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·Review·

Prefrontal dysfunction and a monkey model of schizophrenia

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The prefrontal cortex is implicated in cognitive functioning and schizophrenia. Prefrontal dysfunction is closely associated with the symptoms of schizophrenia. In addition to the features typical of schizophrenia, patients also present with aspects of cognitive disorders. Based on these relationships, a monkey model mimicking the cognitive symptoms of schizophrenia has been made using treatment with the non-specific competitive N-methyl-*D*-aspartate receptor antagonist, phencyclidine. The symptoms are ameliorated by atypical antipsychotic drugs such as clozapine. The beneficial effects of clozapine on behavioral impairment might be a specific indicator of schizophrenia-related cognitive impairment.

Keywords: prefrontal cortex; schizophrenia; monkey model

Introduction

One percent of the adult population, particularly young adults, are affected by schizophrenia. Schizophrenic patients typically present with hallucinations, delusions, withdrawal from social activities, loss of personal care skills, and flat or inappropriate emotional responses to situations[1]. Although many factors have been associated with schizophrenia, including genetic factors, early environmental influences, and neurobiological, psychological, and sociological processes[2-4] that are very important contributory factors, the mechanism underlying this disorder is unknown. Patient data are insufficient for understanding the pathology and etiology of schizophrenia. Further, direct experimentation on human subjects is ethically unacceptable. Thus, animal models have become an indispensable tool for pathological research. Unlike other neurological diseases such as stroke, epilepsy, and Parkinson's disease that can be easily replicated in animals, some of the symptoms of schizophrenia human patients, such as thinking disorders, delusions, and hallucinations, are difficult to replicate in animals. For many years, there has been no appropriate non-human primate model of schizophrenia. In addition to the typical features of schizophrenia, patients present with aspects of prefrontal cognitive disorders involving, e.g., working memory, selective attention, initiating movement, and planning. Based on these relationships, a monkey model of schizophrenia could be developed by mimicking its cognitive symptoms. In this review, we introduce schizophrenia and the prefrontal cortex (PFC) as well as their relationship and discuss the development of a monkey model of schizophrenia, including the methods and behavioral tests of the model.

The Prefrontal Cortex and Schizophrenia

The volume of the human brain is twice that of the chimpanzee, and the PFC, which is the most rostral component of the primate cortex, has expanded most in humans[5,6]. In other species, the PFC functions in voluntary motor control, whereas in primates, it has developed

significantly to include other important functions such as executive functions, conflicting-thought mediation, decision-making (e.g., distinctions of right *versus* wrong or good *versus* bad), prediction of future events, and government of social and emotional control. Further, the PFC in the human brain plays a central role in conscience, intelligence, and personality[5-7]. The PFC has broad connections with many parts of the brain, particularly the sub-regions of the limbic system[10]. The human PFC, which is better developed than in other primates, is the primary contributor to humans having unequalled abilities for planning and abstract reasoning[6,8].

Prefrontal dysfunction plays a role in the expression of the cognitive deficits associated with schizophrenia[9]. The relationship among the PFC, executive dysfunction, and schizophrenia symptoms has been studied, and several studies have shown the existence of abnormalities in the PFC. MRI studies have revealed a decrease in the volume of PFC in schizophrenic patients[10-13], and a postmortem anatomical study found that the cortex of prefrontal area 46 is thinner and the density of neurons in this area is increased[14-16]. In as early as 1986, to study the relationship between prefrontal dysfunction and schizophrenia, medication-free chronic schizophrenia patients and normal controls were used, and the regional cerebral blood flow (rCBF) was measured during performance of a PFC-specific cognitive test, the Wisconsin Card Sorting (WCS) or a simple number-matching (NM) test as the control. During the WCS, there was a clear increase in PFC rCBF in the controls compared with the schizophrenic patients; the PFC was the only region that changed. This finding significantly distinguished patients from controls, whereas during the NM, no region differentiated patients from controls. Further, the PFC rCBF was positively associated with WCS performance in patients, suggesting that the better the PFC functions, the better patients perform[9]. The decreased prefrontal rCBF in schizophrenic patients might be a manifestation of abnormal prefrontal neuronal activity. In addition, considerable effort has been directed at identifying specific neuronal factors that contribute to PFC dysfunction in schizophrenic patients. These findings are consistent with the hypothesis that schizophrenia is associated with complex alterations in the anatomy and function of multiple neuronal populations in the PFC. At the cellular and molecular levels, chronic stress exposure leads to spine loss in the PFC[17,18], particularly in layer III, which harbors the recurrent microcircuits that are most affected in schizophrenia[19]; the interconnection of precise microcircuits in the dorsolateral PFC appears to be associated with schizophrenia. Physiological studies in monkeys indicate that recurrent excitation between PFC pyramidal cells depends on the N-methyl-*D*-aspartate (NMDA) receptors, and several genes associated with NMDA transmission have been linked to schizophrenia [20].

