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Interactive report

Network interactions in schizophrenia — therapeutic implications [1]

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Abstract

Research into the role of neurotransmitters and neural networks in the pathogenesis of schizophrenia has been remarkably successful in recent years. The hypothesis postulating a dopamine dysfunction, which has for a long time been supported only by indirect evidence, has received direct support by means of sophisticated imaging techniques. Interactions between dopamine and several other neurotransmitters in complex neural networks have been revealed, largely thanks to the advent of an array of new pharmacological probes. Two major pharmacological models of schizophrenia, based on hyperdopaminergia and hypoglutamatergia, respectively, are ready for clinical testing. In addition, the hypothesis of network stabilization as a major therapeutic strategy in psychiatry and neurology has now reached the 'proof-of-concept' level. From a therapeutic perspective, several ongoing and forthcoming clinical trials, using drugs acting on dopaminergic, serotonergic and glutamatergic receptors, give rise to optimism.

Keywords: Schizophrenia; Antipsychotics; Neurocircuits; Neurotransmitters; Dopamine; Glutamate

Contents

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1. Introduction — the dopamine hypothesis revisited

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 [6] but has now received more direct support by research using imaging techniques. First, an aberration of the turnover of dopamine in the brain, measured by means of PET following administration of radiolabelled dopa or fluorodopa, has been demonstrated in drug-naive schizophrenic patients, compared to age-matched controls [13,18,22]. Second, SPECT and PET studies, using a sophisticated technique to measure the release of dopamine in the basal ganglia in vivo, have shown that an amphetamine challenge enhances this release significantly more in drug-naive schizophrenic patients than in age-matched controls. Moreover, this elevation correlates to the induction of positive psychotic symptoms [1,4,21].

However, a number of caveats should be considered. Firstly, the data show some scatter, and some of the values observed in the schizophrenic patients are within the normal range. A dopaminergic dysfunction may thus be limited to a subpopulation of patients suffering from this probably heterogeneous disorder. (A few observations suggest that the synthesis of dopamine may actually deviate in the opposite direction in catatonia; compared to other cases of schizophrenia; regarding heterogeneity, see also [16].) Secondly, the abnormal values were obtained in patients who were challenged by amphetamine and/or exposed to the stress inevitably caused by the imaging procedures. Whether a dopamine dysfunction occurs also under minimal stress thus remains to be firmly established.

Thirdly, 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. (personal communication) indicate that the amphetamine-induced release of dopamine in schizophrenic patients in remission is within the normal range. This fits with the clinical experience that patients in remission complain more about the side effects of antipsychotic drugs than during an exacerbation. If a normal baseline dopaminergic function in remission can be corroborated, the implications are important. All agents used today to prevent relapse in schizophrenia are antidopaminergic and should induce a state of hypodopaminergia, provided that baseline dopaminergic function is normal. Hypodopaminergia, with extrapyramidal dysfunction and, perhaps more importantly, a failure of the reward system, resulting in dysphoria and anhedonia, is a most unpleasant and incapacitating condition. To develop drugs capable of preventing relapse without these side effects should be an urgent task. In fact, as will be discussed below, such agents may already exist.

An additional point deals with the interpretation of the data obtained with labelled dopa. The increased synthesis rate of labelled dopamine observed in the schizophrenic patients does not necessarily mean that the rate of endogenous dopamine synthesis is increased. It should be remembered that the rate-limiting step in the synthesis of dopamine is generally assumed to be the hydroxylation of tyrosine rather than the decarboxylation of 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 dopa decarboxylation. The functional significance of this aberration has, however, not yet been fully clarified.

2. 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, and perhaps partly a compensatory phenomenon.

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 radiolabelled 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 [2].

For several years considerable interest has focused on the possible role of glutamate in schizophrenia [14,19]. 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. This receptor is equipped with an ion channel regulating 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. MK-801 and ketamine (an 'uncompetitive' binding), or (competitively) to the same site as glutamate, e.g. AP5, D-CPPene and CGS 19755, 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 (for review, see Ref. [23]).

