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The Major Hallucinogens and the Central Cytoskeleton: An Association Beyond Coincidence? Towards Sub-cellular Mechanisms in Schizophrenia

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Summary — There appears to be a remarkably consistent structural and functional relationship between the phenylethylamine hallucinogens and the microtubule inhibitor colchicine. Such a relationship is not sustained in simple form through to the indoleamine hallucinogens and the indole based Vinca alkaloids. However, LSD and the more potent hallucinogens retain the full potential to disrupt the structure of the brain's cytoskeleton indirectly via serotonin and the raphe system. Serotonin appears to have a direct role in regulating and maintaining microtubules and microfilaments. It appears that a second receptor mediated action is required for full hallucinogenic activity.

It is deduced that cytoskeletal restraints may have a role in governing central information processing. A theory for the cellular mechanisms of thought disorder and drug induced hallucinations is proposed. Schizophrenia may reflect a subtle disorder of central cytoskeletal function.

Introduction

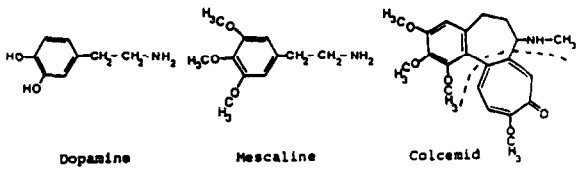
The mode of action of the indoleamine and phenylethylamine hallucinogens has not yet yielded to experimental enquiry. Two dimensions appear to be involved; an increased arousal and disruption of central information processing (1). This paper explores the possibility that aspects of the filtering mechanism might have some structural expression at the cellular level.

The cytoskeleton, a complex dynamic framework of contractile and scaffolding proteins, providing organisation, motility and boundaries to the cell, occupies a strategic position conceivably capable of mediating aspects of such a role. De Brabander et al (2) have argued that microtubules have a primary signal transducing role potentially as relevant as their skeletal functions. Tubulin, a major post-synaptic protein (3), is apparently involved in the maturation and stabilisation of newly formed synapses (4). This predicts that there should be a consistent structural and functional relationship be-

tween major hallucinogens and cytoskeletal proteins or drugs acting on the cytoskeleton.

The phenylethylamines

Such a relationship is most clearly expressed in the case of mescaline and the classical microtubule (m.t.) inhibitor colchicine. There is an obvious structural homology between these two molecules even more transparent in the case of colcemid a potent m.t. inhibitor (5).



Colchicine appears to be a tropolone derivative of mescaline, itself a methoxylated derivative of the neurotransmitter dopamine (5). Mescaline, like colchicine, inhibits fast axon transport (6, 7) and is almost as potent and a less toxic inhibitor than colchicine (5). Harrison et al (5) noted that mescaline acts as a mitosis inhibitor and binds to tubulin, inhibiting its assembly.

Other mescaline derivatives exhibit anti-microtubular activity; indeed the hallucinogenic potency of these substances ranks in the same order as their effectiveness as anti-transport agents (7) (8). A perfectly linear relationship was not found (8). Simple m.t. inhibitors are apparently not generally hallucinogenic. It rapidly becomes clear that a second essential action would appear to be required to elicit full psychotomimetic effects. The dose of mescaline required (typically 500 mgs) would appear adequate when compared to the milligram doses of colchicine used in the treatment of gout (9). In spite of demonstrating that both 5-hydroxy and 5-methoxy derivatives of N,N-dimethyltryptamine, harmaline and 6-methoxy harmaline are all potent m.t. inhibitors, Paulson et al concluded that inhibition of axo-plasmic transport is not correlated with hallucinogenesis. They felt that the previously reported good correlation (7) was coincidental and that inhibition of axon transport is not a property of all the hallucinogens (8). This view was based on the lack of a perfectly linear relationship between anti-transport activity and hallucinogenic potency and the fact that although (−) and (+) enantiomers of 1-(2,5-dimethoxy-4-methyl(phenyl)-2-aminopropane (DOM) are potent inhibitors (−>+), only the (−) enantiomer appears to be active as an hallucinogen; they noted the apparent lack of activity in their system of LSD and N,N-dimethyltryptamine (8). These arguments, whilst they might apply to a one dimensional 'axon transport' model are not valid reasons for rejecting the general proposal. Paulson and McClure assumed that only a single action is required for hallucinogenic effects and that the agent necessarily acts directly. The enormous potency of LSD makes it intrinsically unlikely that it would have a direct effect on the cytoskeleton. If it were to act directly it would need to be an impossibly efficient inhibitor. DOM is the most potent member of its series and in some systems (but admittedly not all) (10) appears to act indirectly via 5HT and the raphe system (11). The relatively inactive enatiomer of DOM may lack a second essential action, either in acting at the raphe or post-synaptically.

