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REVIEW

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Animal models of working memory: insights for targeting cognitive dysfunction in schizophrenia

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Abstract

Background and rationale Working memory performance is considered to be a core deficit in schizophrenia and the best predictor of social reintegration and propensity for relapse. This cardinal cognitive process is critical for human reasoning and judgment and depends upon the integrity of prefrontal function. Prefrontal dysfunction in schizophrenia has been linked to altered dopaminergic and glutamatergic transmission. However, to date, antipsychotics provide no substantial relief from the debilitating cognitive consequences of this disease. *Objectives:* This review examines the key rodent and non-human primate models for elucidating the neural mechanisms of working memory and their neuromodulation. We compare the physiology and pharmacology of working memory between the normal state and experimentally induced models of prefrontal dysfunction and evaluate their relevance for schizophrenia.

Results and conclusions Rodent models have demonstrated the significance of aberrant dopaminergic and glutamatergic signaling in medial prefrontal cortex for working memory. However, there is some question as to the extent to which rodent tests of working memory tap into the same process that is compromised in schizophrenia. Non-human primates provide an unexcelled model for the study of influences on prefrontal function and working memory due to the high degree of homology between human and non-human primates in the relationship between prefrontal cortex and higher cognitive capacities. Moreover, non-human primate models of prefrontal dysfunction including amphetamine sensitization, subchronic phencyclidine, and neurodevelopmental insult are ideal for the analysis of novel compounds for the treatment of cognitive dysfunction in schizophrenia, thereby facilitating the translation between preclinical drug development and clinical trials.

Keywords Spatial working memory · Non-human primate · Prefrontal cortex · Schizophrenia · Dopamine · Animal models

Dr. Goldman-Rakic died before publication of this review, which is dedicated to her memory and her vision.

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Introduction

Keeping track of relevant information and ideas is a constant necessity for the rational interpretation and anticipation of ongoing events. Thus, in order to explain many aspects of human reason and cognition, it has been theorized that a system must exist for the active maintenance and manipulation of information. This construct of working memory incorporates temporary buffers of information and an attentionally constrained central executive—subsystems which are served by distributed neural networks (Baddeley and Hitch 1974; Baddeley 1992; Baddeley and Della Sala 1996). Studies in both human and non-human primates have identified the prefrontal cortex (PFC) as a critical node in these networks. Much of what is known today about the cellular and circuit basis of working memory comes from the work of Goldman-Rakic and colleagues (Goldman-Rakic 1990). The demonstration of a specific anatomical and physiological substrate for different domains of working memory led Goldman-Rakic to postulate that the PFC plays a central role in working memory and disruption of its intrinsic circuitry or functional connec-

tivity with other brain regions could lead to the myriad of cognitive deficits observed in schizophrenia (Goldman-Rakic 1991; Goldman-Rakic and Selemon 1997). Working memory in multiple domains has been tested in both human and non-human primates with a wide variety of cognitive tasks. Each particular task may involve both the transient neural representation of information to guide an immediate response and executive function to varying degrees especially when information held on-line has to be manipulated in order to generate an appropriate response (Perry et al. 2001). Notably, there is evidence for both hypo- and hyperfrontality as a function of working memory load in patients performing tasks which involve these different aspects of working memory function (Weinberger et al. 1986; Callicott et al. 2000; Manoach et al. 2000). Moreover, disruption of dlPFC by dysregulation of dopamine signaling in non-human primates is associated with profound working memory impairments involving both spatial and object domains as well as executive function, consistent with evidence that dopamine signaling appears to be substantially altered in this region in schizophrenia. The above findings strongly suggest that there is a homologous neurobiological substrate for working memory between the two species (Petrides and Pandya 1999; Petrides 2000; Nakahara et al. 2002; Rosano et al. 2002). In conjunction with the PFC, there is much evidence to support the contribution of the hippocampus to the process of working memory. Indeed, the original model of working memory (Baddeley and Hitch 1974) recognized the importance of the interface between the visuospatial sketch-pad and episodic long-term memory. Recently, Baddeley (2000) proposed that a fourth subsystem, the "episodic buffer", is necessary for working memory operations. This limited capacity buffer is postulated to facilitate binding of information from multiple sources into chunks.

While positive and negative symptoms have long been considered the hallmark features of schizophrenia, recent clinical studies have highlighted cognitive dysfunction as a third major diagnostic category which is increasingly considered to be the core deficit of the disorder (Goldman-Rakic 1991, 1994; Andreasen 1997; Green 1997; Weinberger and Gallhofer 1997; Meltzer et al. 1999; Elevag and Goldberg 2000). Indeed, impairment in working memory is the most consistently observed cognitive deficit exhibited by patients with schizophrenia (Park and Holzman 1992; Keefe et al. 1995; Park et al. 1999). Given that working memory is critical for the integrity of the thought process, it can be postulated that the breakdown in the neural circuitry of working memory may underlie the cognitive deficits and associated thought disorder observed in schizophrenia (Goldman-Rakic 1987, 1991). Notably, the extent of cognitive dysfunction in patients with schizophrenia is the best predictor of social functioning, unemployment, and even relapse (Sevy and Davidson 1995; Green 1996; Lysaker et al. 1996; Meltzer et al. 1996; Keks 1997; Meltzer 1999; Smith et al. 1999a, 1999b; Liddle 2000; McGurk and Meltzer 2000). Although atypical antipsychotics tend to improve cognition more than typical antipsychotics (Meltzer and McGurk 1999; Meltzer and Sumiyoshi 2003), there is no consensus that any of the currently available antipsychotics adequately alleviate the debilitating cognitive dysfunction associated with schizophrenia (Green et al. 2002; Sernyak et al. 2003).