The monoamine system, particularly the dopamine (DA) system, is important for prefrontal cognitive function, so many PFC functions are related to the DA system[21]. Dysfunction of the prefrontal monoamine system is associated with mental disorders such as schizophrenia, attention-deficit/hyperactivity disorder, drug addiction, autism, and depression[22-28]. Neurochemical analyses of DA and its metabolites provide evidence that mesoprefrontal DA neurons play a role in prefrontal dysfunction in schizophrenia and that the extent of decrease of DA turnover is directly associated with the severity of cognitive deficits[29-32]. In addition, the density of D1-like receptors in the PFC is decreased in schizophrenic patients who show prefrontal cognitive impairments[32]. On the contrary, DA agonists improve cognitive performance and cognitive activation of blood flow in the PFC of schizophrenic patients, which supports the hypothesis that hypofunction of the mesoprefrontal DA neurons contributes to schizophrenia[21].

Based on these facts, Goldman-Rakic and some scientists suggested that prefrontal dysfunction, particularly the impairment of working memory, is a cause of schizophrenia[14-16, 28-32, 50]. This suggestion led to the development of a novel monkey model of schizophrenia that mimics the cognitive symptoms of schizophrenia.

The Monkey Model of Schizophrenia

Based on this idea, in 1997, Jentsch *et al.* reported the development of a monkey model of schizophrenia using phencyclidine (PCP), a non-specific competitive NMDA receptor antagonist, in which the monkeys exhibit task performance deficits involving prefrontal cognitive function after PCP treatment twice a day for two weeks. In addition, they found that clozapine, an atypical antipsychotic drug, ameliorated the performance deficits. This study showed that the repetition of PCP treatment in monkeys might be

an effective method of studying psychiatric disorders such as schizophrenia, which involves cognitive dysfunction and DA hypo-function in the PFC[33].

Drugs for Developing an Animal Model of Schizophrenia

Three drugs are used for the development of a monkey model of schizophrenia, ketamine, PCP, and MK801. Here, we focus on ketamine and PCP.

Ketamine is an NMDA receptor antagonist that is predominantly used for the induction and maintenance of general anesthesia. Long-term treatment with ketamine can cause a number of impairments in cognitive function. The effects of ketamine are brief, and last no more than a few hours; its hallucinatory effects last ~1 h. At sub-anesthetic doses, ketamine induces a dissociative state[34-38].

PCP is also an NMDA receptor antagonist. It is a synthetic dissociative drug originally developed as a general anesthetic. It is a partial agonist of dopamine D2 receptors, which might explain the psychotic symptoms caused by PCP. In humans, PCP can cause schizophrenia-like symptoms, and it has become a useful tool for developing animal models of this disease[39-43]. The short-term psychotic effects include: visual and auditory hallucinations; feelings of unreality and dissociation from the environment; distorted sense of body and time and space; distorted thinking; anxiety; paranoid thoughts; confusion and disorientation; intense feelings of alienation; depression; bizarre or hostile behavior; and grandiose delusions. The effects of long-term use are the following: chronic and severe anxiety and depression; social withdrawal and isolation; impaired memory; and persistent speech problems, such as stuttering. In monkeys, it is difficult to detect hallucinations with the PCP treatment. The effects of PCP in nonhuman primates include impairments in working memory and motor programming, as well as behavioral inhibition.

