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Gene-Environment Interplay in Schizopsychotic Disorders

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Genetic studies have sought to identify subtypes or endophenotypes of schizophrenia in an effort to improve the reliability of findings. A number of chromosomal regions or genes have now been shown to have had replicated linkage to schizophrenia susceptibility. Molecules involved in neurodevelopment or neurotransmitter function are coded by many of the genes that have been implicated in schizophrenia. Studies of neurotransmitter function have identified, among others, a possible role for GABA, glutamate and dopamine in animal models of schizophrenia. GABA neurons that co-express the calcium binding protein parvalbumin have been implicated as have glutamatergic metabotropic receptors and dopamine D_3 receptors. Stress influences glutamate and dopamine providing another environmental factor that may interact with the influence of genes on neurotransmitter function. Neurotransmitter interactions include influences on signaling molecules and these too have been implicated in forms of learning thought to be affected in schizophrenia. Results continue to unravel the interplay of genes and environment in the etiology of schizophrenia and other psychotic disorders.

Keywords: Dopamine; GABA; Genetics; Glutamate; Parvalbumin; PKA; Schizophrenia; Signaling Molecules; Stress

INTRODUCTION

Multiple genes interacting with multiple environmental factors influence many psychiatric disorders. Perhaps because of this complex etiology, diagnostic classification is less than perfect. This provides a major challenge for genetics researchers who search for associations between genes and phenotypes that may represent identifiable heterogeneous groups. Genetics researchers have risen to this challenge by trying to subtype individuals within phenotypic classifications. This approach has begun to yield some of the first reliable results in genetic studies of psychiatric disorders.

Many of the genes that have begun to be associated with psychiatric phenotypes code for molecules involved in synaptic transmission. Results have begun to converge with the known targets of pharmacotherapy for those conditions to implicate changes in particular neurotransmitter systems in particular neuropsychiatric disorders. Neuroscientific studies of the function of neurotransmitter systems in normal conditions or in animals that model one or more of the phenotypic changes seen in neuropsychiatric disorders therefore complement genetic studies. By identifying environmental factors that influence neurotransmitter function, on the one hand, and phenotypic changes that result from alterations in neurotransmitter systems, on the other, the efforts of those who study neurotransmitter systems go hand-in-hand with those of genetics researchers to discover the interplay of genes and environment in neuropsychiatric disorders.

This paper provides an overview and introduction to this special issue on, "Gene-Environment Interplay in Schizopsychotic Disorders". The ten remaining papers in this journal issue divide quite naturally into two sets. One set of five uses genetic approaches to identify chromosomal regions and genes that might contribute to schizopsychotic phenotypes and the other uses a range of molecular and behavioural approaches to identify the role of various molecules within neurotransmitter and signaling systems in schizophrenic phenotypes or animal models of those phenotypes. Considered together, this collection of papers provides a glimpse into the interplay of genes and environment that leads not only to disordered phenotypes but also to the wide range of phenotypes that collectively are us.

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GENETIC PREDISPOSITION IN PSYCHIATRY

Many studies seek to identify genes that may vary between individuals with a particular disorder and those who do not have the disorder as a means of eventually understanding the etiology and underlying mechanisms of the disorder. The starting point for linkage studies is to identify individuals with the syndrome of interest and then to make genetic comparisons with control individuals. Klein and Stewart (2004) discuss this approach and identify challenges faced by researchers who use it.

A particular syndrome may come about as a result of a variety of genomic or environmental factors; this potential etiological variability will hinder elucidation of underlying genetic causes (Klein and Stewart, 2004). It may be possible to address this problem by identifying differences in individuals within a particular phenotype, for example in response to medication or in developmental course. Klein and Stewart (2004) provide an example from their studies of atypical depression that supports this approach.