There is a strong tradition of evidence that LSD and the indole hallucinogens function at least in part indirectly via 5-hydroxytryptamine (5HT) and the raphe system (11, 12, 13, 14). $5HT_2$ receptors appear to mediate the excitatory effects on arousal of these compounds (15). Yet the existence of cross tolerance between the phenylethylamines and indoleamines and the fundamental similarity of their effects strongly supports a shared mechanism of action.

The indoleamines and the problem of lisuride

LSD and the other indoleamines exert a powerfully selective inhibitory effect on the raphe system (12) abolishing the tonic release of 5HT onto post-synaptic neurones allowing them to escape from its inhibitory effects (12, 13). LSD in this respect acts as an indirect 5HT antagonist but also has a wide range of complex post-synaptic effects. It has long been clear that inhibition of raphe firing is not a sufficient explanation for LSD's psychotomimetic effects (16a). This is clear in the case of lisuride which is more potent than LSD on the raphe but not hallucinogenic in man (14). Again, it appears that other post-synaptic actions, e.g. on glutamate or $5HT_2$ receptors (15) (17) may be involved. This does not detract from the fact that a marked decrease of serotonin release occurs with inhibition of the raphe system and that depletion of 5HT potentiates LSD's effects (13).

Serotonin and the cytoskeleton

There is a large body of evidence that serotonin has a regulatory action on the cytoskeleton. Quay (19) concluded that serotonin was functionally associated with microtubular mechanisms and that these might be more relevant to its mode of action than the usual concepts. This suggestion has received experimental support (20). There is a powerful tendency for chemical messengers to preserve their primitive phylogenetic functions (21). 5HT is strongly associated with cell motility in a wide range of systems, stimulating neuron and glial cell movement and axon transport (22, 24, 25, 26). Woolly and Shaw (23) related this to hallucinogenesis. Serotonin exerts decisive effects on gastrulation, morphogenesis and neurulation (24, 26), processes which reflect cytoskeletal activity (27). Melatonin, N-acetyl-5-methoxytryptamine has direct pharmacological effects on tubulin (28). 5HT stimulates movement (29) and regeneration of cilia (30) which are m.t. dependent processes, mediated, at least in part, by Camp and Calcium (30). Inhibition of ciliary regeneration is characteristic of m.t. inhibitors (31). Pargyline, a non-hydrazine monoamine oxidase inhibitor induces ciliogenesis in normally unciliated adult cat brain cells, possibly mediated via 5HT (32). Emanuelsson (26) has demonstrated a direct consistent humoral association between microfilaments and 5HT released from the yolk granules of Polychaete embryos. Emanuelsson (26) suggested that 5HT's most important function may be to act on and stimulate microfilaments. Buznikov et al (33) noted that sea urchin eggs treated with 5HT antagonists during cleaveage became multi-nuclear, an effect typical of the microflament inhibitor cytochalasin B. The Vinca alkaloids, which are interesting in that vincristine has been reported to occasionally cause hallucinations (34) inhibit binding of 5HT to a high affinity Serotonin Binding Protein (S.B.P) which occurs via a sulphydryl group (35). S.B.P. is an actin like protein concerned with storage and transport of 5HT (16) (35, 36). Serotonin binds to the microfilament protein subunit actin and with even higher affinity to polymerized actin (37, 38).

The raphe neurones are amongst the first to differentiate during the development of the CNS (11). There is strong evidence that 5HT in particular orchestrates embryogenesis (24, 25, 26) actually 'moulding' the construction of its own circuitry. It seems not unreasonable that the raphe system should continue to regulate and maintain the cytoskeleton of its target cells. The mode of action of 5HT on the cytoskeleton is probably complex and likely to operate at different levels. 5HT appears to bind only very weekly to tubulin (35). Nevertheless the interaction is sufficiently real for it to stabilise tubulin-colchicine binding (see Fig. 2 in (39)), a process which seems to reflect on the configuration of tubulin sulphydryl-disulphide bonds (40) and suggests the involvement of microtubule associated proteins (41). The indole hallucinogens therefore have the potential to modulate the cytoskeleton of target cells indirectly by reducing the amount of 5HT released by the raphe system to a sub-critical level. Rapidly turning-over components would be the most sensitive. A large proportion of cytoskeletal proteins are already in the soluble phase (42, 43) so the change would be one of degree. The time course would reflect the different stability of the various components. The fact that psychotomimetic effects may outlast the inhibition of raphe firing (10, 11) would be explained by the time required for subunits to reassemble.

