Translational neuropsychiatry of genetic and neurodevelopmental animal models of schizophrenia

Estudos traducionais de neuropsiquiatria e esquizofrenia: modelos animais genéticos e de neurodesenvolvimento

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Abstract

Psychiatric symptoms are subjective by nature and tend to overlap between different disorders. The modelling of a neuropsychiatric disorder therefore faces challenges because of missing knowledge of the fundamental pathophysiology and a lack of accurate diagnostics. Animal models are used to test hypotheses of aetiology and to represent the human condition as close as possible to increase our understanding of the disease and to evaluate new targets for drug discovery. In this review, genetic and neurodevelopmental animal models of schizophrenia are discussed with respect to behavioural and neurophysiological findings and their association with the clinical condition. Only specific animal models of schizophrenia may ultimately lead to novel diagnostic approaches and drug discovery. We argue that molecular biomarkers are important to improve animal to human translation since behavioural readouts lack the necessary specificity and reliability to assess human psychiatric symptoms.

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Keywords: Translational research, neuropsychiatry, genetic, neurodevelopment, animal model, schizophrenia.

Resumo

Sintomas psiquiátricos são subjetivos por natureza e tendem a se sobrepor entre diferentes desordens. Sendo assim, a criação de modelos de uma desordem neuropsiquiátrica encontra desafios pela falta de conhecimento dos fundamentos da fisiopatologia e diagnósticos precisos. Modelos animais são usados para testar hipóteses de etiologia e para representar a condição humana tão próximo quanto possível para aumentar nosso entendimento da doença e avaliar novos alvos para a descoberta de drogas. Nesta revisão, modelos animais genéticos e de neurodesenvolvimento de esquizofrenia são discutidos com respeito a achados comportamentais e neurofisiológicos e sua associação com a condição clínica. Somente modelos animais específicos de esquizofrenia podem, em último caso, levar a novas abordagens diagnósticas e descoberta de drogas. Argumentamos que biomarcadores moleculares são importantes para aumentar a tradução de animais a humanos, já que faltam a especificidade e a fidelidade necessárias às leituras comportamentais para avaliar sintomas psiquiátricos humanos.

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Palavras-chave: Pesquisa traducional, neuropsiquiatria, genética, neurodesenvolvimento, modelo animal, esquizofrenia.

Introduction

According to a prediction of the World Health Organization (WHO) neuropsychiatric disorders including schizophrenia, depression, bipolar disorder and dementia, will be the greatest factor contributing to disease-adjusted life years by the year 2030[1]. Epidemiological studies have calculated a lifetime morbidity risk for schizophrenia of approximately 1%[2]. Fundamental research into the psychopathology of this disorder and drug development during recent years has yielded few answers and more questions. One of the major reasons for this lack of progress appears to result from the diversity of psychiatric disorders, which often overlap in subjectively evaluated symptoms.

Clinical research calls for animal models as a necessary first step towards a deeper understanding of psychopathology and to provide tools for successful drug discovery. However, current models are only able to mimic certain psychiatric symptoms and it is questionable if we will ever be able to mirror and evaluate a multifaceted disorder such as schizophrenia using animal models. To this end, three categories are now assessed for animal models: construct, face and predictive validity[3].

Construct validity

The degree to which animal models embody and conform to etiological aspects of the disease is termed the construct validity. One difficulty with the study of schizophrenia is that we cannot simply knock out one risk gene in order to generate symptoms. This is because schizophrenia, like most neuropsychiatric disorders, it is a multi-locus and multi-factorial disorder. Also, the precipitating environmental factors are either unknown or cause a range of psychiatric syndromes. This lack of certainty impedes creation of animal models with features specific for one psychiatric disorder with high construct validity.

Face validity

Face validity is the extent to which animal models reflect the main features or symptoms associated with a psychiatric disorder. This has most commonly been assessed using behavioural testing. A major barrier to development of animal models with high face validity is that the primary symptoms of schizophrenia, such as hallucinations, delusions, speech abnormalities and inappropriate behaviour, are

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impossible to model in other species. Nonetheless, several behavioural paradigms have been developed that have some relevance to schizophrenia, including hyperlocomotion, social interaction deficits, effects on prepulse inhibition (PPI), and intra- and extra-dimensional (ID/ED) shifting. The controversial association of hyperlocomotion with schizophrenia positive symptoms is based on its post-pubertal onset and exacerbation with N-methyl-D-aspartate (NMDA) receptor antagonists, indicating subcortical dopamine excess[4]. Social interaction deficits are associated with the negative symptom of social withdrawal in patients which has been shown to have predictive power for the development of schizophrenia in children[5-7].