Schizophrenia has an enormous economic impact that is largely attributable to the lack of adequate therapeutics targeted to treat the key cognitive symptoms as evidenced by the fact that up to 90% of patients are unemployed. Thus, it cannot be overemphasized that the best predictor for those suffering from schizophrenia to reintegrate into society is their level of cognitive abilities, particularly working memory. To this end, Davidson and Keefe (1995) have suggested that a new class of drugs should be developed that are targeted towards treating the cognitive deficits in the disease rather than the psychotic symptoms. This is the challenge for drug development in the treatment of schizophrenia. As such, the intention of the present article is to review animal models of working memory and cognitive dysfunction in order to foster research on both the nature of the disease process in schizophrenia and the development of novel pharmaceutical strategies targeted toward improving cognitive function in patients.

Rodent models of working memory

Molecular neuroscience research (such as gene knockouts) may be far more accessible and/or efficient in the rodent than in the non-human primate. Therefore, it is important to recognize the advantages and potential limitations of rodent models for studying the distributed neural systems involved in working memory and their relevance to the understanding and treatment of cognitive deficits in schizophrenia. Furthermore, it is equally necessary to identify the parameters which affect performance in the tasks purported to test working memory. Possible confounds in such tasks include the use of sensory cues, postural bias, and covert use of a directional movement bias, especially in left/right response choices. Many of the rodent tasks however, have been designed to avoid such pitfalls and have provided important information on the circuitry and neuropharmacology of working memory.

Excitotoxic damage to the ventral hippocampus in neonates provides a model that clearly demonstrates concordance with dopaminergic and prefrontal dysfunction in schizophrenia (Lipska and Weinberger 2000). The cardinal feature of this model is the postpubertal emergence of behavioral and neurochemical abnormalities. As such, this model addresses the neurodevelopmental hypothesis (Lillrank et al. 1995), which has proven to be a valuable conceptual framework for the synthesis of a wide range of evidence supporting aberrant changes in brain development in schizophrenia (see Knable et al. 1995; Weinberger 1996; Raedler et al. 1998). However, this hypothesis has been criticized for not taking into

account progression of abnormalities following an early pathology (Woods 1998). In fact, it has been suggested that particular degenerative processes occur in the early stages of the disease coincident with emergence of psychotic symptoms (Lieberman 1999).

Lesions of the ventral hippocampus in neonates, but not in adults, induce the same deficits in working memory as medial PFC (mPFC) lesions in adult rats performing continuous delayed alternation and discrete paired trial variable-delay alternation tasks (Lipska et al. 2002). It has been questioned whether performance on the former task is selectively dependent on working memory due to its repetitive nature (Green and Stanton 1989), whereas the latter task requires constant updating of information and response on a trial-by-trial basis (Aultman and Moghaddam 2001). Neonatal ventral hippocampal-lesioned (NVH) rats also show a similar deficit prior to puberty in the radial arm maze (Chambers et al. 1996) where spatial working memory is assessed by measuring the frequency of re-entries into previously baited arms and reference memory is tested by the frequency of visits to baited arms that are not part of a previously learned set (Zhang and O'Donnell 2000). Following NVH, rats are also impaired in remembering the location of the submerged platform (session-unique) in the Morris water-maze, an alternative test of working memory (Le Pen et al. 2000). Thus, multiple measures of working memory in rodents provide concordant evidence that interference with normal development in the functional circuitry of ventral hippocampus and PFC induces a postpubertal emergence of cognitive deficits consistent with findings in schizophrenia. Evidence for a role for mPFC in this process stems from studies that have shown alterations in gene expression, neuronal morphology and neurochemistry in mPFC following NVH, consistent with the neuroanatomical connections between ventral hippocampus and mPFC in the rat (see Lipska and Weinberger 2000).

Notably, NVH lesions in rodents also induce a postpubertal onset of deficits in sensorimotor gating or pre-pulse inhibition (PPI; Chambers et al. 1996; Le Pen et al. 2000; Daenen et al. 2003), a consistent feature in schizophrenia spectrum disorders (Swerdlow et al. 1994; Braff et al. 2001; Geyer et al. 2001). However, pharmacological activation/disruption of either ventral hippocampus (Bast et al. 2001) or mPFC (Japha and Koch 1999) also produces PPI deficits in adult rats, suggesting that a progressive disruption of functional circuitry is not obligatory for induction of this deficit. Another important feature of the NVH lesion model is that it involves distinct changes in mesocortical and nigrostrital dopamine function in adulthood (Lipska et al. 1995; Lillrank et al. 1999) as evidenced by the finding that these rats display exaggerated apomorphine-induced locomotor activity and stereotopy that can be suppressed by both haloperidol and clozapine. Since direct injection of amphetamine (AMPH) into striatum or accumbens induces stereotopy or hyperlocomotion, respectively, in the marmoset (Annett et al. 1983), it can be posited that the mechanism by which antipsychotics ameliorate these symptoms in the NVH model is by elevation of dopamine in PFC. Such a mechanism may have an important bearing on the postulated action of atypical antipsychotics in schizophrenia (Youngren et al. 1999; Ichikawa et al. 2001). In this respect, it is interesting to note that prefrontal pyramidal neurons are rendered hyperexcitable to stimulation of mesocortical neurons but not to stimulation of thalamic afferents in this model (O'Donnell et al. 2002).

