Pharmacology Biochemistry & Behavior, Vol 24, pp 359–363 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Effects of Hallucinogenic Drugs on Serotonergic Neuronal Systems

ROBERT B McCALL

Cardiovascular Diseases Research, The Upjohn Company, 7243-209-3, Kalamazoo, MI 49001

McCALL, R B *Effects of hallucinogenic drugs on serotonergic neuronal systems* PHARMACOL BIOCHEM BEHAV **24**(2) 359–363, 1986 —Studies indicate that hallucinogens markedly suppress the discharge of serotonin containing neurons in the dorsal raphe nucleus Forebrain neurons receiving a major serotonergic input are relatively insensitive to hallucinogens These actions of hallucinogens are not sufficient to explain the psychoactive effects of these drugs Evidence is presented to indicate that hallucinogens sensitize serotonin and norepinephrine receptors in the facial nucleus This receptor sensitizing effect is common to all, and specific for, hallucinogens It is suggested that a mechanism of receptor sensitization might account for the altered perceptual reactivity produced by hallucinogens

Serotonin Hallucinogens d-Lysergic acid diethylamide Mescaline Facial motor nucleus

BASED upon the structural similarity between the hallucinogen d-lysergic acid diethylamide (LSD) and serotonin (5-HT), Gaddum [14] and Wooley and Shaw [34] independently proposed that the potent psychoactive effects of LSD might be mediated by an action on 5-HT receptors in the central nervous system However, it was not until Dahlstrom and Fuxe localized 5-HT containing perikarya to the brain stem raphe nuclei and identified the areas of projection of these neurons using fluorescence histochemical techniques that the effects of hallucinogens on 5-HT pathways could be studied directly [11,13] Using microelectrode recording techniques, Aghajanian and co-workers were the first to examine the effects of intravenous (IV) LSD on 5-HT neuronal firing recorded from the dorsal raphe nucleus [2,3] They found that LSD (10–50 μg/kg) produced a complete but reversible inhibition of 5-HT neuronal discharges Similarly, the indoleamine hallucinogens psilocin and N,N-dimethyltryptamine (DMT) inhibited raphe firing [3,4] In contrast, the non-hallucinogenic analog of LSD, brom-LSD, failed to reduce 5-HT unit activity More recently, Mosko and Jacobs [26] demonstrated that 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), an idoleamine with weak hallucinogenic properties, also depressed raphe neuronal firing

In order to determine if hallucinogens acted directly on 5-HT neurons to suppress their firing, Aghajanian and co-workers studied the effect of microiontophoretically applied LSD on raphe cells [1, 4, 6] They found that small ejecting currents of dilute LSD profoundly suppressed the firing of serotonergic neurons Direct application of 5-HT also inhibited raphe firing (Fig 1, upper trace), although LSD was much more than 5-HT in its inhibitory effects Iontophoretic application of psilocin, DMT and 5-MeODMT also dramatically inhibited the discharges of 5-HT cells [4,12] These data indicate that hallucinogenic indoles act as agonists at receptors located on 5-HT perikarya and dendrites (i e , autoreceptors [7]) in order to produce their inhibitory effects

