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NMDA receptor hypofunction model of schizophrenia

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Abstract

Several decades of research attempting to explain schizophrenia in terms of the dopamine hyperactivity hypothesis have produced disappointing results. A new hypothesis focusing on hypofunction of the NMDA glutamate transmitter system is emerging as a potentially more promising concept. In this article, we present a version of the NMDA receptor hypofunction hypothesis that has evolved from our recent studies pertaining to the neurotoxic and psychotomimetic effects of PCP and related NMDA antagonist drugs. In this article, we examine this hypothesis in terms of its strengths and weaknesses, its therapeutic implications and ways in which it can be further tested. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Recently, several research groups have begun to examine the potential role of the NMDA glutamate receptor system in schizophrenia. Original findings relevant to this inquiry date back to the 1950s when the dissociative anesthetic phencyclidine (PCP) was observed to induce a schizophrenia-like psychotic state in human subjects (Luby et al., 1959). These observations established PCP psychosis as an interesting drug model for studying schizophrenia. However, the link to NMDA glutamate receptors was not suspected until thirty years later when David Lodge and colleagues (Lodge and Anis, 1982; Lodge et al., 1987) generated evidence strongly implicating blockade of NMDA glutamate receptors as the primary mechanism by which PCP disrupts brain function. Subsequent evidence that numerous other drugs, which block NMDA glutamate receptors, all trigger acute psychotic reactions, prompted us and others to propose that a disturbance in NMDA glutamate receptor function might model the pathophysiology of schizophrenia.

Different research groups have developed different hypotheses revolving around the NMDA receptor hypofunction concept. The hypothesis presented here is one that we have developed in the course of investigating a pathomorphological neurotoxic syndrome induced in the adult rat brain by PCP and various other NMDA antagonists, all of which trigger psychotic reactions in adult humans. In this article, we will discuss the strengths and weaknesses of our hypothesis in terms of how well it can explain the cardinal signs and symptoms and natural course of schizophrenia, and will also address ways in which this hypothesis can be further tested.

2. The hypothesis

Simply stated, the hypothesis proposes that NMDA receptor hypofunction (NRHypo), the condition induced in the human or animal brain by an NMDA antagonist drug, might also be viewed as a model for a disease mechanism which could explain the symptoms and natural course of schizophrenia. The disease mechanism itself might involve dysfunction of the NMDA receptor or downstream effects that can be modeled by blocking NMDA receptors. One typical consequence

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of blocking NMDA receptors is excessive release of Glu (Moghaddam et al., 1997; Adams and Moghaddam, 1998) and acetylcholine (ACh; Hasegawa et al., 1993; Giovannini et al., 1994; Kim et al., 1999) in the cerebral cortex. It has been proposed that this excessive release of excitatory transmitters and consequent overstimulation of postsynaptic neurons might explain the cognitive and behavioral disturbances associated with the NRHypo state (Olney and Farber, 1995; Moghaddam et al., 1997; Adams and Moghaddam, 1998). It is assumed that both genetic and nongenetic factors can contribute to the NRHypo state and that this state is instilled in the brain early in life as a latent condition with the potential to erupt and trigger psychotic manifestations in adulthood but not usually in pre-adult life. We propose that it usually lacks the potential to produce psychotic symptoms in pre-adult life because certain maturational changes in the brain's circuitry have to occur before its pathological potential can be expressed. After these maturational changes have occurred, the NRHypo state has the potential to trigger the full spectrum of schizophrenia-type symptoms and, in extreme cases, to cause ongoing structural pathology and clinical deterioration.

3. Evidence supporting the hypothesis

3.1. Psychosis associated with the NRHypo state

Although it can be debated whether the psychotic reaction to PCP is identical in all respects to a schizophrenic psychosis, most investigators agree that the similarities in several major symptom categories are quite impressive, that a PCP psychosis is diagnostically difficult to differentiate from schizophrenia (Yesavage and Freeman, 1978) and that PCP mimics the symptoms of schizophrenia more faithfully than do other psychotomimetic drugs, including LSD and amphetamines (Javitt and Zukin, 1991). PCP has also been shown to trigger a prolonged recrudescence of acute psychotic symptoms in stable chronic schizophrenia patients, and representatives of other drug categories, including LSD, do not reproduce this phenomenon (Rosenbaum et al., 1959; Cohen et al., 1962). In addition, a long list of NMDA antagonists, essentially all that have been adequately tested in humans, can trigger a florrid psychotic reaction that is qualitatively similar to a PCP psychosis (Domino and Luby, 1981; Kristensen et al., 1992; Herrling, 1994; Krystal et al., 1994; Grotta et al., 1995; Malhotra et al., 1996; Muir et al., 1997; Newcomer et al., 1999a). Some of these drugs block NMDA receptors by a competitive mechanism at the glutamate recognition site outside the ion channel and some by a noncompetitive mechanism inside the ion channel. Since the single feature that all of these drugs have in common is that they induce an NRHypo state, it is reasonable to propose than an NRHypo state, if present in the brain of a schizophrenic patient, could explain significant elements of the mental disturbances characteristic of that illness.