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) identified seven domains of cognitive dysfunctions in schizophrenia patients including specific tests for measurement of these: working memory, verbal memory, visual learning, attention/vigilance, abstract reasoning, social cognition and speed of processing[8-10]. Unlike the changing intensity of psychosis, cognitive symptoms tend to accumulate and treatment of these has been found to be a better predictor of therapeutic efficiency and patient outcome than treatment of positive or negative symptoms[11]. Learning and memory tasks are translatable to rodents and numerous behavioural paradigms are available. Sensorimotor gating deficits are considered endophenotypes of schizophrenia, belonging to the category of cognitive impairments. Such deficits are related to the inability of schizophrenia patients to ignore irrelevant stimuli, and are believed to mirror the positive symptoms causing learning deficits and cognitive fragmentation in schizophrenia[12-14]. Human gating defects include reduced P50 auditory evoked potential suppression and inhibition of the startle reflex (both measurements of PPI), and abnormal smooth eye pursuit, which may reflect fundamental causes for the clinical expression of schizophrenia[15,16]. An advantage of such tests is the homology between the human and the animal test conditions[17]. More recently, a rodent analogue of the Wisconsin card sorting test (attentional set shifting task) has been developed[18]. Performance in this task measures prefrontal function and is impaired in schizophrenia patients.

Although all of these behavioural hallmarks have translational features, they are not likely to be disease-specific[19-21]. Furthermore, all existing animal models represent only distinct features of the disease. Considering the complexity of the disorder, it remains questionable whether we will achieve creation of an ideal model. Therefore, there is an urgent need for identification of translatable molecular markers in order to increase confidence in the validity of available animal models.

Predictive validity

The utility of a model in the prediction of drug efficacy in the clinic is termed the predictive validity. Assessment of this aspect is compromised by our limited knowledge of drug effects. Since the first antipsychotic drugs were discovered serendipitously based on dopamine receptor blockade, all new drugs have been developed in models chosen for their predictive validity as dopamine antagonists. However, recent studies have demonstrated the influence of antipsychotics on multiple neurotransmitter systems and signalling cascades, and progress has been made in moving model development away from dopamine pathways.

Aim of this review

This review focuses on relevant behavioural and neurophysiological findings in currently used animal models of schizophrenia from the perspective of translational neuropsychiatry. Our goal is not to list all models but to focus on differential etiological theories of schizophrenia and on the models which target these pathways. Following the assumptions of the Research Domain Criteria (RDoC) project launched by the NIMH, clinical neuroscience research will yield biomarkers to extend the view on psychiatric symptoms and improve patient management[22]. We believe that the correlation of schizophrenic patients and psychiatric animal models will result in a greater insight in psychopathology and provide the research tools essential for novel drug discovery strategies.

Reciprocity of research: finding the "right" aetiology

Many different views on the aetiology of schizophrenia have emerged and it is now believed that the pathogenesis results from an interaction of genetic and environmental risk factors[3]. The neuropathological features of the disorder include dysregulation of neurotransmitter systems (primarily dopamine and glutamate)[23,24], hypofrontality[25] and hippocampal synaptic deficits[26]. All of these have been followed by construction of relevant animal models resulting in a range of findings. The aetiological validity of an animal model can only be considered as a measurement of the precision of our knowledge of human pathogenesis[27,28]. In spite of the great diversity of aetiological findings in schizophrenia research, some aspects have been more reproducible in epidemiological studies. This includes genetic heritability and vulnerability during neurodevelopment which form the main focus of this review (Figure 1)[29-31].