The inhibitory effect of LSD on 5-HT cell firing is not sufficient to explain its psychedelic actions, since 5-HT also suppresses raphe neuronal discharges However, Aghajanian and Haigler [4,17] found that forebrain neurons receiving a major serotonergic input (e g , ventral lateral geniculate, the basolateral and cortical amygdala and the optic tectum) are relatively insensitive to LSD at iontophoretic ejection currents that are highly effective in the raphe (Fig 1) In contrast, iontophoretic 5-HT is approximately equipotent in depressing activity of 5-HT neurons and neurons in postsynaptic areas which receive a major serotonergic input (Fig 1) Psilocin, DMT and 5-MeODMT also preferentially inhibit raphe firing as compared to the discharge of neurons in postsynaptic forebrain areas [4,12] In these studies, the degree of preference to the 5-HT autoreceptor correlated well with hallucinogenic potency The preferential inhibitory action of hallucinogens on raphe cells suggests that these agents could release postsynaptic forebrain neurons from a tonic inhibitory influence In agreement with this prediction, low intravenous doses of LSD accelerates the discharge rate of neurons in postsynaptic areas which receive an inhibitory 5-HT input (Fig 1, [15, 18, 27]) These studies led to the hypothesis that indole hallucinogens produced their psychoactive effects by acting preferentially upon 5-HT autoreceptors in the dorsal raphe, allowing postsynaptic neurons to escape from the tonic inhibitory action of 5-HT neurons Since the visual and limbic systems are densely innervated by 5-HT axons, the hallucinogen-induced disinhibition in these areas could account for two of the major consequences of hallucinogenic action visual hallucinations and alterations of affect

Although the "disinhibition" hypothesis laid the framework for much investigation, certain problems exist with the theory [22] First, the inhibitory action of LSD on raphe neurons is relatively transient, while the psychedelic effects of the drug are prolonged [9,32] Moreover, the time course of the behavioral and raphe neuronal effects of LSD in the free-moving cat do not correlate [19,29] Second, al-

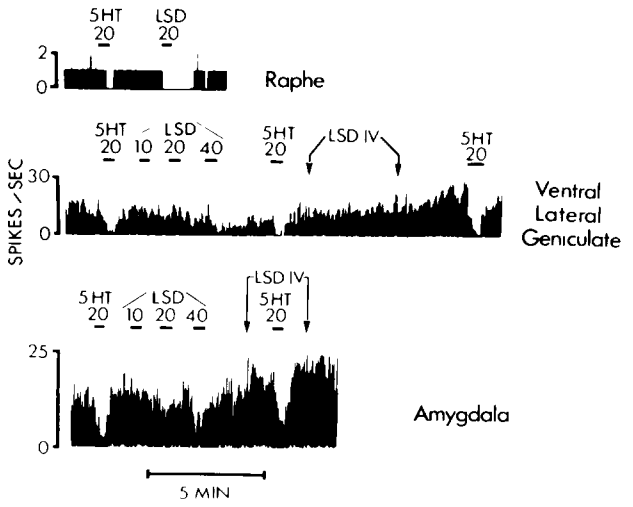

FIG 1 Comparison of the response of a neuron in the dorsal raphe nucleus with that of neurons in the ventral lateral geniculate and the basolateral nucleus of the amygdala to microiontophoretic administration of 5-HT and LSD LSD preferentially inhibited 5-HT neurons 5-HT inhibited 5-HT neurons and postsynaptic neurons to a similar degree In this and the following figures, the horizontal bar indicates the iontophoretic ejection period, the number over the bar represents the ejecting current The ordinate represents the integrated firing rate in spikes per second Reprinted by permission of The Williams and Wilkins Co , Baltimore, MD Copyright 1974