Possible Genetic Monkey Models of Schizophrenia in the Near Future

Besides drug models, studies involving twins have shown that schizophrenia is a heritable disorder and several schizophrenia-related genes have been revealed. For example, disrupted in schizophrenia 1 (*DISC1*) was one of the first genes discovered to be involved in schizophrenia. Anatomically, DISC1 knockin mice show increased lateral ventricle size, reduced cortical and hippocampal size like those found in schizophrenic patients[51]. Also, the expression of several proteins changes in the brain of schizophrenic patients such as “dysbindin” encoded by the gene *DTNBP1*, which is thought to be one of the most promising candidate genes for schizophrenia[52]. Another gene is *NRG1* which codes for a growth factor crucial to the development of the nervous system. Partial knockout of NRG1 in mice causes social interaction problems, reduced prepulse inhibition, and higher levels of spontaneous locomotion. These symptoms are reduced by clozapine[51].

It used to be quite difficult to perform genetic manipulation in monkeys, but at present, these techniques are rapidly developing in nonhuman primates[53,54]. Thus it will be possible to develop genetic monkey models for schizophrenia by genetic manipulation techniques in the near future.

Behavior Testing

The major prefrontal function is executive function, which includes planning and regulating, which are difficult to model in animals. Here, we describe two methods of detecting cognitive dysfunction in animal models.

The object retrieval detour (ORD) task The ORD task measures inhibitory control, which is a component of executive function. The main compartment of the test apparatus is put in front of the monkey. In the main compartment, there is a transparent plastic reward box that is open on one side. The open side of the box can be oriented directly toward, to the right side, or to the left side of the monkey, and the monkey can reach the box in all positions. This box can also be placed at the center or on the right or left side of the main compartment (Fig. 1). In this task, the monkey is required to retrieve food, which is placed in the reward box as a reward. The difficulty of the task performance is set up in the following three ways: the placement of the reward box within the main compartment, the orientation of the open side of the reward box, and the location of the food reward within the reward box (e.g., near or far from the opening). To perform this task, a monkey must inhibit the tendency to reach directly toward the food. To inhibit this tendency, several PFC functions are required. The motor performance in the ORD task is sensitive to impairments of the PFC and the dopamine system[44-49].

The delayed-response (DR) task DR tasks are normally used to investigate working memory processes. Providing