Structure-activity relationships

The structural requirements of the hallucinogens are not particularly strict (44, 45). A much better correlation is given by their pronounced electron donating properties (45), the indole, methoxy and hydroxy groups injecting electrons into the molecule (45). 5HT occupies a mid-range of electronic energy (45).

The remarkable and striking tendency for the whole range of both hallucinogens and microtubule inhibitors to possess numerous methoxy groups and/or indole rings suggests that the activity of microtubule inhibitors is also related to a common mode of action and ability to denote electrons. According to Deysson (46), colchicine interferes with m.t. assembly by blocking a stage in the hydrogen transport chain. However it does not react directly with SH groups (47). An aqueous extract of yeast totally prevents colchicine from inhibiting mitosis in plant cells (47), this protective action being due to nicotinamide and riboflavin. Nicotinamide alone is protective in higher doses (47). Deysson (47), suggests that the fixing of colchicine to tubulin modifies, via an allosteric action, the site where the hydrogen carrier should become at-

tached in order to permit the oxidation of the SH group required for the formation of normal tubulin dimers. This would still be possible in the presence of excess carrier (47). Given the electronic properties of the methoxy groups it seems more probable that the hinderance is an electronic one, the inhibitor generating a local electrostatic barrier which hinders intra-subunit interchange governing and allosteric change. In the case of 5HT, because of its intermediate energy level, such interchange might be facilitated. The indole based Vinca alkaloids, which bind tubulin at a different site to colchicine (34) are also sensitive to yeast extract which supports a similar mechanism (46). 5HT and other tryptophan derivatives are well known for their ability to form stable charge-transfer complexes with riboflavin and nicotinamide adenine dinucleotide (48, 49, 50). The structure of LSD, which according to Cerletti (51) represents a double molecule comprising a 5HT-like part jointed to a nicotinamide-like part, can then be seen to be mirroring such a mechanism in a remarkably vivid way. This juxtaposition can also be seen in the Harmala alkaloids and in vestigial form in dimethyltryptamine. The effects of LSD are partly antagonised by nicotinic acid or nicotinamide (52). This type of complex-formation could also conceivably operate at the raphe (or post-synaptic) 'LSD recognising site', integrating 5HT and nicotinamide-like activity. The psychoses related to nicotinamide deficiency may be relevant here. Adrenochrome, which like adrenolutin is a mitosis inhibitor (53, 54) and probably hallucinogenic (55), also complexes with nicotinamide and has an affinity for SH groups (56). The structure-activity relationship that emerges explains the transition from direct through mixed and indirectly acting and how mechanisms for control of polymerization may have been integrated.

Discussion

There appears to be a remarkably consistent and direct relationship between the phenylethylamine hallucinogens and tubulin. This relationship is more complex in the case of the indoleamine hallucinogens; these appear to have an equal potential to disrupt the central cytoskeleton indirectly via 5HT and the raphe system. Platelet derived 5HT maintains actin's support of microvascular integrity, (57, 58) apparently also involving $5HT_2$ mechanisms (57, 58). The evidence linking 5HT to the control of two major components of the cytoskeleton is particularly intriguing. It seems unlikely that a set of such clear associations would arise by chance or be devoid of biological significance. Consideration should be given to possible 'structural' effects of neurotransmitters. The correlations suggest that the major hallucinogens may disrupt the molecular organisation of cytoskeletal elements, and to use the term coined by Smythies (59) in a similar context, 'literally fragment the delicate neuronal fabric on which thought depends'. If disruption of the central cytoskeleton is necessary for psychotomimetic effects it cannot be a fully sufficient cause; a second action would still appear to be required to explain the activity of these compounds. This is no worse than the already existing objection that inhibition of raphe firing may be necessary but is not a sufficient explanation for LSD's effects (16a). Related to this is the issue of tolerance, and the inactivity of lisuride. Tolerance to LSD does not occur at the raphe (10), implying that it occurs at a post-synaptic site. Whilst it is possible that the cytoskeleton and the mechanisms controlling it may have some ability to reorganise, the implication has to be that the lesioning of the central cytoskeleton (which would still be predicted to occur with the non-hallucinogenic lisuride) would produce an unproductive, latent defect. There is evidence that tolerance to LSD is not complete in all respects (60). Possibly it is only when the system is put under load by the parallel throughput of electrical traffic that the defect can be manifested. The analogy of the effects of administering methylphenidate (61) to release productive symptoms in schizophrenics may be relevant. The hallucinatory activity of dreaming has been related by Hobson and McCarley (62) to a scanning of memory circuits related to brain stem electrical activity.

The $5HT_2$ effects on startle appear to be critical (15) but themselves appear related to the control of the cytoskeleton, (58) suggesting these actions may be linked.

