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From Humans to Animals: Animal Models in Schizophrenia

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1. Introduction

Schizophrenia is one of the most devastating psychiatric disorders. Schizophrenia affects 1.1% of the population or 51 million people (NIMH). Schizophrenia is a disorder that affects multiple brain regions and systems. Symptoms include positive symptoms, negative symptoms and cognitive deficits. Much research has focused on two neurotransmitter systems, dopamine and glutamate. Postmortem studies examining morphology have found alterations in dendrites and spines in the prefrontal cortex and the hippocampus, changes in cell number in volume in the thalamus and alterations in protein expression in the prefrontal cortex. Genetic studies have found a number of genes associated with schizophrenia including but not limited to DISC1, neuregulin1, and Dysibindin 1. The current hypothesis based on the postmortem work and genetic studies suggests the etiology of schizophrenia has its origins in development. The changes in dendrites and spines observed in the prefrontal cortex and hippocampus without a change in cell number could occur as a result of alterations in calcium signaling levels in development due to alterations in synaptic input into the prefrontal cortex and hippocampus. The various genes that have been shown to be altered in schizophrenia are also involved in neurodevelopment. DISC1, neuroregulin 1 and Dysbindin 1 have all been shown to be involved in neurite outgrowth and differentiation (Ghiani et al, 2010; Kamiya et al, 2005; Pitcher et al, 2011; Sebat et al., 2009; Wiliams et al., 2010). These data support the above hypothesis that schizophrenia is a neurodevelopmental disorder that may or may not have a genetic predisposition. In order to better understand the etiology of the disease, research needs good models with which to test theory. Genetic models, chemical lesions, and physical lesions have been used to produce animal models to mimic human disorders and are becoming the hallmark of translational research. Animal models in the past have been used to understand how the nervous system develops by using lesions to examine pathways or genetic knockouts to examine the role of genes in development and function of the nervous system. The use of animal models is not limited to basic research but is also used by pharmaceutical companies to test drugs to treat diseases to determine their viability. Whatever their use, animals provide us with a unique way in which to view how the nervous system develops, functions and what happens when development goes wrong. This chapter will focus on the use of animal models as a potential method to study neuropsychiatric disorders.

2. Animal models

Over 50 animal models have been described in the past 30 years (Tseng et al., 2009). The first models tended to be pharmacological constructs linked to dopamine and glutamate. The issue with these models is that they leave out certain aspects of the disorder such as the idea that schizophrenia is a disorder founded in development, cognitive deficits as well as alterations in neuroanatomy and interactions between systems. A review by Harrision (2011) suggests that the problem with modeling schizophrenia is that since it is a disorder that involves so many brain regions, how does one choose a target for the lesion? Schizophrenia therefore, appears to be a disorder involving circuits (Fig 1). One way to choose a target is by picking a brain region shown to be altered anatomically or by choosing a gene whose expression is involved in the development of the structures shown to be altered in schizophrenia. With this in mind two of the most consistent postmortem findings in schizophrenia are lateral ventricular enlargement and a decrease in volume and cell number in the thalamic medial dorsal nucleus. Several models have been designed around these two findings and will be discussed in this chapter. The use of knock out mice to model schizophrenia has also been very popular. The mouse model for Dysbindin 1 has shown much promise in the field of schizophrenia.