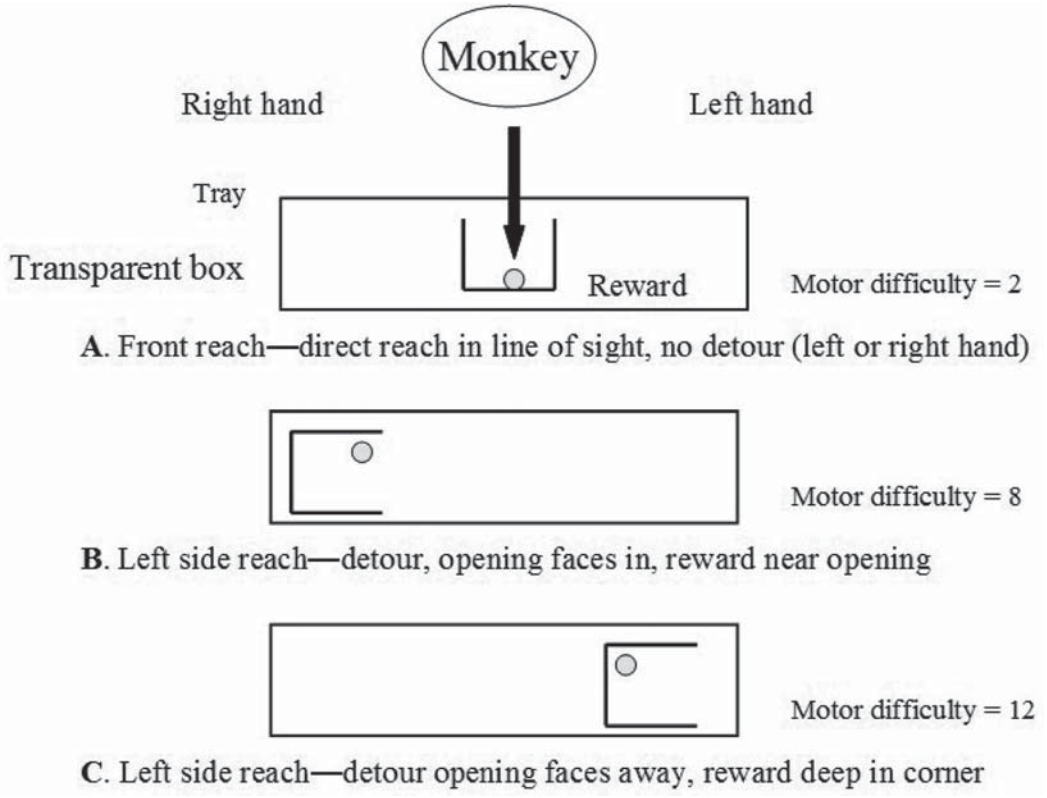

Fig. 1. The object retrieval detour task consists of attempting to retrieve a food reward placed in a transparent box that has one open side. The open side can be oriented toward, to the right, or to the left of the monkey[33].

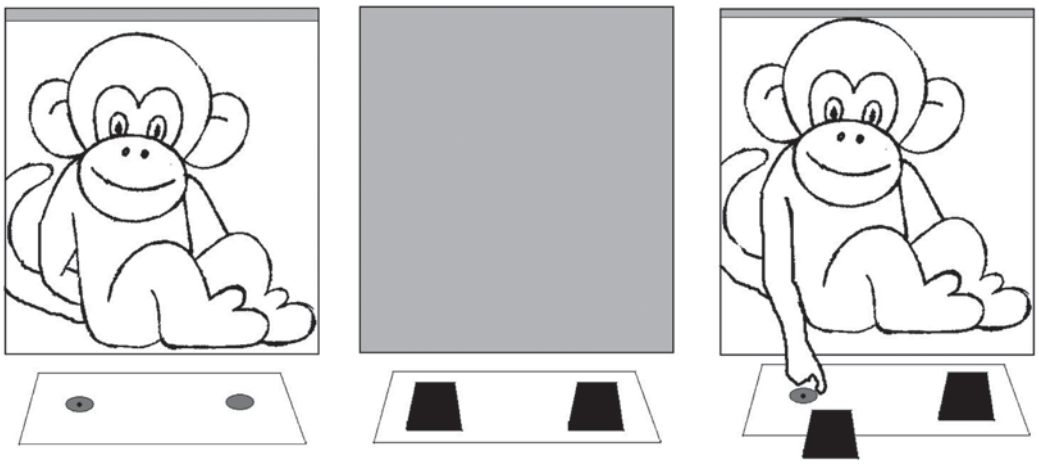

Fig. 2. In the delayed-response task, the monkey watches an experimenter place a food morsel in one of two wells (left); both wells are then covered. Subsequently, a screen is lowered for an interval of a few seconds to several minutes (the delay) (middle). When the screen is raised, the monkey gets only one chance to uncover the well containing food and receive the reward (right)[55].

different stimuli in different trials creates a task in which the test animal must remember varieties of the cue from trial to trial using working memory.

In a typical DR task, the monkey must choose from two wells, only one of which contains food (Fig. 2). With a delay (from a few seconds to several minutes) by lowering and raising a screen between the monkeys and the wells, the monkeys have only one chance to uncover the well to receive the reward after watching the placement of the food[9].

The repetition of PCP administration induces behavioral and biological impairments similar to those of schizophrenia. It has been reported that clozapine ameliorates the symptoms of schizophrenic patients refractory to treatment. Thus, clozapine would have an effect on the behavioral improvement of animals previously treated with PCP. The beneficial effects of clozapine on behavioral impairment might be a “specific indicator” of schizophrenia-related cognitive impairment.

Conclusion

The PFC is implicated in cognitive functioning and schizophrenia, and there is a close relationship between prefrontal dysfunction and the symptoms of schizophrenia. In addition to the typical features of schizophrenia, patients present with aspects of cognitive disorders. Based on these relationships, a monkey model of schizophrenia could be developed by mimicking the cognitive symptoms, which are ameliorated by atypical antipsychotic drugs such as clozapine. The beneficial effects of clozapine on behavioral impairment might be a “specific indicator” of schizophrenia-related cognitive impairment.

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