3. Glutamatergic control of dopamine 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 (Fig. 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 a slight overweight of the brake. Thus a reduced glutamate function, induced e.g. by MK-801, may cause some elevation of dopamine release. But if dopamine release is enhanced dramatically, e.g. by amphetamine, a negative feedback regulation appears to be activated, leading to a strong overweight of the brake. This can be demonstrated in experimental animals by superimposing an NMDA antagonist upon amphetamine. Then the release of dopamine is markedly enhanced [26]. 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, leading to a weakened negative feedback control. In fact, co-treatment with the NMDA antagonist ketamine has been found to cause enhancement of the amphetamine-induced dopamine release in humans, as demonstrated by means of SPECT (Laruelle, personal communication).

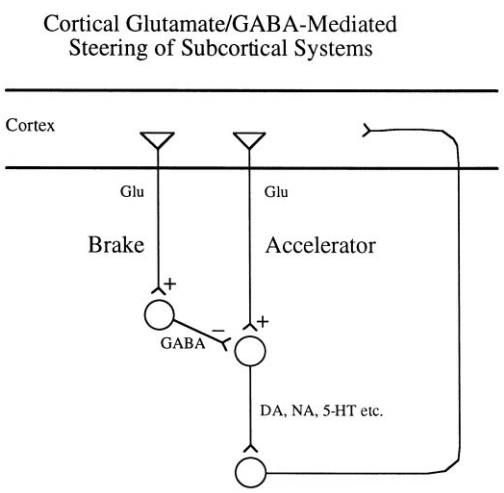

Fig. 1. Hypothetical scheme showing the cortical regulation of the activity of the monoaminergic brainstem neurons by means of a direct glutamatergic pathway ('accelerator') and an indirect glutamatergic/gabaergic pathway ('brake'). The outcome of a glutamatergic failure will partly depend on the balance 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.

Treatment of experimental animals with NMDA antagonists alone has given ambiguous results. For example, in the previously quoted work of Miller and Abercrombie [26] 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. 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 [32]. 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. Interesting in this context is the above-mentioned possibility of a reduced presynaptic dopamine function in schizophrenia, tentatively suggested to be a compensatory response to hypoglutamatergia.

NMDA receptor antagonists appear to stimulate 5-HT turnover and release more consistently than dopaminergic activity (see [25]). This is of special interest in view of the striking effect of the selective 5-HT2A antagonist M100907 [28] on the behavioral stimulation induced by NMDA-receptor antagonism [24]. This effect can be seen after doses of M100,907 which are unable to influence the activity of normal mice. In fact, hyperserotonergia appears to be a prerequisite for this antagonism [24]. This remarkable profile of M100,907 is very different from that of neuroleptic agents and may have important therapeutic implications. The postmortem observations suggesting a presynaptic hyperserotonergia in paranoid schizophrenic patients [16] 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 due to a concomitant blockade of the dopamine transporter. However, the psychostimulation 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 [27]. Interestingly, in this study PCP was found to enhance the release of glutamate, and this effect was antagonized by LY354740. This phenomenon will be commented below.

4. Glutamate-dopamine interaction at the postsynaptic (striatal) level

Carlsson and Carlsson [8] 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 and Carlsson (1992) 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 presumably 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 farfetched 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 responsible for the positive symptoms. However, failure of the glutamatergic control of the direct striatothalamic pathways may also contribute to the complex negative symptomatology.

Our subsequent work revealed a dramatic synergism between a variety of monoaminergic agonists and MK-801 or other NMDA receptor antagonists [7,9,10]. 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 LSD, a 5HT2 agonist. A synergy between muscarinic and NMDA receptor antagonists was also demonstrated. Since 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, illustrating the interaction between several neurotransmitters to form networks of psychotogenic pathways (Fig. 2).

