Of rats and schizophrenia

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Surprisingly (or not), I am sometimes greeted with skeptical grins from members of the audience at seminars when I explain that I use rats, mice and guinea pigs to attempt to understand the causes of schizophrenia. (Yeah, right, a schizophrenic rat!) This has prompted me to reflect on a few of the significant contributions to the understanding and treatment of schizophrenia that have been made and are currently being made through work with rats and other laboratory animals.

Animal models continue to be useful in understanding how clinically effective antipsychotic drugs work, from the initial finding that typical neuroleptic drugs are effective in schizophrenia because of dopamine D_2 receptor blockade[1] to newer notions, for example, that second-generation antipsychotic drugs may also affect neurodegeneration, synaptic plasticity and remodelling.[2] In addition to leading to improved therapeutics, this type of knowledge can also provide impetus toward understanding aspects of the pathophysiology of schizophrenia. The interaction of neuroleptics with dopamine receptors was the key component of the rationale for the still-prevailing theory that schizophrenia involves a dysregulation of brain dopamine function,[1] while the discovery that the psychotomimetic, phencyclidine, blocks N-methyl-D-aspartate (NMDA) receptors[3] led to the idea of glutamatergic hypofunction in schizophrenia. With respect to existing neuroleptics, animal models have contributed significantly toward understanding the mechanisms involved in such deleterious side effects as extrapyramidal symptoms, tardive dyskinesia and, more recently, metabolic effects resulting in weight gain. Recent reports that clozapine has greater antipsychotic efficacy than other atypical neuroleptic drugs for treatment-nonresponsive schizophrenia[4] and that weight gain induced by clozapine correlates with antipsychotic response[5] indicate that much is still unknown about mechanism of action of existing antipsychotic medications. Animal models are certain to play a key role in investigating novel possibilities, such as the notion that metabolic effects somehow contribute to clozapine's antipsychotic efficacy.

Of course, preclinical work in laboratory animals continues to spearhead the search for innovative drug therapy in schizophrenia. In addition to illuminating the search for agents interacting with various combinations of neurotransmitter sites, animal models are central to the development of additional/alternative therapeutic approaches, such as the current search for enhancers of cognition and perception .[6,7] In this respect, animal models of learning, memory, attention, sensorimotor information processing and social recognition have not only increased our understanding of the modulation of these cognitive processes but also provide requisite tools in the search for compounds to enhance function.

Although some people might easily agree that lower animals could be useful in predicting drug efficacy, there appears to be more hesitation in conceding that animals could be used to understand the pathophysiology and causes of such a consummately human disorder as schizophrenia. I agree that we will never be able to model the complete disorder of schizophrenia in a rat — there is no such thing as a schizophrenic rat or even an animal model of (the whole of) schizophrenia. However, to borrow a term from the genetic literature, what one can model in laboratory animals are "endophenotypes" relevant to schizophrenia.[8] Because of the inherent complexity of psychiatric disorders and the heterogeneity of diagnostic categories, psychiatric geneticists have proposed that it may be simpler and more fruitful to search for genes for "subclinical traits" or "facets" of the phenotype of schizophrenia (endophenotypes) — these may involve fewer genes. Similarly in animal modelling, one can model a variety of endpoints or endophenotypes characteristic of schizophrenia and seek to understand their physiology and regulation. With respect to etiology, one can attempt to understand genetic and environmental factors involved in modulating these specific endophe-

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notypes or traits relevant to schizophrenia. Given our deepening understanding of pathological features of schizophrenia at multiple levels of resolution, the spectrum of traits relevant to schizophrenia that can be modelled in animals is fast increasing. Such abnormalities include changes in psychological function/behaviour (e.g., working memory, selective attention, set shifting, social interaction); psychophysiological measures (e.g., prepulse inhibition of startle, evoked brain potentials); brain structure (e.g., ventricular and brain regional volume, neuronal density or migration, oligodendrocyte number or structure); neurochemistry (dopamine, glutamate, GABA, serotonin); and, at a molecular level, changes in the expression of a wide variety of gene products. Abnormalities in some of these traits may be present in not only schizophrenia but might also represent pathophysiological processes common to several psychiatric disorders.