3.2. Structural brain changes associated with the NRHypo state

We have found in experimental animal studies that if the increased release of Glu and ACh induced by NRHypo is pronounced, certain postsynaptic neurons can develop either reversible or irreversible morphological changes, depending on the duration and severity of the NRHypo state (Olney and Farber, 1995). We propose that moderately increased neurotransmitter release and associated overstimulation of postsynaptic neurons can explain cognitive and behavioral symptoms in schizophrenia. If the NRHypo state and associated excitatory transmitter release is unremittingly severe on a chronic basis, it can lead to neurodegenerative changes that would explain the deterioration seen in some patients. For research purposes, creating a drug-induced NRHypo state in the rodent brain provides a highly effective means of identifying neuronal populations that are at risk of being hyperstimulated and eventually injured or killed as a consequence of the NRHypo state. Findings indicate that a protracted NRHypo state can trigger neuronal injury throughout many corticolimbic brain regions (Ellison and Switzer, 1993; Ellison, 1994; Corso et al., 1997; Horvath et al., 1997; Wozniak et al., 1998). If the severe NRHypo state is relatively brief, the pathological changes are limited to a reversible vacuole reaction affecting cytoplasmic organelles in specific neurons of the posterior cingulate and retrosplenial cortex (Olney et al., 1989), whereas a prolonged severe NRHypo state causes irreversible degeneration and death of neurons in many corticolimbic brain regions (Corso et al., 1997; Fig. 1). Presumably many of these hyperstimulated neurons might be instrumental in producing psychotic symptoms. Finally, this animal model provides an opportunity to test pharmacological approaches for preventing the NRHypo state from hyperstimulating and injuring neurons. A careful analysis of the pharmacological interventions that are protective can also provide insights into the circuitry and receptor mechanisms that mediate this pathological process.

If NRHypo-related hyperstimulation is present in the brain of a schizophrenia patient, then it is reasonable to propose that psychotic symptoms could be produced by mild hyperstimulation accompanied by either no pathological changes or a limited and reversible reaction. However, sustained levels of severe hypersti-

