CHAPTER 5

Neurophysiologic Properties of Psychotomimetics

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A. Introduction

In recent years, physiologic studies on psychotomimetic drugs (e.g., psychedelics, stimulants, and deliriants) have focused increasingly upon actions at the single neuron level. This trend has been fostered by the mapping of a number of neuronal systems in the central nervous system according to neurotransmitter content. Of prime importance to investigations on psychedelic and stimulant drugs has been the mapping of monoaminergic neurons in the brain by the formaldehyde-condensation histochemical method of FALCK and HILLARP (DAHLSTRÖM and FUXE, 1965). By means of this and related methods it has been possible to identify the location of the cell bodies, axons, and terminal fields of the major monoaminergic pathways (i.e., noradrenergic, dopaminergic, and serotonergic). Similarly, the mapping of central cholinergic pathways has been crucial to investigating the actions of the antimuscarinic drugs, which produce a state of delirium.

This emerging histochemical knowledge has had an inevitable impact on physiologic approaches to the investigation of psychotomimetic drugs. Many psychotomimetic drugs are closely related in chemical structure to known neurotransmitters in the brain (e.g., the monoamines or acetylcholine). This review will place emphasis on single-cell recording studies dealing with the actions of psychotomimetic drugs on chemically related, histochemically identified neuronal systems. Wherever possible an effort will be made to establish correlations between the single-cell studies and relevant biochemical and behavioral data. The more general physiologic actions of psychotomimetic drugs have been reviewed by BRAWLEY and DUFFIELD (1972).

As defined above, the scope of this review is limited by the fact that several psychotomimetic drugs (e.g., the tetrahydrocannabinols and phencyclidine) have no obvious chemical relationship to any known neurotransmitters. On the other hand, major sections will be devoted to the indoleamine and phenethylamine group of psychedelic drugs and the stimulant drugs; these drugs are chemically related to the monoamines and have been studied extensively within histochemically identified monoaminergic systems. The delirium-inducing anticholinergic (antimuscarinic) drugs also will be considered since their actions have been studied within identified central cholinergic pathways by single-cell recording techniques.

B. Psychotomimetic Drugs and Related Neurotransmitters

I. Psychedelics

The psychedelic class includes D-lysergic acid diethylamide (LSD), the O- and *N*-methylated indoleamines, mescaline, the methoxyamphetamines, and several mari-

juana derivatives (e.g., Δ^9-tetrahydrocannabinol). These drugs, which are sometimes referred to as "hallucinogens," produce an altered state of perception, cognition, and affect without inducing the profound confusion and disorientation which are typical of a "toxic" or "organic" psychosis. It has been proposed that the psychedelic state represents an appropriate model for incipient phases of certain acute psychosis but not for chronic stages of schizophrenia (BOWERS and FREEDMAN, 1966).

On a single-cell level, LSD and the simple indoleamine hallucinogens will be discussed together as they appear to have many actions in common. Mescaline and the methoxyamphetamines will be considered separately as they differ from the indoleamine group in many of their cellular actions despite their similar overall effects on behavior. A similar analysis of the sites of action of the tetrahydrocannabinols is not possible since these compounds have not been linked as yet to any specific neurotransmitter systems.

1. LSD and the Simple Indoleamines

a) Background

Partly because of its structural similarity to the endogenous indoleamine serotonin (5-hydroxytryptamine; 5-HT), it has been thought that LSD might act upon 5-HT receptors in the CNS (GADDUM, 1953; WOOLLEY and SHAW, 1954; FREEDMAN, 1961). More recently, it has been found by single-cell recording and microiontophoretic techniques that there are at least three types of central 5-HT receptors in the mammalian brain: inhibitory postsynaptic, facilitatory postsynaptic, and autoreceptors (AGHAJANIAN et al., 1975; AGHAJANIAN and WANG, 1978; MCCALL and AGHAJANIAN, 1979). The actions of hallucinogenic drugs at each type of 5-HT receptor will be reviewed.

b) Actions at Autoreceptors and Inhibitory Postsynaptic Receptors

The first direct evidence for an effect of LSD on the physiologic activity of a histochemically identified neuronal system came with the demonstration that small intravenous doses of LSD inhibit the firing of 5-HT neurons in the raphe nuclei of rats (AGHAJANIAN et al., 1968; AGHAJANIAN et al., 1970). Initially, it was suggested that LSD might inhibit 5-HT neurons through a negative feedback circuit by acting as an agonist on postsynaptic neurons (AGHAJANIAN et al., 1968; ANDÉN et al., 1968). However, subsequent studies have shown that LSD has a powerful direct inhibitory action upon 5-HT neurons in the raphe when applied by microiontophoresis (AGHAJANIAN et al., 1972; BRAMWELL and GONYE, 1976). Moreover, the inhibition of 5-HT neurons by LSD is more pronounced than its inhibitory effect upon neurons receiving an identified serotonergic input in several visual and limbic areas (HAIGLER and AGHAJANIAN, 1974a; DEMONTIGNY and AGHAJANIAN, 1977). In contrast, 5-HT itself shows no such preferential activity. The 2-bromo derivative of LSD, which has minimal hallucinogenic effects, also fails to show such preferential action (AGHAJANIAN, 1976). By inhibiting 5-HT neurons directly, LSD could release postsynaptic neurons from a tonic inhibitory 5-HT influence; such a release or disinhibition might account for the sensory, cognitive, and other disturbances caused by LSD. The finding of increased activity of some neurons in the lateral geniculate nucleus, amygdala, and other areas after low doses of LSD is consistent with this idea (MOURIZ-GARCIA et al., 1969; GUILBAUD et al., 1973; HORN and MCKAY, 1973; HAIGLER and AGHAJANIAN, 1974a).