Gift of our ancestors: genes

Genetically modified rodents have become important research models in medical sciences in recent years. Modern molecular methods allow for targeted gene approaches and can help in discovering the neurobiological effects of genes and their interplay on behaviour. Genome-Wide Association Studies (GWAS) have facilitated identification of risk factors including single nucleotide polymorphisms, copy number variations and structural or allelic variants, and these can be mirrored in animal models. The heritability of schizophrenia has been estimated to be around 73% to 90%, based on twin studies and currently around 30 risk alleles have been identified[32-34]. Among the polymorphism- and chromosomal-based schizophrenia mouse models are the phenotypically-well characterized disrupted in schizophrenia 1 (DISC1), neuregulin 1 (NRG1), proline dehydrogenase (PRODH) and 22q11 mutants[35]. Further models are represented by dysbindin (DTNBP1) and reelin (RELN) knock-outs[36,37]. As with all genetic models, the resulting experimental findings should be considered with care since schizophrenia appears to be an oligogenetic disease with multiple small risk genes accumulating to a give a particular phenotype[38-40].

DISC1

DISC1 was first discovered due to its co-segregation with psychiatric disorders in a Scottish family and it has been found to be an important vulnerability factor for schizophrenia and other mental disorders in diverse populations[41,42]. DISC1 has been shown to play an essential role in pre- and post-natal neurodevelopment, particularly in synaptogenesis, synaptic plasticity and neuronal migration[43]. The commonly used 129S6 Sv/Ev mouse strain has been shown to carry a 25bp deletion in exon 6 of this gene, which may result in a working memory deficit[42]. Disorganization and impaired plasticity of neurons may be the cause of the cognitive deficits found in DISC1 mice[26]. The N-ethyl-N-nitrosourea (ENU)-induced *Disc1* missense mutation, L100P, produced schizophrenia-like behavioural impairments in PPI, latent inhibition and hyperlocomotion which could be blocked by administration of typical and atypical antipsychotics[44]. Working memory deficits were also reported for a mouse model of complete DISC1 deletion[45]. The Q31L missense mutation resulted in the generation of mice with deficits in working memory and diminished social interaction, and this could be blocked with clozapine[44]. Both mutant strains showed reduced volumes of different brain structures[38,46,47]. Consistent with these findings, DISC1 has been shown to be developmentally regulated[47,48]. At the molecular level, reduced DISC1 binding to the cAMP-specific 3',5'-cyclic phosphodiesterase 4B (PDE4B) has been demonstrated. PDE4B is a phosphodiesterase