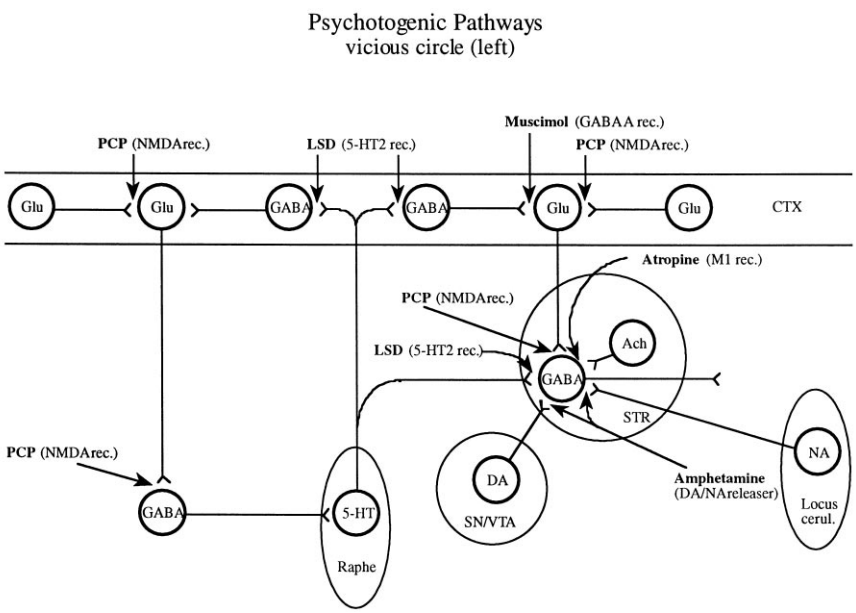

Fig. 2. Schematic diagram illustrating potential psychotogenic pathways and sites of action of psychotogenic and antipsychotic agents. The striatal complexes (STR, the centrally located circle) are composed of the dorsal and ventral striatum /pallidum. The striatum receives glutamatergic inputs from all parts of the cerebral cortex as well as serotonergic, dopaminergic and noradrenergic inputs from the lower brainstem. Cholinergic interneurons are located in the striatum. Striatopallidal chains of gabaergic neurons project to the thalamus, not shown in this figure, but see Fig. 3. Amphetamine and PCP are supposed to be psychotogenic by acting on striatal dopamine release and blocking NMDA receptors, respectively. These actions are partly located in the (limbic) striatum, partly in other sites. For example, PCP may act by blocking cortical NMDA receptors as well, e.g. in the hippocampus, as indicated in the Figure, leading to reduced tone in corticostriatal glutamatergic pathways. The 5-HT_2 agonist LSD may act by stimulating GABAergic interneurons in the limbic cortex, thereby reducing corticostriatal glutamatergic tone [15]. LSD also seems to act on neurons in the striatum. The GABA A receptor agonist muscimol, which also appears to be psychotogenic [31], may likewise act by reducing corticostriatal glutamatergic tone. Anticholinergic agents appear to act by blocking predominantly muscarinic M_1 receptors (modified from [6]).

5. The thalamic filter

Carlsson [5] 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 (Fig. 3). These neurotransmitters are predominantly, though not entirely, antagonistic to each other, the former being inhibitory and the latter stimulating, 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.

The above-mentioned hypothesis [5] focused 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 [3]. This difference could have important consequences for a differential responsiveness of the direct and indirect pathways to drugs (cf. [11]).

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 focused 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. As to the metabotropic receptors, the recent observations of Moghaddam and Adams [27] briefly referred to above, are most interesting. They found that the behavioral stimulation caused by PCP could be antago-