Three simple indoleamine hallucinogenic drugs, psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine), DMT (*N*,*N*-dimethyltryptamine), and 5-methoxy-*N*,*N*-dimethyltryptamine also have a preferential inhibitory action upon 5-HT neurons as compared to postsynaptic neurons in the lateral geniculate (ventral nucleus) and amygdala (AGHAJANIAN and HAIGLER, 1975; DEMONTIGNY and AGHAJANIAN, 1977). On the other hand, there is only a slight difference between the pre- und postsynaptic actions of bufotenine (5-hydroxy-*N*,*N*-dimethyltryptamine). In general, these results parallel the known hallucinogenic (or psychotogenic) actions of these compounds. Except for LSD and some of its congeners, psilocin is the most potent of the indoleamine hallucinogens that have been tested in human subjects (WOLBACH et al., 1962). The effects of another powerful indoleamine hallucinogen, psilocybin (4-phosphoryl-*N*,*N*-dimethyltryptamine) are most probably mediated through its rapid metabolic conversion to psilocin (HORITA, 1963). The physiologic effects of DMT are similar to those of LSD and psilocin except for its lesser potency (SZARA, 1956; ROSENBERG et al., 1964). On the other hand, even high doses of bufotenine have little hallucinogenic action (FABING and HAWKINS, 1956; TURNER and MERLIS, 1959). Perhaps part of the reason for bufotenine's low hallucinogenic activity is the fact that is penetrates the brain poorly (SANDERS and BUSH, 1967). It is also possible that bufotenine has low activity as an hallucinogen because it differentiates less well between pre- and postsynaptic serotonergic sites than do psilicin, DMT, and 5-methoxy-*N*,*N*-dimethyltryptamine.

In general, these results are compatible with the hypothesis that LSD and the simple indoleamine hallucinogens could produce their hallucinogenic effects by acting preferentially upon 5-HT autoreceptors on or near the soma 5-HT neurons in the raphe nuclei. Two possible physiologic functions can be suggested for 5-HT autoreceptors. The autoreceptors could mediate the effects of 5-HT axon collaterals (or dendrodendritic junctions) within or between the various raphe nuclei. Recently, direct physiologic evidence for recurrent or collateral inhibition has been provided by studies in which the major ascending 5-HT pathway was activated antidromically during the recording of 5-HT cells which originate in the raphe (WANG and AGHAJANIAN, 1977, 1978). Another possible function of 5-HT autoreceptors is suggested by the finding that LSD blocks 5-HT release from isolated brain slices (CHASE et al., 1967; FARNEBO and HAMBERGER, 1971; HAMON et al., 1974). Thus, the autoreceptors that are sensitive to LSD may be involved in a local negative feedback regulation of 5-HT release from serotonergic terminals.

Figure 1 summarizes the differential actions of indoleamine hallucinogens at autoreceptors and postsynaptic inhibitory 5-HT receptors.

c) Actions at Facilitatory Postsynaptic 5-HT Receptors

Motoneurons of the brain and spinal cord receive a dense 5-HT input (DAHLSTRÖM and FUXE, 1965). Recently, it has been found that excitation of facial and other motoneurons by various means (e.g., stimulation of motor cortex, iontophoresis of glutamate) is markedly facilitated by 5-HT (MCCALL and AGHAJANIAN, 1979). By itself 5-HT has no excitatory action on the normally quiescent motoneurons. The facilitatory action of 5-HT is characterized by a long latency of onset and persistence for extended periods beyond the cessation of iontophoresis. The interpretation of this data for fa-

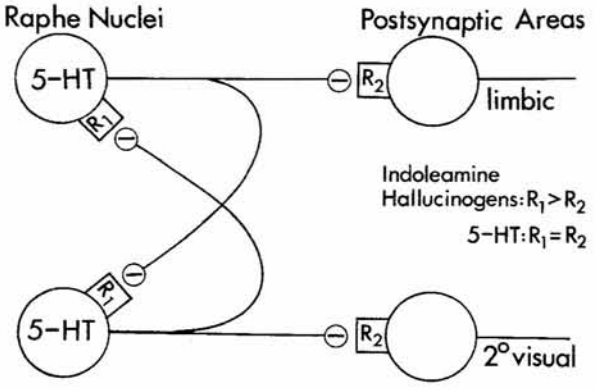

Fig. 1. A hypothetical circuit diagram of the differential localization of 5-HT autoreceptors R_1 and inhibitory (−) postsynaptic 5-HT receptors R_2. 5-HT autoreceptorts are shown in relation to inhibitory 5-HT axon collaterals within the raphe nuclei; postsynaptic 5-HT receptors are shown in relation to postsynaptic neurons in limbic and 2° visual areas