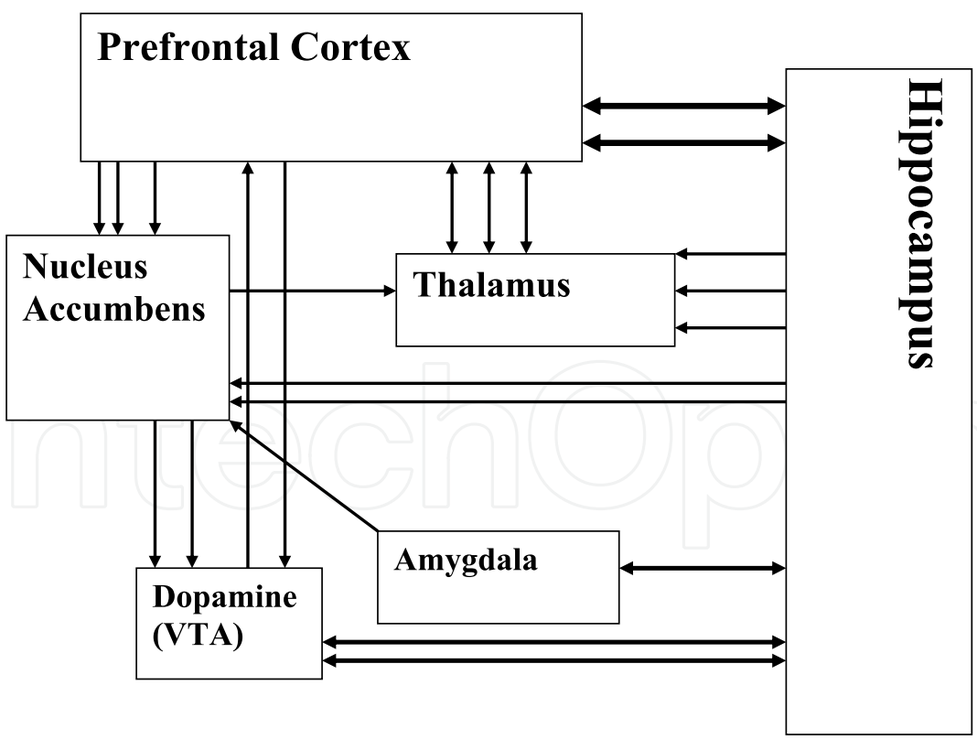

Fig. 1. Schematic showing the circuits thought to be involved in schizophrenia (Tseng et al, 2009).

3. Animal models involving the hippocampus

Lesions of the ventral hippocampus in the rat involve using iobotinic acid to cause a bilateral excitotoxic lesion at postnatal day 7 (Lipska et al, 2002; Becker et al, 1999; Sams-Dodd et al, 1997). One such model involves the neonatal damage of the rat ventral hippocampus; typically, ibotenic acid, causing an excitotoxic lesion, is applied to the ventral hippocampus at postnatal day 7 (Lipska et al 2002; Becker et al, 1999; Sams-Dodd et al, 1997). The animals are allowed to mature and are tested for social interactions (Sams-Dodd et al, 1997), aggression (Becker et al, 1999), and performance in working memory tasks (Lipska et al 2002). This model mimics a spectrum of behavioral features of schizophrenia; it produces functional pathology in other brain regions also implicated in schizophrenia, such as the striatum, the nucleus accumbens, and the prefrontal cortex (PFC). Furthermore, the social and functional effects are not evident until the rat subjects reach adolescence, thus mimicking the timing of onset of symptoms (for review see Lipska, 2004 and Tseng et al, 2009). Following the bilateral lesion at P7 the behaviors emerge in a manner consistent with schizophrenia. Negative symptoms such as aggression and deficits in grooming appear prior to puberty. The cognitive symptoms such as deficits in various types of memory appear at the onset of puberty and the positive symptoms appear late in adolescence (Tseng et al, 2009). This delayed emergence of behaviors mimics that observed in schizophrenia. This model appears to be consistent with many of the behavioral aspects of schizophrenia; however, it lacks construct validity, as schizophrenics do not have a lesion in their hippocampus similar to that seen in the model. Postmortem studies have reported morphometric abnormalities in the hippocampal formation, such as decreased volumes (Falkai & Bogerts, 1986; Heckers et al, 1991) and decreased number of neurons and smaller pyramidal cells in schizophrenia (Falkai & Bogerts, 1986; Jonsson et al, 1999). Other studies have not been able to replicate such findings (Heckers et al, 1991; Walker et al, 2002). Further discrepancy is seen in the morphological evaluation of this model which reports an increase in synaptic density, number of branches, and dendritic length in the pyramidal cells of the PFC (Robinson and Kolb, 1997), which contradicts the compromised morphological evidence in schizophrenia (Byne W et al; 2001, Jones L, Mall N, Byne W; 1998, Bunney WE and Bunney BG; 2000, Schindler MK et al; 2002, Jonsson SAT et al; 1999; Broadbelt et al, 2002, Kalus, 2000; Black et al, 2004; Pierri et al, 2001; Garey et al, 1998; Glantz and Lewis, 2000). Although the discrepancy in anatomical findings between this model and schizophrenia are great, it prevails to be an attractive model because of its implications in the dopaminergic system, a neurotransmitter system known to be affected in this disorder and a major target for therapeutic agents. Recent investigations using this model examined cell excitability in PFC neurons, and it was concluded that the PFC dopamine-glutamate interactions were altered after puberty in the lesioned rats (Tseng et al, 2007). Specifically, the PFC neurons showed enhanced excitability in lesioned animals, which contradicts the common concept of hypofrontality, characteristic of schizophrenic subjects. While the model may have its inconsistencies, the approach using neurodevelopmental damage has merits in developing models for schizophrenia.