On the mechanism of drug induced hallucinations

It may be premature to extend preliminary evidence of correlations of molecular structure to a general theory of drug induced hallucinations. However, a speculative broad framework can be developed from Crick's (63) reformulation of in-

formation storage and ultra-fast-memory — (thought) as being mediated via actin dependent shape changes in the dendritic spines, i.e. having a cytoskeletal basis. The post-synaptic cytoskeleton extends into the dendritic spine, acytoskeletal organelle — Siekevitz (64) considers there is overwhelming evidence that short term changes in synaptic conductance are reflected in synaptic structure.

Crick (63) attempting to define the site of the memory engram, discusses his hypothesis in static terms but this omits consideration of an equally important aspect of such a system when considered in its dynamic mode. Agents inducing activation or 'twitching' of the dendritic spines distributing a parallel throughput of electrical traffic, could generate the undulating 'stuff' ofillusions, hallucinations and perceptual disturbances. Changes in the proportions (63) due to contractions of the actin containing dendritic spines (eg. 65) would critically modulate the electrical cable properties (Hebbian weightings) of synapses thereby selecting a 'channel' of favoured cell to cell communication. This immediately suggests a role for the dendritic spine in determining the route of connectivity of neuronal connections. This would be at a stage initially preliminary to the fixing of more permanent synaptic structural changes required for the storage of the memory engram which may involve the post-synaptic density apparatus — a cytoskeletal organelle of as many as 30 proteins (64). Actin-induced shape changes might appear too rapid and labile to be a viable candidate for a long term memory store.

A distinction between a microfilamentous or microtubular site of action may be artificial. Once mechanical stability of proportions has been lost multiple and divergent 'channels' could easily arise, providing a simple model for thought disorder. A shift in proportions of dendritic spines (e.g. altered uniformity or a shift in size or speed of response) could have lasting effects on information processing. This could explain the long term effects, e.g. on visual processing (66, 67) or how thought disorder may persist after apparent recovery from psychosis. The model would account for the response complexity of thought disorder, due to an excess of 'scintillating' connections and negative symptoms due to a relative inability to activate appropriate synaptic connectivity. The actions of the hallucinogens could become permanently 'fixed' in the brain if closely related consolidating steps involved in memory storage, depending on the cell nucleus, become activated, consolidating structural synaptic changes (eg. 68, 85). Garcia Ramos (69, 70, 71) has produced direct evidence that mescaline acts at apical dendrites, and related this to the mechanism of memory. The existence of flashbacks and the large memory content of hallucinations (72), more or less requires some close tie up between the hallucinogens and the brain's memory system (73).

The general concept of a dynamic yet stable 'synaptic mechanical sub-matrix' biasing and switching the brain's more transient electrochemical traffic, possessing both long term and rapid plasticity, reflecting and containing the history of its owner, could form the more or less familiar biological substrate manifested at the psychological level as the ego boundary. Descriptions of the subjective effects of hallucinogens (16) emphasize the loss of boundaries and structure to thought and perception and stress themes of fragmentation or disintegration. The most economical explanation that becomes available may be the boldly literal, that these drugs loosen mechanical restraints that underlie these boundaries, governing the flow of impulses by a subtle 'focusing' effect, and that this cytoskeletal substrate may form the domain within which higher order concepts of the ego boundary and construct theory can be accommodated. Fischman (13) has discussed how serotoninergic outflow appears to be related to maintenance of the ego boundary.

Speculation on the nature of schizophrenia

The fact that the hallucinogens do not provide perhaps more than an overlapping model for schizophrenia (eg. 1, 13, 60) does not mean that a knowledge of the mode of action of these drugs could not provide highly relevant insights into the cellular mechanisms that govern thought and perception.

In Ciompi's view, (74) the symptom complex of the schizophrenias represents a process in which psychotic symptoms evolve out of a basic defect in information processing, due to an abnormally low 'channel capacity'. Extrapolation would suggest that the ability to channel information may in part depend on an efficient neuronal cytoskeleton. The complex nature of the cytoskeleton suggests vulnerability to viral, environmental and genetic factors (75).

The concept is not far removed from

Feinberg's (76) suggestion of a 'defective synaptic pruning' in schizophrenia. Feinberg does not approach the fundamental question of how information would be channelled, but stresses the important of a trophic factor for maintaining synaptic integrity (suggestive of the role postulated for 5HT in maintaining synaptic tone) and the likelihood of embryonic morphogenetic processes continuing to exert effects on information processing into maturity (76). Haracz (77, 78) attempting to integrate the many faces of schizophrenia has reviewed evidence for a 'nonspecific' defect of neuronal plasticity, not dissimilar to Conacher's (79) 'stuck synapse' concept. Haracz reviews the evidence for subtle structural deviations in schizophrenia and the potential for developmental and life experiences and various types of kindling processes to impose structural 'imprints', particularly on dendritic spine morphology. However there is evidence that the 'plasticity' of neurones is itself ultimately a product of the dynamic properties of the cytoskeleton (43) suggesting a sub-cellular lesion 'mid-way' between the biochemical and the structural levels.