cial motoneurons is simplified by the fact that there are no interneurons within the facial nerve nucleus itself. Thus, 5-HT presumably facilitates through an action on synaptic inputs or on the motoneuron itself. The classic 5-HT antagonists (e.g., methysergide and cyproheptadine), which are not consistently or selectively effective at inhibitory 5-HT receptors (CURTIS and DAVIS, 1962; BLOOM et al., 1972; HAIGLER and AGHAJANIAN, 1974b; SEGAL, 1976), selectively and powerfully block the facilitatory effects of 5-HT on facial motoneuron excitation. Norepinephrine (NE) also facilitates motoneuron excitation, but via a different receptor as its effect is blocked by α-adrenoceptor antagonists but not by 5-HT antagonists (MCCALL and AGHAJANIAN, 1979). Previous studies have reported "excitatory" actions of 5-HT on unidentified spontaneously active brain stem neurons (e.g., BOAKES et al., 1970). In the latter area, as in the facial nerve nucleus, responses to 5-HT tended to be delayed and prolonged. Based on the facial nerve studies, these apparent excitations induced by 5-HT could be interpreted alternatively as representing a facilitation of tonic excitatory inputs. The excitatory effects of 5-HT on brain stem neurons have been reported to be blocked by LSD (BOAKES et al., 1970). However, since the existence of a 5-HT input to the latter neurons has not been established, the physiologic relevance of these findings must await further study. In contrast, the facilitation of facial neuron excitation by 5-HT as well as by NE is greatly enhanced by low intravenous doses of LSD (e.g., 10 μg/kg) (MCCALL and AGHAJANIAN, 1980). The iontophoresis of LSD at low currents, which by themselves have no effect, also enhances 5-HT facilitation; at higher currents LSD temporarily antagonizes the response. Thus, in small amounts LSD appears to sensitize these receptors to the facilitatory effects of 5-HT. Interestingly, mescaline also sensitizes and/or acts as an agonist at motoneuron 5-HT receptors despite the fact that it acts differently from LSD at certain other 5-HT receptors (see below). These sensitizing or facilitating effects on motoneuron excitability could account for the enhancement of certain spinal reflexes by LSD (ANDÉN et al., 1968) and mescaline (MAJ et al., 1977). The interaction of hallucinogenic drugs with the facilitation of motoneuron excitability by 5-HT is depicted in Fig. 2.

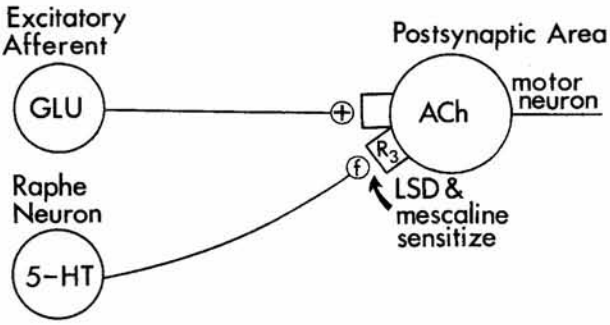

Fig. 2. A diagrammatic representation of the interaction between a hypothetical excitatory (+) glutaminergic *GLU* input to a cholinergic motor neuron *ACh* and a facilitatory 5-HT input *f* acting at a receptor R_3 on the motor neuron. The facilitatory R_3 receptor could also be located presynaptically (i.e., on the excitatory nerve terminal). LSD and mescaline are shown to sensitize the facilitatory 5-HT receptor R_3

d) Indoleamine Hallucinogens, 5-HT Neurons, and Behavior

Recently, TRULSON and JACOBS (1978, to be published, a) have examined the behavioral effects of hallucinogenic drugs in awake, freely moving cats, while simultaneously recording the activity of 5-HT neurons. Both LSD and 5-methoxy-*N*,*N*-dimethyltryptamine decreased the activity of 5-HT neurons in a dose-dependent manner in association with increases in behaviors that are characteristically produced by hallucinogenic drugs in cats (e.g., the limb flick response). In the case of 5-methoxy-*N*,*N*-dimethyltryptamine, the onset, offset, and peak of the behavioral effects were temporally correlated with changes in neural activity. The results with LSD were in general similar to those seen with 5-methoxy-*N*,*N*-dimethyltryptamine. However, in the case of LSD the behavioral effects outlasted the depression in 5-HT neuronal activity. Furthermore, when LSD was readministered the next day, it produced little or no behavioral effect, but the depression in 5-HT cell activity was as large as that on the first day. Thus, it appears that while LSD may be having its primary effect by depressing the firing of 5-HT neurons, it might also produce changes in postsynaptic neurons that can both outlast the primary effect and modify responses to subsequent injections. Such changes could involve alterations in the sensitivity of postsynaptic 5-HT receptors to LSD, 5-HT, or both (TRULSON et al., 1977; TRULSON and JACOBS, to be published, b).

e) Comparison of LSD with Lisuride, a Nonhallucinogenic ergoline

Lisuride is an ergoline derivative which is structurally similar to LSD. However, unlike LSD, lisuride does not produce hallucinations in man and, in fact, has recently been evaluated for use in the prophylaxis of migraine headache (HERRMANN et al., 1977) and in the treatment of hyperprolactinemic states (LIUZZI et al., 1978; HOROWSKI et al., 1978). In common with some but not all chemically related ergot alkaloids (BURKI et al., 1978; FUXE et al., 1978), lisuride reduces 5-HT and dopamine (DA) turnover and, at higher doses, increases NE turnover (KEHR, 1977; PIERI et al., 1978). These and other biochemical observations have led to the conclusion that lisuride is a potent 5-HT and DA receptor agonist and a somewhat weaker NE receptor antagonist.

Recently, as previously demonstrated for LSD, extremely small doses of lisuride have been found to produce a rapid, dose-dependent suppression of 5-HT neuronal activity (ROGAWSKI and AGHAJANIAN, to be published). In microiontophoretic experiments, both lisuride and LSD produce a complete suppression of most raphe units studied, but, for equivalent iontophoretic currents, the recovery with lisuride is more prolonged. These results suggest that lisuride, like LSD, has a direct agonist action at 5-HT autoreceptors. However, since drugs interacting with central adrenoceptors have been found to indirectly influence to activity of raphe serotonergic neurons (SVENSSON et al., 1975; GALLAGER and AGHAJANIAN, 1976; BARABAN et al., 1978), the possibility that lisuride's action is in whole or in part mediated via an action at adrenergic receptor sites cannot be excluded. In any case, the response of raphe neurons appears to be highly selective since units in the locus ceruleus are not depressed by the drug.