The use of excitatory lesions of the entorhinal cortex (EC) has furthered investigation of the effects on the dopaminergic system. It was observed that an EC lesion resulted in the

enhancement of methamphetamine-induced dopamine release in the nucleus accumbens and basolateral amygdala (Uehara, et al 2007), implying dysregulation in the dopaminergic neurotransmission in the limbic regions. Although these models offer great insight into circuitry of the dopaminergic system and potential for development of therapeutic agents, it is evident that models based on manipulations of the dopamine system have limited promise. They can imitate a spectrum of schizophrenic behaviors, but they fall short on morphological and physiological findings.

Keeping with the idea that schizophrenia is a disease that affects circuits, another mesiotemporal limbic area used for lesion studies is the amygdala. The amygdala receives projections from the hippocampus and projects to the nucleus accumbens (Fig. 1). A model put forward by Francine Benes examines the effects of altering the circuitry between the amygdala and the hippocampus. The non-competitive GABA-A receptor antagonist picrotoxin was infused into the basolateral complex of the amygdala. This was done to mimic a GABA defect in this region. This model shows alterations in GABAergic neurons in the CA2/3 region of the hippocampus similar to that seen in schizophrenia (Berretta and Benes 2006; Berretta et al, 2009). Daenen et al, (2001) examined several behaviors in rats following a lesion of the amygdala at P7 or P21. The lesions at P7 but not P21 showed alterations in locomotor stereotypy (Daenen et al, 2001) as well as play (Daenen et al, 2002) and exploratory activities (Woletrink et al, 2001). These lesion studies tend to find deficits in social behavior (Becker et al, 1999; Sams-Dodd et al, 1997), working memory (Lipska et al, 2002), and abnormalities in locomotor stereotypy (Daenen et al 2001, 2003). Daenen et al, (2003) also lesioned the ventral hippocampus at P7 and P21 and examined the response to acoustic startle and found that the lesions had no effect on the response to acoustic startle. A final study examined the effect of a mesiotemporal limbic lesion on the expression NAA, a neuronal viability marker in the PFC, and they found a developmental effect in the early-lesioned animals, which was absent from the animals lesioned as adults (Bertolino et al, 1997). In humans, these temporal association areas have widespread connections with the medial dorsal nucleus of the thalamus and the pulvinar nucleus of the thalamus (Byne et al, 2001), which has also been implicated in schizophrenia (Byne et al, 2002; 2001) (Fig. 2). When one looks at the brain regions involved in schizophrenia and the circuits involved, one target region emerges as a location to target in modeling schizophrenia, the medial dorsal nucleus of the thalamus. This nucleus receives multiple inputs from the hippocampus as well as the amygdala and projects to the prefrontal cortex as well as other regions involved in schizophrenia.