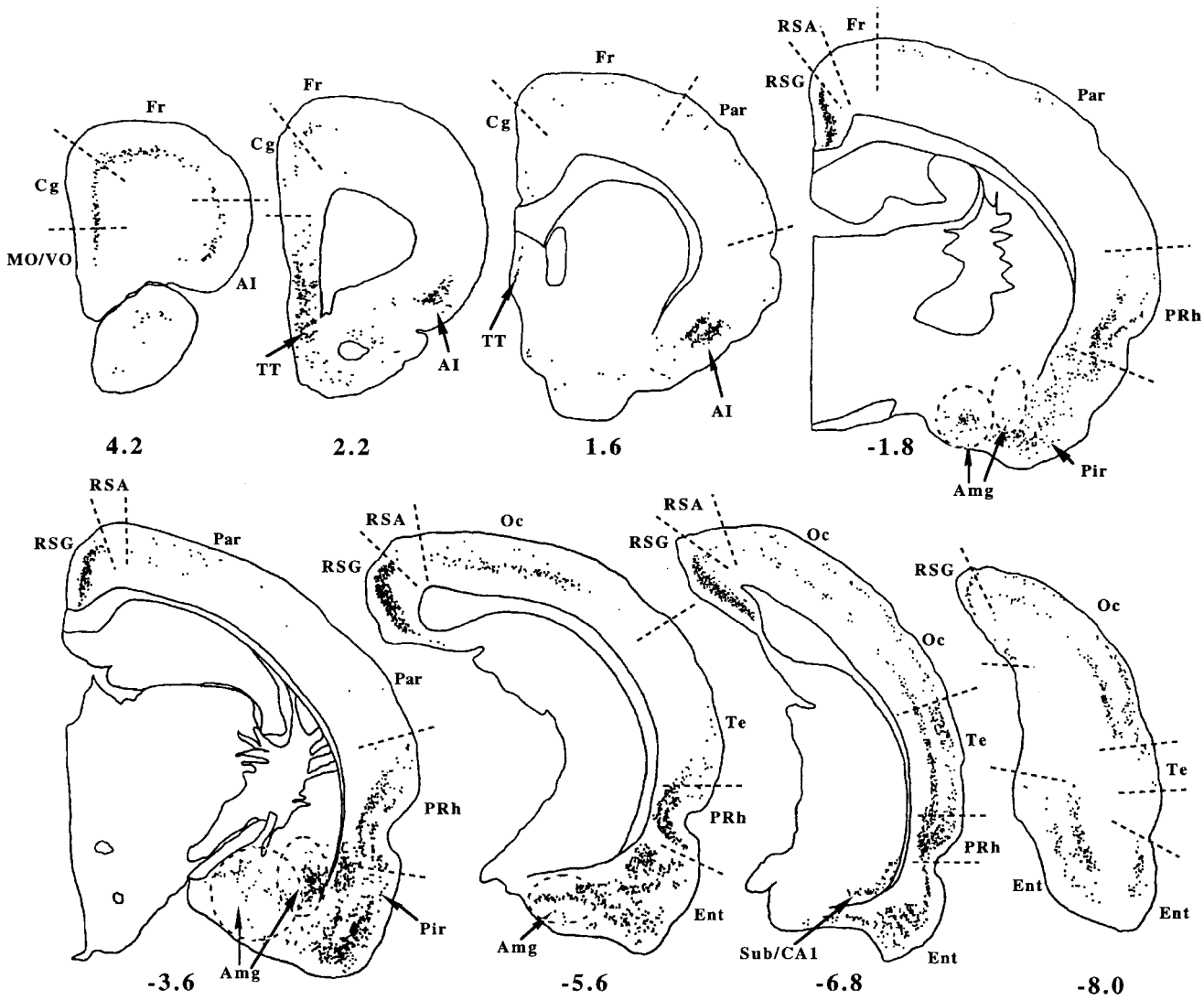

Fig. 1. Schematic representation of the distribution of degenerating neurons at eight rostrocaudal levels of the adult rat brain 4 days following treatment with a high dose of an NMDA antagonist. These cell plots illustrate the neuronal populations that are primarily at risk to degenerate when the NMDA receptor system is rendered profoundly hypofunctional. At risk populations include pyramidal and multipolar neurons in the prefrontal, posterior cingulate and retrosplenial, occipital, temporal, parietal, entorhinal, perirhinal and piriform cortices and in the anterior olfactory nucleus, taenia tecta, amygdala and hippocampus. Rostro-caudal level and anatomical nomenclature are from Paxinos and Watson (1986). The number under each cell plot is the distance in mm from Bregma. AI: agranular insular cortex, Amg: amygdala, Cg: anterior cingulate, Ent: entorhinal cortex, Fr: frontal cortex, MO/VO: medial orbital/ventral orbital cortex, Oc: occipital cortex, Par: parietal cortex, Pir: piriform cortex, PRh: perirhinal cortex, RSA: retrosplenial agranular cortex, RSG: retrosplenial granular cortex, Sub/CA1: subiculum/CA1 field of hippocampus, Te: temporal cortex, TT: taenia tecta. Note: The area designated as RSG is the equivalent to the region referred to herein as PC/RS. See Corso et al. (1997) for histological documentation of this degeneration pattern.

mulation could cause psychotic manifestations accompanied by ongoing structural pathology that may vary from negligible and undetectable changes to extensive changes that are readily detectable by brain imaging methods. Regarding glial scarring, although it is accepted as a general rule that neurodegenerative reactions in the adult brain produce scarring, NRHypo-induced neurodegeneration in the adult rat brain is an exception to that rule. Studies employing histochemical stains for glial fibrillary acidic protein (astrocyte stain) or for activated microglia have shown that when a high percentage of the neuronal population in the posterior cingulate cortex is destroyed by treatment with an NMDA antagonist drug there is a transient increase in the markers for these two types of glia lasting for several days and soon thereafter these markers return to normal (Fix et al., 1995). Thus, the observation that structural brain changes in schizophrenia are not associated with evidence for gliosis could signify either that the changes occurred during development or that they occurred by an NRHypo mechanism during adulthood. Our NRHypo hypoth-

esis proposes that structural brain changes can occur both during development and in adulthood.

3.3. Mechanism by which the NRHypo state triggers psychosis and the potential for structural brain changes

Our evidence suggests that blockade of NMDA receptors triggers a complex network disturbance featuring inactivation of inhibitory neurons and consequent disinhibition of excitatory pathways as the core mechanism by which psychotogenic NMDA antagonist drugs injure neurons in various corticolimbic brain regions. We propose that the same core mechanism and neural network disturbance underlie both the psychotoxic and neurotoxic effects of NMDA antagonist drugs, the psychotoxic effects being triggered by a relatively mild network disturbance and the neurotoxic effects requiring a more severe disturbance. Supporting this proposal is evidence that several classes of drugs that prevent the neurotoxic effects in rats also attenuate the psychotomimetic effects in humans, and evidence that both the neurotoxic effects in rats and psychotomimetic effects in humans have the same age dependency profile (discussed below).

3.3.1. Complex polysynaptic network disturbance is the pathophysiological mechanism

Using NMDA antagonist drugs as tools for inducing an NRHypo state in animal brain, we have learned that many classes of drugs, including $GABA_A$ agonists, muscarinic antagonists, nonNMDA Glu antagonists, sigma agents, α_2-adrenergic agonists, $5HT_{2A}$ agonists and novel antipsychotics such as clozapine and olanzapine, abort the mechanism by which the NRHypo state damages the brain (Olney et al., 1991; Farber et al., 1993; Farber and Olney, 1995; Ishimaru et al., 1995; Farber et al., 1996, 1997, 1998; Jevtovic-Todorovic et al., 1997). This has provided insight into the neural circuitry that mediates this neurotoxic process (Fig. 2) and implicates transmitter receptors of at least seven different types (NMDA Glu, nonNMDA Glu, m_3-muscarinic, α_2-adrenergic, $GABA_A$, sigma and $5HT_{2A}$).