In contrast to its depressant effects in the raphe, lisuride, in somewhat higher doses, causes an activation of noradrenergic neurons in the locus ceruleus. This activation is consistent with the increased turnover of NE reported after corresponding higher doses in biochemical studies. Pharmacologic agents with α-adrenoceptor blocking properties, such as piperoxan, which activate the locus ceruleus (CEDARBAUM and AGHAJANIAN, 1976) have been reported to produce anxiety or fear in human subjects (GOLDENBERG et al., 1947; SOFFER, 1954). It is therefore of interest to note that one of the most prominent side effects of lisuride is its anxiety-producing or "dysphoric" action (ITIL et al., 1975). LSD also causes an activation of locus ceruleus neurons and has been reported to decrease NE levels and accelerate NE turnover (FREEDMAN, 1963; DIAZ et al., 1968; LEONARD and TONGE, 1969; STOLK et al., 1974), but both the physiologic and biochemical effects are less pronounced than with lisuride (PIERI et al., 1978).

Lisuride's action on dopaminergic neurons is not as clear-cut as its effects on the other two monoaminergic systems. The majority of cells tested are depressed by low doses of the drug, but in many cases this response is only partial and a small proportion of the cells were excited (ROGAWSKI and AGHAJANIAN, to be published). Similar effects of LSD on dopamine cells have been reported (CHRISTOPH et al., 1977).

In summary, lisuride resembles LSD in its effects on 5-HT and other monoaminergic neurons, except for a more prominent effect of lisuride on noradrenergic neurons.

f) Conclusions

Considerable evidence has now accumulated that LSD and the simple indoleamine hallucinogens can inhibit directly the firing of 5-HT neurons through a preferential action on 5-HT autoreceptors. In general, the first-dose effect of these drugs on hallucinogen-specific behaviors in cats correlates well with their ability to suppress 5-HT cell activity, although the behavioral effects of LSD seem to outlast changes in firing rate. In any case, by directly suppressing 5-HT cell activity these drugs could produce a psychedelic–hallucinatory state by disinhibiting postsynaptic neurons in various postsynaptic areas where 5-HT is inhibitory (e.g., in limbic and 2° visual nuclei of the brain; HAIGLER and AGHAJANIAN, 1974a). One problem with this hypothesis is the fact that ergoline drug lisuride, which is even more powerful than LSD in inhibiting 5-HT neurons, is not hallucinogenic. However, lisuride might share some properties with in-

directly acting agents that suppress 5-HT cell firing (e.g., α-adrenergic antagonists) and therefore would not express hallucinogenic activity. In any case, it will be of theoretical interest to further investigate pharmacologic differences between lisuride and LSD which could reveal drug actions critical for psychotomimetic activity.

Finally, the discovery of receptors at which LSD and mescaline can sensitize the facilitatory action of 5-HT opens a new approach to the study of these drugs on single cells. Thus far, these sensitizing effects of psychedelic drugs have been observed directly only on motoneurons. If similar effects can be found in sensory pathways, then sensitization, in distinction to disinhibition, might account for the altered perceptual reactivity induced by this drug.

2. Mescaline and Methoxyamphetamines

a) Background

As the effects of LSD and mescaline (3,4,5-trimethoxyphenylethylamine) on autonomic function and behavior are similar (WOLBACH et al., 1962), it generally has been assumed that these two drugs share a common site of action. In various species, cross tolerance occurs between LSD and mescaline (BALESTRIERI and FONTANARI, 1959; APPEL and FREEDMAN, 1968). A metabolic mechanism does not seem to account for such cross tolerance since prior treatment with mescaline does not reduce brain levels of LSD (WINTERS, 1971). Several investigators (SNYDER and RICHELSON, 1968; KANG and GREEN, 1970; NICHOLS et al., 1977) have proposed that mescaline may assume a conformation resembling a portion of the LSD molecule. Taken together, these data suggest that LSD and mescaline may act on the same receptor site in the CNS. Single-cell studies to test this hypothesis have dealt mainly with actions in the serotonergic and noradrenergic systems.

b) Mescaline, Methoxyamphetamines, and 5-HT Neurons

Systemic administration of mescaline (2–4 mg/kg, i.v.) has been found to inhibit a subpopulation of 5-HT neurons located within the ventral portion of the dorsal raphe nucleus and adjacent areas of the median raphe nucleus (AGHAJANIAN et al., 1970). A similar subpopulation of raphe neurons are inhibited by 2,5-dimethoxy-4-methylamphetamine (DOM). When LSD is administered systemically in doses comparable to those that produce behavioral effects, the firing of serotonergic neurons in the raphe nuclei of the brain stem is reversibly inhibited (see above). When LSD is administered microiontophoretically a similar inhibition is obtained (AGHAJANIAN et al., 1972). These data, coupled with the fact that after the systemic administration of mescaline a subpopulation of raphe neurons is inhibited (AGHAJANIAN et al., 1970), indicate that there may exist a subpopulation of raphe neurons that would be inhibited by the microiontophoretic application of mescaline. However, this expectation is not borne out by studies in which the effects of microiontophoretically and systemically applied mescaline are compared (HAIGLER and AGHAJANIAN, 1973). Although some raphe neurons are partially depressed by the microiontophoretic application of mescaline, this effect may represent a local anesthetic action and is not correlated with the inhibition produced by mescaline given intravenously. On the other hand, some raphe cells are unaffected by the microiontophoretic application of mescaline but are

completely inhibited by the systemic administration of mescaline. The failure to obtain a response to mescaline, even under extreme conditions, from cells that are very sensitive to systemic mescaline does not support the view that the action of systemic mescaline on these raphe neurons is a direct one. In contrast, certain cortical neurons are highly responsive to the direct application of mescaline with no reported local anesthetic effect (BRADSHAW et al., 1971). In the raphe there is no correlation between response to mescaline and NE administered microiontophoretically (HAIGLER and AGHAJANIAN, 1973) as has been reported for cortical cells (BRADSHAW et al., 1971). Moreover, in the raphe there is no relationship between responses to i.v. mescaline and responses to NE given iontophoretically.