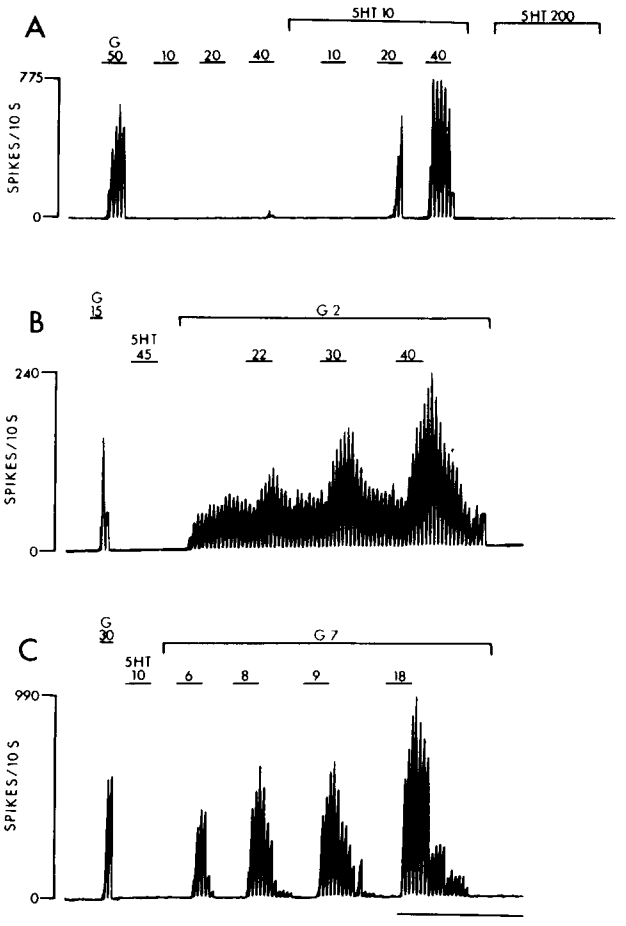

FIG 2 Facilitation of glutamate-induced excitation of facial motoneurons by 5-HT A 5-HT (10 nA) reduced the threshold required for glutamate-induced activation of unit 5-HT (200 nA) failed to directly excite neuron B Facilitating effect of 1-min pulses of 5-HT on glutamate-induced excitation (G2 nA) of motoneuron C Facilitation of the subthreshold excitatory effect of glutamate (G7 nA) by 5-HT

though tolerance develops to the behavioral effects of LSD [9, 29, 32], no such tolerance develops to the inhibitory effect of LSD on 5-HT neurons [30] Third, the phenethylamine hallucinogen mescaline and LSD are thought to act at the same receptor site to produce their psychoactive effects [9, 32, 33] However, mescaline does not directly suppress the firing of 5-HT neurons in the dorsal raphe [16] Finally, the ergoline derivative lisuride, produces a direct, rapid dose-dependent suppression of the spontaneous activity of 5-HT neurons [20,28] In fact, lisuride is approximately 5–10 times as potent as LSD in inhibiting raphe firing Importantly, however, lisuride does not possess hallucinogenic properties Taken together, these data suggest that an agonist action at 5-HT autoreceptors and the subsequent release from tonic inhibition in postsynaptic forebrain areas may be insufficient to explain the mode of action of hallucinogens

An alternative possibility is that hallucinogens act on postsynaptic 5-HT receptors to produce their psychedelic effects In this regard, McCall and Aghajanian have characterized a third type of 5-HT receptor in the central nervous system located on facial motoneurons [5, 23–25] As illustrated in Fig 2, they found that microiontophoretic application of 10–200 nA pulses of 5-HT lasting from 1 to 10 min failed to activate the normally quiescent facial motoneurons However, 5-HT markedly potentiated the excitatory effect of iontophoretically applied glutamate on these neurons (Fig 2A) One minute pulses of iontophoretic 5-HT also enhanced the subthreshold (Fig 2B) and threshold (Fig 2C) excitatory effects of glutamate In addition, 5-HT (5–10 nA) dramatically facilitated the excitatory effects of afferent nerve stimulation Like 5-HT, norepinephrine (NE) also markedly facilitated excitatory inputs to facial motoneurons [23] Peripheral 5-HT antagonists (i e , methysergide, metergoline, cyproheptadine and cinanserin) which fail to block the inhibitory effects of 5-HT in the raphe and forebrain areas [7], antagonized the facilitating effects of 5-HT but not NE [25] Thus, in the facial nucleus, 5-HT functions in a manner that is not analogous to direct excitation, but rather acts as a gain setter to enhance the effects of excitatory inputs Furthermore, the data indicate that the receptor mediating the facilitating effects of 5-HT in the facial nucleus is distinct from those found in the dorsal raphe and postsynaptic forebrain areas

