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INTERACTIONS BETWEEN MONOAMINES, GLUTAMATE, AND GABA IN SCHIZOPHRENIA: New Evidence

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■ **Abstract** In spite of its proven heuristic value, the dopamine hypothesis of schizophrenia is now yielding to a multifactorial view, in which the other monoamines as well as glutamate and GABA are included, with a focus on neurotransmitter interactions in complex neurocircuits. The primary lesion(s) in schizophrenia does not necessarily involve any of these neurotransmitters directly but could deal with a more general defect, such as a faulty connectivity of developmental origin. Nevertheless, a precise identification of neurotransmitter aberrations in schizophrenia will probably provide clues for a better understanding of the disease and for the development of new treatment and prevention strategies.

INTRODUCTION

The dopamine hypothesis of schizophrenia has guided schizophrenia research for several decades and has clearly proven its heuristic value. However, despite emerging direct evidence supporting a dopaminergic dysfunction in schizophrenia, this hypothesis is now yielding to a multifactorial view, in which the other monoamines as well as glutamate and GABA are joining up. Research in this area tends to focus on neurotransmitter interactions in complex neurocircuits. The primary lesion(s) in schizophrenia may not even involve any of these neurotransmitters directly but could deal, for example, with a more general defect in connectivity, perhaps of developmental origin (1). Nevertheless, the identification of neurotransmitter aberrations in schizophrenia, now underway, is likely to bring clues for understanding the fundamental nature of the disease as well as for the development of new treatment and prevention strategies.

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This review starts out with the present state of dopamine research in schizophrenia. It then brings in the evidence for a role of glutamate in this disease and discusses the possibility of changes in one neurotransmitter being primary or secondary to those occurring in another. In this context serotonin and noradrenaline must also be considered. The review largely focuses on pharmacological evidence and discusses the two animal models that currently seem to be the most relevant, that is the hyperdopaminergia and the hypoglutamatergia models. Postmortem and imaging data are referred to only briefly, although much fascinating work is ongoing in this area. The integration of such data with the pharmacological evidence may well turn out to point to important directions for future research but will have to be left out of this review, because of space limitations.

DOPAMINE: Still a Cornerstone

In recent years important progress has been made in basic schizophrenia research. The dopamine hypothesis of schizophrenia, which postulates a dopaminergic dysfunction in this disorder, has for a long time been supported only by indirect pharmacologic evidence (2), but has now received more direct support from two different lines of research, both using imaging techniques. First, it has been shown that the synthesis of labeled dopamine or fluorodopamine in the brain, measured by means of positron emission tomography following administration of radiolabeled L-3,4-dihydroxyphenylalanine (L-DOPA) or fluoro-L-DOPA, is increased in drug-naive schizophrenic patients, compared with age-matched controls (3–5). Second, single photon emission computed tomography and positron emission tomography studies, using a sophisticated technique to measure the release of dopamine in the basal ganglia in vivo, have shown that following an amphetamine challenge, this release is elevated in drug-naive schizophrenic patients compared with age-matched controls, and that this elevation correlates to the induction of positive psychotic symptoms (6–8). In an additional series of experiments Laruelle et al (9), using the single photon emission computed tomography technique with α-methyltyrosine as a tool, have obtained evidence that the unchallenged release of dopamine is elevated in schizophrenic patients compared with controls.

Although these novel data are impressive, a number of caveats should be remembered. First, although statistically significant aberrations of dopamine synthesis and release have been demonstrated in schizophrenic patients, the data show a considerable scatter with some of the values observed within a normal range. Thus, a dysfunction of dopamine may be limited to a subpopulation of patients suffering from this probably heterogeneous disorder. (A few observations suggest that the aberration of dopamine synthesis may actually go in the opposite direction in catatonia, compared with other cases of schizophrenia.) Interestingly, the elevated dopamine release correlated with a good response to antipsychotic drugs.

Secondly, it must be remembered that the abnormal values were obtained in patients who were exposed to the stress inevitably caused by the imaging procedures. Whether a dopamine dysfunction also occurs under minimal stress thus remains an open question.

Third, the patients examined were in acute episodes, and the situation may be different in chronic schizophrenic patients between episodes. In fact, recent observations by Laruelle et al (9) indicate that the amphetamine-induced release of dopamine in schizophrenic patients in remission is within the normal range. This tallies with the clinical experience of patients in remission complaining about the side effects of antidopaminergic drugs more than they do during an exacerbation. If the level of dopaminergic function is normal in patients in remission, the practical implications are obvious. All agents used today to prevent relapse in schizophrenia are antidopaminergic and should thus induce hypodopaminergia in such patients. This is a most unpleasant and incapacitating condition that leads to extrapyramidal side effects and, perhaps more importantly, to a failure of the reward system, resulting in dysphoria and anhedonia and to a cognitive deficit. To develop drugs capable of preventing relapse without these side effects should be an urgent task. In fact, as is discussed below, such agents may already be underway.

An additional point deals with the interpretation of the data obtained with labeled L-DOPA. An increased synthesis rate of labeled dopamine does not necessarily mean that the rate of endogenous dopamine synthesis is increased. The rate-limiting step in the synthesis of dopamine is generally assumed to be the hydroxylation of tyrosine rather than the decarboxylation of L-DOPA. A cautious interpretation of these interesting observations would thus be that there seems to exist in central dopaminergic neurons of schizophrenic patients a metabolic aberration involving the rate of L-DOPA decarboxylation. The functional significance of this aberration has not yet been fully clarified. However, these findings agree with the observations by Laruelle et al (9) regarding unchallenged dopamine release. Taken together, the data thus support the assumption of an elevated baseline release of dopamine in schizophrenic patients.

Finally, this elevation of dopamine release in schizophrenia is not necessarily a primary phenomenon, but could be secondary to, for example, hypoglutamatergia. In support of this it has been found in rats as well as in humans that drugs that block N-methyl-D-aspartic acid (NMDA) receptors are capable of enhancing the spontaneous and especially the amphetamine-induced release of dopamine. The latter effect could be due to blockade of a negative feedback mechanism (see below).

On the whole, these recent data tend to support treatment strategies involving dopamine. However, most of the efforts made in recent years using such strategies have been discouraging. These efforts have largely focused on the D4 and partly also on the D3 and D1 subtypes. A general feeling seems to prevail that the D2 subtype is no longer an attractive target for an improved antipsychotic therapy.

DOPAMINERGIC STABILIZERS: A Promising Novel Therapeutic Approach

Is the therapeutic potential of dopaminergic agents exhausted? Several reasons support the view that this is far from the case. First, the roles of the various subtypes of dopamine receptors need to be explored further. However, perhaps even more important will be ongoing attempts to reach a deeper understanding of the function of these receptors. This may open up entirely new ways of improving this function and optimizing the receptors' abilities to cope with aberrations in neural circuits. In support of this prediction some recent observations in our research group are briefly mentioned.

We have developed a series of compounds capable of stabilizing the dopaminergic system without inducing the hypodopaminergia so ominous for the currently used antipsychotic drugs. Some of these new drugs are partial dopamine-receptor agonists, acting on the D2 family of receptors. A number of partial dopamine-receptor agonists, developed by us and by others, are now in clinical trials and seem to offer promise [for recent clinical data on (−)-3PPP, see Ref. 10; several of the partial dopamine receptor agonists studied so far are less suitable as probes because of their poor selectivity, e.g the ergolines terguride and SDZ 208-912]. Others are pure antagonists, again acting on the D2 family of receptors, and can thus readjust elevated dopamine functions, but in contrast to the currently used antipsychotic agents, they do not cause hypodopaminergia. On the contrary, they antagonize subnormal dopamine function. The reason for this aberrant pharmacological profile seems to be that their action on different subpopulations of dopamine receptors differs from that of the currently used drugs. Thus, whereas they exert a strong action on dopaminergic autoreceptors, they have a weaker effect postsynaptically and seem unable to reach a subpopulation of postsynaptic dopamine receptors (11–13).