4. Animal models and the thalamus

Thalamic association nuclei, such as the medial dorsal nucleus (MD) (Paxinos G, 1986), which have connections to many regions involved in schizophrenia (Paxinos G, 1986; Kuroda et al, 1998), represents an important relevant target for lesion studies (see figure 2).

Normal development of the cerebral cortex is dependent upon reciprocal connections with the thalamus. The close association between the MD and the PFC and EC initiates early in development. The cortical plate differentiates from a densely packed zone of immature cells into lamina, resembling future cortical layers (van Eden 1986); axons from early postmitotic

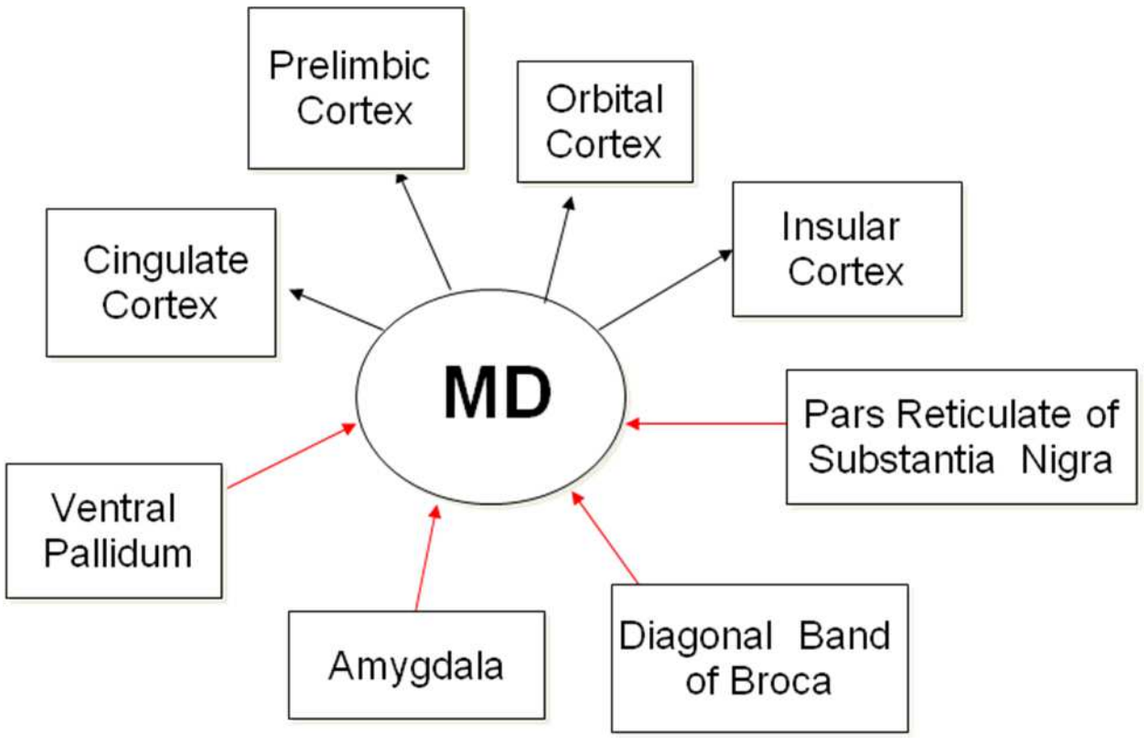

Fig. 2. Circuitry formed by the MD in rats. MD projects to cortex and receives feedback, as well as projections from subcortical structures.