It is well known that some persons diagnosed with depression fail to respond to tricycle antidepressants (TCAs) or electroconvulsive therapy but do respond to monoamine oxidase inhibitors (MAOIs). MAOI-responders were defined as suffering from atypical depression and were described as having a number of phenotypic features (e.g., histrionic, marked lethargy) not seen in typical depression and as lacking some of the phenotypic features of typical depression (e.g., weight loss, early morning waking). These observations provided an example of a diagnostic group that can be subdivided on the basis of their response to medication (Klein and Stewart, 2004).

Liebowitz *et al.* (1988) elaborated on this distinction to identify an atypical features modifier of major depression. They found that patients classified with the phenotypic markers of atypical depression were more responsive to a MAOI than to a TCA or placebo. Further studies confirmed these findings (Quitkin *et al.*, 1988; 1990) and identified further distinctions between patients with atypical depression vs. patients with the melancholic form including family history, perceptual asymmetry, sleep electroencephalogram and hypothalamic-pituitary-adrenal function (review: Klein and Stewart, 2004). However, even with all these distinctions, some patients diagnosed with atypical depression responded to TCAs.

Additional features that might distinguish subsets of individuals within the atypical depression group included age of onset of illness and chronicity. Using these features, Stewart *et al.* (1999) found that the subgroup with either onset after age 20 yr or not having a chronic illness was more likely to respond to TCAs whereas the subgroup with onset prior to age 20 yr and a chronic illness responded similarly to TCAs or placebo. The authors went on to show a number of differences in pathophysiology and in family histories in these further subgroups of atypical depressives (Klein and Stewart, 2004).

Results make it clear that psychiatric diagnoses may be identifying groups consisting of subgroups with different pathophysiological and genetic bases for the observed syndromes. This provides a considerable challenge to genetic linkage studies that rely on these diagnoses to classify probands in their studies.

GENES IN SCHIZOPSYCHOTIC DISORDERS

Much evidence contributes to the consensus that schizophrenia is a genetic disorder and that it is genetically complex (Kendler and Diehl, 1993), implying that schizophrenia involves the interaction of a large number of genes. Riley (2004) clearly acknowledges the challenges of diagnostic imprecision in his review of linkage studies of schizophrenia. He begins by reviewing family, twin and adoption studies. The observation that lifetime morbid risk rises from the population value of about 1% to closer to 10% in siblings and offspring of schizophrenic persons and then to about 50% in monozygotic twins provides clear evidence of genetic mediation of schizophrenia but the less than perfect concordance in monozygotic twins further shows that schizophrenia is not genetically determined but that it is a complex disorder determined by genes, environment and their interaction.

Riley (2004) states that, "Misclassification of affected individuals causes great loss in power to detect genetic effects", in agreement with the limitations of linkage studies resulting from diagnostic imprecision identified by Klein and Stewart (2004). One approach to dealing with this problem is to perform several analyses on the same data using different definitions of the illness for each. This approach has the benefits of possibly identifying different genes that are linked with different ranges of pathology without making assumptions about the range of pathology attributable to a particular gene.

Linkage studies identify chromosomal regions (in the order of tens of millions of base pairs) that segregate with a trait in multiple families. They are especially limited in the case of complex traits that are influenced by multiple genes. Besides the problem of fuzzy diag-

nostic boundaries already alluded to above, the genetic study of schizophrenia is dogged by the presence of phenocopies, *i.e.,* the presence of schizophrenia-like symptoms produced by drugs of abuse or other conditions. Furthermore, family samples may present a random variation of predisposing genes; this variation may be responsible for the widespread failure to replicate results of linkage studies (Riley, 2004).

Within the framework of the challenges and limitations of linkage and association studies of schizophrenia, Riley (2004) reviewed the relevant literature in an effort to identify regions and genes that have been shown to have had replicated linkage to schizophrenia susceptibility. This effort yielded 8 promising regions. Candidate genes in these regions included the following: 1) the gene for catechol-*O*-methyl transferase, an enzyme involved in the degradation of catecholamines including dopamine; 2) the gene for neuroregulin that affects the expression and activation of neurotransmitter receptors including glutamate receptors; 3) the gene for dystrobrevin binding protein, with unknown function in the central nervous system; 4) a region of chromosome 13q14-q32 that contains the gene for the serotonin 5-HT_{2A} receptor; and 5) a gene for the alpha7 nicotinic cholinergic receptor subunit. He concluded that the emergence of these replicated findings is the most important development in the genetics of schizophrenia in recent years.