In subhuman primates, in which Parkinsonism had been induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, one member of this class, named (S)-(−)-3-(3-(methylsulfonyl)phenyl)-1-propylpiperidine [(−)-OSU6162], given in single doses, could prevent L-DOPA-induced dyskinesias without interfering with the therapeutic movement response. In subsequent trials on Parkinsonian patients the same kind of response was observed (14; J Tedroff, personal communication). Subsequent trials on patients with Huntington's disease (15) showed a marked reduction of choreatic movements, considerably outlasting the presence of the drug in the blood. These observations support the view that drugs of this class are capable of stabilizing dopaminergic function; that is, they are able to alleviate signs of hyperdopaminergia without inducing any signs of reduced dopaminergic function. If these findings can be extrapolated from neurology to psychiatry, these agents should possess antipsychotic activity without any concomitant signs of hypodopaminergia. Forthcoming trials with such agents in schizophrenia will answer this question. A preliminary study on a few schizophrenic patients, using

a double-blind crossover design, has demonstrated an antipsychotic action of (S)-(−)-3-(3-(methylsulfonyl)phenyl)-1-propylpiperidine [(−)-OSU6162] (16).

BEYOND DOPAMINE

In view of the close interaction between neurotransmitters in the brain, it is unlikely that dopamine is the only neurotransmitter showing dysfunction in schizophrenia. As already indicated, the change in dopaminergic function may even be secondary to aberrations elsewhere. In any event, there are good reasons to study the function of several other neurotransmitters in schizophrenia, such as noradrenaline, serotonin, acetylcholine, glutamate, and GABA. These neurotransmitters are more difficult to study in the living intact brain than dopamine. Least difficult would perhaps be serotonin because it seems possible to study it using the same kind of approach as for dopamine; that is, to administer radiolabeled precursor (5-hydroxytryptophan) and measure the turnover of serotonin. Such a study has been carried out in depressed patients, and an aberration was actually demonstrated (17).

For several years considerable interest has focussed on the possible role of glutamate in schizophrenia (18, 19). One reason for this is the discovery that phencyclidine (PCP, "angel dust"), which can induce a psychotic condition mimicking schizophrenia, perhaps even more faithfully than the amphetamines, is a powerful antagonist on one of the glutamate receptor subtypes, namely the NMDA receptor (20). This receptor is equipped with an ion channel that regulates the penetration of calcium and other cations into the neuron. PCP binds to a specific site in this channel, thereby blocking the function of the receptor. A number of other NMDA antagonists are available, binding to different sites of the receptor molecule, such as to the "PCP site," e.g. (+)-5-methyl-10,11-dihydro-5H-dibenzo-(a,d)-cyclohepten-5,10-imine hydrogen maleate = dizocilpine (MK-801) and ketamine (an "uncompetitive" binding), or to the same site as glutamate, e.g. DL-2-amino-5-phosphonopentanoic acid (AP5), 3-(2-carboxypiperazine-4-yl)-1-propenyl-1-phosphonic acid (D-CPPene), and cis-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755) (a competitive binding), or to still another site on the NMDA receptor, where glycine functions as an additional agonist. An example of antagonists acting at the glycine site is D-cycloserine (a mixed agonist-antagonist). All these different NMDA antagonists appear to be psychostimulants, at least in rodents, and psychotogenic in humans.

GLUTAMATERGIC CONTROL OF MONOAMINE RELEASE

At first the psychotogenic action of glutamate antagonists was suggested to be mediated by an increased catecholaminergic activity. Dopamine neurons, like other monoaminergic brainstem neurons, seem to be controlled by corticofugal

glutamatergic neurons either directly or via gabaergic interneurons, acting as accelerators and brakes, respectively (Figure 1). Hypoglutamatergia may then cause an increase or a decrease in dopamine function, depending on whether the effect on the brake or the accelerator would predominate. Normally there appears to be a balance between the accelerator and the brake, perhaps with slightly more effect on the brake. Thus, a reduced glutamate function, induced e.g. by MK-801, may cause some elevation of dopamine release. However, if dopamine release is enhanced dramatically, e.g. by amphetamine, a negative feedback regulation appears to be activated, leading to a much greater effect on the brake. This can be demonstrated in experimental animals by superimposing an NMDA antagonist upon amphetamine. Then the release of dopamine is markedly enhanced (21). This phenomenon is of clinical interest because it opens up a possibility to explain the previously mentioned, enhanced amphetamine-induced release in schizophrenic patients. This enhancement could be due to a glutamate deficiency that leads to a weakened negative feedback control. In fact, cotreatment with the NMDA antagonist ketamine has been found to cause enhancement of the amphetamine-induced dopamine release in humans, as demonstrated by means of single photon emission computed tomography (9).

Treatment of experimental animals with NMDA antagonists alone has given variable results. For example, in the previously cited work of Miller & Abercrombie (21) a slight, not dose-dependent release of dopamine, studied by microdialysis, was observed in rats, following treatment with MK-801. Using the same technique, other laboratories have found similar, more or less impressive effects of this agent. In fact, different portions of the dopaminergic system have been found to respond differentially to treatment with MK-801 (22). As to the competitive NMDA antagonists, the available evidence suggests that these agents, if anything, inhibit dopamine release, and this decrease is concomitant with behavioral stimulation (23). Thus, we have to look for a mechanism other than increased dopamine release to account for at least an important part of the psychostimulant and psychotogenic action of NMDA antagonists.

NMDA receptor antagonists appear to stimulate 5-HT turnover and release more consistently than dopaminergic activity (24). This is of special interest in view of the striking effect of the selective 5-HT2A antagonist R(+)-a-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (M100907) (25) on the behavioral stimulation induced by NMDA-receptor antagonism (26). This effect can be seen after doses of M100907 that are unable to influence the activity of normal mice. In fact, hyperserotonergia appears to be a prerequisite for this antagonism (26). This remarkable profile of M100907 is very different from that of neuroleptic agents and may have important therapeutic implications. The postmortem observations that suggest a presynaptic hyperserotonergia in paranoid schizophrenic patients (27) are of interest in this context.

PCP, which is a somewhat less selective NMDA antagonist than MK-801, does indeed cause a fairly pronounced release of dopamine, probably owing to a concomitant blockade of the dopamine transporter. However, the psychostimulation

