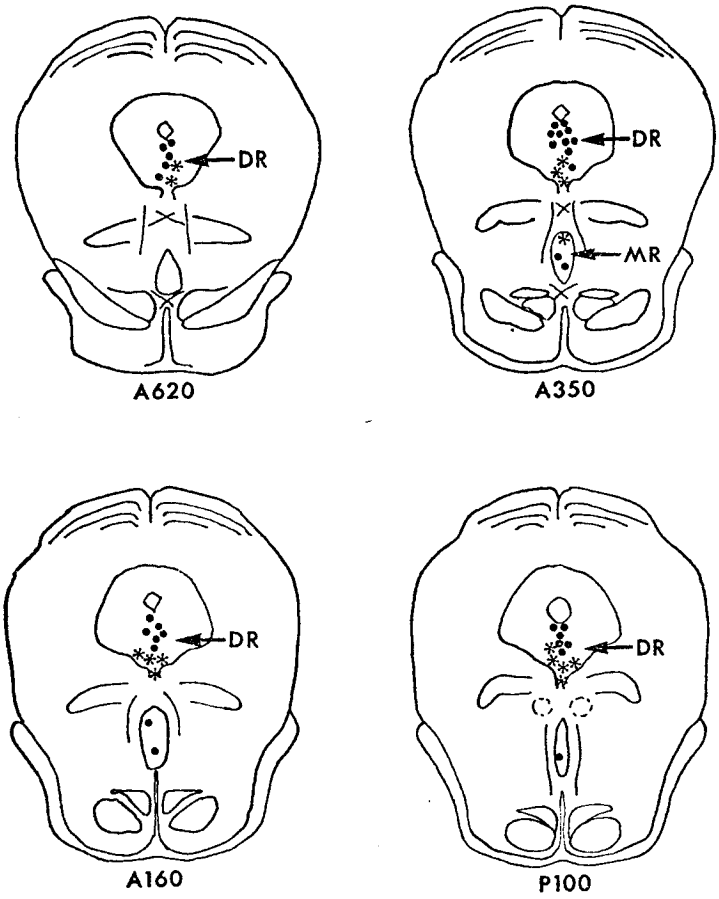

FIG. 8. Summary of histologic data showing loci of units and their responses to mescaline. The units illustrated are those included within frontal planes A620, A350, A160 and P100 (after König and Klippel, 1963). *, indicates units inhibited by mescaline; ●, units not inhibited by mescaline. The units not inhibited by mescaline were inhibited by LSD. Almost all the units that were inhibited by mescaline were located in the ventral portion of the dorsal raphe nucleus.

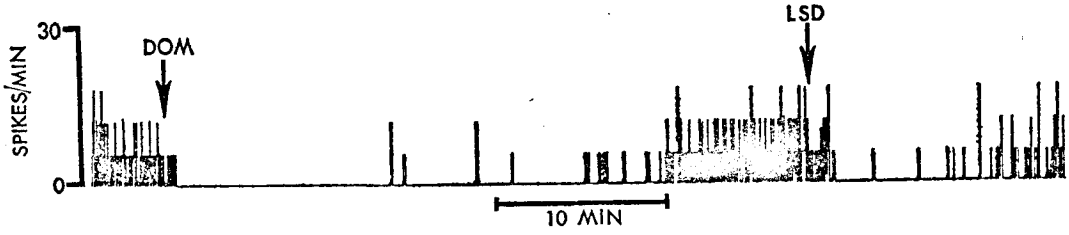

FIG. 9. Inhibition of a raphe unit by DOM. DOM, in a dose of 0.25 mg/kg, produced a prolonged inhibition of this unit. Once unit had recovered, LSD (10 μg/kg) was given and also produced inhibition. This unit was in the ventral portion of the dorsal raphe nucleus.

common the property of inhibiting at least some raphe units are related in various other respects. For example, LSD and mescaline, the prototype drugs in their respective categories, have similar behavioral effects and have been shown to exhibit cross-tolerance in man (Balestrieri and Fontanari, 1959; Wolback *et al.*, 1962) and rat (Appel and Freedman, 1968). The more restricted category of drugs that inhibit all raphe units (*viz.*, LSD, BOL and DMT) have in common a N-methylated

indolethylamine nucleus. Although BOL is commonly regarded as lacking in central activity, it does produce a partial LSD-like effect in man at 100 times the dose of the parent compound (Isbell *et al.*, 1959). It is interesting that the inhibitory effect of BOL on raphe units was also usually only partial. The drugs whose inhibitory effect is confined to the ventral portion of dorsal raphe nucleus (*i.e.*, mescaline and DOM) are derivatives of phenethylamine or α-methylphenethylamine. Interestingly, the psychotogenic potency of a series of substituted phenethylamines has been correlated with their tendency to approximate the ring configuration of lysergic acid (Snyder and Richelson, 1968). It should be noted that unsubstituted α-methylphenethylamine (*i.e.*, amphetamine) never inhibits raphe units and actually accelerates some (Foote *et al.*, 1969). Mescaline, and even more strikingly DOM, accelerate some raphe units (*e.g.*, in dorsal portion of dorsal raphe), and thus resemble amphetamine in this regard.

