Neuropharmacology 62 (2012) 1308–1321

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

To poly(I:C) or not to poly(I:C): Advancing preclinical schizophrenia research through the use of prenatal immune activation models

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ARTICLE INFO

Article history:
Received 1 November 2010
Received in revised form
5 January 2011
Accepted 7 January 2011

Keywords:
Animal model
Cognition
Cytokines
Dopamine
Glutamate
Prevention
Prodromal

ABSTRACT

The neurodevelopmental hypothesis of schizophrenia has been highly influential in shaping our current thinking about modeling the disease in animals. Based on the findings provided by human epidemiological studies, a great deal of recent interest has been centered upon the establishment of neurodevelopmental rodent models in which the basic experimental manipulation takes the form of prenatal exposure to infection and/or immune activation. One such model is based on prenatal treatment with the inflammatory agent poly(I:C) (=polyriboinosinic-polyribocytidilic acid), a synthetic analog of double-stranded RNA. Since its initial establishment and application to basic schizophrenia research, the poly(I:C) model has made a great impact on researchers concentrating on the neurodevelopmental and neuroimmunological basis of complex human brain disorders such as schizophrenia, and as a consequence, the model now enjoys wide recognition in the international scientific community. The present article emphasizes that the poly(I:C) model has gained such impact because it successfully accounts for several aspects of schizophrenia epidemiology, pathophysiology, symptomatology, and treatment. The numerous features of this experimental system make the poly(I:C) model a very powerful neurodevelopmental animal model of schizophrenia-relevant brain disease which is expected to be capable of critically advancing our knowledge of how the brain, following an (immune-associated) triggering event in early life, can develop into a "schizophrenia-like brain" over time. Furthermore, the poly(I:C) model seems highly suitable for the exploration of novel pharmacological and neuro-immunomodulatory strategies for both symptomatic and preventive treatments against psychotic disease, as well as for the identification of neurobiological mechanisms underlying gene–environment and environment–environment interactions presumably involved in the etiology of schizophrenia and related disorders.

This article is part of a Special Issue entitled 'Schizophrenia'.

1. Introduction

Schizophrenia is a chronic form of psychotic illness that affects approximately 1% of the population worldwide (Tamminga and Holcomb, 2005; Tandon et al., 2009). It is characterized by profound disturbances in mental functions, emotions and behavior, and it undermines basic human processes of perception and judgment. Multiple lines of evidence suggest that the etiology of schizophrenia involves aberrant neurodevelopmental processes, in which primary cerebral insults or pathological processes occur during early brain development long before the illness is clinically expressed (Murray and Lewis, 1987; Weinberger, 1987; Lewis and Levitt, 2002; McGrath et al., 2003; Rapoport et al., 2005; Fatemi and Folsom, 2009). According to the neurodevelopmental hypothesis of schizophrenia, an interaction between early neurodevelopmental disturbances and peri-adolescent brain maturation seems to be necessary in order to trigger the onset of full-blown psychotic behavior, which typically emerges during adolescence or early adulthood. Recent advances in brain imaging techniques have led to an important refinement of the neurodevelopmental hypothesis of schizophrenia by underlining the importance of progressive brain changes that occur during and subsequent to the onset of full-blown psychosis (Rapoport et al., 2005; Hulshoff Pol and Kahn, 2008; Wood et al., 2008).

Despite the growing consensus that schizophrenia is a brain disorder, a comprehensive neurobiological account of the disease (including the etiology, neuropathology, pathophysiology, psychopharmacology and genetics) remains a considerable challenge to

Abbreviations: AMPH, amphetamine; GD, gestation day; IL, interleukin; LI, latent inhibition; LPS, lipopolysaccharide; poly(I:C), polyriboinosinic-polyribocytidilic acid; PPI, prepulse inhibition; TNF, tumor necrosis factor.

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doi:10.1016/j.neuropharm.2011.01.009

clinicians and scientists alike. Furthermore, the available symptomatic treatment of schizophrenia is only partially successful, and therefore the development of novel therapeutic strategies is clearly warranted (Tamminga, 1999; Kapur and Remington, 2001; Buchanan et al., 2007; Remington et al., 2010). Besides a direct exploration of these issues in human subjects, basic research in animals represents a fruitful approach to study the neurobiological basis of brain and behavioral disturbances relevant to schizophrenia, and to establish and evaluate novel pharmacological therapies for their treatment. Indeed, the use of animal models allows a stringent experimental control of subjects in genetically homogenous populations and facilitates the identification of neurobiological factors contributing to distinct forms of schizophrenia-related brain and behavioral abnormalities. Furthermore, animal models provide indispensable tools to test hypotheses which cannot be directly addressed in human subjects for technical and ethical reasons, including the verification of causal relationships in epidemiological studies.

It needs to be emphasized that the attempt to model any human psychiatric conditions in animals has always been met with some skepticism, and schizophrenia is a particularly illustrative case (Boksa, 2007; Low and Hardy, 2007). The obvious reason for this is that the clinical manifestation of schizophrenia in humans includes symptoms such as hallucinations, delusions and major thought disorders, which are specific to humans and impossible to ascertain without structured interviews. Hence, it is impossible to mimic a complex human brain disorder such as schizophrenia in animals. However, one fruitful experimental approach is to focus on individual behavioral, physiological and neuroanatomical phenotypes of the disorder, rather than to model the entire syndrome (Lipska and Weinberger, 2000; Tarantino and Bucan, 2000; Arguello and Gogos, 2006).