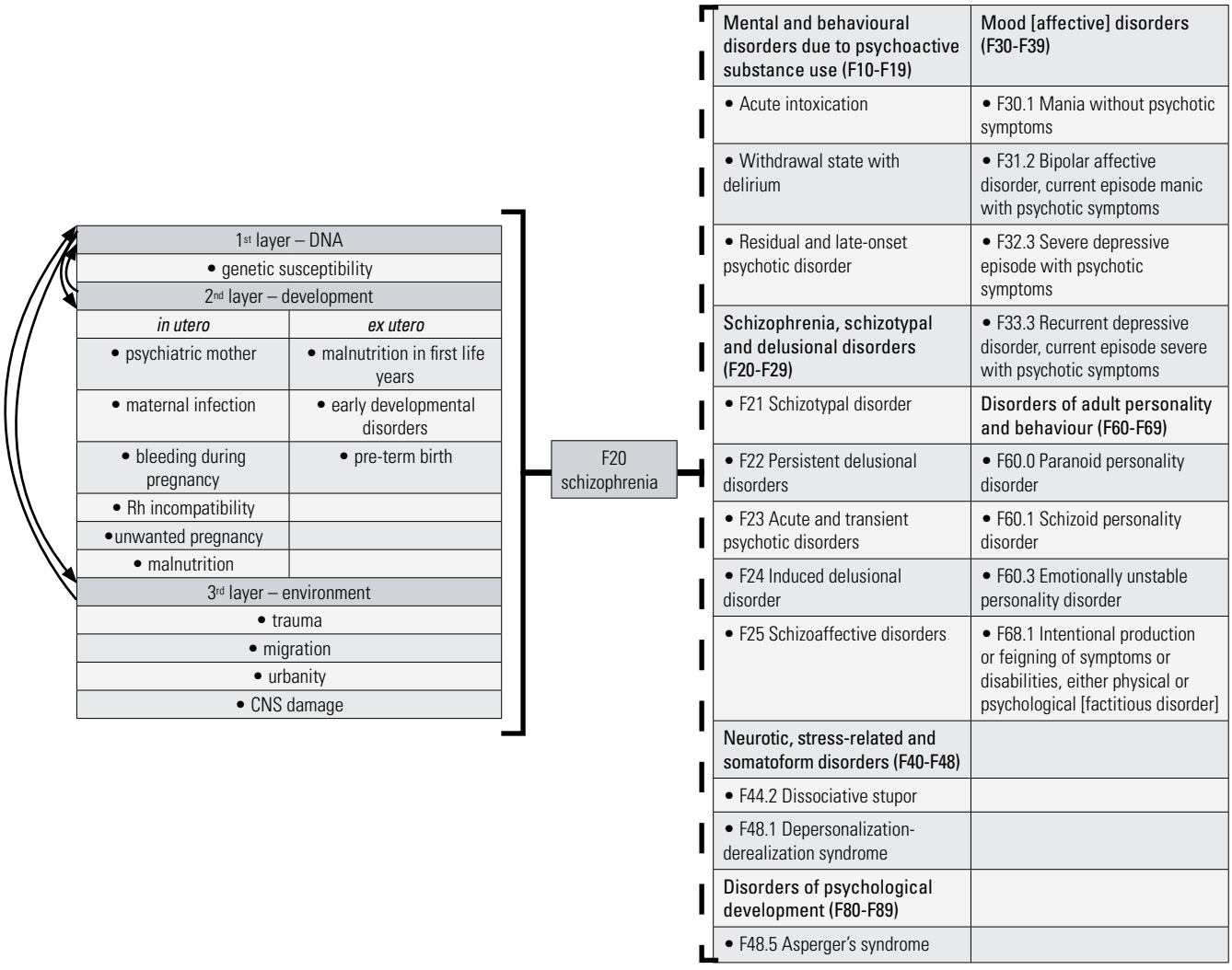

Figure 1. Complications in the aetiology and diagnosis of schizophrenia. (Left) Risk factors for developing schizophrenia – arrows indicate interaction between the different layers of vulnerability, for example epigenetic changes due to experience of trauma. (Right) Selection of possible non-organic psychiatric differential diagnoses with ICD-10 codes[202] to be considered before the diagnosis of schizophrenia is possible.

which has been implicated in animal models with learning and memory impairments[44,49,50]. Polymorphisms of PDE4B have been reported to be associated with schizophrenia in human GWAS[51]. Approaches with mutated human DISC1 in mice have resulted in reports of hyperlocomotion, diminished reward learning, impairments in social interaction and declarative memory and increased aggression[52-54]. Structural abnormalities in this model have been reported such as enlarged ventricles and decreased dendritic arborisation, with decreased expression of lissencephaly 1 (LIS1) and synaptosomal-associated protein 25 (SNAP-25)[53]. LIS1, DISC1 and nuclear distribution protein nudE-like 1 (NDEL1) have been shown to be part of a molecular interaction complex relevant in neurodevelopment[55-58]. Morphological changes in DISC1 mice have been observed including reduced prefrontal cortex volume and impaired growth and dendritic orientation in the dentate gyrus, correlating with findings in human schizophrenia studies[59-61].

NRG1

NRG1 has been implicated by GWAS as a risk factor of schizophrenia[62]. The roles of NRG1 and its various isoforms include synaptogenesis, myelination, glia-neuron interactions, glial cell formation, NMDA receptor-regulated neuronal migration and glutamatergic signalling at a range of neurodevelopmental stages[63-65]. Behavioural abnormalities have been observed in mice lacking one of the NRG1 isoforms, including reduced fear conditioning and lower locomotor activity[66,67]. Some of these effects have been shown to be reversed by administration of atypical antipsychotics[68]. Behavioural analyses of NRG knockout mice have shown decreased sensorimotor gating and social interaction, with increased aggression[69-72]. Molecular analyses of the NMDA receptor in NRG1 knockout mice revealed an overall decrease and hypophosphorylation which could be reversed by clozapine treatment[62,73].