More recently, McCall and Aghajanian studied the effects of hallucinogens on the facilitating action of 5-HT and NE in the facial nucleus [24] Intravenous administration of LSD (10–100 μg/kg) had no effect by itself on the glutamate-induced excitation of facial motoneurons In contrast, the facilitation of facial motoneuron excitation by iontophoretically applied 5-HT and NE was enhanced approximately 10-fold by low doses of LSD (5–10 μg/kg, IV, Fig 3A, Table 1) Similarly, iontophoresis of LSD at low currents (2–7 nA) failed to effect the glutamate-induced excitation of motoneurons, but markedly enhanced the facilitation of fa-

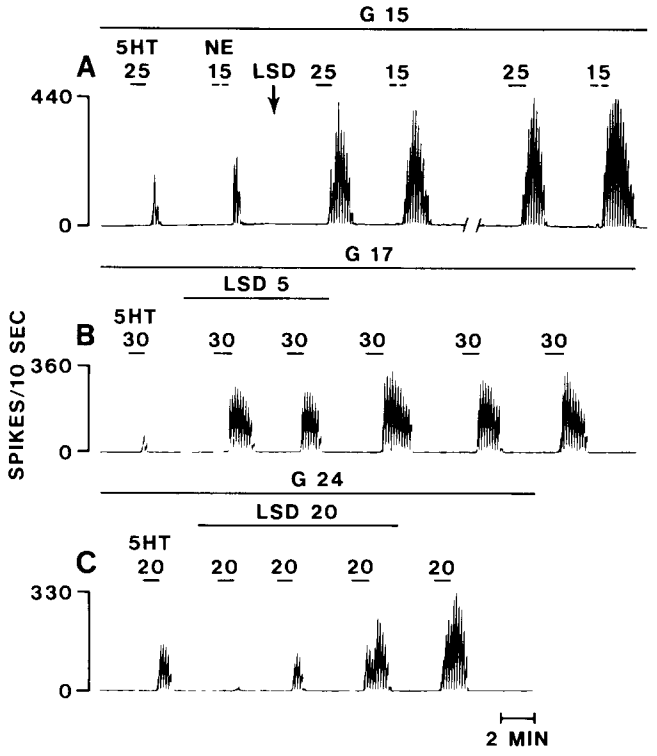

FIG 3 LSD potentiates the facilitating effect of iontophoretically applied 5-HT and NE on glutamate (G)-induced facial motoneuron excitation A Intravenous LSD (10 μg/kg) immediately enhances the response to 5-HT and NE, an effect lasting at least 4 hours (slashed baseline) B Iontophoretically applied LSD (5 nA) also enhances the effect of 5-HT C Higher ejecting currents of LSD (20 nA) temporarily depress the response to 5-HT