With respect to the pathophysiology of schizophrenia, animal experimentation has been pivotal in contributing to our knowledge of the regulation of the neuronal circuitry thought to be dysregulated in the disorder. To mention a few examples, a huge body of research in rodents and other animals has elucidated the mechanisms of sensitization of dopamine neurons to psychostimulant drugs and stress, providing profound insights into the functioning of dopamine neurons and the mechanisms involved in dopaminergic hyperactivity.[9,10] Work by Goldman-Rakic[11] and colleagues, using mainly nonhuman primates, but also ferrets, has produced a detailed delineation of the role of the prefrontal cortex in working memory and its modulation by dopamine. Pioneering electrophysiological studies in rats by Anthony Grace and others[12,13] have outlined functional interactions in the neurocircuitry involving the ventral tegmental dopamine neurons, prefrontal cortex, hippocampus, amygdala and nucleus accumbens — key regions involved in the pathophysiology of schizophrenia. Prompted by the work of Lipska and Weinberger,[14] numerous groups have contributed to work in rodent models, showing that perinatal disruption of brain regions such as the hippocampus and prefrontal cortex can lead to a constellation of endophenotypes at adulthood that are characteristic of schizophrenia, including dopaminergic hyperactivity.

Regarding the causes of schizophrenia, extensive ongoing animal experimentation is aimed at further understanding both genetic and environmental risk factors and their interaction. Genetic studies in human populations have provided significant evidence for potential susceptibility genes for schizophrenia; however, in several cases, little was initially known about the function of these genes (e.g., DISC-1, dysbindin) in neurodevelopment and behaviour. It is mainly through the use of animal models that we are able to detect what these genes do. Experimentation in normal animals can provide information on the basic biology of these genes and their proteins, such as their localization and cellular function.[15] After this, genetically engineered and naturally occurring mutant mice can be particularly useful in providing requisite information about the neurodevelopmental, behavioural and molecular consequences of dysregulation in specific susceptibility genes.[15,16] In a different approach, instead of starting with known susceptibility genes and trying to find what they do, one can start with a trait known to be abnormal in schizophrenia (e.g., prepulse inhibition [PPI] of startle) and search for the genes modulating that trait. Continuous traits (which, like height or PPI, can assume any value) are amenable to searching for genes modulating the trait using the statistical methods of quantitative trait locus analysis in inbred strains of rodents, followed by fine mapping strategies and identification of candidate genes for the trait[17,18] and, possibly, for schizophrenia.

In the case of environmental factors, whereas human epidemiological studies can reveal an association between an environmental risk factor and the development of schizophrenia, animal modelling can be used to address whether that environmental factor can actually cause changes in brain development that are relevant to schizophrenia.[19] For example, reports over many years have documented an increased incidence of schizophrenia after maternal infection with viruses such as influenza and other infectious agents during pregnancy. Several laboratories have now embarked on animal studies to characterize the exact brain changes wrought in offspring following maternal viral or bacterial infection.[20] Even more importantly, these animal models can be used to investigate the mechanisms underlying the effects of maternal infection. One might question whether effects of the mother's infection are caused by actions of cytokines (the chemical mediators of inflammation); or by the effects of fever on neurodevelopment; or perhaps the effects are caused by more generalized factors, such as the release of glucocorticoid stress hormones during the infection. Such questions would be difficult to address directly in human populations and may provide insight, for example, on whether prevention of the infection is necessary or whether prevention of fever and/or the inflammatory reaction is sufficient for fetal protection.

Another example of an environmental risk factor associated with the precipitation of psychotic symptoms, which is quite amenable to investigation using animal models, is chronic cannabis use during adolescence. Recent work on the central nervous system (CNS) effects of cannabinoids in rats indicates these compounds have effects that could potentially contribute to psychosis, including a complex modulation of dopaminergic transmission that can lead to an enhanced sensitization of dopamine neurons and the ability to alter dendritic structure in the prefrontal cortex.[21,22] Long-term cannabis exposure to adolescent rats has been shown to impair memory and social interaction, whereas perinatal lesion to the prefrontal cortex in combination with cannabis exposure during the adolescent period exacerbates aspects of these deficits.[23] The latter experiments illustrate how animal models can begin to assess the additive or interactive effects of combinations of risk factors or lesions purported to contribute to the development of schizophrenia.

Exactly how early environmental risk factors might cause lasting changes in CNS function is poorly understood at a molecular level. However, studies with animal models are providing novel insights into how this may come about. An example is the work of Meaney, Szyf and colleagues[24] who

have investigated how variation in the maternal care of rat pups can produce lasting changes in the CNS of those offspring. They showed that variation in maternal care alters the chromatin structure in the brains of offspring by altering histone-DNA interactions regulating the DNA methylation state of specific genes (the glucocorticoid receptor gene).[24] This epigenetic regulation provides a mechanism for long-term, relatively stable (but still reversible) changes in gene expression in response to experiences during early development. It is likely that similar types of mechanisms may mediate the effects of other early environmental experiences, including some of those putatively involved in causing schizophrenia and other psychiatric disorders.