3.3.2. Disinhibition is the core principle

An important lesson we have learned from the above studies is that Glu functions not only as a straightforward excitatory agent in the brain, but as a major regulator of inhibitory tone. Glu achieves this by tonically activating NMDA receptors on GABAergic, serotonergic and noradrenergic neurons, thereby driving these neurons to inhibit the activity of major excitatory pathways (both glutamatergic and cholinergic) that convergently innervate primary neurons in cerebrocortical and limbic brain regions (Fig. 2). These primary neurons use Glu as transmitter and

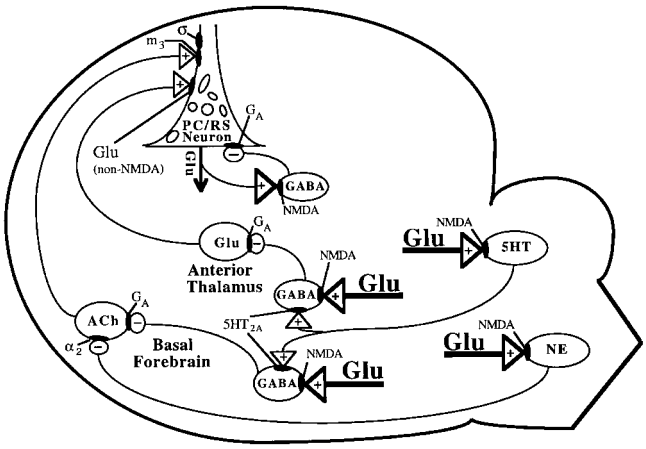

Fig. 2. To explain NRHypo-induced neurotoxicity of posterior cingulate and retrosplenial (PC/RS) neurons, we propose that Glu acting through NMDA receptors on GABAergic, serotonergic and noradrenergic neurons maintains tonic inhibitory control over multiple excitatory pathways that convergently innervate PC/RS neurons. Systemic administration of an NMDA receptor antagonist (or NRHypo produced by any mechanism) would simultaneously abolish inhibitory control over multiple excitatory inputs to PC/RS neurons. This would create chaotic disruption among multiple intracellular second messenger systems, thereby causing derangement of cognitive functions subserved by the afflicted neurons, as well as eventual degeneration of these neurons. This circuit diagram focuses exclusively on PC/RS neurons. However, we hypothesize that a similar disinhibition mechanism and similar but not necessarily identical neural circuits and receptor mechanisms mediate damage induced in other corticolimbic brain regions by sustained NRHypo. (+) = excitatory input; (−) = inhibitory input; ACh = acetylcholine; NE = norepinephrine; σ = sigma binding site; 5HT = serotonin; $\alpha_2 = \alpha_2$ subtype of adrenergic receptor; $G_A = GABA_A$ subtype of GABA receptor; $m_3 = m_3$ subtype of muscarinic cholinergic receptor; nonNMDA = nonNMDA subtype of Glu ionotropic receptor; NMDA = NMDA subtype of Glu receptor. $5HT_{2A} = 5HT_{2A}$ subtype of 5HT receptor.

they regulate their own firing by sending a recurrent inhibitory collateral to an NMDA receptor on a GABAergic neuron that feeds back onto the primary neuron. When the NMDA receptors in the overall network are blocked or impaired, it results in a complex disinhibition syndrome in which the major excitatory pathways are released from inhibition, which causes them to hyperstimulate the primary corticolimbic neurons. In addition, the feedback inhibitory loop is inactivated due to the NMDA receptor blockade so that it fails to regulate the firing of the primary neurons. Thus, the primary neurons are being excessively stimulated through disinhibited excitatory inputs at the same time that they have lost control over their output to many other neurons, an excellent formula for disrupting normal mental functions and producing unmodulated noise in corticolimbic circuits; in other words, a formula for producing mental aberrations, like positive psychotic symptoms. Since the NRHypo state involves dysfunction of both NMDA receptors and

muscarinic cholinergic receptors and both of these receptor systems are implicated in the mediation of memory functions, we can begin to understand cognitive and especially memory impairments produced by NMDA antagonist drugs (Newcomer et al., 1999a,b) as well as disturbances in cognition that have been described as an early manifestation of a schizophrenic illness. If the excessive excitatory input to the primary neurons is persistent and severe enough it will injure and eventually kill these neurons, thereby silencing their firing upon other neurons. This may explain the progressive clinical deterioration observed in some patients, including the manifestation of certain enduring negative symptoms, positive symptom 'burnout' and progressive cognitive impairments.

3.3.3. Role of dopamine

Our circuit diagram (Fig. 2) implicates many different transmitter receptors as intrinsic components of the NRHypo network, each receptor system exerting either an excitatory or inhibitory influence contributing to the dynamic equilibrium of the network. Conspicuously absent from the list of intrinsic components is the D_2 dopamine receptor, the single receptor system that has dominated schizophrenia research for the last several decades. Does this signify that D_2 receptors play no role in the NRHypo model? No, quite the contrary. We have found no evidence that D_2 receptors function internally within the network, but we postulate that they may be exceedingly important extrinsic regulators of the network. However, conceptually we hold a position that appears to be at odds with the prevailing viewpoint. Numerous investigators in recent years have begun shifting the emphasis of their research from the DA to the NMDA receptor system, and the strategy being followed most frequently is to search for evidence that the NMDA receptor system wields an influence over the DA system, thereby causing dysfunction of the DA system to explain psychotic symptom formation. According to our concept (see Olney and Farber, 1995) the type of interaction between the DA and NMDA systems that could best explain psychotic symptom formation would be one in which the DA system wields influence over the NMDA system. Specifically, we postulate that at critical points in the circuitry that mediates NRHypo effects, D_2 receptors may regulate the release of Glu at NMDA receptors. If so, in schizophrenia a genetically determined aberration in the DA system causing hyperinhibition of Glu release would result in an NRHypo state that can explain psychotic symptom formation, and treatment with a D_2 antagonist would normalize Glu release, relieve the NRHypo state and attenuate the psychosis (thus explaining why D_2 antagonists are beneficial in schizophrenia). Paul Greengard and colleagues (Greengard et al., 1998) have recently reported evidence that in many brain systems DA receptors do regulate the NMDA receptor system as we have proposed.