In addition to the genes identified by Riley (2004), Blackwood and Muir (2004) reviewed results of linkage studies implicating a region of chromosome 1 and the candidate genes *Disrupted in Schizophrenia 1* (DISC1), DISC2 and RGS4 in schizophrenia. In agreement with the previous authors, Blackwood and Muir (2004) pointed out the importance of strict adherence to standard clinical diagnostic criteria in identifying individuals to include in an experimental group for a linkage study. They also discussed the importance of identifying subgroups as, for example, has been done in factor analytic studies of schizophrenic patients that have identified three dimensions of the disorder (Liddle, 1987; Andreasen *et al.*, 1995). They discussed the use of "endophenotypes" to identify intermediate biological traits within a diagnostic classification and they provide results of genetic studies of electrophysiological endophenotypes in schizophrenia.

In electrophysiological studies, cognitive event-related potentials include the long latency P300 observed in the "odd-ball" task. P300 amplitude is reduced in schizophrenic patients and their relatives (Blackwood *et al.*, 1991). In one particular family a balanced chromosomal translocation between chromosomes 1 and 11 segregated with major psychiatric illness including schizophrenia (St. Clair *et al.*, 1990; Blackwood *et al.*, 2001). The breakpoint in chromosome 1 affected the genes DISC1 and DISC2 and was linked to a phenotype that included schizophrenia and affective disorder. As DISC1 is expressed in limbic regions including the hippocampus and in the neocortex during early development where it may affect neuritic growth (Miyoshi *et al.*, 2003; Morris *et al.*, 2003; Ozeki *et al.*, 2003), results supported neurodevelopmental hypotheses of schizophrenia that suggest that genetic and/or environmental events early in development confer a susceptibility to the disorder (e.g., Weinberger, 1995; Palomo *et al.*, 2002).

Personality traits may provide another endophenotype identifiable within particular psychiatric illnesses. Thus, the possible genetic relationship between neuroticism and major depression and between schizotypy and schizophrenia has been studied (Fanous and Kendler, 2004). Neurotocism is one of the three factors identified by Eysenck and Eysenck (1985) for explaining individual differences in personality; it has been shown in a number of studies to be related and possibly genetically linked to major depression (e.g., Fanous *et al.*, 2002). Association studies of major depression have focused on genes associated with the serotonin system (Celada *et al.*, 2002) and some studies have looked at the possible association of serotonin system genes with neurotocism; both positive and negative results have been reported. Results to date provide some hints that neurotocism may serve as a useful endophenotype for major depression but further studies are needed.

Schizotypy refers to personality traits that are like some of those seen in schizophrenia but attenuated, for example, odd speech, magical thinking, illusions, social isolation and ideas of reference. Cannon *et al.* (2002) suggested that biological endophenotypes shared by schizotypy and schizophrenia might be more specific indicators of underlying genetic influences than those that are specific to schizophrenia, the latter possibly reflecting environmental influences. Studies have shown that first-degree relatives of schizophrenic probands have a higher likelihood of having schizotypal personality disorder (Kendler *et al.*, 1993). This finding and results from genetic studies suggest that the same genes that confer a risk for schizophrenia may influence endophenotypes based on personality (Fanous and Kendler, 2004).

Another approach to identifying genes that may be associated with schizophrenia is to look for genes that predict a good response to antipsychotic medication.

For example, recent studies suggest that variations in the gene that codes for the dopamine D_2 receptor (DRD2) may influence clinical efficacy of some antipsychotic drugs (Malhotra *et al.*, 1999; Suzuki *et al.*, 2000; 2001; Shafer *et al.*, 2001; Mata *et al.*, 2002) and some studies have reported that polymorphism of the gene for the 5-HT_{2A} receptor is associated with response to clozapine (Arranz *et al.*, 1995). As studies continue to advance understanding of the relationships between clinical phenotypes and particular genetic loci, they will provide additional bases for the study of genetic contributions to antipsychotic drug responses.