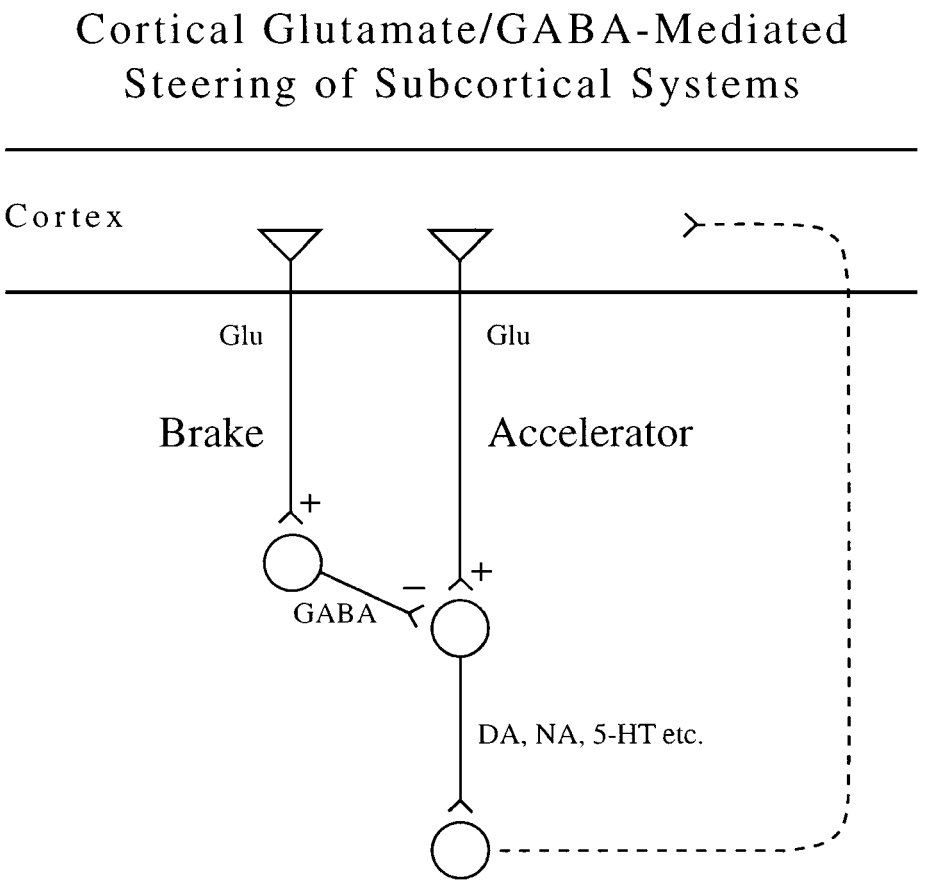


Figure 1 Hypothetical scheme showing the cortical regulation of the activity of the monoaminergic brainstem neurons by means of a direct glutamatergic pathway (accelerator) and an indirect glutamatergic/gabaergic pathway (brake). The outcome of a glutamatergic failure partly depends on the balance between the accelerator and the brake. If the latter predominates in the cortical regulation of a dopaminergic pathway, for example, such failure will lead to an elevated activity of this pathway. As indicated, feedback loops probably exist, at least partly mediated via the striatum and the thalamus. If, for example, the release of dopamine is enhanced by amphetamine, the feedback regulation will increase the activity of the brake, which will counteract the amphetamine-induced release. If the brake fails after treatment with an NMDA-receptor antagonist, or in the case of a hypothetic glutamatergic deficiency in schizophrenia, the amphetamine-induced release of dopamine will be enhanced. A similar failure may occur in chronic abuse of central stimulants, leading to "sensitization" (cf. GABA: AN ACHILLES HEEL). (From Ref. 45)

caused by PCP does not depend so much on this release, because it can be nearly abolished by LY354740, a group-II metabotropic glutamate receptor agonist, despite the fact that this agonist leaves the enhanced dopamine release unchanged (28). Interestingly, in this study PCP was found to enhance the release of glutamate, and this effect was antagonized by LY354740. This phenomenon is commented on below.

Many antipsychotic agents, especially some so-called atypical antipsychotics, possess adrenergic receptor-blocking properties, and the possible contributory role of this blockade has been recognized ever since our original report in 1963 (29). Recent observations tend to corroborate this contention. Thus, in the hypoglutamatergia model of schizophrenia the α_1-adrenergic antagonist prazosine could antagonize the behavioral stimulation and normalize the firing pattern of dopaminergic neurons in a manner somewhat similar to M100907 (22). The atypicality of clozapine and other more recently introduced antipsychotic agents may thus depend not only on antiserotonergic but also antiadrenergic properties. Other properties such as affinity for cholinergic receptors may have to be considered as well.

Recently, Gessa (30) presented convincing evidence that the extracellular dopamine measured by means of microdialysis in rat prefrontal cortex is largely derived from noradrenergic neurons. In fact, we have observed for a long time in our laboratory that there exists a very close correlation between extracellular dopamine and noradrenaline in rat frontal cortex. Thus, variations in dopaminergic tone in this region should be looked at as an expression of locus ceruleus neuron activity and may then be regulated very differently from the dopaminergic neurons.

GLUTAMATE-MONOAMINE INTERACTIONS AT THE POSTSYNAPTIC (STRIATAL) LEVEL

Carlsson & Carlsson (31) reported that MK-801, given systemically, is capable of inducing motor activity in mice completely depleted of dopamine and noradrenaline (by pretreatment with reserpine plus α-methyltyrosine). Subsequently, Svensson & Carlsson (32) showed that competitive NMDA-receptor antagonists were also active under these conditions, and that not only systemic but also local treatment with NMDA antagonists in the nucleus accumbens could induce movements in spite of virtually complete monoamine depletion.

The local administration of NMDA receptor antagonists in the nucleus accumbens of monoamine-depleted mice induced a fairly normal motility pattern, but systemic treatment with these drugs caused a highly abnormal motility, i.e. compulsory forward locomotion with apparently total loss of the ability to switch between different behavioral patterns. Systemic treatment will inhibit NMDA receptors not only in the basal ganglia but also, for example, in the cerebral cortex, where the failure of glutamatergic association pathways could lead to loss of important functions, such as the ability to select appropriate behavioral programs. If glutamatergic deficiency is a relevant pathogenetic mechanism in schizophrenia

and if this includes the cerebral association pathways, it is not far-fetched to propose that this could lead to important consequences, involving cognitive disturbances, loss of flexibility, ambivalence and other behavioral aberrations, perhaps mainly belonging to the sphere of negative schizophrenic symptomatology. Hypofrontality could also be a result of failure of cortical association pathways, and these could be especially vulnerable in so far as they engage chains of glutamatergic pathways. Thus, it may be speculated that glutamatergic failure in the cerebral cortex may lead to negative symptoms, whereas glutamatergic failure in the basal ganglia could be resposible for the positive symptoms. However, failure of the glutamatergic control of the so-called direct striatothalamic pathways may also contribute to the complex negative symptomatology (see below).

Our subsequent work revealed a dramatic synergism between a variety of monoaminergic agonists and MK-801 or other NMDA receptor antagonists, all of them already in low dosage (33–35). This was true, for example, of apomorphine; a mixed D1/D2 agonist, SKF 38393; a selective D1 agonist, clonidine; an α_2-adrenergic agonist; and a 5HT2 agonist, LSD. A synergy between muscarinic and NMDA receptor antagonists was also demonstrated. Because these phenomena could be demonstrated in the absence of monoamines, the synergism must be assumed to occur postsynaptically, and then presumably in the ventral striatum. The exact mechanism of this synergism is not clear. It may occur locally or involve some kind of loop-mediated regulation.

Based on these observations, we have proposed a hypothetical scheme that illustrates how the interaction between several neurotransmitters forms networks of psychotogenic pathways (Figure 2).

GABA: An Achilles Heel?

Besides the glutamatergic neurons, the GABAergic neurons form by far the dominating neuronal cell population in the brain, and it is hard to imagine any neuronal circuitry that does not involve GABA. A reduction of GABAergic neurons has been observed in, for example, limbic and prefrontal cortical regions of schizophrenic brains post mortem, as well as an increase in the density of $GABA_A$ receptors (36). Moreover, GABAergic neurons have been found to be especially vulnerable to, for example, glucocorticoid hormones, and also to glutamatergic excitotoxicity. Certain glutamatergic neurons seem to occur in increased number in, for example, the cingulate gyrus of schizophrenic brains, and this, in conjunction with a postulated role of stress in the pathogenesis of schizophrenia, would strengthen the assumption of an important role of GABA in schizophrenia, at least as a vulnerability factor. A GABAergic dysfunction might arise in the course of the disorder during adulthood or, for example, in utero or neonatally as a consequence of obstetric complications or other stressful events. In either case the activation of negative feedback circuits during psychosis or stress may well have a deleterious impact on vulnerable interneurons, resulting in longlasting and perhaps lifelong sensitivity changes.