A novel neurodevelopmental model of immune activation during pregnancy in the rodent (Zuckerman et al. 2003) produces a postpubertal disruption of latent inhibition that can be reinstated by both haloperidol and clozapine. Notably, a similar loss of latent inhibition has been reported in schizophrenia and this may be particularly relevant for the difficulties in selection of relevant versus irrelevant information (Feldon and Weiner 1992; Braunstein-Bercovitz et al. 2001; Escobar et al. 2002). Similar to NVH lesions, adult rats which experienced immune activation in utero show an enhancement of AMPH-induced locomotor activity that has parallels with the enhanced release of striatal dopamine in response to AMPH shown by patients with schizophrenia (Laruelle et al. 1996; Breier et al. 1997). These animals also show aberrant morphological changes in the hippocampus and entorhinal cortex. Thus, there appears to be a disturbance of the dopaminergic regulation of frontostriatal function in adult rats that have experienced a neurodevelopmental insult that involves the hippocampus. These rodent models should therefore be considered highly significant for the analysis of novel compounds in the treatment of what is postulated to be a similar disturbance in schizophrenia. However, the demonstration of a postpubertal onset of deficits in spatial working memory is required for the immune activation model to have full impact on preclinical research.

An alternative approach to the study of drug action in the rodent relevant to cognitive dysfunction can be found in two pharmacological models, AMPH and phencyclidine (PCP). Both AMPH and non-competitive NMDA antagonists (PCP and MK-801) produce deficits in spatial working memory in rodents performing spatial delayed alternation or delayed match-to-position tasks which have relatively short delays (<60 s). For example, in the study of Aultman and Moghaddam (2001) MK-801 impaired performance independent of delay when the delay ranged from 1 to 40 s. Moreover, mGluR2/3 activation or low doses of an AMPA/kainate antagonist all produced a delay-dependent impairment in the task, in support of the hypoglutamatergia hypothesis of frontostriatal dysfunction in schizophrenia. Note however, that both PCP and AMPH require the intervention of a considerably greater between-trial delay in order to have an impact on working memory as assessed in the radial arm and water mazes (Buresova and Bures 1982; Beatty and Rush 1983; Butelman 1990; Blokland et al. 1998). Whereas PCP clearly induces deficits in PPI, its impact on spatial working memory is debatable. Subchronic PCP has been reported to produce deficits in delayed alternation in the

T-maze (Jentsch et al. 1997b), but it has been found to have no effect on spatial working memory in the radial arm maze (Li et al. 2003). Furthermore, in rodents there is conflicting evidence on whether subchronic PCP/ketamine or AMPH induce deficits in either spatial working memory or PPI that persist after cessation of treatment (Jentsch et al. 1997b; Martinez et al. 1999; Stefani and Moghaddam 2002; Becker et al. 2003). Nonetheless, further study of the pharmacology of deficits in working memory and PPI in these models will provide an important basis for the evaluation of the effects of novel pharmacological compounds on gene expression, cell physiology, and signaling systems.

An important factor in rodent tests of working memory is the degree to which this form of memory can be dissociated from reference memory by specific task/behavioral parameters. For example, in the radial arm maze AMPA receptor knockout mice show deficits in spatial working memory but not spatial reference memory (Schmitt et al. 2003), the latter being dependent upon intact hippocampal function. Rodent tasks purported to test working memory may involve episodic memory and recruit the hippocampus to varying degrees especially when encoding takes place over a number of trials and retention intervals are long (minutes versus seconds). Thus, it may be postulated that as the length of delay or the number of items to be remembered increases, temporary forms of consolidation may become involved in order to sustain behavioral performance in working memory tasks (Antonova et al. 2001; Kesner and Rolls 2001; Bhalla 2002) which may depend upon the hippocampus and utilization of episodic buffers in working memory. Thus, the circuitry being tested in rodent models of working memory may differ as a function of the extent to which the hippocampus is recruited by the task. In order to directly test the same mechanisms of working memory that operate in humans, it is vital to translate preclinical studies via the non-human primate where this circuitry can be fully determined and the tasks designed to assess working memory are identical between the two primate species.

Non-human primate models of working memory

The nature of the tasks employed to investigate the key cognitive functions in non-human primates that may relate to a primary dysfunction of PFC in schizophrenia is of critical importance. In this regard, there is little doubt that there are critical measures of working memory in the non-human primate that have direct bearing on cognitive functions affected in schizophrenia (Park and Holzman 1992; Park et al. 1999). Here, we review the leading primate models of working memory and discuss their relationship to prefrontal function and the distributed architecture of cognition.