22q11

In schizophrenia research, several studies have been performed on the chromosomal microdeletion at 22q11.2 (22q11DS), which results in velocardiofacial syndrome (VCFS), with palatal abnormalities, heart defects, microcephaly and deformation of thymus or parathyroid glands. Some of the cognitive abnormalities observed in patients with 22q11DS are thought to originate in the prefrontal cortex and hippocampus including deficits in attention, working memory, executive function and short-term verbal memory[74-76]. Approximately 25% of 22q11DS patients suffer from schizophrenia or schizoaf-

fective disorder[77-79]. Also, 6% of early onset schizophrenia patients have the same microdeletion[80,81]. Several genes in this chromosomal region have been associated with schizophrenia including proline dehydrogenase (PRODH), catechol O-methyl transferase (COMT) and guanine nucleotide-binding protein subunit beta-like protein 1 (GNB1L)[82-84]. The COMT enzyme has been reported to modulate degradation of dopamine in the brain and therefore its absence could be responsible for working memory deficits[75]. Mutations of PRODH have been shown to produce neurotransmitter abnormalities in glutamatergic and dopaminergic pathways of genetically modified mice[75]. Selective deletion of PRODH in mice has been shown to lead to deficits in sensorimotor gating, with decreased glutamate, aspartate and GABA levels in the frontal cortex[85]. Proline has been implicated in modulation of neurotransmission especially in the glutamatergic system, which could lead to the psychotic symptoms observed in patients[86-88]. 22q11DS mouse models present with a loss of glutamatergic synapses, decreased spine density, decreased CA1 pyramidal neuron complexity and reduced neurogenesis in the subventricular zone. The same mice show behavioural abnormalities in PPI, hyperlocomotion, fear conditioning and working memory[89-94]. 22q11DS is the only confirmed recurrent structural mutation associated with schizophrenia identified to date[95].

Mutations in neuronal signal transmission pathways

Neurotransmitter deficits have been modelled using genetic methods. Higher dopamine concentrations in the synaptic cleft can be simulated by knock-out of the dopamine transporter (DAT). Such mice have been classified as models of schizophrenia as they are hyperactive in novel environments, express excessive stereotypic behaviour, reduced reward learning, deficits in sensorimotor gating, working and declarative memory, and show circadian rhythm impairments[96-99]. The modified neuron-oscillatory properties caused by DAT knock-out have also been shown to influence the serotonergic system, possibly as compensation for the hyperdopaminergia[100,101]. The hypothalamic-pituitary-adrenal axis in these mice is dysregulated, resulting in anterior pituitary hypoplasia[102], similar to effects seen in schizophrenic patients[103]. Also, approximately 50% lower concentrations of D1 and D2 postsynaptic receptor mRNA have been described in the striatum of these animals as well as downregulation of preproenkephalin A (PENK) and upregulation of dynorphin (PDYN)[96,97]. Following the glutamate hypothesis, a mutant mouse strain has been created with a 90% reduction in NMDA receptor 1 (NR1) expression, resulting in social and sexual behavioural deficits and similar symptoms to the DAT knock out mouse. These include impaired circadian rhythm, memory and gating deficits, diminished reward learning and increased locomotion[104-107]. These symptoms could be reduced with haloperidol and clozapine treatment[104]. Reduced NMDA-signalling induced by gene knockdown resulted in impaired habituation of the auditory startle response, similar to that induced by phencyclidine (PCP) administration, and mimicking the sensory overload believed to be experienced by many schizophrenic patients[106,108]. The observed loss of parvalbumin-positive neurons in NMDA deficient mice has also been linked with schizophrenia-like symptoms and has been reported for hippocampal interneurons[21,109,110].

Vulnerability of our youth: neurodevelopment

The existence of an environmental component of schizophrenia was demonstrated by the finding that identical twins show a concordance of approximately 50%[111]. The neurodevelopmental character of schizophrenia was postulated based on epidemiological, human *post-mortem* tissue and imaging studies[112]. Neurodevelopmental animal models include maternal immune activation, prenatal malnutrition, the interruption of neurogenesis by methylazoxymethanol (MAM) and the neonatal ibotenic acid lesion of the ventral hippocampus[113,114]. Additional models are represented by the exposure of pregnant mice to unpredictable stress, maternal separation or birth complications[115-117]. All of these models have revealed behavioural deficits associated either with positive, cognitive or negative symptoms of schizophrenia, and alterations in the dopaminergic, glutamatergic, GABAergic and serotonergic systems[118-124].