Of course, an essential step in clarifying the etiology of schizophrenia is understanding the gene–environment interactions contributing to the disorder. Animal modelling is on the verge of investigating such interactions. Further elucidation of genes involved in schizophrenia is certain to lead to models incorporating multiple genetic and environmental insults for the disorder.

This has been a very selective description of some ways in which the humble laboratory rodent and other animals are contributing remarkably to our understanding of brain mechanisms relevant to schizophrenia. The value of animal research rests in its interplay with human research. Ideally, experiments with humans (with their inherent limitations) point the way for detailed mechanistic studies in animals, with key findings in animals leading back to further validation experiments in human populations.

In closing, I would contend that animal models play a crucial role in the process of understanding, treating and preventing schizophrenia. I leave you with reference to some more extensive recent reviews evaluating the usefulness and future directions of animal modelling in relation to schizophrenia.[25,26]

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References

1. Seeman P. Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse* 1987;1:133-52.
2. Bai O, Zhang H, Li XM. Antipsychotic drugs clozapine and olanzapine upregulate bcl-2 mRNA and protein in rat frontal cortex and hippocampus. *Brain Res* 2004;1010:81-6.
3. Anis NA, Berry SC, Burton NR, et al. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* 1983;79:565-75.
4. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006;163:600-10.
5. Bai YM, Lin CC, Chen JY, et al. Association of initial antipsychotic response to clozapine and long-term weight gain. *Am J Psychiatry* 2006;163:1276-9.
6. Hagan JJ, Jones DN. Predicting drug efficacy for cognitive deficits in schizophrenia. *Schizophr Bull* 2005;31:830-53.
7. Hajos M. Targeting information-processing deficit in schizophrenia: a novel approach to psychotherapeutic drug discovery. *Trends Pharmacol Sci* 2006;27:391-8.
8. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636-45.
9. Laruelle M. The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. *Brain Res Brain Res Rev* 2000;31:371-84.
10. Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Brain Res Rev* 1997;25:192-216.
11. Goldman-Rakic PS, Castner SA, Svensson TH, et al. Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology (Berl)* 2004;174:3-16.
12. Grace AA, Rosenkranz JA. Regulation of conditioned responses of basolateral amygdala neurons. *Physiol Behav* 2002;77:489-93.
13. Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res Brain Res Rev* 2000;31:330-41.
14. Lipska BK. Using animal models to test a neurodevelopmental hypothesis of schizophrenia. *J Psychiatry Neurosci* 2004;29:282-6.
15. Ishizuka K, Paek M, Kamiya A, et al. A review of Disrupted-In-Schizophrenia-1 (DISC1): neurodevelopment, cognition, and mental conditions. *Biol Psychiatry* 2006;59:1189-97.
16. Chen J, Lipska BK, Weinberger DR. Genetic mouse models of schizophrenia: from hypothesis-based to susceptibility gene-based models. *Biol Psychiatry* 2006;59:1180-8.
17. Flint J, Valdar W, Shifman S, et al. Strategies for mapping and cloning quantitative trait genes in rodents. *Nat Rev Genet* 2005;6:271-86.
18. Darvasi A. Dissecting complex traits: the geneticists' "Around the world in 80 days." *Trends Genet* 2005;21:373-6.
19. Boksa P. Animal models of obstetric complications in relation to schizophrenia. *Brain Res Brain Res Rev* 2004;45:1-17.
20. Boksa P, Luheshi GN. On the use of animal modeling to study maternal infection during pregnancy and prenatal cytokine exposure as risk factors for schizophrenia. *Clin Neurosci Res* 2003;3:339-46.
21. Rodriguez De Fonseca F, Gorriti MA, Bilbao A, et al. Role of the endogenous cannabinoid system as a modulator of dopamine transmission: implications for Parkinson's disease and schizophrenia. *Neurotox Res* 2001;3:23-35.
22. Kolb B, Gorny G, Limebeer CL, et al. Chronic treatment with Delta-9-tetrahydrocannabinol alters the structure of neurons in the nucleus accumbens shell and medial prefrontal cortex of rats. *Synapse* 2006;60:429-36.
23. Schneider M, Koch M. The effect of chronic peripubertal cannabinoid treatment on deficient object recognition memory in rats after neonatal mPFC lesion. *Eur Neuropsychopharmacol* 2007;17:180-6.
24. Szyf M, Weaver IC, Champagne FA, et al. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. *Front Neuroendocrinol* 2005;26:139-62.
25. Arguello PA, Gogos JA. Modeling madness in mice: one piece at a time. *Neuron* 2006;52:179-96.
26. Powell CM. Miyakawa. Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? *Biol Psychiatry* 2006;59:1198-207.