A possible explanation for the lack of correlation between the effect of mescaline given systemically or microiontophoretically would be that an active metabolite is formed in the periphery when the drug is given by the systemic route. Therefore, when mescaline is applied very close to the cell it would be relatively ineffective since there would be no opportunity for it to be metabolized. Two metabolites of mescaline that have been studied in man (i.e., *N*-acetylmescaline and 3,4,5-trimethoxyphenylacetic acid) do not produce physiologic and psychological effects (CHARLAMPOUS et al., 1966). The primary metabolite of mescaline in rats is 3,4,5-trimethoxyphenylacetic acid (MUSACCHIO and GOLDSTEIN, 1967). The possibility that mescaline must be converted to this metabolite in rats before it is effective on raphe cells has not been ruled out. However, the blockade of mescaline metabolism by iproniazid does not prevent certain of its behavioral effects (SMYTHIES et al., 1967). Moreover, in the single-cell experiments, the onset of the inhibition of firing in the raphe cells is within 30–40 s after the i.v. injection of mescaline, suggesting that if an active metabolite is formed this must occur extremely rapidly to be responsible for the inhibition.

In conclusion, it would appear that the effects of systemically administered mescaline upon 5-HT cells are via an indirect mechanism since the only direct mescaline effect obtainable was of a local anesthetic type. Furthermore, it appears that responses to mescaline by either route are unrelated to response to NE. As both LSD and mescaline can inhibit cells in the raphe nuclei when given systemically, but only LSD readily produces an inhibition in these cells when applied microiontophoretically, it would appear that they differ in their mode of action upon raphe cells. On a biochemical level, LSD and mescaline also differ as LSD but not mescaline depresses the metabolism of brain serotonin (FREEDMAN et al., 1970). The possibility remains that LSD and mescaline share a common site of action in some other area of the CNS.

c) Mescaline, Methoxyamphetamines, and Noradrenergic Transmission

In the periphery, mescaline can have both agonistic and antagonistic actions on adrenergic receptors (CLEMENTE and LYNCH, 1968). When applied to unidentified brain stem neurons, mescaline at high iontophoretic currents blocks responses to catecholamines (GONZALEZ-VEGAS, 1971). In the cerebral cortex, mescaline (again at high iontophoretic currents) exerts both excitatory and depressant actions (BRADSHAW et al., 1971; BEVAN et al., 1974). Regardless of the direction of change, the effects of mescaline have a higher correlation with the effects produced by NE than with those produced by 5-HT. However, mescaline is a much weaker "agonist" than either of the endogenous amines and its effects are not antagonized in a specific way by adrenergic or serotonergic antagonists.

Of course, it is possible that mescaline and methoxyamphetamine have their effects on monoamine transmission through an indirect action, such as on uptake (DENGLER et al., 1961) or release of endogenous transmitter (TILSON and SPARBER, 1972), rather than through a direct action on receptors. Mescaline, as well as LSD and the simple indoleamine hallucinogens, induces a decrease in levels of NE in brain (BARCHAS and FREEDMAN, 1963; DIAZ et al., 1968; LEONARD and TONGE, 1969). However, NE metabolite patterns are not altered in a consistent fashion, indicating that the various psychotomimetic drugs may not share a common effect on brain NE neurons (STOLK et al., 1974).

Recently, the effects of mescaline on the firing pattern of single NE neurons of the locus ceruleus have been studied in rats (AGHAJANIAN, 1980). In low systemic doses (1–4 mg/kg) mescaline has a dual action on these neurons. It induces a suppression of baseline firing rate while reactivity to peripheral stimuli remains the same or increases. NE neurons of the locus ceruleus respond to a noxious stimulus applied anywhere on the body by an initial activation followed by a period of suppressed activity (CEDARBAUM and AGHAJANIAN, 1978 a). The activation appears to be via direct spinal afferents, although some relay neurons may be involved (CEDARBAUM and AGHAJANIAN, 1978 a and b). There is evidence that the postactivation suppression in firing is mediated by NE released from a direct axon-collateral negative feedback system (AGHAJANIAN et al., 1977; CEDARBAUM and AGHAJANIAN, 1978 a). Mescaline prolongs the period of postactivation inhibition and thus behaves like desipramine, an inhibitor of NE uptake (AGHAJANIAN et al., 1978). As in the case of desipramine, the extended postactivation suppression induced by mescaline can be reversed by the presynaptic ($\alpha 2$) adrenoceptor antagonist piperoxan (AGHAJANIAN, in preparation). However, mescaline differs from desipramine, amphetamine, and the $\alpha 2$-agonist clonidine as the latter drugs depress reactivity to peripheral stimuli (AGHAJANIAN, 1980). Mescaline also differs from the $\alpha 2$-antagonist piperoxane; the latter diminishes postactivation collateral inhibition, but does not increase the initial reactivity to peripheral stimuli. Thus, mescaline possesses a unique action upon NE neurons which cannot be classified according to simple agonism or antagonism. Microiontophoretic results are consistent with this view: mescaline does not directly depress the firing of NE neurons (except at high iontophoretic currents), nor does it antagonize the depressant effects of NE.