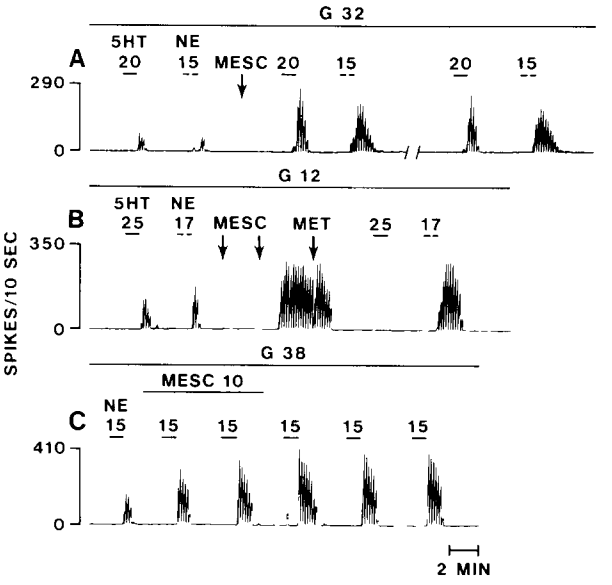

FIG 4 Mescaline potentiates the facilitating effect of iontophoretically applied 5-HT and NE on facial motoneurons A A low dose of mescaline (1 mg/kg, IV) enhances the effects of 5-HT and NE without directly activating the cell The action of mescaline lasts at least 2 hours B Metergoline (100 μg/kg, IV) blocks the enhancement of glutamate excitation which is produced by higher doses of mescaline (6 mg/kg, IV), metergoline also blocks 5-HT but the response to NE is enhanced C Iontophoretically applied mescaline (10 nA) potentiates the facilitating effect of NE on facial motoneurons

TABLE 1

INFLUENCE OF INTRAVENOUS HALLUCINOGENS AND NONHALLUCINOGENS ON THE FACILITATING EFFECT OF 5-HT AND NE ON FACIAL MOTONEURONS

Drug	Number of Animals*	Dose	% Control 5-HT	% Control NE
LSD	8	10 μg/kg	1026 ± 93†	976 ± 109†
Mescaline	6	1 mg/kg	763 ± 120†	913 ± 168†
Psilocin	5	1 mg/kg	497 ± 46†	491 ± 72†
DMT‡	5	1 mg/kg		469 ± 48
Lisuride	5	40 μg/kg	102 ± 4	102 ± 2
Methysergide	5	1 mg/kg	0	98 ± 6

*One neuron was tested per animal
†$p<0.02$, Student's t-test
‡Animals were pretreated with metergoline (100 μg/kg, IV)

cial motoneuron excitation by 5-HT (Fig 3B) Higher ejecting currents of LSD (15–40 nA) produced a transient block of the effect to 5-HT which was followed by an enhanced response (Fig 3C) The most remarkable feature of LSD's effect was that even a brief exposure of the hallucinogen sensitized responses to 5-HT and NE for several hours (Fig 3A)

Low doses of mescaline (0 5–1 0 mg/kg, IV) also potentiated the effect of 5-HT and NE, but did not alter the glutamate-induced excitation of facial motoneurons Again, the potentiating effects of mescaline lasted several hours (Fig 4A) Higher doses of mescaline (6–10 mg/kg, IV) acted directly to facilitate the glutamate-induced excitation of facial motoneurons This effect was blocked by the 5-HT antagonist metergoline, indicating that at high doses mes-

caline acts as a 5-HT agonist in the facial nucleus (Fig 4B) In animals pretreated with metergoline, iontophoretic mescaline potentiated the facilitating effect of NE (Fig 4C) Thus, the data in Figs 3 and 4 indicate that low doses of LSD and mescaline, in the absence of an effect of their own, markedly increase sensitivity to both 5-HT and NE in the facial nucleus

To determine if the sensitizing action of LSD and mescaline is specific for hallucinogens, the effects of two indoleamine hallucinogens, psilocin and DMT, and two nonhallucinogenic ergot derivatives, lisuride and methysergide, were studied Like LSD, psilocin (0 5–2 0 mg/kg, IV) markedly potentiated the effect of 5-HT and NE on motoneurons but had no direct action when given alone (Table 1) In contrast, DMT (0 5–2 0 mg/kg, IV) facilitated the glutamate-induced excitation of motoneurons by itself This effect was blocked by metergoline DMT was unlike mescaline in that a 5-HT sensitizing action could not be differentiated even at low doses from the 5-HT agonist activity Nevertheless, in animals pretreated with metergoline, DMT (like mescaline) potentiated the facilitating effect of NE (Table 1) Thus, it appears that the ability to potentiate the facilitating effect of 5-HT and NE may be common to all of the psychedelic hallucinogens Importantly, the nonhallucinogens lisuride and methysergide failed to potentiate the facilitating effects of 5-HT and NE (Table 1)