Spatial delayed response task

Delayed response is the classical test of spatial working memory. In this task, monkeys are tested in a sound-attenuated Wisconsin General Testing Apparatus (WGTA) and one of two or more spatially displaced wells is baited, the wells are covered with identical plaques, and an opaque screen lowered for variable delays randomized across trials. During the delay, the monkey must hold on-line information regarding the spatial location of the baited well in order to respond appropriately and be rewarded. Task difficulty/memory load is increased by either increasing delay lengths or increasing the number of spatially displaced wells (i.e. the spatial resolution). Note that there is a potential confound in this task given that the monkeys may change their posture according to the spatial location of the baited well. However, this is rarely observed. Keefe and colleagues (1995) developed a pen and paper version of this task, which is sensitive to the detection of deficits in spatial working memory in patients with schizophrenia.

Based on the extensive work in the non-human primate, many insights have been gained into the functional neural circuitry and neuropharmacology of spatial working memory. Ablation, excitotoxic damage, or cooling of the principal sulcus region of dlPFC in primates produces profound impairments in delayed response performance (Butters et al. 1971; Bauer and Fuster 1976; Passingham 1985; Goldman-Rakic 1987; Fuster 1997; Levy and Goldman-Rakic 1999). These studies demonstrated that the PFC is a key node in the functional neural circuitry of working memory. Insight into the neuropharmacology that underlies working memory was first discovered by Brozoski and colleagues (1979). In this study, a critical role for dopamine in working memory was demonstrated by the finding that 6-hydroxydopamine (6-OHDA) lesions of dlPFC in monkeys produced delay-dependent impairments in performance. Note, 6-OHDA lesions reduced performance dramatically (<50% of controls at a 20-s delay) and levodopa treatment markedly improved performance in lesioned animals by some 35%, indicating the strength of dopaminergic modulation of working memory. The integrity of dopamine in PFC has also been shown to be critical for acquisition of the spatial delayed response task but not for performance of a spatial self-ordered sequencing task (Collins et al. 1998). Using the delayed response task in non-human primates, the inferior parietal cortex, caudate nucleus, dorsomedial nucleus of the thalamus, and hippocampus have also been identified as key nodes in the circuitry of spatial working memory (Isseroff et al. 1982; Friedman and Goldman-Rakic 1988, 1994; Collins et al. 2000; Sybirska et al. 2000).

Delayed match-to-sample: a test of object working memory

Delayed matching-to-sample (DMS) is the classical test of object working memory. Monkeys are typically tested in the WGTA using session- and trial-unique three-dimensional objects. After a variable delay during which the opaque screen is lowered, the monkey has to remember and respond to the choice stimulus that matches the sample. Modern computerized versions of this task have been incorporated into the CANTAB battery (Weed et al. 1999). Numerous studies in the non-human primate have demonstrated that DMS relies upon the integrity of ventrolateral PFC (vlPFC) as well as medial temporal lobe, including hippocampus. Lesions or cooling of either PFC or inferior temporal cortex impair DMS performance (Bauer and Fuster 1976, 1978; Horel et al. 1987; Cirillo et al. 1989; George et al. 1989; Gaffan and Murray 1992; Easton et al. 2001). It is of note that low dose AMPH potentiates the effects of cooling of PFC in monkeys performing DMS (Bauer and Fuster 1978). 2-Deoxyglucose autoradiography has been used to show considerable activation of lateral perirhinal cortex in this task (Davachi and Goldman-Rakic 2001). Like spatial working memory, recent evidence indicates that patients with schizophrenia show impairments in object working memory (Spindler et al. 1997; Coleman et al. 2002; Park et al. 2003) consistent with the findings that both PFC and hippocampus are part of the functional circuitry compromised in the disease (Weinberger et al. 1986; Selemon et al. 1995; Harrison 1999; Arnold 2000). However, it has been postulated that deficits in object working memory may be in part, attributable to impairments in perceptual processing (Tek et al. 2002). Nevertheless, object working memory may represent an important component of working memory based on information from the ventral visual stream as compared to spatial working memory which relies upon information from the dorsal stream (Wilson et al. 1994).

Attentional set-shifting: an analogue of the Wisconsin card sorting task

Attentional set-shifting invokes cognitive processes that recruit both executive function and maintenance/manipulation of visual data. Both components of working memory are compromised in schizophrenia as highlighted by impaired performance on the Wisconsin Card Sorting Task (WCST) (Berman et al. 1986; Weinberger et al. 1986; Park 1997). Medicated patients are also impaired on a computerized attentional set-shifting task in which they have to ignore the previously relevant dimension and switch to a new one (Elliot et al. 1995). WCST performance in patients is positively correlated with CSF concentrations of homovanilic acid (HVA; Weinberger et al. 1988; Kahn et al. 1994), suggesting that there may be a relationship between dopamine turnover in the brain and performance. Attentional set-shifting relies on the ability to make extradimensional shifts in response (e.g. color to shape) as the appropriate dimension is shifted back and forth during the task. A computerized version of this task has been used in the marmoset to show disruption of performance following excitotoxic lesions of PFC (Dias et al. 1996). Furthermore, a version of this task has been incorporated into the CANTAB battery of neuropsychological tests (CeNeS, Cambridge, UK) for use in both human and non-human primate studies (Weed et al. 1999). In a recent fMRI study, performance of the identical attentional set-shifting task recruited homologous regions of vlPFC in both human and non-human primates (Nakahara et al. 2002). Attentional set-shifting recruits areas 45,12, and 47 of vlPFC consistent with imaging and single unit recording studies implicating involvement of this region in object working memory (Haxby et al. 1996) and categorization or familiarity of visual stimuli (Petrides et al. 2002). To date however, the cellular mechanisms that subserve set-shifting have not been directly investigated. Notably, while fundamental aspects of cognitive processing in set-shifting and spatial working memory are differentially regulated by the prevailing level of dopamine stimulation in PFC (Roberts et al. 1994; Elliot et al. 1997), set-shifting is impaired in dopamine dysfunctional states including schizophrenia (Daniel et al. 1991; Owen et al. 1993; Robbins et al. 1998). Thus, in the evaluation of novel compounds targeted to treat cognitive dysfunction in schizophrenia, it is important to include a battery of tasks that tap into the distributed functional circuitry that is compromised and to recognize that these systems may be differentially modified by signaling at selective receptor subtypes.