d) Conclusions

Mescaline and the methoxyamphetamines do not fit into any simple category as agonists or antagonists with respect to either 5-HT or NE neurons. Indeed, the enhancement of NE-neuronal reactivity in relation to a reduction in baseline activity which is produced by mescaline represents an effect unlike that seen with known adrenergic agonists or antagonists that act at that site. Recent single-cell recording studies show that low doses of LSD (5 μg/kg, i.v.) also enhance reactivity of NE neurons to peripheral stimuli (AGHAJANIAN, in preparation). These findings are reminiscent of the earlier studies that show an activating effect of low doses of LSD on evoked potentials in specific sensory systems (PURPURA, 1956). Moreover, the activation of EEG by LSD is enhanced by increased external stimuli (BRADLEY and KEY, 1958). Similarly, clinical reports show that the subjective effects of LSD are accentuated with increased environmental stimulation (ELKES et al., 1954; COHEN and EDWARDS, 1964). Further-

more, the ECoG-activating effect of the psychedelic drugs differs from the stimulants, such as amphetamine, that activate the ECoG independently of the level of ambient stimulation (BRADLEY and ELKES, 1957). More recently, it has been shown that LSD (DAVIS and SHEARD, 1974; MILIARESSIS and ST-LAURENT, 1974) and mescaline (GEYER et al., 1978) enhance startle responses to acoustic and tactile stimuli, respectively. Thus, the mechanisms by which LSD or mescaline enhance NE-cell reactivity to peripheral stimuli may offer a clue to an understanding of mechanisms these psychedelic drugs may have in common.

II. Stimulants

In large doses, the amphetamine and other stimulants can induce a psychosis that bears a close clinical resemblance to spontaneous paranoid psychoses or paranoid schizophrenia (CONNELL, 1958; BEAMISH and KILOH, 1960; BELL, 1965; ELLINWOOD, 1967). Because of their obvious similarity in chemical structure to the catecholamines, the amphetamines have long been presumed to act via these neurotransmitters (SNYDER, 1972). Single-cell recording and microiontophoretic studies support the concept that amphetamine acts indirectly through the release or blockade of reuptake of endogenous catecholamines (e.g., BOAKES et al., 1972; BUNNEY et al., 1973; GROVES et al., 1976).

Several studies have indicated that paranoid symptoms can be elicited in human subjects with similar doses of L- and D-amphetamine (ANGRIST et al., 1971; JANOWSKY and DAVIS, 1976). These results suggest that brain systems in which the two isomers have nearly equal actions may be involved in mediating the psychotomimetic effects of these drugs. Thus, a major strategy in approaching their biochemical, behavioral, and physiologic actions on catecholaminergic neurons has been to compare relative potencies of the amphetamine isomers in various test systems (SNYDER et al., 1974).

1. Comparison of Amphetamine Isomers on the Activity of NE and DA Neurons

Most (SVENSSON, 1971; COSTA et al., 1972; FERRIS et al., 1972; SCHEEL-KRÜGER, 1972; HARRIS and BALDESSARINI, 1973; JORI et al., 1973; THORNBURG and MOORE, 1973; HOLMES and RUTLEDGE, 1976; PETERSON and SPARBER, 1976) but not all (ROFFMANN et al., 1978) recent biochemical and behavioral studies have indicated that D- and L-amphetamine are approximately equipotent in the NE system, but that D-isomer is much more potent than the L-isomer in the DA system. Similar differences have been found in single-cell recording studies (BUNNEY et al., 1975). DA neurons of the substantia nigra (zona compacta) are 5–20 times more sensitive to the depressant effect of D- and L-amphetamine given intravenously. On the other hand, the potency of L-amphetamine in depressing the firing of NE neurons is equal to that of D-amphetamine. From these results it would appear that low doses of L-amphetamine have a preferential action on the firing of NE as opposed to DA neurons. There is evidence from single-cell studies that the depression of DA cell firing by D-amphetamine is mediated indirectly by a postsynaptic neuronal feedback circuit (BUNNEY and AGHAJANIAN, 1976). An alternative view is that D-amphetamine depresses the firing of DA neurons by releasing DA locally from dendrites (GROVES et al., 1975). In this case, the local

"self-inhibitory" effect of DA could be mediated by DA autoreceptors (AGHAJANIAN and BUNNEY, 1977). In either case, the much greater effect of D-amphetamine on DA cells firing correlates with the greater potency of this isomer in affecting the firing of postsynaptic striatal neurons innervated by the DA neurons of the zona compacta (REBEC and GROVES, 1975). Comparisons between D- and L-amphetamine have been made on NE-innervated postsynaptic neurons in the cerebellum (WISE and HOFFER, 1977); the two isomers have an equal ability to inhibit Purkinje cell discharge in this region. If D- and L-amphetamine prove to have equal actions at other postsynaptic NE sites as well, then the NE rather than DA system would seem more likely to be responsible for the amphetamine-induced paranoid psychosis. However, new data on differential actions of D- and L-amphetamine within subgroups of DA neurons necessitates a modification of this conclusion (see below).

2. Differential Actions of Amphetamine Isomers on Striatal and Nonstriatal DA Systems

It hat been proposed by a number of investigators that while the nigrostriatal DA system is involved in extrapyramidal motor functions, the nonstriatal mesocortical and mesolimbic DA projection systems, which arise in the ventral tegmental area, may be involved in schizophrenia (COSTA and GESSA, 1977). In a recent single cell recording study, the potencies of L- and D-amphetamine in decreasing the firing of DA neurons in both the substantia nigra (A 9) and the ventral tegmentum area (A 10) were compared (BROWDER et al., to be published). In agreement with previous results (BUNNEY et al., 1975), the firing rate of A 9 neurons is much more sensitive to D- and than L-amphetamine. In addition, the dose-response of A 10 cells to D-amphetamine is comparable to that of A 9 cells.