3.4. Genetic mechanisms that might contribute to an NRHypo state

We do not have evidence for a specific genetic mechanism that produces an NRHypo state in schizophrenia, but clearly there are many ways in which various transmitter systems could be genetically altered to give rise to a network disturbance that would render critical components of the NMDA receptor system hypofunctional. This would include a primary disturbance in the DA system, which causes DA to hyperinhibit the release of Glu at NMDA receptors, thereby rendering the NMDA receptor system hypofunctional. In addition, various NRHypo 'equivalent' conditions could similarly produce the relevant network disturbance, such as a primary disturbance in the GABAergic system that prevents Glu from acting through NMDA receptors on GABAergic neurons to regulate inhibitory tone. In this case the NMDA receptor system itself might be normal or even hyperfunctional (not hypofunctional) but the network disturbance caused by the GABAergic deficit would manifest as an NRHypo-type of disinhibition syndrome. Similarly, a primary disturbance in noradrenergic or serotonergic neurons could result in an NRHypo 'equivalent' condition. In all such cases, the NRHypo (or NRHypo 'equivalent') genetic disturbance might be sufficient in itself to cause a phenotypically expressed schizophrenic illness. Or, it could merely establish an NRHypo predisposition that requires the contribution of a nongenetic factor for phenotypic expression.

3.5. Nongenetic mechanism by which the NRHypo state may be instilled in the developing brain

During a specific stage in development, the synaptogenesis stage, neurons with NMDA receptors are exquisitely sensitive to Glu stimulation, and the amount of Glu stimulation must be regulated within narrow bounds, because either too much or too little can be lethal for the NMDA receptor-bearing neuron. Too much Glu stimulation results in *excitotoxic* neurodegeneration (Ikonomidou et al., 1989), and too little Glu stimulation results in *apoptotic* neurodegeneration (Ikonomidou et al., 1999). In either case, the neurons deleted from the brain are neurons that have NMDA receptors on their surface and the deletion of these NMDA receptor-bearing neurons produces an NRHypo state.

Hypoxia/ischemia, which causes excessive amounts of Glu to be released at NMDA receptors, is a prime example of too much Glu stimulation causing an exci-

totoxic lesion leading to an NRHypo state. We propose that this type of lesion can be triggered in the developing brain by a mechanism as simple as compression of the umbilical cord.

Exposure of the in utero fetus to an NMDA antagonist drug is a prime example of too little Glu stimulation causing apoptotic neurodegeneration leading to an NRHypo state. We have shown (Ikonomidou et al., 1999) that exposure of the developing rodent brain in vivo to any of several NMDA antagonists (e.g., MK801, PCP, CPP, ketamine) in doses that maintain blockade of NMDA receptors for 4 or more hours during the synaptogenesis period triggers a massive wave of apoptotic neurodegeneration deleting millions of neurons from several major regions of the developing brain (all major divisions of the cerebral cortex, several thalamic nuclei, hippocampus, caudate nucleus, globus pallidus, nucleus accumbens). In addition, we have recently discovered (Olney et al., 1998, 1999; Price et al., 1999) that administering ethanol, which is known to have NMDA antagonist properties, to immature rats, mice or guinea pigs during the synaptogenesis period induces a pattern of apoptotic neurodegeneration similar to but more extensive than that induced by other NMDA antagonist drugs. Doses of ethanol that maintain blood ethanol levels in the 180 mg% range for 4 or more hours are sufficient to trigger this neurodegenerative syndrome. These new findings support the interpretation that developing neurons depend on NMDA receptor stimulation for survival and are programmed to commit suicide (die by apoptosis) if deprived of this stimulation for several consecutive hours during synaptogenesis. Thus, we use the acronym, NRD (NMDA receptor deprivation), to refer to this developmental neuropathology mechanism. NMDA antagonists, by blocking NMDA receptors, deprive neurons of critical Glu receptor input and, thereby, delete millions of neurons that would not otherwise be deleted from the developing brain.

3.6. Consequences of instilling an NRHypo state in the developing human brain

It is well known that exposure of human fetuses to ethanol can cause neurodevelopmental deficits [fetal alcohol syndrome (FAS) or fetal alcohol effects (FAE), depending on severity], and our new evidence signifies that one major mechanism by which ethanol causes such deficits is by deleting NMDA receptor-bearing neurons from the fetal brain. Thus, the FAE/S provides an instructive example of a human neurodevelopmental brain disorder in which widely distributed NRHypo neuropathology is instilled in the developing brain during synaptogenesis (third trimester of pregnancy).