Physiological correlates of working memory

Spatial working memory can also be tested with an oculomotor version of the classic delayed response task (or ODR). Critically, patients with schizophrenia show pronounced impairments on this task (Park and Holzman 1992; Park et al. 1999). In physiological experiments in non-human primates, a trial is initiated by fixation of a central stimulus for a period of 0.5 s, at which point a stimulus is illuminated in one of eight or more peripheral target locations for 0.5 s while the monkey continues to fixate. A delay period of some 2–3 s then follows, during which the monkey must continue to fixate while holding on-line the target location to be remembered. At the end of this delay, removal of the central stimulus signals the monkey to make a saccade directly to the remembered target location in order to obtain reward. The position of the targets varies pseudorandomly across trials and therefore must be remembered on a trial-by-trial basis. In this task, neurons can be functionally characterized according to their sensory, mnemonic, and response-related activity in terms of mean firing rates and spatial tuning (Funahashi et al. 1990). A large proportion of neurons in dlPFC areas 46 and 8A show spatially tuned

delay activity or "memory fields" comprising of varying degrees of excitatory responses for preferred target locations and inhibitory responses for targets in the opposite direction (Funahashi et al. 1989; Rao et al. 1999). Fuster and colleagues were among the first to identify the delay activity of prefrontal neurons in monkeys performing manual delayed response tasks (Fuster and Alexander 1971; Fuster 1973). ODR offers the advantage of systematically controlling eye position and studying the neuronal response to multiple locations in the visual field. Neuronal populations within both dlPFC and inferoparietal cortex have been shown to possess almost identical cue, delay, and response-related properties, asserting the integral role of this circuitry in spatial working memory (Chaffee and Goldman-Rakic 1998). In this task, Funahashi et al. (1993) demonstrated that microlesions within dlPFC produce "mnemonic schotomas" in the contralateral visual field in memory- but not sensory-guided saccades. These data, taken together with the finding that failure of a clearly responsive delay cell in dlPFC to sustain firing throughout the delay period predicts an error in saccadic response (Funahashi et al. 1989), strongly suggest that neurons in this region constitute the cellular substrate of spatial working memory. This is an ideal system for the examination of the effects of local and systemic drug action on memory-related neuronal responses (Williams and Goldman-Rakic 1995; Williams et al. 2002a), the strength of inhibitory processes in relation to spatial tuning and trial epoch (Rao et al. 1999, 2000; Constantinides et al. 2002), as well as recurrent excitation between pyramidal cells, an integral component of persistent activity shown to be modulated by dopamine (Williams et al. 2002b). Therefore, the impact of various receptor/transmitter/signaling systems on the operations of working memory at the level of PFC can provide vital information for the development of novel compounds targeted to treat cognitive deficits in schizophrenia.

Neuromodulation of working memory in animal models

Dopamine

Neuromodulation of cellular mechanisms in working memory have been studied directly within dlPFC. Single unit recordings in this region have revealed that the firing of neurons in the ODR task is subject to significant neuromodulation by direct iontophoretic application of dopamine (Sawaguchi et al. 1988). The D_1 receptor has been shown to play a critical role in this modulation by acting on multiple sites within prefrontal circuitry to regulate mnemonic processing. Consistent with the fact that D_1 receptor binding is 10–20 times higher and more widely distributed than that of the D_2 receptor in primate dlPFC (Lidow et al. 1991), it has been shown that local microinjections of selective D_1, but not D_2, antagonists into dlPFC disrupts memory but not visually guided saccades (Sawaguchi and Goldman-Rakic 1991, 1994). Williams and Goldman-Rakic (1995) discovered that prefrontal D_1 signaling operates within a critical range (see Lidow et al. 1998) by revealing that iontophoresis of low concentrations of a selective D_1 antagonist dramatically enhance the strength and tuning of delay activity or "memory fields" of pyramidal neurons in dlPFC, but excessively high concentrations have the opposite effect. This study provided definitive evidence that the D_1 receptor directly regulates the cellular mechanism of spatial working memory such that the optimal level of D_1 receptor occupancy may vary with increasing demands on this process (Granon et al. 2000). This "inverted-U" relationship has been verified at the behavioral level. Acute or repeated D_1 agonist administration improves working memory performance in dopamine deficient monkeys (Arnsten et al. 1994; Castner et al. 2000a; Castner and Goldman-Rakic, in press), whereas the preferential elevation of prefrontal dopamine by noise-induced or drug-induced stress produces profound cognitive deficits which are reversed by D_1 antagonist administration (Murphy et al. 1996; Arnsten and Goldman-Rakic 1998). Computational models that attempt to explain the role of dopamine in optimizing working memory on the basis of a local neuronal network provide an accurate representation of the concentration dependent action of dopamine on prefrontal circuitry (Brunel and Wang 2001; Durstewitz and Seamans 2002; Tanaka 2002).