Surprising, however, A 10 cells are at least as sensitive to the depressant action of L- as D-amphetamine. These data show that the various DA nuclei are not pharmacologically homogenous. Moreover, as the two amphetamine isomers have similar potencies on A 10 neurons, the mesolimbic and mesocortical DA systems represent a possible site through which the stimulant drug could produce a paranoid psychosis.

III. Deliriants

A delirious state (or toxic psychosis) is characterized by confusion, disorientation, memory deficits, and hallucinations. When produced by nonspecific toxic agents the delirium is often accompanied by generalized metabolic dysfunctions. The antimuscarinic drugs (e.g., atropine and scopolamine), which block cholinergic transmission at muscarinic receptor sites, are of particular pharmacologic interest as model psychotomimetic agents since they can reliably induce a delirious state in normal subjects without also inducing concomitant metabolic disturbances (e.g., KETCHUM et al., 1973). As the antimuscarinic drugs have a structural relationship to the neurotransmitter acetylcholine (ACh) (ABOOD and BIEL, 1962), it may be hypothesized that the antimuscarinic drugs act upon cholinergic receptors in the brain, as they do in the periphery. A further clue about central mechanisms of action comes from the fact that anticholinesterase agents such as physostigmine, which block the hydrolysis of ACh, are able to reverse the delirium produced by antimuscarinic drugs (KLEINWACHTER,

1864; FORRER and MILLER, 1958; CROWELL and KETCHUM, 1967; GOLDNER, 1967; DUVOISIN and KATZ, 1968; HEISER and GILLIN, 1971; KETCHUM et al., 1973). These clinical findings clearly link the psychotomimetic effects of the antimuscarinic drugs to cholinergic mechanisms.

With the discovery of presumptive cholinergic pathways in the brain by means of acetylcholinesterase (AChE) straining (SHUTE and LEWIS, 1963) combined with more specific biochemical assays (LEWIS et al., 1967) it has become possible to apply single-cell recording techniques to the investigation of the actions of antimuscarinic drugs on central cholinergic neurotransmission.

1. Antimuscarinic Drugs and Central Cholinergic Pathways

Perhaps the best-characterized cholinergic pathway in brain lies within the septohippocampal projection. Some of the evidence is as follows: (1) ACh is located in the hippocampus and ACh levels are greatly reduced following lesions of the medial septum that interrupt the septohippocampal tract (KUHAR et al., 1973); (2) stimulation of the medial septal nucleus results in the release of ACh from the dorsal hippocampus (ROMMELSPRACHER and KUHAR, 1974; SMITH, 1974; DUDAR, 1975); (3) choline acetyltransferase, the enzyme necessary for the synthesis of ACh, is localized to the neuropil adjacent to the pyramidal cell layer of the hippocampus (FONNUM, 1970); (4) the activity of this enzyme in the hippocampus is decreased by medial septal lesions (LEWIS et al., 1967; KUHAR et al., 1973); (5) AChE, the enzyme responsible for the degradation of ACh, is localized to the neuropil adjacent to the pyramidal cells (SHUTE and LEWIS, 1966; STORM-MATHISEN and BLACKSTAD, 1964); and (6) septal lesions result in a marked decrease in AChE activity in the hippocampal cell layer (LEWIS et al., 1967; STORM-MATISEN, 1972; MELLGREN and SREBRO, 1973). It should be noted, however, that there is not as yet a universally accepted histochemical method for cholinergic neurons (e.g., by using choline acetyltransferase as a marker).

The hippocampus has been linked with the functions of memory (SCOVILLE, 1957; VICTOR et al., 1961), learning (MEISSNER, 1966), and spatial orientation (OLTON and ISSACSON, 1968; O'KEEFE and DOSTROVSKY, 1971; MAHUT and ZOLA, 1973). As these are major functions disrupted by the antimuscarinic drugs, the hippocampus represents a relevant system for exploring the mechanism of action of their drugs. Hippocampal pyramidal cells are exceedingly sensitive to the excitatory action of ACh and muscarinic agonists, but not to nicotinic agonists applied by microiontophoresis (HERZ and NACIMENTO, 1965; BISCOE and STRAUGHAN, 1966; BIRD and AGHAJANIAN, 1975 and 1976; SEGAL, 1978). Muscarinic antagonists (i.e., atropine, scopolamine, and quinuclidinyl benzylate) totally and selectively block ACh excitation of hippocampal cells. Some but not all nicotinic antagonists are also effective, suggesting cholinergic receptors of the hippocampus are of the mixed type (BIRD and AGHAJANIAN, 1976; SEGAL, 1978). Similar findings have been reported for the cerebral cortex (KRNJEVIĆ and PHILLIS, 1963), which also receives a cholinergic projection from the septal area. Excitatory responses to ACh are also blocked by antimuscarinic drugs in the lateral geniculate nucleus (PHILLIS et al., 1967). The latter observation may be of interest in relation to the visual hallucinatory phenomenon induced by these drugs. Taken together, these studies establish that antimuscarinic drugs have powerful anticholinergic actions in identified or presumed central cholinergic pathways.