Relationship to the dopamine hypothesis of schizophrenia

The Dopamine hypothesis demonstrates the extent to which insights can be gained from a comparison of molecular structures. The hypothesis presented is based on a comparable and complementary set of observations and could be viewed as an extension of the Dopamine hypothesis but extrapolated in an unfamiliar direction. Put crudely mescaline resembles a version of Dopamine with in-built (or enhanced) cytoskeletal activity. Dopamine leads to a localised significant decrease in the number of microtubules associated with pituitary secretory granules and this is supposed to account for its inhibition of prolactin secretion (80, 81). It is of particular interest that this D_2 receptor activity, which correlates well with neuroleptic action, should be mediated via microtubules, supporting the concept previously hinted at by the structure of Dopamine and mescaline for some antagonistic biological relationship between Dopamine and microtubules.

Kindling

A challenge is presented by the finding of a high incidence of psychoses indistinguishable from schizophrenia in patients with chronic temporal lobe epilepsy (TLE) (82). Lynch and Baudry, (83, 84, 85) in attempting to explain long term potentiation in the hippocampus, have suggested that repetitive stimulation results in long lasting morphological remodelling of synapses. There is a complementary argument about kindling — in which repeated sub-convulsive electrical stimuli lead to seizures. Kindling appears to induce phosphorylation of proteins, akin if not identical to those found in the post synaptic density concerned with its shape (64). In TLE a structural change in the dendritic spines might become manifest in the 'final kindled state', (64) potentially compromising the system's ability to channel information. This implies a distinctly different type of cytoskeletal lesion in paranoid schizophrenia (remodelling) to that proposed for the major hallucinogens (disintegration).

Experimental suggestions

Space permits only a brief discussion of a complex issue. Approaches might include examining the effects of hallucinogens on directly visualised animal brain cytoskeletons using fluorescent antibody techniques, the co-administration of M.T. and/or microfilament inhibitors and $5HT_2$ agonists. Examination of the fate of labelled amphetamine derivatives in primate models of amphetamine psychosis, looking for tubulin binding, would address itself more directly to schizophrenia. Agents capable of stabilising microtubules such as a heavy water and strains of rats with genetically different level of brain tubulin and the possible effects of LSD on mescaline tubulin binding would represent additional approaches. The hypothesis could be disproved by the demonstration of a non-raphe hallucinogen with cross-tolerance to mescaline but with no effect on the cytoskeleton. Analysis of comparative dendritic spine morphology in suitably fixed and stained schizophrenic brain tissue should receive attention.

Conclusion

The highly organised nature of the brain indicates the importance of structure in predetermining information traffic. The argument presented is essentially simple; that maintenance of correct dynamic structural integrity remains crucial to proper processing and ordering of impulse traffic down to a rather fine

level of discrimination, indeed that this occurs down to a subcellular level of structural organisation, the neuronal cytoskeleton. The recruitment of subcellular structural features would maximise the information processing (switching) power available and enable this to be integrated with processes mediating storage.

Direct support for this is provided by the structure of the major hallucinogens which are considered to disrupt constraints on central information processing. Evidence is reviewed that these drugs have a clear potential to disrupt the structure of the central cytoskeleton, although this would appear to be not sufficient to fully explain their activity. $5HT_2$ receptor mediated effects themselves apparently also related to the control of cytoskeletal activity appear to be involved. A second line of argument is based on the idea of the memory engram having a structural basis, centred around the dendritic spine and post-synaptic density (a cytoskeletal 'organelle').

The contraction of actin containing spines would alter short term weightings and connectivities of synapses, sometimes supplemented by longer term structural changes representing the memory engram. In the course of deposition and retrieval of memory traces, common steps of processing are likely. The memory engram may represent a fossil of the final stages of earlier processing, implying a role for actin in the dendritic spine and the post-synaptic density apparatus in channelling information. Actin induced shape changes, critically influencing the connectivity of neuronal networks, might simplify the apparent complexity required for thought, memory and perception. The possibility that schizophrenia may reflect a subtle disorder of cytoskeleton mediated neuronal connectivity would appear worthy of investigation.