In a recent study (Famy et al., 1998), a large cohort of human subjects with a childhood diagnosis of FAE/S were studied as adults and it was determined that a very high percent (72%) of these individuals required psychiatric care for diverse adult-onset disorders, including a 40% incidence of psychosis. To fully appreciate the potential significance of this observation, an additional aspect of our recent findings must be factored in. We have found that different neuronal groups become sensitive to the NRD mechanism at different times within the synaptogenesis period (because each group has its own schedule for forming synaptic connections). Therefore, different combinations of neuronal groups will be deleted from the brain by a NRD event, depending on whether the event occurs in the early, mid or late phase of the synaptogenesis period. It follows that the NRD mechanism can produce a wide variety of dysfunctional syndromes, each having its own constellation of neurobehavioral disturbances. Presumably certain patterns of neuronal loss would be more conducive to producing a psychotic behavioral outcome than others. Therefore, in the Famy et al. study it is possible that the 40% of FAE/S individuals who displayed psychotic symptoms as adults were a subgroup who were exposed to ethanol at a time when a psychotogenic combination of NMDA receptor-bearing neurons were at peak vulnerability for being deleted by the NRD mechanism.

To establish the relevance of these observations to schizophrenia, it is not necessary to prove that fetal ethanol exposure by itself causes an adult psychotic disorder mimicking all features of schizophrenia. It is sufficient to view ethanol as a nongenetic factor which can act in concert with genetic factors to tip the balance and potentially cause a genetic predisposition for schizophrenia to be clinically expressed.

3.7. Schizophrenia and NRHypo disturbances have the same age dependency profile

If the NRHypo state is already present in the schizophrenic brain during infancy and childhood, why does it not begin to trigger psychotic and neurotoxic effects until early adulthood? This fundamental enigma of schizophrenia is readily explained by the nature of the NRHypo mechanism. It depends on a chain reaction initiated by an interference in one transmitter system which triggers a change in a second transmitter system, then a third and so on until an end point is reached which involves hyperactivation and neuropsychotoxic impingement upon neurons that are at the end of the synaptic series. This chain of events cannot occur unless the entire series of synaptic connection is in place, which we postulate does not happen until late adolescence. Evidence supporting this postulation is as follows: (1) administering NMDA antagonist drugs in doses that induce a profound NRHypo state causes cerebrocortical neuronal injury in adult animals but

not in fetal, infant or juvenile animals (Farber et al., 1995); (2) administering NMDA antagonist drugs in high doses triggers psychotic reactions in adult but not pre-adult humans (e.g., ketamine, an NMDA antagonist used in anesthesia, triggers a psychotic reaction in human adults but not in children, and for this reason ketamine is used much more frequently today in pediatric than adult anesthesia; Reich and Silvay, 1989). The fact that schizophrenia also shares this age dependency profile (onset of susceptibility in young adulthood) lends credibility to the proposal that an NRHypo mechanism may play a role in schizophrenia.

4. Explanatory power versus inconsistencies and shortcomings of the model

Most investigators agree that both genetic and non genetic factors play a role in the pathogenesis of schizophrenia but progress has been slow in identifying specific mechanisms, either genetic or nongenetic, that can explain various features of the disease process, including adult onset of psychosis, heterogeneity of presenting symptom complexes, chronicity of the mental dysfunction and occurrence of structural brain changes. Most investigators agree that structural brain changes are a key feature of schizophrenia, but there is very little agreement regarding the nature, regional distribution, timing or origin of such changes and it is not known precisely how the structural changes relate to the mental disturbances.

Our hypothesis identifies mechanisms, both genetic and nongenetic, which individually or in combination might resolve many of these issues and provide a plausible explanation for many of the fundamental features of schizophrenia. The NRHypo hypothesis addresses these issues first by demonstrating that specific structural changes can occur in the developing human brain that instill an NRHypo state, which has the potential to give rise in adulthood to a polysynaptic network disturbance that can produce both psychotic disturbances and ongoing structural brain changes. Thus, it resolves the vexing issue of whether the structural brain changes occur during development or in adulthood, by concluding that this is not an either/or issue — structural changes can occur both during development and in adulthood. It also resolves an issue revolving around an argument that structural brain changes in schizophrenia can only be of developmental origin because they are not accompanied by gliosis. This becomes a nonissue by the demonstration that the NRHypo type of neurodegeneration can occur in the adult brain without enduring gliosis.

Our hypothesis resolves the age of onset issue by evidence that the NRHypo state is not capable of triggering psychoneurotoxic effects until adulthood (the putative reason being that the pre-adult brain lacks the wiring to support the mechanism by which these effects are triggered). If our hypothesis is correct that an NRHypo mechanism causes the structural brain changes (in adulthood), this would help in understanding the nature, regional localization, timing and origin of such changes because we have published extensive evidence clarifying the nature and extensive regional distribution of structural changes induced in rat brain by the NRHypo state. On the other hand, this hypothesis raises new questions about the nature of childhood-onset schizophrenia.

An important way in which the NMDA antagonist-induced NRHypo model fails to mirror schizophrenia precisely is that NMDA antagonist drugs render NMDA receptors hypofunctional throughout the brain, and this disrupts every brain circuit containing NMDA receptors, but we assume that in schizophrenia the defect state will be more selective for specific circuits or subcomponents within specific circuits. Heterogeneity of presenting symptoms may be partially explained by differences in the severity of the network disinhibition, or differences in the specific corticolimbic circuits that are affected by the NRHypo state.

Heterogeneity of symptoms may also be explained by the demonstration that when an NRHypo state is instilled in the developing brain it has the potential to produce a variety of different neurobehavioral symptom complexes depending on whether this occurs during the period of synaptogenesis, and exactly when during this period. This is necessarily so because when it is instilled at one stage it is associated with one pattern of neuronal degeneration and when it is instilled at another stage it is associated with a different pattern of neuronal degeneration. Chronicity of mental dysfunction is explained by the fact that when the NRHypo state is instilled during development it is instilled as a permanent change in the structural makeup of the brain, altering subsequent brain development, so that circuit changes remain present in the brain throughout life as a generator of adult-onset mental disturbances.