2. Action of Physostigmine in Cholinergic Pathways

Since physostigmine, a AChE inhibitor, can reverse the delirium produced by antimuscarinic drugs, its effect on transmission in known central cholinergic systems may be relevant to its clinical action. In normal animals, physostigmine greatly enhances the excitatory effect of ACh on neurons in several brain regions such as the lateral geniculate nucleus (PHILLIS et al., 1967) and the hippocampus (BIRD and AGHAJANIAN, 1975). When the septohippocampal pathway is lesioned, causing a depletion of AChE, a marked increase occurs in sensitivity to ACh but not carbachol (which is resistant to hydrolysis by AChE). In the lesioned animals, with the loss of presynaptic AChE, physostigmine no longer enhances ACh excitation (BIRD and AGHAJANIAN, 1975). These results show that denervation supersensitivity to ACh in the septohippocampal pathway is due primarily to decreased inactivation of ACh by presynaptic AChE. An implication of this finding is that AChE inhibitors can substantially increase the amounts of ACh at physiologically active sites. The therapeutic effect of physostigmine and other AChE inhibitors in reversing the delirium induced by antimuscarinic drugs may thus be explained by the fact that the action of ACh in the hippocampus and possibly other areas of the brain is so critically modulated by AChE.

3. Deliriants as a Model for Human Memory Disorders

Based on the fact that antimuscarinic drugs impair memory processes and anticholinergic drugs improve certain aspects of memory function, it has been suggested that diminished cholinergic transmission may underlie certain human memory disorders (DAVIS and YAMAMURA, 1978, for review). In support of this hypothesis, an age-related decrease in the central cholinergic enzymes choline acetyltransferase and AChE has been observed (MCGEER and MCGEER, 1976). These decrements are more severe in patients with Alzheimer's type senile dementia (PERRY et al., 1977). Thus, the possibility arises that drugs or precursors that enhance central cholinergic transmission might be useful in patients with senile or presenile dementias.

C. General Conclusions

As can be seen from the foregoing review, drugs within each of the major subgroups of psychotomimetics have dramatic effects on single-cell activity in chemically identified neuronal systems. Furthermore, each major subgroup appears to be separable according to transmitter-specific actions as follows:

I. Stimulants

Based on a large body of biochemical, behavioral, and physiologic evidence, the effects of stimulants (e.g., D- and L-amphetamine) within catecholaminergic systems can be attributed to a single overall action: the enhancement of the synaptic availability of NE or DA through a release and/or block of the reuptake of these catecholamines. However, a major question remains as to which of the several neuronal systems in which the stimulants have actions are most responsible for the psychotomimetic effects of these drugs. The noradrenergic system and the mesolimbic and mesocortical

DA systems have been implicated in the psychotomimetic effects of D- and L-amphetamine by virtue of the fact that they affect neuronal activity in these systems to a similar degree and have approximately equal effects in eliciting a paranoid psychosis. On the other hand, D-amphetamine, which has much greater activity than the L-isomer in the nigrostriatal DA system, can be linked to disturbances in extrapyramidal motor functions. However, several caveats should be mentioned. Knowledge about relative psychotomimetic potencies of D- and L-amphetamine is based on clinical studies involving relatively few subjects; ultimately further confirmation will be required. Furthermore, even if the nigrostriatal DA system could be ruled out in psychotogenesis, the remaining catecholamine pathways (both NE and DA) project so extensively within the brain that a multitude of other sites remain to be considered. Thus, much work needs to be done to define more precisely which brain systems are most closely involved in the psychotomimetic effects of the stimulant drugs.

II. Deliriants

As in the case of the stimulants, the central effects of the delirium-inducing antimuscarinic drugs can be attributed to a single action: the blockade of cholinergic transmission at muscarinic receptors. Moreover, certain of the major cholinergic pathways in the brain project to regions whose presumed functions are similar to functions that are disturbed in states of delirium. For example, the hippocampus, which receives the cholinergic septohippocampal projection, has been implicated in aspects of memory and orientation. However, the precise manner in which the cholinergic inputs modulate hippocampal function is not known. Moreover, the complete delineation of cholinergic systems in the brain has been hampered by the lack of a workable, specific histochemical method for mapping. A more complete picture of central cholinergic pathways will be needed to assess all possible sites at which the antimuscarinic drugs could be acting to induce the multiple disturbances seen in delirium.

III. Psychedelic Drugs

In contrast to the stimulants and deliriants, the effects of psychedelic drugs cannot as yet be attributed to a single action. In fact, at least two different types of mechanisms have been hypothesized by which the psychedelic drugs could act. The first can be termed the "5-HT disinhibitory" hypothesis, which applies best to LSD and the simple indoleamine hallucinogens. According to this hypothesis these hallucinogens, by directly inhibiting 5-HT neurons, would release postsynaptic neurons (e.g., in limbic or 2° visual areas) from tonic 5-HT influences, allowing hallucinatory and other psychedelic phenomena to emerge. However, there are seeming difficulties with the disinhibitory hypothesis as a unitary explanation. First, lisuride also appears to inhibit 5-HT neurons by acting at autoreceptors, yet it is not an hallucinogenic drug. Secondly, despite the fact that mescaline and the methoxyamphetamines have psychedelic effects that are very similar to those of LSD, they do not act upon 5-HT autoreceptors. On the other hand, both LSD and mescaline are similar in enhancing the responsivitity of noradrenergic neurons to peripheral stimuli. Furthermore, in some recent single-cell studies it has been observed that mescaline and LSD do share certain facilitatory actions. For example, they both directly sensitize facilitatory 5-HT recep-

tors found on motoneurons. Thus, the psychedelic drugs can have a facilitatory as well as inhibitory and disinhibitory actions on a single-cell level. It remains for future research to ascertain the degree to which each of these mechanisms contributes to the final common behavioral effects of the two major classes of psychedelic drugs.

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