The hallucinogens appear to potentiate the effects of monoamines on facial motoneurons by increasing the sensitivity of 5-HT and NE receptors [24] The mechanism by which hallucinogens sensitize 5-HT and NE receptors is not known However, the fact that LSD and 5-HT appear to bind to different 5-HT receptor sites [10] suggests the possibility that drug induced changes in receptor sensitivity could occur through interactions between 5-HT and LSD binding sites In any case, a sensitization of 5-HT and NE receptors located on motoneurons [23,31] likely accounts for the enhancement of spinal reflexes produced by hallucinogens [8,21] If the sensitizing effects of hallucinogens described above occurs in sensory pathways in the central nervous system, then a mechanism of receptor sensitization, in distinction to disinhibition, might account for the altered perceptual reactivity produced by these drugs Support for a receptor sensitizing effect of hallucinogens stems from the fact that indoleamine and phenethylamine hallucinogens act in a similar fashion in the facial nucleus, while lisuride has no effect Furthermore, the time course of the LSD enhanced effects of 5-HT and NE in the facial nucleus parallels the prolonged behavioral effects of this drug in the free moving cat [29] These observations raise the interesting possibility that relatively long-term changes in the sensitivity of noradrenergic and/or serotonergic receptors may be involved in the psychedelic actions of hallucinogens

REFERENCES

1 Aghajanian, G K LSD and 2-Bromo-LSD Comparison of effects on serotonergic neurones and on neurones in two serotonergic projections areas, the ventral lateral geniculate and amygdala *Neuropharmacology* **15**, 521–528, 1976

2 Aghajanian, G K , W E Foote and M H Sheard Lysergic acid diethylamide Sensitive neuronal units in the midbrain raphe *Science* **161** 706–708, 1968

3 Aghajanian, G K , W E Foote and M H Sheard Action of psychotogenic drugs on midbrain raphe neurons *J Pharmacol Exp Ther* **171**· 178–187, 1970

4 Aghajanian, G K and H J Haigler Hallucinogenic indoleamines Preferential action upon presynaptic serotonin receptors *Psychopharmacol Commun* **1**: 619–629, 1975

5 Aghajanian, G K and R B McCall Serotonergic synaptic input to facial motoneurons Localization by electromicroscopic autoradiography *Neuroscience* **5**· 2155–2162, 1980

6 Aghajanian, G K , J A Rosecrans and M H Sheard Serotonin Release in the forebrain by stimulation of midbrain raphe *Science* **156**, 402–403, 1967

7 Aghajanian, G K and R Y Wang Physiology and pharmacology of central serotonergic neurons In *Psychopharmacology A Generation of Progress* edited by M A Lipton A DiMascio and K F Killam New York Raven Press, 1978, pp 171–183

8 Andén, N E , H Corrodi, K Fuxe and H T Hokfe Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide *Br J Pharmacol Chemother* **34** 1–7 1968

9 Appel, J B and D X Freedman Tolerance and crosstolerance among psychotomimetic drugs *Psychopharmacologia* **13**: 267–274, 1968

10 Bennett, J P and S H Snyder Serotonin and lysergic acid diethylamide binding in rat brain membranes Relationship to postsynaptic serotonin receptors *Mol Pharmacol* **12** 373–389, 1976

11 Dahlstrom, A and K Fuxe Evidence for the existence of monoamine-containing neurons in the central nervous system I Demonstration of monoamines in the cell bodies of brainstem neurons *Acta Physiol Scand [Suppl]* **232**: 1–55, 1964

12 De Montigny, C and G K Aghajanian Preferential action of 5-methoxytryptamine and 5-methoxydimethyltryptamine on presynaptic serotonin receptors A comparative iontophoretic study with LSD and serotonin *Neuropharmacology* **16**· 811–818, 1977

13 Fuxe, K Evidence for the existence of monoamine-containing neurons in the central nervous system IV The distribution of monoamine terminals in the central nervous system *Acta Physiol Scand [Suppl]* **247**: 37–85, 1965