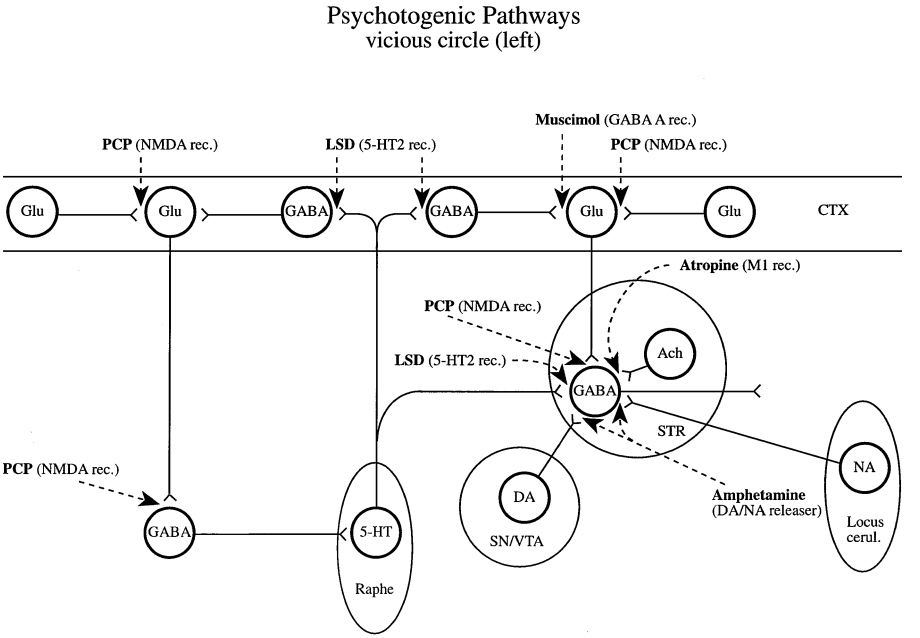


Figure 2 Schematic diagram illustrating potential psychotogenic pathways and sites of action of psychotogenic and antipsychotic agents. The striatal complexes (STR, the centrally located circle) are composed of the dorsal and ventral striatum/pallidum. The striatum receives glutamatergic inputs from all parts of the cerebral cortex as well as serotonergic, dopaminergic, and noradrenergic inputs from the lower brainstem. Cholinergic interneurons, located in the striatum, seem to cooperate with glutamate to some extent. Striatopallidal chains of GABAergic neurons project to the thalamus, not shown in this Figure (but see Figure 3).

Amphetamine and PCP are supposed to act psychotogenically by enhancing striatal dopamine release and blocking striatal NMDA receptors, respectively. These actions are partly located in the (limbic) striatum and partly in other sites. For example, PCP may act by blocking cortical as well as striatal NMDA receptors as well (e.g. in the hippocampus, as indicated in the figure) leading to reduced tone in corticostriatal glutamatergic pathways. The 5-HT2 agonist LSD may act by stimulating GABAergic interneurons in the limbic cortex, thereby reducing corticostriatal glutamatergic tone (46). LSD also seems to act on neurons in the striatum. (In contrast to this coupling in the limbic, piriform cortex, 5-HT2 receptors located presynaptically in prefrontal cortex on glutamatergic nerve terminals, seem to stimulate glutamate release, an effect that is counteracted by metabotropic glutamate autoreceptors (see Ref. 47)). The GABA A receptor agonist muscimol, which also appears to be psychotogenic (48), may likewise act by reducing corticostriatal glutamatergic tone. Anticholinergic agents appear to act by blocking predominantly muscarinic M1 receptors. (Modified from Ref. 2)

THE THALAMIC (AND EXTRATHALAMIC) FILTER

Carlsson (37) proposed that psychomotor activity and psychotogenesis depend, inter alia, on an interplay between dopamine and glutamate pathways projecting to the striatum from the lower brainstem and cortex, respectively (Figure 3). These neurotransmitters are predominantly, though not entirely, antagonistic to each other, the former being inhibitory and the latter stimulatory, when acting on striatal GABAergic projection neurons. These GABAergic projection neurons belong to so-called indirect striatothalamic pathways, which exert an inhibitory action on thalamocortical glutamatergic neurons, thereby filtering off part of the sensory input to the thalamus to protect the cortex from a sensory overload and hyperarousal. Hyperactivity of dopamine or hypofunction of the corticostriatal glutamate pathway should reduce this protective influence and could thus lead to confusion or psychosis.

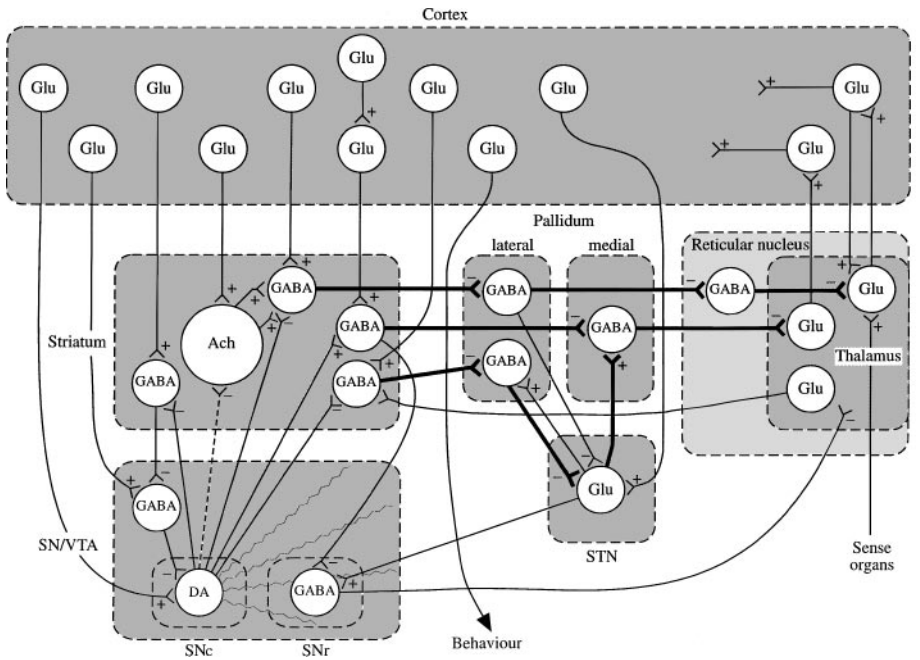


Figure 3 Neurocircuitries of the basal ganglia. Detail of the striatopallidothalamic pathways. Among these, the top and bottom pathways drawn with thick lines contain three GABAergic neurons and are referred to as "indirect," i.e. inhibitory, pathways. The pathway in between contains two GABAergic neurons and is referred to as "direct" (modified from Ref. 33). SN, substantia nigra; VTA, ventral tegmental area; STN, subthalamic nucleus; Glu, glutamate. Ach, acetylcholine; DA, dopamine.