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References

1. Claridge G. Animal models of schizophrenia; the case for LSD-25. Schiz. Bull., 4, 186–209 (1978)
2. De Brabander M. Microtubules in mammalian cell shape and surface modulation; an alternative hypothesis. Cell Biology Int. Reports, 1, 453–461 (1977)
3. Westrum L. E., Gray E. G. Microtubules and membrane specialisations. Brain Res., 105, 547–550 (1976)
4. Cronly-Dillon J., Percy G. W. Effect of visual experience of tubulin synthesis during a critical period of visual cortex development in the hooded rat. J. of Physiology, 293, 469–484 (1979).
5. Harrisson C. M. H., Page B. M., Keir H. M. Mescaline as a mitotic spindle inhibitor. Nature, 260, 138–139 (1976).
6. Paulson J. C. McClure W. O. Inhibition of axoplasmic transport by mescaline and other trimethoxyphenylalkylamines. Mol. Phar., 9, 41–50 (1973)
7. Paulson J. C., McClure W. O. Microtubules and axoplasmic transport. Brain Res., 73, 333–337 (1974a)
8. Paulson J.C., McClure W. O. The lack of correlation between hallucinogenesis and inhibition of axoplasmic transport. Mol. Phar., 10, 419–424 (1974b)
9. British National Fomulary, p. 311 No. 7 (1984)
10. Trulson M. E., Heym J., Jacobs B. L. Dissociations between the effects of hallucinogenic drugs on behaviour and raphe unit activity on freely moving cats. Brain Res. 215, 275–293 (1981)
11. Jacobs B. L., Trulson M. E. Mechanisms of action of LSD. Amer. Scient. 67, 396–404 (1979)
12. Haigler H. J., Aghajanian G. K. Serotonin receptors in the brain. Fed. Proc., 36, 2159–2164 (1977).
13. Fischman L. G. Dreams, Hallucinogenic Drug States, and Schizophrenia: a Psychological and Biological Comparison. Schiz. Bull., 9, 73–94 (1983).
14. White F. J., Appel J. B. LSD and Lisuride; Differentiation of their neuropharmacological actions. Science., 216, 535–537 (1982)
15. Davis M. Mescaline: excitatory effects on acoustic startle are blocked by serotonin antagonists. Psychopharm. 93, 286–291 (1987)
16. Freedman D. X. The psychopharmacology of hallucinogenic agents. Ann. Rev. Med., 20, 409–417 (1969)

16a. Freedman D. X. Mode of action of hallucinogenic drugs. In Handbook of Biological Psychiatry, part IV. van Praag H. M. et al (Eds) Marcel Dekker N.Y., p. 859–884 (1981)

17. McCall R. B., Aghajanian G. K. Hallucinogens potentiate response to derotonin and norepinephrine in the facial motor nucleus. Life Sciences, 28, 1149–56 (1980)
18. McCall R. B. Neurophysiological effects of hallucinogens on serotinergic neuronal systems. Neurosc. Biobehav. Rev., 6, 509–514 (1982)
19. Quay W. B. Comparative physiology of serotonin and melatonin. Advances in Pharmacology, 6A, 283–297 (1986)
20. Emanuelsson H., Palen K. Effects of L-Trytophan on morphogenesis and growth in the early chick blastoderm. W. Roux's Arch., 177, 1–17 (1975)
21. Roth J., Le Roith D., Shiloach J., Rosenzweig J. L., Lisnak M. A., Hanranhova J. The evolutionary origins of hormones. New Eng. J. Med., 306, 523–527 (1982)
22. Geiger R. S. Effect of catecholamines, serotonin and serum from schizophrenics on adult mammalian cortical brain tissue in culture. In Serological Func. in Schiz. Heath R. G. (Ed.), Harper and Row, 159–183 (1963)
23. Woolly D. W., Shaw E. Serotonin in mental processes. Ann. N.Y. Acad. Sci., 66, 649–66 (1956)
24. Gustafson T. Effect of drugs on morphogenetic movements in the sea urchin. In Ciba Foun. Symp., 14, 271–285 (1973)
25. Lauder J. M., Wallace J. A., Krebs H. Roles for serotonin in neuro-embryogenesis. Advances in Exp. Med. and Biology, 133, 477–506 (1979)