For many years, a preoccupation with dopamine has dominated research in the schizophrenia field. The NRHypo hypothesis provides an alternate conceptual framework that has additional explanatory power, including the ability to explain, in NRHypo terms, why DA antagonists are therapeutically beneficial in schizophrenia. If this concept is correct, it does not depreciate the importance of DA but opens new paths for progress toward understanding how dysfunction of the DA, NMDA and many other transmitter systems may contribute to the pathophysiology of schizophrenia.

An apparent inconsistency between the NRHypo model and schizophrenia is that some of the pharma-

cological agents (e.g. GABA agonists) that prevent the neuropsychotoxicity of NMDA antagonist drugs are not routinely used as monotherapy in schizophrenia, although they may be used as important adjunctive agents (Wolkowitz and Pickar, 1991; Hollister et al., 1993; Carpenter et al., 1999). Since the initial pathological event that renders NMDA receptor-bearing GABAergic neurons defective in schizophrenia is proposed to occur in prenatal life, it must be recognized that complex plastic changes during brain development will occur, further altering the damaged network and potentially drastically altering responsivity of the network to decades-later pharmacological interventions. For example, if the developmental lesion consists of depletion of NMDA receptor-bearing GABAergic neurons, this will instill a permanent NRHypo state and will ensure that the circuit depicted in Fig. 2 will function abnormally throughout life. It is a circuit that is bereft of a key component required for maintenance of inhibitory balance. If GABA agonist drugs are applied 20 years later in adulthood to correct the imbalance, this will not likely be as successful because the GABA receptors with which the drug must interact will have been deleted from the brain or will have been reconnected in some aberrant manner. The NMDA antagonist-induced NRHypo model involves transiently inducing the NRHypo state in the normal adult brain and simultaneously reversing this state by co-administration of another drug. This obviously is quite different from permanently instilling an NRHypo state in the developing brain by the depletion of developing neurons, and 20 years later after extensive aberrant rewiring has occurred, applying drugs to the altered nervous system to reverse symptoms produced by the initial deletion of developing neurons plus all of the subsequent pathological alterations.

5. Approaches for testing the model

5.1. Pharmacological approaches

As discussed above, because the proposed defect in schizophrenia is developmental, this complicates and may effectively sabotage certain seemingly rational treatment approaches. However, if we are correct in postulating that specific excitatory receptors on the surface of primary cerebrocortical neurons are being hyperstimulated and that this contributes substantially to either psychotic or neurodegenerative manifestations of the illness, blocking these excitatory receptors might be of therapeutic value. Evidence supporting this proposal is provided by Tandon and colleagues who have shown that anti-muscarinic therapy may ameliorate negative symptoms of schizophrenia (Tandon and Greden, 1989; Tandon et al., 1991). In addition, it is possible that anti-muscarinic therapy prescribed for control of extrapyramidal symptoms in recent decades has prevented or diminished the progressive downhill course that some schizophrenic patients would have experienced in the absence of such treatment. This could explain any decreases in recent decades in the average severity of illness observed for patients with this disorder. This possibility should be further studied systematically, perhaps by both retrospective and prospective research designs. Regarding the other main excitatory receptor system (nonNMDA Glu) that would be rational therapeutic targets, the hypothesis remains entirely untested, in that there have not been any selective nonNMDA Glu antagonists available for testing. However, currently some antagonists of the Glu-AMPA receptor are being entered into clinical trials for the treatment of stroke and head trauma. These agents cross-react with both AMPA and kainate receptors, so it is possible that they might be therapeutically beneficial in schizophrenia either as antipsychotic agents or as therapies to prevent deterioration.

In animal studies, an effort should be made to further clarify the interactive relationship between the dopamine and NMDA receptor systems. Specifically, evidence should be sought that DA receptors regulate the release of Glu at certain NMDA receptors within the neural network depicted in Fig. 2.

In rodent studies, we are currently applying microdialysis methods to corroborate the role of ACh and Glu in the neurotoxic effects of NMDA antagonist drugs. Thus far, we have found that systemic administration of such drugs to the adult rat causes massive elevation of ACh in the posterior cingulate cortex and that clonidine, an α_2 adrenergic agonist that protects against NMDA antagonist neurotoxicity in the posterior cingulate cortex prevents the elevation of ACh (Kim et al., 1999). Others have found that NMDA antagonists cause an excessive release of Glu in corticolimbic areas (Moghaddam et al., 1997; Adams and Moghaddam, 1998). Additional valuable information can be obtained by further application of microdialysis methods.

In human studies by several research groups an NRHypo-inducing drug (ketamine) has been administered to human volunteers in low doses that produce very mild and rapidly reversible psychotomimetic symptoms, then various drugs that are known to prevent NRHypo neurotoxicity are co-administered with ketamine in an attempt to suppress the emergence of psychotomimetic symptoms. Thus far, clozapine, guanabenz (an α_2 adrenergic agonist) and lamotrigine (prevents NRHypo neurotoxicity by an unknown mechanism) have been tested in this paradigm and have been shown to be effective in suppressing the expression of psychotomimetic symptoms (Anand et al., 1997; Malhotra et al., 1997; Newcomer et al., 1998).