neurons of the cortical subplate pioneer the pathway from the cortex toward subcortical targets, prior to neurons from cortical layers V and VI migrating into position (Molnar 2000). By postnatal day 4 and 5, layer V can be distinguished from the upper cortical plate containing the elements to become layers II and III. The first evidence of retrograde labeling from PFC to MD becomes apparent at this time (Van Eden 1986). The arrival of the MD afferent fibers in the upper cortical plate precedes the completion of layer III differentiation, occurring on postnatal days 9 to 10 (Van Eden 1986). The predominant thalamic input to the PFC is from the medial dorsal nucleus (Negyess et al., 1998, Kuroda 1995a, 1995b). Afferents from the MD synapse on spines and dendritic shafts of pyramidal cells in the PFC (Negyess et al., 1998). Myelination of the axons from the MD to the PFC occurs approximately in the second decade of life (Molnar 2000). Developmental maturation of neurons is activity-dependent (Van Pelt et al., 1996, Kossel et al., 1997, Baker et al., 1997); an early lesion of the MD could therefore result in abnormal development of the PFC. In particular, a decrease in thalamic input to PFC may result in decrease of calcium-mediated stimulation of dendritic remodeling. Binding of glutamate to the N-methyl-D-Aspartate (NMDA) receptor causes an influx of calcium, which triggers the release of calmodulin from the calcium binding protein neurogranin (Ramakers et al., 2001), allowing for calmodulin to bind to calcium. Calcium-calmodulin can activate calcium calmodulin kinase (CaMK) II (Petit et al., 1998), CaM kinase, and CaM Kinases I and IV (Petit et al., 1998). CaMK II has been shown to be important in controlling spine formation (Petit et al., 1998), as well as neuronal arborization, both pre- and post-synaptically (Ramakers et al., 2001, Petit et al., 1998, Kater et al., 1988). CaMK II also phosphorylates MAP2, which in turn promotes dendritic branching.

Dephosphorylation of MAP2 by calcineurin promotes dendritic elongation (Ramakers et al., 2001, Petit et al., 1998, Kater et al., 1988). Current postmortem studies of the PFC have shown a decrease in neurogranin and calmodulin in areas 9 and 32 (Broadbelt et al., 2006, 2008). These data suggest possible alterations in calcium signaling in the PFC. Thus, changes in proteins involved in calcium signaling may lead to changes in dendritic arbors and spines, which are critical to neuronal function, leading to possible alterations in integration of synaptic inputs. Thus information transfer between cells can be altered. In addition, these data suggest that the medial dorsal nucleus is a potential target for a lesion during development that may result in alterations similar to those seen in schizophrenia.

Research has shown that two of the most consistent findings in schizophrenia are volume and cell loss in the MD of the thalamus and enlarged anterior and posterior horns of the lateral ventricles (Pakkenberg; 1990, 1992, Popken et al 2000, Young et al 2000, Byne et al 2001, 2002, Lewis et al 2001). Previous MD lesion studies have primarily looked at the effect of the lesions on behavior (Volk & Lewis 2003; Van Eden et al, 1994; Isseroff et al, 1982). Studies have shown that a lesion of the MD leads to impairments in spatial memory tasks in rats (Isseroff et al, 1982) as well as in monkeys (Aggleton et al., 1983). This spatial memory loss is qualitatively similar to that seen after damage of the prefrontal cortex (Isseroff et al, 1982). MD lesions can also affect working memory as assessed by radial maze tests (Aggleton, 1983; Stokes1990). These findings are consistent with reports of working and spatial memory deficits in schizophrenic patients (Perry et al, 2001). An embryonic animal lesion model for schizophrenia includes intrauterine radiation of rhesus monkeys during thalamic neurogenesis, which results in a 25% loss of thalamic volume, neuron loss, and nonuniform damage to the thalamic complex (Schindler et al, 2002). Although this model is simulating the consistent finding of neuron loss and decreased volume in the thalamus (Pakkenberg; 1990, 1992, Popken et al 2000, Young et al 2000, Byne et al 2001, 2002, Lewis et al 2001), it offers too many variables as the entire fetus is subjected to radiation and thus a spectrum of possible side effects. Several studies showed alterations in working and short-term memory in adult rats following early N-methyl-D-aspartate (NMDA) receptor inhibition in the MD (Garter et al., 1992, Sicar et al., 1998, 2003, Stefani et al., 2005, Wang et al., 2001 for review see Pehrson et al., 2007).