Understanding D_1 receptor modulation of prefrontal cortical function and working memory is pivotal to the generation of novel drug strategies targeted toward the core cognitive deficits in schizophrenia. A common mechanism of action of chronic neuroleptic treatment is to reduce prefrontal activation (Potkin et al. 1994; Vita et al. 1995; Miller et al. 1997; Liddle et al. 2000; Ngan et al. 2002) and to downregulate D_1 receptors in primate PFC (Lidow et al. 1994, 1997). Therefore, it is conceivable that the up-regulation of D_1 binding potential in dlPFC that is negatively correlated with working memory performance in schizophrenia (Abi-Dargham et al. 2002) is representative of excessive D_1 signaling in PFC, parallel to that found in non-human primates under conditions of acute stress (Arnsten and Goldman-Rakic 1998). Alternatively, the contradictory reports of down-regulation of D_1 binding in dlPFC that is also correlated with cognitive performance (Okubo et al. 1997) may be associated with the hyperactivation of this region in patients performing the N-back task which typically requires that the subject remember stimuli presented one, two, or three trials previously (Callicott et al. 2000; Manoach et al. 2000). This may reflect insufficient dopamine/D_1 signaling, parallel to that which occurs in non-human primate models of dopamine deficiency or in patients with Parkinson's disease. Physiological studies of non-human primate models of normal and aberrant cognitive function can help to further elucidate the relationships between prefrontal dopamine levels and

the extent of recruitment of prefrontal neurons engaged in working memory.

Serotonin

A major distinction in antipsychotic targets of action is the high affinity of atypical antipsychotics at the serotonin 5-HT_{2A} receptor which is densely localized within the neocortex in humans (Hall et al. 2000). This receptor is of interest due to its known involvement in hallucinogenesis (Aghajanian and Marek 1999) and the facilitation by this receptor of excitatory glutamatergic transmission onto pyramidal neurons in PFC is suspected to be a potential mechanism for disruption of prefrontal function in cognition (Aghajanian and Marek 2000). In monkeys performing the ODR task, local 5-HT_{2A} stimulation increases surround inhibition of prefrontal pyramidal neurons, which at low levels improves their spatial tuning but at higher levels diminishes their memory fields (Williams et al. 2002a). Iontophoresis of 5-HT_{2A} antagonists, including MDL100,907, directly attenuates memory fields of both pyramidal neurons and putative inhibitory interneurons. This physiological evidence for deleterious effects of prefrontal 5-HT_{2A} blockade on cognition stands in contrast to the proposed benefit of the 5-HT_{2A} antagonist properties of atypical antipsychotics (Schmidt et al. 1995). However, it has been proposed that an important mechanism for their clinical efficacy might be the elevation of prefrontal dopamine release (Youngren et al. 1999; Ichikawa et al. 2001; Liegeois et al. 2002). Thus, the recent report of significant amelioration of positive symptoms at low but not high doses of MDL100,907 (De Paulis 2001) may reflect beneficial elevation of prefrontal dopamine and deleterious blockade of prefrontal 5-HT_{2A} receptors, respectively. These findings strongly support the use of the physiological approach to investigate serotonergic neuromodulation of prefrontal circuitry subserving working memory processes. Thus, selective cognitive testing and physiological recordings in non-human primate models can provide an invaluable platform for evaluating the impact of pharmacological treatments targeted to alter D_1 and 5-HT_{2A} signaling on working memory performance.

Non-human primate models of prefrontal dysfunction

Subchronic PCP

Support for the PCP model stems from findings on the effects of non-competitive NMDA antagonists in normal healthy volunteers and patients with schizophrenia. For example, acute exposure to ketamine in healthy volunteers produces symptoms resembling those of schizophrenia (Javitt and Zukin 1991; Krystal et al. 1994; Abi-Saab et al. 1998) and increases activation in dlPFC areas 46 and 9 (Vollenweider et al. 1997). Acute ketamine also exacerbates positive symptoms in neuroleptic-free patients with schizophrenia (Malhotra et al. 1997). Furthermore, PCP abuse in humans can lead to a psychotic-like state not altogether different from AMPH psychosis (Ellinwood 1967; Snyder 1972, 1973; Rainey and Crowder 1975; Fauman et al. 1976; Allen and Young 1978).