Some antipsychotic drugs induce weight gain providing another phenotype for pharmacogenetic studies. One advantage of this phenotype is that it can be defined precisely and reliably. Furthermore, much evidence suggests that weight gain is heritable (reviewed by Malhotra, 2004). A polymorphism of the 5-HT_{2C} receptor gene has been found to be associated with weight gain produced by the antipsychotics risperidone, clozapine or chlorpromazine (Reynolds *et al.*, 2002; 2003). These studies provide further clues to possible genes that may play a role in schizophrenia.

The identification of genes that produce susceptibility to schizophrenia will lead to several new lines of research including rational drug design, characterization of genotype-phenotype relationships, identification of environmental risk factors that interact with specific genes and effective prevention research in high-risk individuals (Riley, 2004).

NEUROTRANSMITTER SYSTEMS STUDIES

Gamma-aminobutyric acid (GABA) neurons in the cortex also express calcium-binding proteins including parvalbumin (PV), calbindin and calretinin. PV is expressed late in development making GABA/PV neurons vulnerable to sudden or excessive increases in calcium concentrations during early development. One of the hypotheses about the pathogenesis of schizophrenia is that an insult takes place during early development that leads to the eventual appearance of symptoms (Weinberger, 1995; Palomo *et al.*, 2002). Evidence suggests that GABA/PV neurons may be affected by an early developmental insult in schizophrenia.

In the cortex of the brains of deceased schizophrenic patients, deficits have been found in some types of GABAergic neurons (Benes *et al.*, 1991; Akbarian *et al.*, 1995). More recently, Beasley and Reynolds (1997) found that GABA neuronal deficits in the cortex were in neurons expressing PV; these neurons normally inhibit the firing of corticofugal pyramidal cells. Results were consistent with the hypothesis that these neurons have an early vulnerability and may be relatively selectively damaged leading to increased risk for schizophrenia.

GABA/PV neurons also were found to be deficient in the hippocampus. Benes *et al.* (1998) had shown that the number of interneurons in the post mortem hippocampus of schizophrenic patients was reduced and subsequent studies showed that peptides co-localized with GABA also were reduced (review: Reynolds *et al.*, 2001). In particular, neurons co-localizing GABA and PV were reduced in number by over 50% (Zhang and Reynolds, 2002). Results were consistent with the hypothesis that GABA/PV neurons are vulnerable to calcium toxicity during early development and that damage to them is associated with the development of schizophrenia in late adolescence or early adulthood.

Neurodevelopmental hypotheses of schizophrenia have been strengthened by the discovery of animal models involving a perinatal insult and subsequent behavioural changes after but not before sexual maturity. For example, Lipska and Weinberger (2002) found that rats receiving ventral hippocampal injections of a glutamate *N*-methyl-D-aspartate (NMDA) receptor agonist on postnatal day 7 (P7) showed enhanced responses to pro-dopaminergic agents after sexual maturity at P65 but not before sexual maturity at P35. Results were consistent with the neurodevelopmental hypothesis of schizophrenia.

Another animal model of schizophrenia involves sub-chronic treatment with the glutamate NMDA receptor antagonist phencyclidine (PCP). Sub-chronic PCP leads to increased motor activity and stereotyped behaviors (Jentsch and Roth, 1999; Powell and Geyer, 2002) and to cognitive impairments such as deficits in learning and memory (Jentsch *et al.*, 1997) suggestive of both positive and negative symptoms, making it an excellent animal model of schizophrenia (Luby *et al.*, 1962; Allen and Young, 1978; Javitt and Zukin, 1991). Adding to the attractiveness of the sub-chronic PCP model of schizophrenia is the recent observation that these animals also show changes in GABAergic neurons. Thus, Reynolds *et al.* (2004) found a significant deficit in GABA/PV cells in the hippocampus following sub-chronic PCP. Although this GABA/PV cell deficit would have been induced in adulthood rather than during early development, results of postmortem studies of the brains of schizophrenic patients and those of PCP-treated rats converge to suggest a deficit in a subset of hippocampal and possibly cortical GABAergic neurons in schizophrenia.