26. Emanuelsson H. Localisation of serotonin in cleavage embryos of Ophryotrocha Labronica le Greca and Baccit. W. Roux's Arch., 175, 253–275 (1974)
27. Kafunkel P. The activity of microtubules and microfilaments during neurolation in Xenopus. J. Cell Biology, 47, 102a–103a (1970)
28. Piezzi R. S., Cavicchia J. C. Effects of cold and melatonin on the microtubules of the toad sciatic nerve. Anatom. Rec., 200, 115–120 (1981)
29. Gosselin R. E. Cilioexcitatory activity of serotonin. J. Cell. and Comp. Phys., 58, 17–25 (1961)
30. Rodriguez N., Renaud F. L. On the possible role of serotonin in the regulation of regeneration of cilia. J. Cell Biology, 85, 242–247 (1980)
31. Margulis L. Assay For antitubulin drugs in live cells. Oral regeneration in Stentor Coerleus in Microtubules and Microtubule and Microtubules inhibitors. Borgers M., de Brabander M. (Eds.) Elsevier, pp. 453–470 (1975)
32. Milhaud M., Pappasg. D. Cilia formation in the adult cat brain after pargyline treatment. J. Cell Biology, 37, 599–609 (1968)
33. Buznikov G. A., Kost A. N., Kucherova N. F., Mndzhoya A. L., Suvorov N. N., Berdysheya L. V. The role of neurohumours in early embryogenesis. J. Embryology and Exp. Morphology 23, 549–569 (1970)
34. Calabresi P., Parks R. E. Alkylating agents, antimetabolites and other antiproliferative agents III. Vica alkaloids. Ch. 62 in Pharm. basis of Therapeutics. Goodman L. S., Gilman A. (Eds.) 5th ed. Macmillan pp. 1284–86 (1975)
35. Tamir H., Rapport M. M. Effects of neurotoxins in-vitro on the binding of serotonin to serotonin binding protein. Ann. N.Y Acad. Sci., 305, 85–95 (1978)
36. Small D. M., Wurtman R. J. Serotonin binds specifically and saturably to an actin-like protein from rat brain synaptosomes. Proc. N.Y. Acad., Sci. (USA) 81, 959–9631 (1984)
37. Small D. K., Wurtman R. J. Association of serotonin, dopamine or noradrenaline with an actin-like component in pheochromocytoma (PC_{12}) cells. J. Neurochemistry 45(3) (1985a)
38. Small D. K., Wurtman R. J. Binding of serotonin to skeletal muscle actin. J. Neurochemistry, 45(3), 819–24 (1986)
39. Tan L. P., Lagnado J. R. Effects of indole alkaloids and related compounds on the properties of brain microtubular protein. Bio. Soc. Trans., 3, 121–124 (1975)
40. Gillespie E. The mechanisms of breakdown of tubulin in vitro. FEBS Letters, 58, 119–121 (1975)
41. Wiche G., Furthner R. Microtubule association proteins stabilise the colchinine binding activity of tubulin. FEBS Letters, 116, 247–250 (1980)
42. Williams R. C. Jr., Caplow M., McIntosh J. R. Dynamic microtubule dynamics. Nature 324, 106–7 (1986)
43. Lasek R. J., Morris J. R. The microtubule — microfilament network: The balance between plasticity and stability in the nervous system. pp. 329–342 Ch. 30 in Biological Functions of Microtubular and related structures. Ed. H. Sakai, Ac. Press, Tokyo (1982)
44. Kang S., Green J. P. Steric and electronic relationships among some hallucinogenic compunds. Proc. N.A.S (USA) 67, 62–67 (1970)
45. Synder S. H., Merril C. R. A relationship between the hallucinogenic activity of drugs and their electronic configuration. Proc. of N.A.S (USA) 54, 258–265 (1965)
46. Deysson G. Antimitotic substances. Int. Rev. of Cytology, 24, 99–148 (1968)
47. Deysson G. In Microtubules and Microtubule Inhibitors. Borgers M., de Brabander M., (Eds.) Elsevier, pp. 427–452 (1975)
48. Alivasatos S. G. A., Ungar F., Jibril A., Mourkides G. A. Non-enzymatic reactions of indoles with pyridine co-enzymes. Biochimica. et Biophysica. Acta., 51, 361–372 (1961)
49. Isenberg I., Szent-Gyorgyi A. Free radical formation in riboflavin complexes. Proc. N.A.S (USA), 44, 857–862 (1958)
50. Karreman G., Isenberg I, Szent-Gyorgi A. On the mechanism of action of chlorpromazine. Science 130, 1191–1192 (1959)
51. Cerletti. Quoted in Biological Psychiatry. A Review of Recent Advances. Smythies J. R., Coppen A., Kreitman N. (Eds.) Heinemann, London pp. 28 (1968)
52. Goldstein J. A. Niacin and acute psychedelic psychoses. Biological Psychiatry 19(1), 272–273 (1984)
53. Lettre H. Cytochemical studies of cell behaviour — a review. Cancer Res., 12, 847–860 (1952)
54. Dustin P. New aspects of the pharmacology of antimitotic agents. Pharm. Rev., 15, 449-480 (1963)
55. Hoffer A., Osmond H, Smythies J. Schizophrenia; a new approach. J. Mental Science 100, 29–45 (1954)
56. Peacock R. A., Powell W. .S. Adrenochrome and related compounds. Prog. in Med. Chem.. 9, 275–339 (1973)
57. Alexander J. S., Kechtman H. B., Shepro O. Serotonin induced actin bovine polymerisational association with cytoskeletal elements in cultured aortic endothelium. Biochem. Biophys. Res. Comm., 143, 152–158 (1987)
58. Shepro O., Welles S. L., Kechtman H. B. Vasoactive agonists prevent erythrocyte extravasation in thrombocytopenic hamsters. Thrombosis Res., 35, 421–430 (1984)
59. Smythies J. R. Neuroanatomy in relation to Psychiatry. Ch. 14. In Companion to Psychiatric Studies. Vol. 1 Forrest A. (Ed.) Churchill, pp. 309 (1973)
60. Braff D. L., Geyer M. A. Acute and chronic LSD effects on rat startle: data supporting an LSD-rat model of schizophrenia. Biological Psychiatry 15, 909–916 (1980)
61. Davis J. M. A two factor theory of schizophrenia. J. Psy. Res., 11, 25–29 (1974)
62. Hobson J. A., McCarley R. W. The brain as a dream state generator – an activation — synthesis hypothesis of the dream process. Amer. J. Psych., 134, 1235–1348 (1977)
63. Crick F. Do dendritic spines twitch? Trends in Neurosciences, 5, 44–46 (1982)
64. Siekevitz P. The postsynaptic density: a possible role in long lasting effects in the central nervous system. Proc. N.A.S. (USA) 82, 3494–98 (1985)
65. Mattus A., Ackermann M., Pehling G., Byers H. R., Fuziwara K. High actin concentrations in brain dendritic spines and post synaptic densities. Proc. NAS (USA) 79, 7590–7594 (1982)
66. Abraham H. D. A chronic impairment of colour vision in users of LSD. B.J. Psych., 140, 518–520 (1981)
67. Abraham H. D. Visual phenomenology of LSD flashback. Arch. Gen. Psych., 40, 884–889 (1983)
68. Goelet P., Castellucci V. F., Schachers, Kandel E. R. The long and the short of long-term memory – a molecular framework. Nature 322, 419–422 (1986)