Maternal immune activation

Maternal immune activation is considered to be an etiological factor in schizophrenia based on epidemiological studies of influenza infection in mothers of schizophrenia patients, and an increased incidence of schizophrenia among winter births[125-127]. This has been modelled in rodents by infecting pregnant animals with viruses or by administration of the bacterial endotoxin lipopolysaccharide (LPS). Sensorimotor gating was reported to be impaired in male and female offspring of mothers treated with LPS between gestation day 15 and 19, but the effects in male mice were more severe[128]. A reduction of glycogen synthase kinase 3 β (GSK3B) mRNA in the prefrontal cortex was consistent with the findings of human *post-mortem* tissue analyses[128-131]. Male offspring of maternal immune activation showed an increase in tumour necrosis factor α (TNF) throughout their lifespan, as seen in schizophrenia[128,132,133]. Antipsychotics have been shown to reverse the effects of maternal immune activation on the behavioural and serum cytokine levels[134,135]. Maternal infection of rodents with influenza virus has led to deficits in social interaction and acoustic PPI in the offspring[136]. Prenatal influenza infection has been associated with impaired corticogenesis and cell layer disruptions in the hippocampus, together with altered expression of synaptic markers[118,137]. This is similar to the finding of hippocampal pyramidal cell disarray reported in human schizophrenia *post-mortem* studies[138-140]. Because the influenza virus or influenza virus antibodies have not been detected in the fetal brain, it has been hypothesized that the maternal immune response alone is sufficient to generate schizophrenia-like behavioural findings in the offspring[136,141-145]. At the neurotransmitter level, dysfunctions in the dopaminergic and glutamatergic system have been reported, especially in the medial prefrontal cortex and the nucleus accumbens in offspring from mothers subjected to immune challenge[123].

Maternal protein malnutrition

Prenatal malnutrition has been shown to be a risk factor for schizophrenia[146-148]. Maternal malnutrition in rats was followed by attention and gating deficits on the behavioural level but only in female offspring[149]. This was associated with increased ^{3}H-Haloperidol binding in the striatum, as found in studies of male rats following maternal malnutrition[121,149], although there are conflicting reports of this[150]. Increased ^{3}H-MK-801 binding in the striatum and hippocampus was described in the maternal malnutrition model and may reflect a NMDA receptor hypofunction and subsequent up-regulation as postulated by the glutamate hypothesis of schizophrenia[121,151]. Memory deficits in this model were described in terms of susceptibility to interference and extinction, further supporting theories of prefrontal and hippocampal psychopathology[152]. Offspring of malnourished mothers showed reduced social interaction and higher aggressive behaviour, similar to findings in malnourished children[153,154]. Increased concentrations of noradrenaline and dopamine were reported following malnutrition, resulting most likely from tyrosine hydroxylase hyperactivity and this correlated with reduced overall brain and hippocampus size[155]. Additionally $GABA_A$ receptors ($GABA_AR$) have been reported to be decreased in the hippocampus of adult offspring subjected to maternal malnutrition[119].

Interruption of neurogenesis

Administration of the mitotoxin methylazoxymethanol acetate (MAM) to rat dams on embryonic day 17 (E17) interferes with development of schizophrenia-relevant brain regions in the offspring[114,120,156,157]. Several mechanisms of action have been proposed to explain the actions of MAM-E17 treatment, including a decrease in the levels of reelin and the 67 kDa form of glutamic acid decarboxylase