Recent studies have investigated a marker for GABAergic neurons [the synthesizing enzyme glutamic acid decarboxylase-67 (GAD67)] in adult rats that underwent neonatal ventral hippocampal lesions. Results revealed that levels of GAD67, determined using in situ hybridization histochemistry, were reduced (Lipska *et al.*, 2003). These researchers also found that chronic treatment with the antipsychotic haloperidol but not clozapine reversed this deficit. Unfortunately, the hippocampus was not tested. Results converge with those of Reynolds *et al.* (2004) in implicating decreased GABA in animal models of schizophrenia.

Decreased glutamatergic neurotransmission also has been linked to the dopamine hypothesis of schizophrenia. Thus, glutamate NMDA receptor antagonists such as PCP or MK-801 have been found to activate ventral tegmental dopaminergic neurons (Freeman and Bunney, 1984; French *et al.*, 1985). This finding provides a link for understanding the psychotogenic effects of PCP and related agents in the context of the dopamine hypothesis of schizophrenia.

It remains to identify the dopamine receptors possibly involved in the putative hyperfunctioning of dopaminergic systems in schizophrenia. D_2-like dopamine receptors are of three subtypes termed D_2, D_3 and D_4. Some years ago it was shown that the average clinical dose of antipsychotic drugs that was effective in treating schizophrenia correlated with the ability of those drugs to block D_2 receptors (Seeman *et al.*, 1976; Snyder, 1976). Indeed, this observation provides one of the foundation stones of the dopamine hypothesis. More recently, it has been shown that antipsychotic drugs also block D_3 (but not D_4) receptors (Leriche *et al.*, 2004) suggesting that significant D_3 receptor occupancy occurs during antipsychotic treatment. These and related findings have led Sokoloff and his coworkers to suggest that the D_3 receptor may play a critical role in schizophrenia (Schwartz *et al.*, 2000).

It has been found that some of the behavioural effects of glutamate NMDA receptor antagonists such as PCP or MK-801 depend on D_3 receptors. Thus, the D_3 receptor antagonist nafadotride or the D_3 partial agonist BP 897 blocked MK-801 induced hyperactivity (Leriche *et al.*, 2004). Furthermore, MK-801 failed to induce hyperactivity in D_3 receptor knockout mice (Leriche *et al.*, 2004). These findings have led Leriche *et al.* (2004) to suggest that D_3 receptor antagonists may have antipsychotic effects and a preliminary report that they do has appeared (Lecrubier, 2003).

STRESS IN THE ENVIRONMENT

Stress affects both dopamine and glutamate in the brain and therefore may be an environmental factor that interacts with genetic influences in the genesis of psychiatric disorders. Stress is difficult to define but refers to conditions that lead to physiological or psychological strain; it can be stressful to be over stimulated or under stimulated, recalling the classical Yerkes-Dodson inverted U-shaped curve relating stress to performance (Yerkes and Dodson, 1908). Stress contributes to the development of psychiatric disorders and can exacerbate symptoms or lead to relapse after a period of remission; stress affects response to therapy (van Praag, 2002). These effects of stress are consistent with observations that stress affects neurotransmitters implicated in schizophrenia and other psychotic disorders.

It is well known that stress increases brain dopamine levels. Aversive stimuli increase dopamine in the prefrontal cortex and the nucleus accumbens (review: Moghaddam and Jackson, 2004). More recently, it has been found that stress also increases glutamate levels in the medial prefrontal cortex, hippocampus and nucleus accumbens detected using intracerebromicrodialysis in freely moving rats (Lowy *et al.*, 1993; Moghaddam, 1993; Bagley and Moghaddam, 1997). Glutamatergic neurons in the prefrontal cortex regulate dopamine levels there and in the nucleus accumbens by affecting terminal dopamine release and the activity of ventral tegmental dopaminergic neurons (Moghaddam and Jackson, 2004). The mechanisms underlying these effects are complex and probably include glutamatergic influence on GABAergic neurons.