Carlsson's hypothesis (37) focussed on the indirect striatothalamic pathways, which have an inhibitory influence on the thalamus. The corresponding direct pathways exert an opposite, excitatory influence. Both pathways are controlled by glutamatergic corticostriatal fibers, enabling the cortex to regulate the thalamic gating in opposite directions. In other words, they appear to serve as brakes and accelerators, respectively, in analogy to the regulation of monoaminergic brainstem neurons mentioned above. Normally, the inhibitory, indirect pathways seem to dominate over the direct pathways. Thus, NMDA receptor inhibitors are behavioral stimulants. However, the balance between the direct and indirect pathways may vary, depending on the state of the system. Failure of the direct pathway, induced e.g. by glutamatergic deficiency, might contribute to the so-called negative symptomatology of schizophrenia. It has been suggested that the activity of the direct pathways is predominantly phasic, whereas that of the indirect pathways is mainly tonic (38). This difference could have important consequences for a differential responsiveness of the direct and indirect pathways to drugs (39).

Needless to say, the postulated existence of a thalamic filter would not exclude a gating function located in other parts of the brain, e.g. the prefrontal cortex. The impressive sophistication of the gating function, enabling a focussed attention to relevance and novelty at the expense of trivial sensory inputs, would actually speak in favor of a more widely spread location.

Little is known about the role of different receptor subtypes in the respective pathways. As to the glutamatergic receptors, NMDA receptor antagonists, as mentioned, are behavioral stimulants, at least in rodents, and this has been interpreted as the result of a failure of the indirect, inhibitory pathways. AMPA receptor antagonists have been studied less intensely but have been found to act in the same direction as NMDA antagonists in some experiments, whereas they act as antagonists to NMDA antagonists in other experiments (22). As for the metabotropic receptors, the recent observations of Moghaddam & Adams (28), briefly referred to above, are most interesting. They found that the behavioral stimulation caused by PCP could be antagonized by a metabotropic receptor agonist, and at the same time, the PCP-induced elevation of glutamate release was antagonized. The question arises as to whether these data can be accommodated to the model of direct and indirect pathways outlined above. Glutamate release is, generally speaking, much more difficult to measure and interpret than the release of monoamines. For example, glutamate plays an important role in general cell metabolism, in addition to serving as a neurotransmitter. Perhaps glutamate release is predominantly indicative of the activity of the direct pathways, because they seem to be mainly phasic, and release by burst firing may be more likely to show up in microdialysis. Thus, the PCP-induced elevation of glutamate release, as measured by microdialysis, is perhaps indicative of an increased activity of the direct pathway; possibly the metabotropic receptor agonist antagonized this release by stimulating glutamatergic autoreceptors. Of course, such a mechanism is speculative.

As mentioned above, the dopaminergic projections to the indirect striatothalamic pathways appear to be predominantly inhibitory at the cellular level. They

seem to operate largely via dopamine D2 receptors. The dopaminergic projections to the direct pathways, however, seem to be stimulating and mediated via D1 receptors.

COMPARING TWO EXPERIMENTAL SCHIZOPHRENIA MODELS: Therapeutic Implications

As it looks today, the two most important animal models of psychosis are those induced by hyperfunction of dopamine and hypofunction of glutamate. However, one cannot disregard the other monoamines, among them perhaps especially serotonin. There seem to be strong interactions between glutamate and all the monoamines in psychotogenesis, and among them the link between glutamate and serotonin appears to be especially noteworthy. Presumably, several other neurotransmitters will ultimately have to be considered.

To illustrate some remarkable transmitter interactions one can compare the actions of the typical antidopaminergic agent haloperidol and the specific 5-HT2A antagonist M100907 in two models of psychosis (Figure 4). As expected, haloperidol is quite powerful in alleviating the hyperdopaminergic stimulation induced by amphetamine, but it is less efficacious in the hypoglutamatergic behavioral stimulation induced by MK-801. However, M100907 is clearly more powerful in counteracting MK-801 than amphetamine-induced stimulation (40). These observations indicate that serotonin plays a more prominent role than dopamine in the behavioral stimulation induced by hypoglutamatergia.

In behavior studies one must of course pay attention both to the quantitative and qualitative aspects. Using an ethovision system, we have found that MK-801 not only stimulates motility but at the same time changes the behavioral pattern in a direction suggestive of a retrogression to more primitive behavior, with an impoverishment of the behavioral repertoire (M Nilsson, S Waters, N Waters, ML Carlsson, unpublished manuscript; Figure 5).

One can speculate that this retrogression involves a cognitive deficit. Besides, it may be related to another behavioral abnormality induced by MK-801 and related drugs: the loss of habituation (42). It is well known that habituation is also deficient in psychosis.

When haloperidol counteracts the behavioral stimulation induced by hypoglutamatergia, it does so without any clear trend to normalization of the abnormal, primitive movement pattern observed in this condition. In contrast, M100907 can concomitantly normalize the hypermotility and, albeit partially, the behavioral pattern, thus reinstating a richer behavioral repertoire (Figure 5).

Given these results from animal model experiments, the question arises whether one can distinguish between subpopulations of schizophrenic patients responding preferentially to either antidopaminergic or antiserotonergic agents; such subpopulations might then be assumed to be predominantly hyperdopaminergic and hyperserotonergic, respectively, and in the latter case perhaps also hypoglutamatergic.

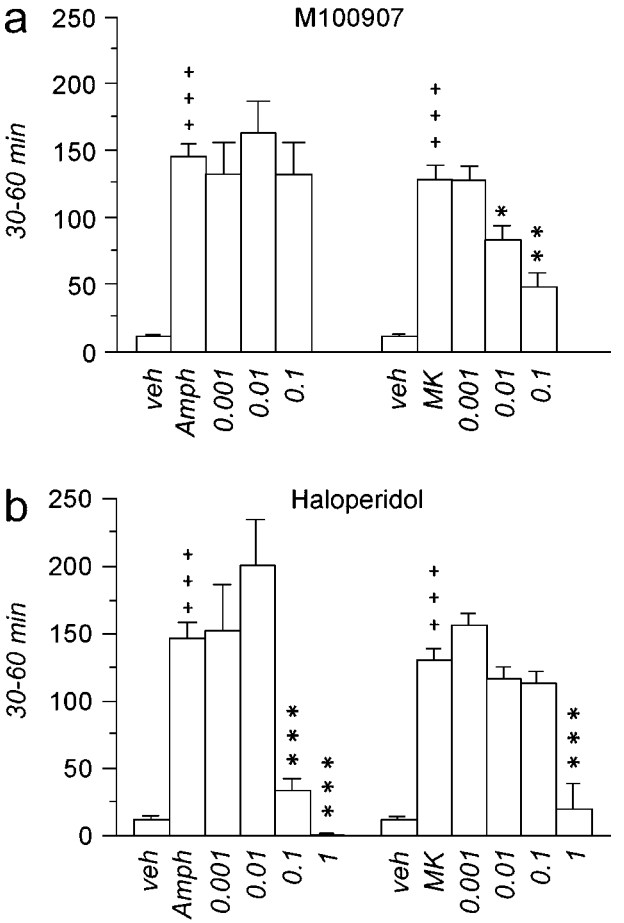


Figure 4 (*a*) Effect of various doses of M100907 (0.001, 0.01, and 0.1 mg/kg) on locomotion stimulated by d-amphetamine (Amph, 3 mg/kg) or MK-801 (0.3 mg/kg). All drugs were given immediately before the animals were placed in the activity meters. Statistics: Mann-Whitney U-test. $+++p < 0.001$ vs vehicle; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs d-amphetamine or MK-801. RS, Spearman correlation coefficient. (*b*) Effect of various doses of haloperidol (0.001, 0.01, 0.1, and 1 mg/kg) on locomotion stimulated by d-amphetamine (Amph, 3 mg/kg) or MK-801 (0.3 mg/kg). All drugs were given immediately before the animals were placed in the activity meters. Statistics: Mann-Whitney U-test. $+p < 0.05$, $++p < 0.01$, $+++p < 0.001$ vs vehicle; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs d-amphetamine or MK-801. RS, Spearman correlation coefficient (from Ref. 45).