(GAD67), as reported in schizophrenic patients, or by methylation of genes critical for neuronal development and plasticity[158-160]. Neuroanatomical findings reported in parallel for the MAM-E17 model and schizophrenic patients include morphological changes in the prefrontal cortex, parahippocampal cortex and hippocampus, reduced size of the medial dorsal thalamus and increased neuron packaging in the frontal lobe[114,161-165]. A decrease in whole brain volume of MAM-E17 rats was mainly focussed on the prefrontal cortex, hippocampus and nucleus accumbens[120]. Cellular disarray in the CA1 region of hippocampus has also been described and is thought to be analogous to hippocampal disarray seen in schizophrenia patients[120,166]. Recently, we carried out a proteomic and metabonomic investigation which showed that MAM-E17 rats have primarily deficits in hippocampal glutamatergic neurotransmission, as seen in some schizophrenia patients[167]. Most importantly, these results were consistent with our finding of functional deficits in glutamatergic neurotransmission, as identified using electrophysiological recordings. At the behavioural level, dysfunctions in sensorimotor gating in MAM-E17 rats have been described in line with findings in schizophrenic patients, implicating frontal dysfunctions and dopaminergic input to the striatum[114,168]. Social interaction deficits have been described to occur before and after puberty in MAM-E17 rats, although hypermotor activity and deficits in spatial working memory and PPI occurred only after puberty[169]. Furthermore, the offspring of MAM-E17 rats displayed working memory deficits in object recognition, as do schizophrenic patients, implicating deficits in the prefrontal cortex[120,170, 171]. Additional evidence for prefrontal abnormalities has been reported by impairments in latent inhibition[120,172-174]. Cortical pyramidal neurons from MAM-E7 offspring failed to reduce their firing frequency as did control neurons if dopamine was artificially injected[175]. This finding has relevance to conditional associative learning which has been described as being impaired in schizophrenia patients[176].

Neonatal hippocampal lesion

The neonatal hippocampal lesion rat model was developed after reports that this region affected mesolimbic dopamine transmission and cortical dopamine turnover in schizophrenia[113]. Ibotenic acid was administered on postnatal day 7 to damage the ventral hippocampus, which connects to the prefrontal cortex, analogous to the human anterior hippocampus. These animals showed hypermotor activity and hyper-responsiveness to stress emerging in adulthood (day 56). Also, the effect could be blocked by haloperidol treatment[113]. Conversely, sensorimotor gating deficits in this model have been shown to be treatable with the atypical antipsychotics clozapine, olanzapine and risperidone but not with the typical antipsychotic haloperidol[177]. This may be a useful model for schizophrenia due to the post-pubertal emergence of PPI deficits, as seen in the human disease, which are thought to result from damage to the prefrontal cortex[17,178,179]. Further behavioural tests have revealed deficits in spatial learning and memory, beginning in the juvenile period[180]. Reduced social interaction has been reported in this model prior to and after puberty, although this effect does not appear to respond to clozapine treatment[181]. This may be relevant in light of studies showing that prodromal individuals demonstrate difficulties in establishing friendships and emotional bonding[5,182-184]. Molecular studies have shown increased AMPA receptor (GRIA3) levels in the prefrontal cortex of ventral hippocampal lesion rats, which may be the cause of striatal dopaminergic hyperactivation[185,186]. Finally, studies on neuronal circuitry in the prefrontal cortex in this model have shown abnormal synaptic responses to excitatory input, which is of interest given the deficit in inhibitory interneurons found in the prefrontal cortex of schizophrenic *post-mortem* tissue[124,187,188].

Translation of animals to humans and back again

Currently, animal behaviours which parallel specific characteristics of psychiatric disorders such as schizophrenia are used in drug development as early indicators of potential treatment efficacy. However, the use of behavioural readouts is limited in disease specificity and this has been regarded as one of the major drawbacks of these approaches[189]. In particular, the assessment of similarities of animal behaviour and patient characteristics can be subjective, leading to problems of bias and irreproducibility. Due to such difficulties, the disease relevance of many animal models for schizophrenia remains dubious.

One means of overcoming these problems is the demonstration that data accumulated from relevant animal model studies are representative of human schizophrenia[190]. A simple approach would be to consider the molecular changes in blood serum or plasma which have been associated consistently with schizophrenia and attempt to correlate these findings with those in animal models of schizophrenia which target particular aspects of the disease. For example similar changes have been identified between specific animal models and human schizophrenia in the case of molecules such as adrenocorticotrophic hormone[191], corticosteroid hormones[192], brain-derived neurotrophic factor[192], interleukin 2[193], interleukin 6[193], kynurenic acid[194] and glutamate[195]. Such parallels in molecular changes may lead to the establishment of construct validity of a given animal model.