Focusing on the relevant circuitry between the MD and the PFC, one study examined the structural and functional effects of a MD lesion on the PFC in the rat (Van Eden et al, 1998). A study using an electrothermal lesion on the MD on the day of birth analyzed prefrontal architecture on day 35, as well as performance on a delayed alternation task. They found no significant gross changes in the PFC, except for local decreases in cortical width. The behavioral ability in spatial task was also examining the morphology in the PFC; they only examined gross morphology and not specific cellular morphology, which is known to be affected in schizophrenic brains (Garey et al, 1998; Broadbelt et al, 2002; Glantz & Lewis 2000). When using animals as models it is important to understand timing of developmental events. In rats, thalamic fibers grow into the cortex between postnatal day 0 and 7 (Wise et al, 1979), and a lesion performed too early may reflect the plastic ability of the brain. An additional MD lesion study looked at whether an acute excitotoxic lesion of the MD on periadolescent monkeys could produce decreased PFC glutamate decarboxylase mRNA expression (Volk & Lewis, 2003). They found that a substantial lesion did not reduce levels of this GABA-synthesizing enzyme in the PFC four weeks after lesions were performed

(Volk & Lewis, 2003). Their inability to see a change in PFC enzymatic levels may have occurred as a result of the acute lesion in prepubescent animals. The connections between the MD and the PFC may have been well established by the time the lesions were performed, therefore, may not accurately reflect the development. Our laboratory is currently developing an animal model for prefrontal cortical development. Our model is based on the interplay between the prefrontal cortex and the MD and that pyramidal cell development is activity dependent. Our data suggest that the model may also model some of the morphological alterations seen in the prefrontal cortex, such as loss of dendrites and spines, and in the hippocampus, such as change in cell density in CA1. Further work examining behavior needs to be performed to more accurately characterize the model as having relevance for studying schizophrenia.

5. Conclusion

While many of the models discussed reflect the ability to express multiple symptoms of schizophrenia from behavior to genetics to morphology, none of the models appear to mimic all of the symptoms. A current review article by Harrison et al., (2011) suggests that the complexity of the disorder makes it very difficult to accurately model schizophrenia. The authors question how you choose your target for alteration when so many targets appear possible. The point is a valid one, as schizophrenia does not present itself the same way in all individuals. Schizophrenia has many symptoms that can be grouped into three categories: positive, negative and cognitive. Schizophrenics may have symptoms from 1, 2 or all 3 categories. Therefore, it may be very difficult to have one model for all of the symptoms exhibited in schizophrenia. Instead several models may need to be used to understand how schizophrenia manifests itself. What does seem to be consistent in all of the research is the agreement that schizophrenia manifests itself during development, which leads to behavioral alterations in late adolescence and early adulthood that may or may not progress throughout the rest of the individual's life. While one model may not fit all of the symptoms of schizophrenia, it may model enough aspects to help us understand how the disease manifests itself and eventually help us come up with better treatments for a complex disorder which affects over 50 million people.

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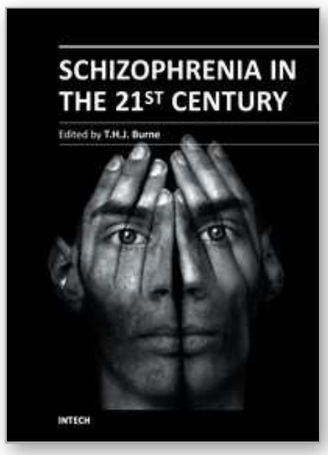

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Schizophrenia is a poorly understood but very disabling group of brain disorders. While hallucinations and delusions (positive symptoms of schizophrenia) feature prominently in diagnostic criteria, impairments of memory and attentional processing (cognitive symptoms of schizophrenia) are attracting increasing interest in modern neuropsychiatry. Schizophrenia in the 21st Century brings together recent findings on this group of devastating disorders. We are still a long way from having effective treatment options, particularly for cognitive symptoms, and lack effective interventions and ways to prevent this disease. This volume covers various current options for therapy, clinical research into cognitive symptoms of schizophrenia and preclinical research in animal models.

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