In parallel with similar efforts in humans, behavioral neuroscience and related research fields have established a wide variety of sophisticated paradigms which allow the assessment of schizophrenia-related traits in experimental models and clinical trials (Barch et al., 2009a,b). Such cross-species translational paradigms have been developed for the identification and characterization of neuropsychological, cognitive and psychopharmacological core dysfunctions implicated in human psychotic disorders (Table 1). These paradigms have been proven valuable and informative experimental tools to assess psychosis-like traits in a variety of lesion-based, genetic or psychopharmacological rodent models (for a review see Gray et al., 1991; Swerdlow and Geyer, 1998; Moser et al., 2000; Weiner, 2003; Castner et al., 2004; Meyer et al., 2005; Arguello and Gogos, 2006).

Over the last two decades, the neurodevelopmental hypothesis of schizophrenia has been highly influential in shaping our current thinking about modeling the disease in animals (Lillrank et al., 1995; Lipska and Weinberger, 2000, 2002; Meyer et al., 2005; Lodge and Grace, 2009; Meyer and Feldon, 2010). The use of selective lesions in adult animals and the acute or chronic administration of psychotomimetic agents are indispensable tools for elucidating the contribution of specific brain regions or neurotransmitters to the genesis of a specific symptom or collection of symptoms, and enjoy some degree of predictive validity, but they may be inaccurate, if not inadequate, in capturing the etiological mechanisms or ontology needed for a heuristic neurobiological account of the disease (Lillrank et al., 1995; Lipska and Weinberger, 2000, 2002; Meyer et al., 2005; Lodge and Grace, 2009; Meyer and Feldon, 2010; see Table 2 for a summary of commonly used validity criteria of animal models). This has motivated the establishment of neurodevelopmental animal models which aim at identifying the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia-like brain" over time. This approach is not only wider in its scope than conventional lesion and drug models, but it also readily lends itself to addressing data and hypotheses concerning the subtle histopathological and neuroanatomical findings revealed in post-mortem and imaging studies, as well as the contribution of genetic and environmental risk factors.

Based on the findings provided by human epidemiological studies, a great deal of recent interest has been centered upon the establishment of neurodevelopmental animal models in which the basic experimental manipulation takes the form of prenatal exposure to infection and/or immune activation (Meyer et al., 2009a; Meyer and Feldon, 2010). Hence, this relatively novel class of "immuno-precipitated" neurodevelopmental animal models has been driven to a great extent by the human epidemiological literature documenting elevated risk for schizophrenia following prenatal exposure to infection and/or inflammation (Brown and Susser, 2002; Fatemi, 2005; Brown, 2006; Brown and Derkits, 2010). In a series of seminal experiments, Fatemi and colleagues have pioneered an experimental animal model of prenatal exposure to human influenza virus in mice (Fatemi et al., 1998a,b, 1999, 2000, 2002, 2004, 2008, 2009; Shi et al., 2003). In this model, pregnant mice are infused intranasally with a sublethal dose of a neurotropic strain of human influenza virus, and the long-term brain and behavioral effects are then evaluated in the resulting offspring relative to control offspring born to sham-treated mothers. As recently reviewed elsewhere (Meyer et al., 2009a; Meyer and Feldon, 2010), the prenatal influenza model in mice seems highly suitable for experimental investigations of the human epidemiological association between prenatal influenza infection and enhanced risk of schizophrenia-related disorders in the offspring (Brown and Susser, 2002; Fatemi, 2005; Brown, 2006; Brown and Derkits, 2010). This model enjoys an appreciable level of face and construct validity for schizophrenia-like brain and behavioral pathology, and it accounts for one of the well-known environmental factors implicated in the infectious etiology of this disorder. Recently, the prenatal influenza model has also been successfully used in a primate species with advanced prenatal corticogenesis, namely the rhesus monkey (Short et al., 2010). The primate influenza model is expected to further enhance the translatability of findings derived from experimental model systems to the human pathological condition.

Another class of animal models of prenatal immune challenge make use of cytokine-releasing agents such as the bacterial endotoxin LPS (=lipopolysaccharide) or the viral-mimic poly(I:C) (=polyriboinosinic-polyribocytidilic acid), or of selected pro-inflammatory cytokines such as interleukin (IL)-1β or IL-6 (reviewed in Meyer et al., 2009a; Patterson, 2009; Boksa, 2010; Meyer and Feldon, 2010). These models have been developed primarily to test whether imbalances in maternal and/or fetal cytokines may be the critical mediators in the link between maternal infection and postnatal emergence of brain and behavioral pathology (Meyer et al., 2009b). Since their initial establishments, the models have made a great impact on researchers concentrating on the neurodevelopmental and neuroimmunological basis of complex human brain disorders such as schizophrenia, and as a consequence, they now enjoy wide recognition in the international scientific community (Fig. 1).

In the present review, we focus on one particular in-vivo animal model of prenatal immune activation, namely the poly(I:C) model in mice, and discuss its validity for preclinical schizophrenia research. We highlight that this model may readily advance our understanding of how the brain, following an (immune-associated) triggering event in early life, can develop into a "schizophrenia-like brain" over time. Furthermore, we emphasize that the mouse poly(I:C) model is highly suitable for the exploration of novel pharmacological and neuro-immunomodulatory strategies for both