The efficient use of reverse translational research seems likely to guide the way for characterization of disease mechanisms and identifying novel drug targets. This is critical as the future clinical need in the field of neuropsychiatry calls for identification of class- or even drug-specific biomarkers matched with novel therapeutic approaches. This could be done by statistical analyses of the complex data generated in proteomic approaches in animals and humans alike. Once discovered and matched, new biomarkers could be used to evaluate the comparability of the animal model and the disease status in humans and treatment effects could be validated more efficiently than with behavioural tests. The goal of these molecular profiling approaches is the identification of cross species signatures of a given human disease. In this way, the best animal models for developing and testing novel therapeutic strategies can be identified.

Conclusions

This review summarized behavioural findings and key features on the morphological, cellular and molecular level in commonly used animal models of schizophrenia generated with genetic and neurodevelopmental approaches. It should be no surprise that none of the listed animal models has been established as the "best" for use in drug discovery, because none are able to mimic the human disease state in all measurable variables. Psychiatric patients present with multiple subtle symptoms, which cannot be measured reproducibly by existing techniques. Therefore, it is not likely that such symptoms can be recapitulated in animal models. In fact, several observations have been made which negatively impact on face validity such as the appearance of higher locomotor activity in some models which has no distinct counterpart in schizophrenic patients[196]. The need for this paradigm change is reflected in the ongoing debate about the introduction of the Diagnostic and Statistical Manual V (DSM-V). Current psychiatric practice includes the assessment of patient symptoms using clinically approved interviews which are not based on the underlying pathophysiology. It should be no surprise that clinical syndromes based on subjective symptoms are a source of misdiagnosis and therefore mistreatments.

To address the problems of combining the next generation of diagnostic rules with the findings of modern neuroscience, the National Institute of Mental Health has initiated the establishment of a classification guide of psychiatric patients for research proposes and for a better incorporation of modern scientific knowledge on the field of neuropsychiatry[22]. The RDoC provides a multidimensional view of "constructs" like behaviourally evaluated cognitive deficits and molecular neurobiological alterations. The major advantage of this approach is the freedom of diagnoses for certain syndromes, circumventing the problem of disease categories. RDoC represents a dimensional system ranging from normality to abnormality. With the exploitation of physiological measures and molecular biomarkers,

this will enable a better integration of animal models in pre-clinical research and enhance their potential to generate value from bench to bedside. Recently new approaches have emerged to integrate new parameters into this process, such as molecular changes in easy accessible peripheral samples (for example saliva) and electrocardiographic measurements for early detection and diagnosis of stress-related psychopathogenesis in humans and for verification of animal models of psychiatric disorders[197].

This review has focussed on the genetic and neurodevelopmental models of schizophrenia. Despite the fact that these were created to model schizophrenia, they represent great variability in their behavioural findings and it is difficult to evaluate them with respect to given symptoms. In the case of human psychiatric disorders, symptoms often overlap between different psychiatric disorders and psychiatrists are faced with a diversity of possible differential diagnoses (Figure 1). Dysfunctions of PPI, for example, have been reported in many neuropsychiatric and even in some non-neuropsychiatric disorders[198].

Molecular findings have been used to show similarities between humans and rodents supporting the view that behaviour alterations are linked to molecular changes[190,199]. Given the reported pool of findings it seems unlikely that a difference in any single molecule would be enough to assign a given animal model to a distinct psychiatric disorder. This is in line with biomarker findings which have focussed on altered patterns rather than changes of single proteins[200]. For example it has been shown that a combination of 51 serum biomarkers can be used in humans to help with the diagnosis of schizophrenia[201]. Further molecular analyses of molecular patterns in psychiatric animal models need to be correlated with human studies to identify signatures associated with specific alterations on the genetic level or with the consequences of environmental insults. The use of biomarkers specific for different symptoms could help in new pharmacological approaches. For example current typical and atypical drugs fail mainly in targeting the negative and cognitive symptoms of schizophrenia[11,182,202]. The study of genetic and neurodevelopmental models could enable us to better identify risk biomarkers and help to initiate research programmes for discovery of novel treatments which target the fundamental pathogenesis instead of the current approach of symptom reduction. The relationship between genetic and environmental impact will probably remain the focus of current neuropsychiatric research over the next decade and the increased use of disease-relevant animal models could lead to new insights. The additional application of the RDoC system into modern approaches with psychiatric animal models could enhance the exchange between the preclinical and clinical stage and help to overcome the current stagnation in translational research.

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