14 Gaddum, J H Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine *J Physiol* **121**, 15, 1953

15 Guilbaud, G , J M Besson, J L Oliveras and J C Liebeskind Suppression by LSD of the inhibitory effect exerted by dorsal raphe stimulation on certain spinal cord interneurons in the cat *Brain Res* **61** 417–422, 1973

16 Haigler, H J and G K Aghajanian Mescaline and LSD Direct and indirect effects on serotonin-containing neurons in brain *Eur J Pharmacol* **21**: 53–60, 1973

17 Haigler, H J and G K Aghajanian Lysergic acid diethylamide and serotonin A comparison of effects on serotonergic neurons and neurons receiving a serotonergic input *J Pharmacol Exp Ther* **188** 688–699, 1974

18 Horn, G and J M McKay Effects of lysergic acid diethylamide on the spontaneous activity and visual receptive fields of cells in the lateral geniculate nucleus of the cat *Exp Brain Res* **17**· 271–284, 1973

19 Jacobs, B L , M E Trulson and W C Stern An animal behavioral model for studying the actions of LSD and related hallucinogens *Science* **194**· 741–743 1976

20 Laurent, J P and L Pieri Lisuride and LSD decrease spontaneous firing of neurons in the raphe *Experientia* **34**· 926, 1978

21 Maj, J , W Palider and A Rawlow The influence of mescaline on the flexor reflex of the hindlimb of the spinal rat *J Pharm Pharmacol* **29**· 177–178, 1977

22 McCall, R B Neurophysiological effects of hallucinogens on serotonergic neuronal systems *Neurosci Biobehav Rev* **6** 509–514, 1982

23 McCall, R B and G K Aghajanian Serotonergic facilitation of facial motoneuron excitation *Brain Res* **169**: 11–27, 1979
24 McCall, R B and G K Aghajanian Hallucinogens potentiate responses to serotonin and norepinephrine in the facial motor nucleus *Life Sci* **26**: 1149–1156, 1980
25 McCall, R B and G K Aghajanian Pharmacological characterization of serotonin receptors in the facial motor nucleus A microiontophoretic study *Eur J Pharmacol* **65**: 175–183, 1980
26 Mosko, S S and B L Jacobs Electrophysiological evidence against negative neuronal feedback from the forebrain controlling midbrain raphe unit activity *Brain Res* **119** 291–303, 1977
27 Mouriz-Garcia, A , R Schmidt and A Arlazoroff Effects of LSD on the spontaneous and evoked activity of retinal and geniculate ganglion cells *Psychopharmacologia* **15**: 382–391, 1969
28 Rogawski, M A and G K Aghajanian Response of central monoaminergic neurons to lisuride Comparison with LSD *Life Sci* **24**. 1289–1298 1979
29 Trulson, M E and B L Jacobs Dissociations between the effects of LSD on behavior and raphe unit activity in freely moving cats *Science* **205**: 515–518, 1979
30 Trulson, M E , C A Ross and B L Jacobs Lack of tolerance to the depression of raphe unit activity by lysergic acid diethylamide *Neuropharmacology* **16**: 771–774, 1977
31 White, S R and R S Neuman Facilitation of spinal motoneuron excitability by 5-hydroxytryptamine and norepinephrine *Brain Res* **188** 119–127, 1980
32 Winters J C Tolerance to a behavioral effect of lysergic acid diethylamide and cross-tolerance to mescaline in the rat Absence of a metabolic component *J Pharmacol Exp Ther* **178**: 625–630 1971
33 Wolbach, A B , E J Miner and H Isbell Comparison of psilocin and psilocybin, mescaline, and LSD-25 *Psychopharmacologia* **3**: 219–223, 1962
34 Wooley, D W and E Shaw A biochemical and pharmacological suggestion about certain mental disorders *Proc Natl Acad Sci USA* **40** 228–231, 1954