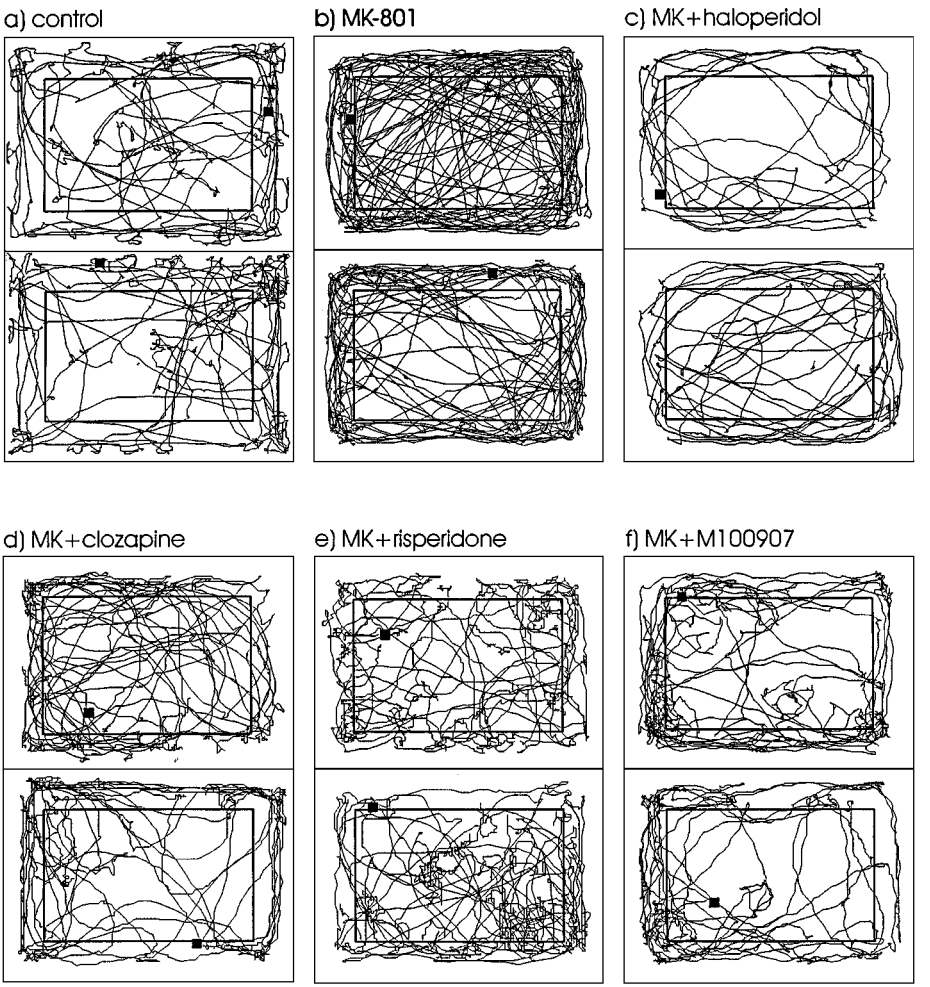


Figure 5 Representative tracks demonstrating the movement patterns of mice during the first 5 minutes of recording in a new environment. Shown in duplicate are tracks from mice treated with (*a*) vehicle, (*b*) MK-801 0.2 mg/kg, (*c*) MK-801 + haloperidol 0.5 mg/kg, (*d*) MK-801 + clozapine 0.03 mg/kg, (*e*) MK-801 + risperidone 0.03 mg/kg, (*f*) MK-801 + M100907 (0.1 mg/kg). Sampling frequency, 12.5 Hz. Doses of antipsychotic drugs were chosen to give approximately the same quantitative motility. (from M Nilsson, S Waters, N Waters, ML Carlsson, unpublished manuscript)

Alternatively, if no such subpopulations can be distinguished, the combined treatment of each individual patient with an antidopaminergic and an antiserotonergic agent might be superior to treatment with either drug alone. This would support the hypothesis that drugs such as clozapine, risperidone, and olanzapine do better than typical neuroleptics because of their combined effect on dopamine and

5-HT2 receptors. However, this may be an oversimplification, in view the "rich pharmacology" of these agents. In any event, we have found that clozapine and risperidone, like M100907, are capable of reinstating a rather sophisticated behavioral repertoire in MK-801-pretreated animals (Figure 5).

Different behavioral patterns can be objectively described using multivariate analysis. 58 different components of movement were defined and counted for individual mice. The data were analyzed by means of principal component analysis and principal least square discriminant analysis. The results can then be described in two-dimensional presentations (M Nilsson, S Waters, N Waters, ML Carlsson, unpublished manuscript; Figure 6). The striking similarity between M100907, clozapine, and risperidone and the difference between these agents and haloperidol are obvious.

Biochemical data visualizing the pattern of neurotransmitter aberrations after treatment with psychotogenic agents also show a striking similarity between M100907 and clozapine and a difference between these agents and haloperidol (43; Figure 7).

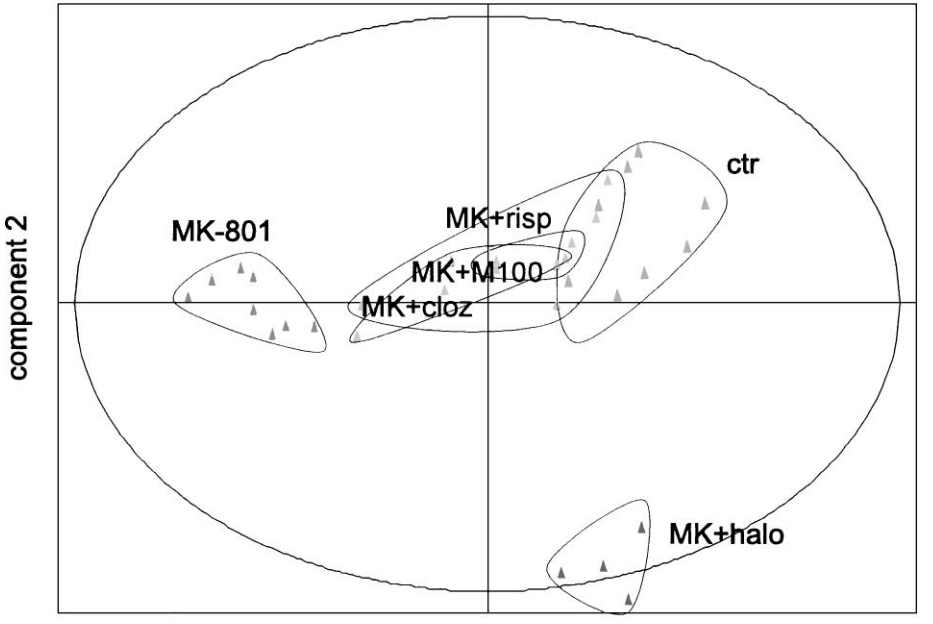
Insofar as M100907 is concerned, our observations are probably clinically relevant because M100907 has recently been reported, in a press release by Aventis, to possess significant antipsychotic activity in extensive phase III studies on schizophrenic patients, thus confirming earlier phase II studies.