The differences we find, in terms of effects on raphe cells between the indolethylamine and the phenethylamine groups may seem surprising in view of their many common effects on behavior and autonomic function. However, recent studies comparing the effects of these various compounds on brain 5-HT metabolism reveal a similar differentiation. LSD and DMT in a wide range of doses induce a moderate lowering of 5-hydroxyindoleacetic acid; whereas, mescaline and DOM lower 5-hydroxyindoleacetic acid just slightly and only at low doses (Freedman *et al.*, 1970). Thus LSD and DMT can be distinguished from mescaline and DOM both in terms of this index of 5-HT metabolism and by their different pattern of action on subgroups of 5-HT-containing neurons.

The anticholinergic drugs (atropine and scopolamine) and phencyclidine represent a third category of psychotogenic drug in that, unlike LSD and mescaline, at least in the doses employed, they did not inhibit any raphe units. This apparent failure of the anticholinergic drugs and phencyclidine to inhibit raphe neurons is of interest in relation to the fact that their behavioral effects are very different from those of LSD or mescaline. The various nonpsychotogenic compounds tested also did not inhibit raphe units. Chlorpromazine has been used to counteract behavioral effects of LSD, although it is not altogether effective in this regard (Isbell and Logan, 1957). In any case, pretreatment with chlorpromazine did not block the LSD inhibition of raphe units.

Spontaneous unit rates in the raphe 24 to 72 hours after *p*-chlorophenylalanine were somewhat higher than in controls but there were not enough cases to ascertain whether or not this difference was significant. This compound produces a selective depletion of brain 5-HT probably by inhibiting tryptophan hydroxylase (Koe and Weissman, 1966). Since *p*-chlorophenylalanine did not prevent the LSD inhibition of raphe units, it would appear that this effect of LSD is not dependent upon the presence of appreciable amounts of 5-HT. This observation is interesting in relation to the finding that the behavioral effects of LSD are not blocked and actually may be enhanced after *p*-chlorophenylalanine (Appel, 1968).

The mechanism by which LSD and related compounds inhibit raphe units is not known. Obviously, a drug given parenterally can act at various sites, and the LSD effect on raphe neurons may be the result of either an indirect or direct action. The possibility of a direct action of LSD on raphe neurons can be studied by iontophoretic application with micropipettes. However, this approach is complicated by the fact that the action of a drug applied iontophoretically may not be the same as when the drug is given systemically. Bradley and Wolstencroft (1965) have shown, for example, that a particular unit may be inhibited by iontophoretically applied amphetamine but excited when the drug is given parenterally. Similarly, we did not find any units in the reticular formation that were inhibited by parenteral LSD, whereas, by the iontophoretic method LSD inhibits a large percentage of units in this and other regions (Bloom *et al.*, 1964; Krnjević and Phillis, 1963; Bradley and Wolstencroft, 1965; Roberts and Straughan, 1967).

It has been suggested that if LSD had a 5-HT-like effect at postsynaptic sites it might inhibit raphe units by a neuronal feedback mechanism (Aghajanian and Freedman, 1968; Aghajanian *et al.*, 1968; Andén *et al.*, 1968). According to this view, LSD acting at 5-HT receptive sites would transmit the false message, "excess 5-HT." Such a postsynaptic effect could in turn lead to a "compensatory" neuronal feedback inhibition of the raphe cells. Although LSD is usually regarded

(mainly from studies in peripheral tissues) as being a 5-HT antagonist, in many systems, particularly at low doses, it can act like 5-HT (Shaw and Woolley, 1956; Costa, 1956; Welsh, 1957; Mansour, 1957; Little *et al.*, 1957; Geiger and Cervoni, 1958; Andén *et al.*, 1968; Banna and Anderson, 1968). Furthermore, electrical stimulation of the raphe nucleus in unanesthetized rats induces behavioral effects similar to those of LSD (Sheard and Aghajanian, 1968; Aghajanian and Sheard, 1968). Thus, there is some precedent for considering the possibility that LSD and related drugs have a direct 5-HT-like action and that the inhibition of raphe units is merely a secondary effect, perhaps mediated by a neuronal feedback circuit. However, there is as yet no *direct* evidence for or against such a hypothesis.

Regardless of whether the effect of LSD or DMT on raphe units is *via* a direct or indirect mechanism, these indole derivatives are characterized by their uniform action on raphe units and thus can be distinguished from mescaline and DOM since the latter drugs affect only a subgroup of raphe neurons. The question arises as to whether the common behavioral and autonomic effects of these two molecular classes of psychotogenic drugs are a function of their overlapping effects on raphe units. In this connection, it is interesting that the relative raphe inhibitory potency of these diverse compounds is roughly comparable to relative behavioral potency in the rat (Appel and Freedman, 1965; Smithies *et al.*, 1967).

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