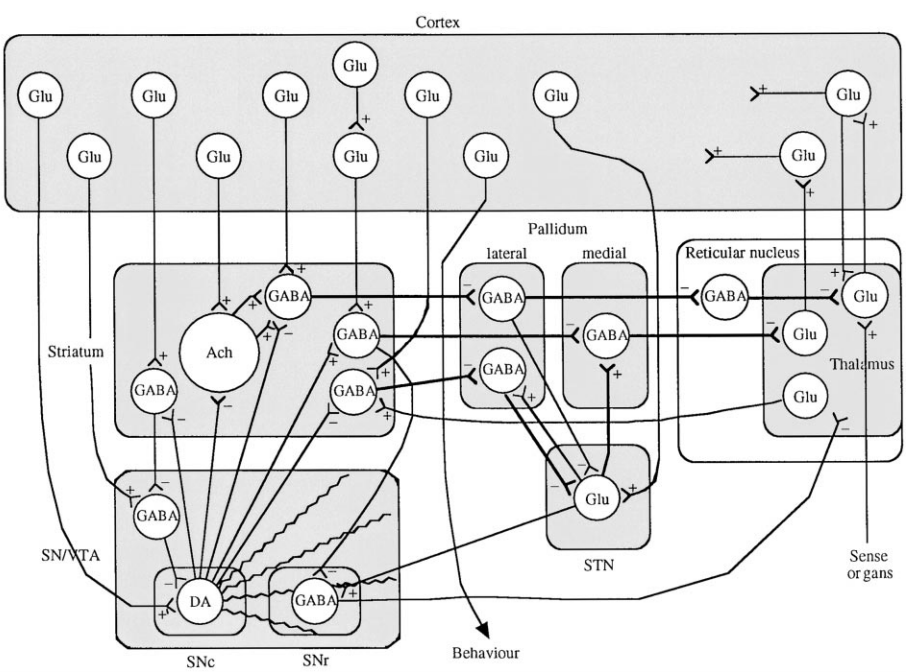

Fig. 3. Neurocircuitries of the basal ganglia. In this figure the striatopallidothalamic pathways are detailed. Among these, the top and bottom pathways drawn with thick lines contain three gabaergic neurons and are referred to as 'indirect' pathways. The pathway in between contains two gabaergic neurons and is referred to as 'direct' (modified from [9]). Explanation: SN = substantia nigra. VTA = ventral tegmental area. STN = subthalamic nucleus. Glu = glutamate. Ach = acetylcholine. DA = dopamine.

nized by a metabotropic receptor agonist, and at the same time the PCP-induced elevation of glutamate release was antagonized. The question arises if 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 e.g. dopamine release. 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 highly speculative.

As mentioned, the dopaminergic projections to the indirect striatothalamic pathways appear to be predominantly inhibitory. 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.

6. Comparing two experimental schizophrenia models — therapeutic implications

At this point it is difficult to choose between the two major pharmacological models of schizophrenia, i.e. the hyperdopaminergia and the hypoglutamatergia model. This choice may have to await clinical trials comparing different pharmacological treatments. Animal data suggest that such a strategy is feasible. Whereas haloperidol turned out to be superior to M100907 in antagonizing amphetamine-induced hyperactivity, the reverse was true of MK-801-induced hyperactivity (Fig. 4, Ref. [12]). As yet it is not clear if M100907 does in fact possess antipsychotic activity; it will have to await the outcome of ongoing phase-3 trials. If the outcome is positive, the interesting question arises if some patients respond better to one type of drugs than to the other and if the reverse is true for other patients. Different patient populations and pathogenetic mechanisms may thus be distinguished. Alternatively, combined treatment will be superior to either treatment alone. This outcome may be predicted by the apparently superior efficacy of clozapine and other ‘atypical’ antipsychotic agents possessing both antidopaminergic and antiserotonergic activity, but the multiple sites of action of the ‘atypical’ group of antipsychotic agents make this prediction uncertain. An alternative interpretation of the ‘superiority’ of clozapine is that this has been demonstrated predominantly in ‘treatment-resistant’ cases of schizophrenia. Maybe many such cases belong to a hypoglutamatergic subpopulation, which would then be expected to respond better to a drug with strong 5HT2-receptor antagonistic properties, such as clozapine.

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, 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 metabotrophic glutamate receptors seem to offer promise.

7. Is the therapeutic potential of dopaminergic agents exhausted?

Several reasons support the view that a lot can be gained by trying to reach a deeper understanding of dopaminergic mechanisms. This may open up entirely new