The advent of a number of agents interacting in different ways with the glutamatergic system, now in different stages of development, is eagerly awaited. Examples of this group of drugs are the glycine agonists (exemplified by D-serine; 44), glycine reuptake inhibitors, AMPA agonists and antagonists, and ampakines. In the case of AMPA ligands it seems at present uncertain if agonists, antagonists, or partial agonists/modulators will be most successful. Finally, drugs acting on different subtypes of metabotropic glutamate receptors seem to offer promise.

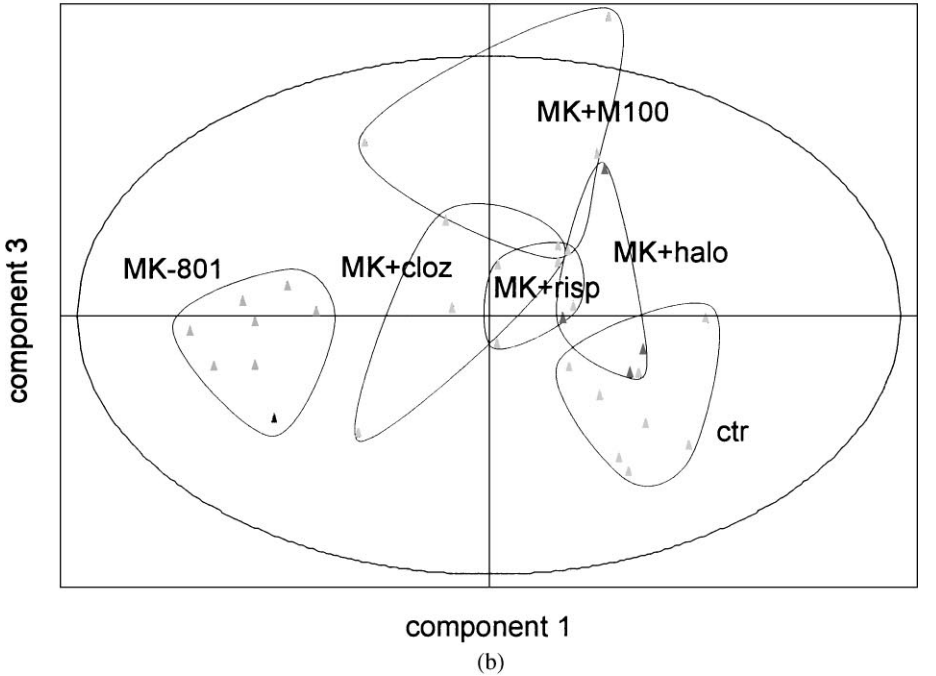
CONCLUDING REMARKS: Outlook

As mentioned in the introduction, the dopamine hypothesis of schizophrenia has received both fairly strong indirect pharmacological and, more recently, direct pathophysiological support. Thus, a dysfunction of the dopaminergic system is

Figure 6 Multivariate analysis of the tracks shown in Figure 5. Note that treatment with MK-801 causes a marked leftward shift along component 1 with little change along component 2 (*a*) or component 3 (*b*), as compared to vehicle-treated controls (ctr). Clozapine (cloz), risperidone (risp) and M100907 (M100), each superimposed upon MK-801, cause similar shifts towards controls along component 1 with only slight changes along component 2. Along component 3 only M100907 caused a modest but noticeable (upward) shift. Haloperidol was similar to the other antipsychotic agents in causing a shift towards normal along component 1 but differed markedly from the others in causing a downward shift along component 2, that is, a movement away from the controls (from M Nilsson, S Waters, N Waters, ML Carlsson, unpublished manuscript).

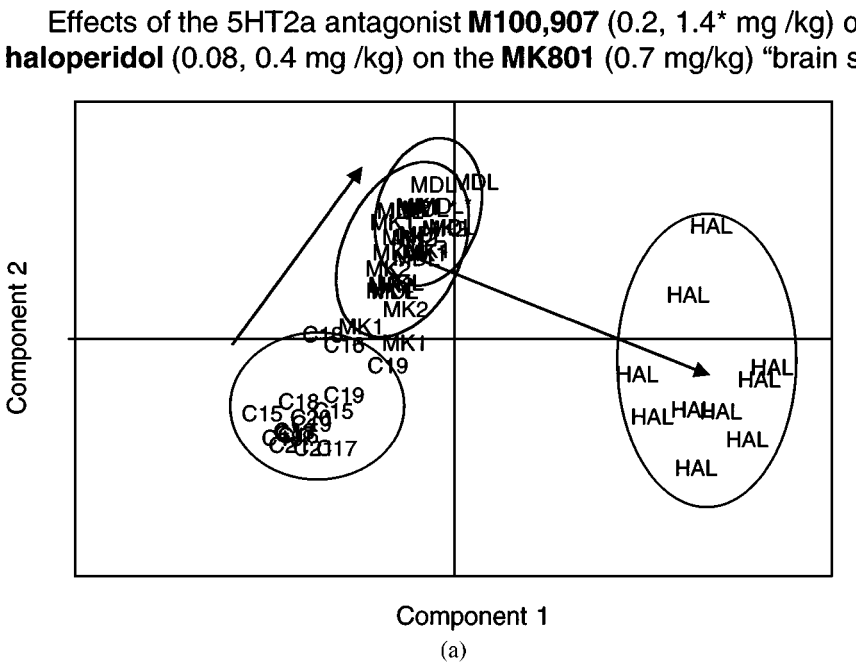

component 2
MK-801
MK+risp
MK+M100
MK+cloz
ctr
MK+halo
component 1

(a)


component 3
MK+M100
MK-801
MK+cloz
MK+risp
MK+halo
ctr
component 1

(b)

probably somehow involved in the disease. However, the role of dopamine in the pathophysiology or etiology of schizophrenia should not be overemphasized. In our original paper (29), which is often quoted as the origin of the hypothesis, we only proposed that major antipsychotic agents might act by blocking receptors for catecholamines. Our data pointed to a particularly strong action on dopamine, but we did not emphasize that. Rather, we proposed that serotonin receptors could also be involved in the antipsychotic action. During a subsequent phase several authors presented data more strongly supporting the role of dopamine, which then

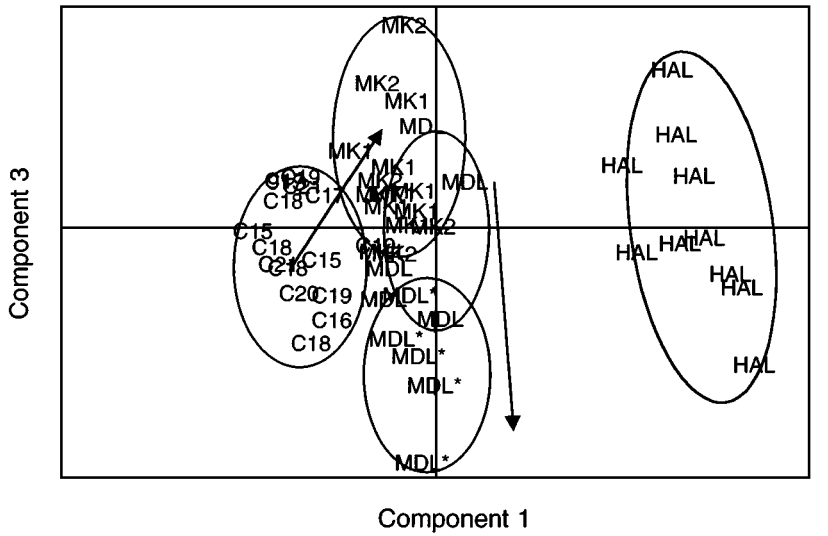


(a)

Figure 7 Multivariate analysis of monoaminergic indices in the brains of rats pretreated with vehicle (C) or MK-801 (0.7 mg/kg s.c.), the latter treatment followed by vehicle (MK), haloperidol (HAL, 0.08 mg/kg s.c.), M100907 (MDL, 0.2 or 1.4* mg/kg s.c.), or clozapine (10 mg/kg s.c.). Each symbol shows the position of an individual rat treated as indicated above. (Modified from Ref. 43.)