69. Garcia Ramos J. Some properties of cortical dendrites as revealed by the effects of mescaline. Acta. Physiologica Lationo Americana 21, 112–120 (1971)
70. Garcia Ramos J. Studies on the mechanism of learning. I. Mescaline and the catecholamine hypothesis. Acta. Physiologica Latino Americana, 23, 94–104 (1973)
71. Garcia Ramos J. The mescaline or strychnine spikes as a tool for physiological and pharmacological studies. Acta. Physiologica. Latino Americano, 27, 16–30 (1977)
72. Asaad G., Shapiro B. Hallucinations: Theoretical and Clinical Overview. Am. J. Psych., 143, 1088–97
73. McGee R. Flashbacks and memory phenomena. A comment on "flashback phenomena — clinical and diagnostic dilemmas". The J. Nervous and Mental Disease, 172, 272–278
74. Ciompi L. Is there really a schizophrenia? The long term course of psychiatric phenomena. B.J. Psych., 145, 636–640 (1984)
75. Cook R. H., Ward B. E., Austin J. H. Familian Alzheimer Disease. Neurology 29, 1402–1412 (1979)
76. Feinberg I. Schizophrenia: caused by a fault in programme synaptic elimination during adolescence? J. Psych. Res. 17, 319–334
77. Haracz J. L. A neuronal plasticity hypothesis of schizophrenia. Neurosci. Beh. Rev., 8, 55–71 (1984)
78. Haracz J. L. Neural plasticity in schizophrenia. Schiz. Bull., 11, 191–229 (1985)
79. Conacher G. N. The "stuck synapse" as a model for schizophrenia. B.J. Psych., 146, 672 (1985)
80. Warchol J., Warchol T. The influence of dopamine on prolactin cells. Acta. Medica Polona 20, 467–468 (1979)
81. Ravindra R., Grosvenor C. E. Microtubules are mobilised in the lactating rat anterior pituitary gland during suckling. End., 118, 1194–1199 (1986)
82. Slater E., Beard A. W. The schizophrenia — like psychosis of epilepsy. I. Psychiatric Aspects. B.J. Psych., 109, 95–150 (1963)
83. Lynch G., Baudry M. The biochemistry of memory: A new and specific hypothesis. Science 224, 1057–1063 (1984)
84. Burns N. R. Skeleton key to memory. News and Views. Nature 313, 178–179 (1985)
85. Fagg G. E. et al. Excitatory amino acid symptom mechanisms and neurological functions. Trends in Pharm. Sci., 7(9), 357–363 (1986)