While a single low dose of lorazepam does not suppress ketamine-induced psychotomimetic symptoms (Krystal et al., 1998), higher doses do attenuate the psychotomimetic effects induced by anesthesic doses of ketamine (Dundee and Lilburn, 1978) supporting the practice in anesthesiology of using agents that promote $GABA_A$ neurotransmission, including benzodiazepines and barbiturates, to attenuate ketamine-induced reactions (Magbagbeola and Thomas, 1974; White et al., 1982; Reich and Silvay, 1989). Finally, haloperidol, a D_2 antagonist, does not suppress ketamine-induced psychosis (Krystal et al., 1999) just as antagonism of D_2 receptors does not suppress NRHypo neurotoxicity in the rat (Farber et al., 1993). All of these observations are consistent with the assumption that the same receptor mechanisms and neural network disturbance underlie NRHypo neurotoxicity and NRHypo psychotomimetic effects. Therefore, continued investigation using this research strategy is warranted and should provide further valuable insight into mechanisms and neural pathways that mediate psychotic symptom formation in humans.

The finding that clozapine and olanzapine are quite effective in preventing the neurotoxic action of NRHypo-inducing drugs should be explored systematically to clarify specifically which and how many transmitter receptor systems mediate this protective action. We postulate that several receptors may be critical for conferring protection in the animal model, and once these receptors are identified, drugs that interact selectively with each identified receptor should be administered individually and in combination to schizophrenic patients in well designed and carefully controlled studies, to determine whether the same combination of receptors that mediate neuroprotection in the animal model mediate the therapeutic benefits of these drugs in schizophrenia.

5.2. Neurohistological, neuropathological and neuroimaging approaches

We propose that disinhibition is the core principle underlying NRHypo effects and that there are a large number of pathological mechanisms that could make this principle operative. In essence, any mechanism that impairs or interferes with the maintenance of inhibitory tone in the type of network illustrated schematically in Fig. 2 would qualify. Although the network in Fig. 2 is derived from observations pertaining to an NRHypo neurotoxic syndrome preferentially affecting primary neurons in the posterior cingulate cortex, we hypothesize that a similar disinhibition mechanism and similar but not necessarily identical neural circuits and receptor mechanisms mediate damage that we have shown can be induced in other corticolimbic brain regions by the NRHypo mechanism (Fig. 1). Thus, the search in human brain for the pathomorphological substrates of schizophrenia should not be limited to a specific network subserving the posterior cingulate cortex but should have a broader focus that includes similarly organized circuits subserving and interconnecting a variety of corticolimbic brain regions.

An appropriate test of the NRHypo model would be to conduct histological studies on post mortem schizophrenia brains using transmitter-specific marker techniques to trace defects to specific types of neurons or receptor systems within the type of circuitry depicted in Fig. 2. As an aid to interpreting such studies it is essential that we have accurate information regarding the normal wiring of such circuits (e.g., Jakab and Goldman-Rakic, 1998; Mrzljak et al., 1998; Muly et al., 1998; Williams and Goldman-Rakic, 1998).

In currently ongoing studies at Washington University NRHypo-inducing drugs are being administered to nonhuman primates and the brains are studied by PET neuro-imaging. In addition, monkey studies are being conducted to clarify susceptibility of the primate brain to NRHypo-induced neuropathological changes and to correlate NRHypo-induced metabolic changes in various regions of the primate brain (neuro-imaging observations) with neuropathological changes in these regions. Based on information gained from monkey studies, it may be possible in the future to conduct more informative neuro-imaging studies in humans.

5.3. Neurodevelopmental approach

Our recent finding that various patterns of neurodegeneration can be induced in the developing brain by transient blockade of NMDA receptors during the synaptogenesis period and that this instills an NRHypo state in the developing brain provides an opportunity to induce various NRHypo-instilling patterns of neurodegeneration in the developing animal brain and determine what constellation of neurobehavioral sequelae is produced by each pattern of neuronal loss.

6. Summary

Here we have discussed the NRHypo concept which explains schizophrenia on the basis of genetic and/or nongenetic mechanisms instilling an NRHypo state with related circuit disinhibition in the developing brain, and this state remaining quiescent until early adulthood when maturational changes in brain circuitry make the brain vulnerable to the psychotogenic and neurotoxic potential of the NRHypo state. It assumes that if the

NRHypo state is relatively mild only the psychotogenic potential will be expressed, but if the NRHypo state is particularly severe and of long duration, both the psychotogenic and neurotoxic potential will be expressed, which will result in a chronic psychosis complicated by ongoing structural brain changes and the potential for clinical deterioration. If this concept is correct, chronic treatment with certain drugs, including olanzapine, clozapine, lamotrigine, α_2 adrenergic agonists and perhaps antimuscarinic agents, would be advisable based on our studies which show that these drugs effectively arrest the neurotoxic process associated with the NRHypo state. In general, our animal model for NRHypo-associated neurotoxicity provides an opportunity to test pharmacological approaches for preventing the NRHypo state from hyperstimulating and injuring neurons. A careful analysis of the pharmacological interventions that are protective can also provide insights into the circuitry and receptor mechanisms that mediate this pathological process.

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