In non-human primates, both acute and subchronic PCP are used to model key symptoms associated with schizophrenia. Acute PCP produces deficits in spatial (Boyce et al. 1991; Rupniak et al. 1991) and object working memory (Baron and Wenger 2001) as well as PPI in monkeys (Linn and Javitt 2001) and the latter deficit is reversible by clozapine (Linn et al. 2003). Prior subchronic PCP exposure produces impairments in the object retrieval/detour task, which is thought to be dependent upon the integrity of corticostriatal function and this deficit is associated with a reduction in dopamine turnover in both dlPFC and striatum (Jentsch et al. 1997a, 1999a, 2000). Of note, acute administration of either a D_4 antagonist or clozapine ameliorates this deficit (Jentsch et al. 1997a, 1999b). Subchronic PCP also produces behaviors reminiscent of other hallmark symptoms of schizophrenia including psychomotor depression and hallucinatory-like behaviors (Linn et al. 1999). At the same time, however, this regimen actually tends to increase affiliative behavior, in contrast to the effects of repeated AMPH (see below) and the social withdrawal that is prominent in schizophrenia. Another important element of PCP, especially in cases of repeated administration, is the established evidence of primary neurotoxicity involving cingulate and retrosplenial cortices and secondary degeneration in other limbic regions including hippocampus (Corso et al. 1997; Ellison et al. 1999). While the circuitry involved in this neurotoxicity may also be compromised in schizophrenia, the issue must be raised as to whether resulting neuropathology induced by subchronic PCP can be fully ameliorated by subsequent pharmacotherapies.

Chronic AMPH

It has been well established that chronic AMPH administration in non-human primates elicits a subset of behaviors reminiscent of the positive symptoms of schizophrenia (Ellinwood et al. 1973; Ellison et al. 1981; Ridley et al. 1982; Ellison and Eison 1983). These behaviors include hypervigilance, abnormal tracking, grasping or manipulation of "thin air", and checking the environment as if in response to non-apparent stimuli and have been referred to as psychotomimetic (Sams-Dodd and Newman 1997) or hallucinatory-like (Ellison et al. 1981; Ellison and Eison 1983; Nielsen et al. 1983a, 1983b). As such, they provide a close approximation to visual or auditory hallucinations in both AMPH psychosis and schizophrenia (Ellinwood 1967; Snyder 1972, 1973). There have been two particular criticisms of this model. Continuous and/or high dose AMPH exposure induces neurotoxicity of the nigrostriatal dopamine system (Ellison et al. 1978; Ellison and Ratan 1982; Ridley et al.

1983), inconsistent with the known neuropathology of schizophrenia and secondly, chronic AMPH has not been considered to be associated with negative-like symptoms. The latter is actually mistaken, as in fact, repeated AMPH in non-human primates consistently induces negative-like symptoms including social withdrawal and long-lasting psychomotor depression (Annett et al. 1989; Knobbout et al. 1996; Palit et al. 1997; Castner and Goldman-Rakic 1999a). The former criticism is harder to dispute since it is well documented that continuous treatment or administration of doses in excess of 2 mg/kg per day in monkeys is sufficient to induce nigrostriatal damage (Ricaurte and McCann 1992).

AMPH sensitization

Repeated, intermittent escalating low-dose AMPH exposure (AMPH sensitization) in rodents circumvents the neural toxicity associated with continuous or high dose exposure while producing a homologous behavioral phenotype at the high doses of the escalating regimen or in response to an acute low dose challenge after repeated exposure (see Robinson and Becker 1986; Kalivas and Stewart 1991). Castner and Goldman-Rakic (1999a) have exploited AMPH sensitization to create a novel non-human primate model relevant to schizophrenia which encompasses all of the symptoms induced by continuous and/or high dose exposure without the obligatory damage to the nigrostriatal system. In this model, sensitized monkeys show evidence of both positive-like and negative-like symptoms off drug including hallucinatory-like behaviors and a persistent psychomotor depression (Castner and Goldman-Rakic 1999a; Castner et al. 2000b). Furthermore, this model produces the third hallmark symptom, and possibly core deficit of schizophrenia, i.e. a profound, long-lasting impairment in working memory (Castner and Goldman-Rakic 1999b). The nature of the cognitive deficits are of critical importance as they are highly related to the integrity of prefrontal cortical function and like subchronic PCP there is a significant reduction of dopamine turnover in dlPFC and striatum (Jentsch et al. 1997a, 1999a; Castner et al. 2001). Moreover, in AMPH sensitized monkeys the reduction in prefrontal dopamine turnover is associated with profound deficits in spatial working memory and these deficits persist for several months even with pretraining (Castner and Goldman-Rakic 2000) and "permanently" without pretraining (Castner and Goldman-Rakic 1999b). Furthermore, aspiration of dlPFC in monkeys blocks AMPH sensitization of hallucinatory-like behaviors, raising the possibility that prefrontal function and dysfunction and its working memory correlates may have a significant role to play in the ontogeny of certain symptoms of psychosis (Castner and Goldman-Rakic 2003). Therefore, we suggest that AMPH sensitization in the non-human primate is a robust, stable, and validated model in which to study the impact of novel compounds targeted for the treatment of cognitive deficits in schizophrenia. It is of note that a mechanism analogous to sensitization has been postulated to play an etiological role in the emergence of symptoms of schizophrenia during adolescence and early adulthood (Lieberman et al. 1997).