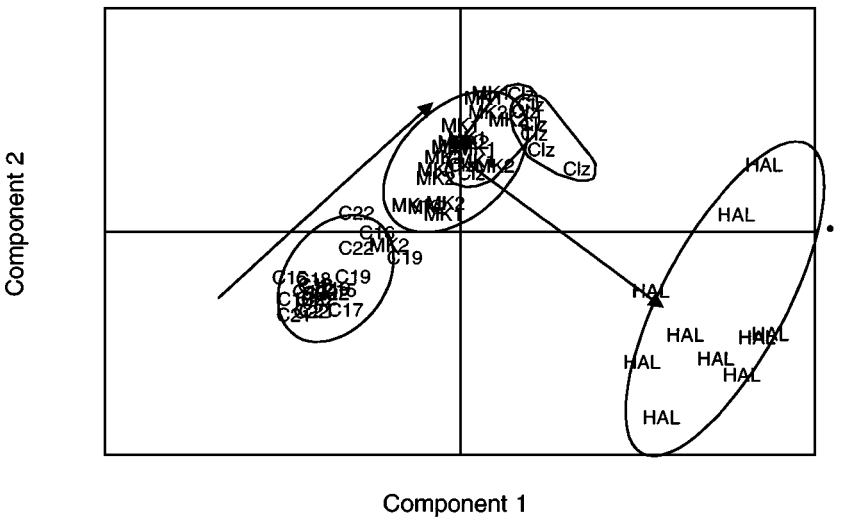
MK-801 gives rise to a slight rightward movement along component 1 (X-axis) and a more pronounced upward movement along component 2 (Y-axis, *a*) and component 3 (Y-axis, *b*). Subsequent treatment with M100907 produces slight and nonsignificant changes along components 1 and 2 but a marked, dose-dependent downward movement along component 3. *c* and *d* show the corresponding changes induced by clozapine. Note the remarkable similarity between the effects of M100907 and clozapine. Haloperidol differs from the other two antipsychotic agents in causing a marked rightward shift along component 1 without any significant shift in components 2 or 3.

Effects of the 5HT2a antagonist **M100,907** (0.2, 1.4* mg /kg) or **haloperidol** (0.08, 0.4 mg /kg) on the **MK801** (0.7 mg/kg) "brain state"



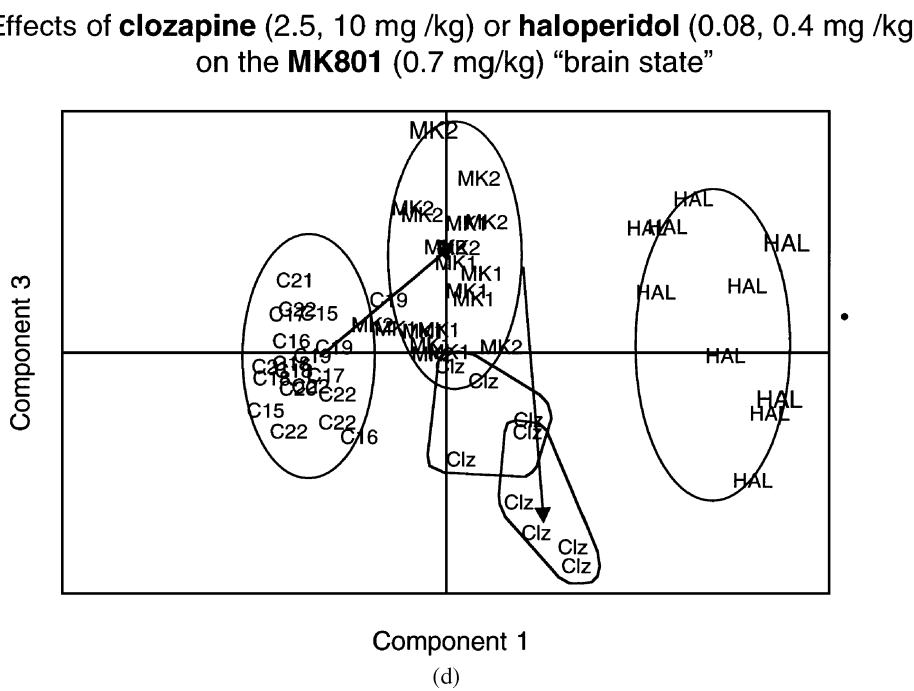
(b)

Effects of **clozapine** (2.5, 10 mg /kg) or **haloperidol** (0.08, 0.4 mg /kg) on the **MK801** (0.7 mg/kg) "brain state"



(c)

Figure 7 (*Continued*)



(d)

Figure 7 (*Continued*)

came to dominate the scene for a couple of decades. It was not until the 1980s that glutamate started to attract attention in this context. This was largely due to the discovery that PCP, a strongly schizophrenia-mimicking agent, is an antagonist on the glutamatergic NMDA receptors. In parallel with this development there was an impressive growth of knowledge regarding the neuroanatomy of pathways of potential psychotogenetic interest. Thus, during the past decade a new direction of research has emerged, focusing upon the interaction of a variety of neurotransmitters in complex neurocircuits engaged in the control of major mental functions, such as affect, emotions, and cognition and their involvement in reward-directed and other complex behavior. Rather than trying to identify a single culprit in psychotogenesis the emphasis is now moving towards trying to understand these interactions and how imbalances in such circuitry can arise, perhaps mainly on a multifactorial basis. From such a perspective it seems reasonable to look upon schizophrenia as a syndrome of heterogeneous etiology and pathophysiology. Evidence quoted in this review argues for a role of not only dopamine and glutamate but also serotonin, noradrenaline, and GABA. There is now overwhelmingly convincing evidence that a primary disturbance in one neurotransmitter system will inevitably influence several other systems. To try to establish, in a given case, the order in which a complex chain of events has arisen and thus to identify the origin,

would in general seem unrealistic. A more modest aim would be to try to describe aberrations in the patterns of physiological and biochemical events and to try to correlate such aberrations to behavioral changes.

Just as reductionism has emphasized the search for an individual culprit among the neurotransmitters, it has led to attempts to identify a particular brain region, such as the prefrontal cortex or the temporal lobe, as the site of the schizophrenic lesion. Rather compelling evidence for a role of both these and a number of other regions has been advanced. Again, to account for all the evidence it will probably be useful to look for a more complex disease model in which many different brain regions in the upper and lower brainstem, the basal ganglia, and the limbic cortex, as well as the neocortex, are engaged and interact in complex circuitries. To define the contribution of different brain regions to psychotogenesis it may again prove useful to apply a pattern recognition approach.

For pattern recognition, multivariate analysis is an essential tool. In our own research we use this tool for describing aberrations in neurotransmitter neurochemistry as well as in behavior in animal disease models. We have also used it for describing the biochemical aberrations occurring in schizophrenic brains post mortem. Recently we have started to apply multivariate analysis on biochemical measurements related to neurotransmitter function, using positron emission tomography methodology, in humans belonging to different diagnostic groups, either untreated or following therapeutic interventions. One goal is to correlate the patterns observed in animal models to those observed in different diagnostic categories of patients, in either case with or without therapeutic interventions. We feel confident that this will bridge the gap between animal and human research and speed up the development of novel therapeutic procedures.

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