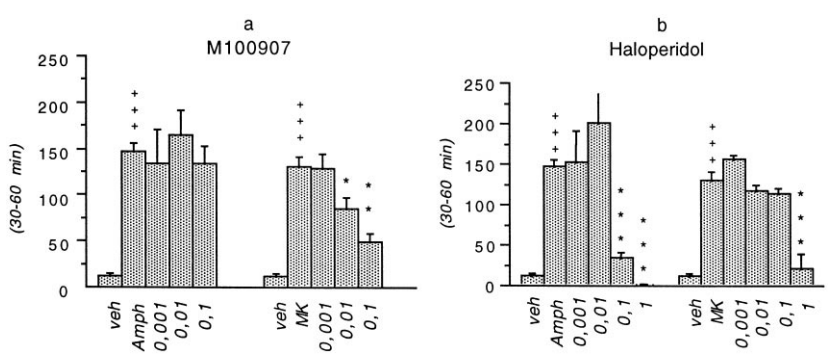

Fig. 4. (A):Effect of various doses of M100907 (0.001; 0.01; 0.1 mg/kg) on locomotion stimulated by D-amphetamine (Amph, 3 mg/kg) or MK-801 (0.3 mg/kg). All drugs were given immediately before the animals were placed in the activity meters, Statistics: Mann–Whitney U-test. + + + $p < 0.001$ vs. vehicle; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. D-amphetamine or MK-801. (B): Effect of various doses of haloperidol (halo, 0.001; 0.01; 0.1; 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, except D-CPPene which was given 60 min prior to the injection of haloperidol. 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 (from [12]).

ways to improve dopaminergic functions, e.g. by optimizing the receptors' ability to cope with aberrations in neural circuits. In support of this prediction some recent observations in our research group will be briefly mentioned.

We have developed a series of compounds which are capable of stabilizing the dopaminergic system in different ways without inducing the hypodopaminergia that seriously limits the utility of 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, for example, see [20]; a number of other partial agonists, such as the ergolines terguride and SDZ 208-912, are fairly unselective and thus less suitable for concept testing). Others seem to be pure antagonists on the D2 family of receptors, and can thus antagonize dopaminergic hyperfunction, but in contrast to the currently used antipsychotic agents they do not cause hypodopaminergia. In fact, they rather tend to antagonize subnormal dopamine function. Although the reason for this aberrant pharmacological profile is not yet fully understood, one reason may 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 [17,29,30]. In subhuman primates, in which Parkinsonism had been induced by MPTP, one member of this class, named (−)-OSU6162, has been found capable of preventing L-dopa-induced dyskinesias without interfering with the therapeutic movement response, and in subsequent trials on Parkinsonian patients the same kind of response was observed (J. Tedroff et al., unpublished data). Subsequent trials on patients with Huntington's disease 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 tone, that is, they are capable of alleviating signs of hyperdopaminergia without reducing dopaminergic function below the baseline level. 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.

8. Concluding remarks

Although remarkable progress has been made regarding the role of neural networks and neurotransmitters in schizophrenia, the available data can offer themselves to a variety of interpretations. In summarizing the data presented above we would like to present the following, tentative interpretation. While a number of subpopulations with different pathogenesis may exist among schizophrenic patients, a mechanism involving a glutamatergic deficiency appears to deserve special attention. This deficiency may well be secondary to, for example, a failure of connectivity arising at an early developmental stage. A glutamatergic deficiency located to the cortical association pathways could be responsible for a variety of cognitive and negative symptoms, even though failures of subcortical mechanisms located to, for example, the 'direct' striatothalamic pathways, may contribute.

A glutamatergic deficiency can bring about important aberrations of subcortical pathways. For example, the responsiveness to dopamine may become exaggerated, leading to an elevated dopamine function, and this may or may not cause a compensatory reduction of presynaptic dopaminergic activity. On the other hand, there is evidence of elevated serotonergic activity, probably located both pre- and postsynaptically, and both dopaminergic and serotonergic dysfunctions will probably contribute significantly to the positive, and presumably also to the negative symptomatology.

In addition, considerable attention will in the future have to be directed to the evolution of the disease process, trying to explain, for example, why psychotic episodes appear to lead to persisting deterioration. This raises the issue of possible excitotoxicity, perhaps caused by episodes of excessive glutamatergic function.

Regardless of the relevance of the picture given above, future research must attempt to incorporate into the overall thinking the events upstream as well as downstream to the receptors, on which the present discussion has been focusing. In addition, more attention must be directed to other neurotransmitters, such as acetylcholine, gaba and neuropeptides, which for reasons of space limitation have been largely or completely omitted in this review.

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