Neurodevelopmental models

There are two major non-human primate models relevant to the neurodevelopmental hypothesis, fetal X-irradiation and NVH lesions. In the first model (Algan and Rakic 1997), X-irradiation is delivered to the fetus in utero during critical periods of neuronal development, e.g. between embryonic days 33 and 40, during which time thalamic relay neurons are being generated that will send projections to neocortex. There are several aspects of this model that accurately simulate key deficits found in schizophrenia. Notably, there is a delayed postpubertal onset of spatial working memory deficits (Castner et al. 1998) analogous to that observed in schizophrenia (Selemon et al. 1995). X-irradiated monkeys also have >20% reduction in thalamic volume (Schindler et al. 2002), and this deficiency may be related to craniofacial dysmorphogenesis consistent with abnormalities observed in patients (Young et al. 2000; Gelowitz et al. 2002). While this model shows promise for its relevance to schizophrenia, further research is necessary with regard to the ability of pharmacotherapy to alleviate working memory deficits.

The second neurodevelopmental approach in non-human primates entails NVH lesions as in rodents. Similar to the other models, this manipulation approximates a subset of behavioral abnormalities that resemble those found in schizophrenia. NVH lesions in rhesus monkeys produce a delayed, postpubertal onset of social withdrawal and an increase in the expression of locomotor stereotypies (Beauregard and Bachevalier 1996). Furthermore, this neurological insult is also associated with a postpubertal onset of impairments in specific aspects of memory such as relational learning, consistent with the postpubertal emergence/exacerbation of cognitive deficits in schizophrenia (Bachevalier et al. 1999). It has been hypothesized that the range of deficits shown in this model provides evidence of dysfunction in brain regions distant from the site of the initial insult such as PFC and basal ganglia. Notably, adult monkeys with NVH lesions show evidence of dysregulation of striatal dopamine and neuropathology of dlPFC as measured by N-acetyl-aspartate, a marker of neuronal function (Bertolino et al. 1997; Saunders et al. 1998) potentially akin to that observed in schizophrenia (Breier et al. 1997; Bertolino et al. 1999). Thus, this model has promise for studying both the etiology as well as the treatment of schizophrenia. However, the underlying neuropharmacology of the deficits involved and their relation to working memory needs to be fully characterized in order to prove useful for evaluating novel pharmacotherapies targeted towards cognitive deficits.

Conclusions

From the above review, it is evident that subchronic PCP, AMPH sensitization, and neurodevelopmental insult are the best models for testing novel compounds for the treatment of cognitive deficits in schizophrenia when used in comparison with the study of normal neural mechanisms in working memory. Although these models have been studied in both primates and rodents, the probes used to test the impact of these manipulations on neural circuitry and cognition can be inconsistent between species. Part of this problem is due to the neuroanatomical differences between rodents and primates in the functional circuitry that is recruited by different working memory tasks, particularly in relation to the mPFC in the rodent. Moreover, the magnitude of cognitive deficits and the extent of recovery or restoration of function by various pharmacological treatments seen in these and other non-human primate models are substantial and significant in typically small sample sizes (n=4–6). Therefore, the non-human primate models of cognitive dysfunction relevant to schizophrenia provide an essential platform for the analysis of the development of different aspects of behavioral symptoms and their underlying cellular mechanisms. This can best be accomplished through an integrated approach that combines selective cognitive tasks identical to those that can be used in clinical trials in conjunction with functional imaging and single unit recording in these tasks. In addition, it is important to have a measure of signal processing dysfunction, which has been identified across all three species. PPI and perhaps latent inhibition fulfill this requirement. Therefore, it is important in models of prefrontal dysfunction to contrast the impact on working memory performance as compared to sensorimotor gating and to determine the extent to which the underlying neural circuitry in the two processes overlaps. Furthermore, this integrated approach can be applied in longitudinal studies to provide insights into the etiology, as well as the impact of pharmacological intervention relevant to key symptoms. Thus, for example, the neurodevelopmental models provide the opportunity to investigate prefrontal and medial temporal lobe function longitudinally before, during, and after puberty. Therefore, it should be possible to determine the temporal relationship between the emergence of cognitive deficits and those that are considered positive- or negative-like. Moreover, this temporal pattern can also be examined for deficits in relation to sensorimotor gating and latent inhibition. By these means, we can gain greater insights into the cognitive sequelae of prefrontohippocampal disruption and the dependence of positive and negative symptoms on pre-existent cognitive dysfunction. Such insights may help us to better ascertain the specific pharmacological/circuit targets by which new drugs can be formulated to alleviate all of the hallmark symptoms of schizophrenia. On the other hand, the pharmacological models also provide the opportunity for studying both the underlying causes that generate these symptoms as well as the pharmacotherapies for their alleviation. The demonstrated durability of the AMPH sensitization model for the induction and persistence of the hallmark symptoms of schizophrenia provides a platform for pharmacotherapy in the treatment of the core deficit in spatial working memory, facilitating the investigation of both acute and chronic drug therapies targeted for this purpose. Critically, this model has already been put to the test with the demonstration that chronic administration of a dopamine D_1 antagonist can produce a long-lasting alleviation of the deficit in spatial working memory (Castner and Goldman-Rakic 1999b). In conclusion, non-human primate models of cognitive dysfunction, by virtue of their direct relationship with human cognition and working memory, can provide critical information on the efficacy of novel compounds and accelerate the discovery of new drugs for treating the core deficit in schizophrenia.

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