As discussed above, agents that decrease glutamatergic NMDA receptor stimulation (e.g., PCP) lead to increased dopamine neuronal activity. Stress *increases* prefrontal cortical levels of glutamate but also increased dopamine levels. It remains the task of future studies to unravel the mechanisms underlying these superficially contradictory finding.

ROLE OF GLUTAMATE RECEPTORS

As already discussed, alterations in glutamatergic neurotransmission have been implicated in schizophrenia (Coyle *et al.*, 2003; Konradi and Heckers, 2003; Krystal *et al.*, 2003; Moghaddam, 2003). Glutamate receptors have been shown to be of two major types termed ionotropic and metabotropic. There are eight identified metabotropic glutamate receptors (mGluRs) (Pin and Duvoisin, 1995). Of these, mGluR5 has been implicated in schizophrenia. Thus, gene linkage studies impli-

cate mGluR5 in an abnormal translocation on chromosome 11 that is linked to schizophrenia (Devon and Porteous, 1997). Postmortem studies of the brains of schizophrenic patients have shown increased numbers of mGluR5 in pyramidal layers of area 11 of the prefrontal cortex further implicating alterations in this mGluR subtype in schizophrenia (Ohnuma *et al.*, 1998). These findings implicate mGluR5 in schizophrenia.

A reliable phenotypic marker of schizophrenia is impairment in sensory-motor gating, often measured with the use of pre-pulse inhibition (PPI). In this paradigm, startle responses are measured electromyographically following the presentation of a sudden, brief, intense stimulus. If this startle stimulus is preceded (e.g., 100 ms before) by a brief mild stimulus, the prepulse, the startle response is significantly attenuated. Rats and mice similarly show PPI usually measured with whole-body startle in an apparatus outfitted with an accelerometer and appropriate electronic circuitry (Geyer *et al.*, 1990). Impairments in PPI have often been used as an animal model of this feature of schizophrenia. Thus, PPI is impaired by treatment with agents that enhance dopaminergic neurotransmission, thought to mimic the putative dopaminergic hyperfunctioning of schizophrenia, and dopamine receptor antagonist drugs that are effective antipsychotic agents reverse the deficits produced by pro-dopaminergic agents (Geyer *et al.*, 2001). Results suggest that impairments of PPI in animals provide a valid model of this phenotypic marker in schizophrenia.

Ionotropic glutamate receptors have been shown to play a role in PPI as receptor antagonists such as PCP that act at one subtype of these receptors, the NMDA receptor, also produce PPI impairments (Mansbach and Geyer, 1989). As already mentioned above, when these agents are given to normal humans, they produce cognitive changes similar to some of the positive and negative symptoms of schizophrenia (Luby *et al.*, 1962; Allen and Young, 1978; Javitt and Zukin, 1991); this observation further links glutamate and schizophrenia and further strengthens the validity of PPI as a phenotypic marker.

More recently, the mGluR5 receptor, previously implicated in schizophrenia (see above), has been shown to play an important role in PPI. In studies using genetically altered mice, it has been shown that mice lacking the mGluR5 receptor from birth [mGluR5 knock out (KO) mice] are impaired in PPI (Brody and Geyer, 2004). As rearing conditions have been shown to alter PPI (Powell and Geyer, 2002), Brody and Geyer (2004) examined the effects of this variable on PPI in mGluR5 KO mice but found no significant effect. In related studies they examined the effects of systemic or central (intracerebroventricular) injections of the mGluR5 receptor antagonist MPEP on PPI in normal (wild type) mice; results revealed no effect. The observation that the deletion of the mGluR5 receptor from birth but not acute blockade of this receptor in adulthood led to PPI deficits led Brody and Geyer (2004) to conclude that the PPI impairments observed in mGluR5 KO mice resulted from the effects of this receptor deletion on neurodevelopment. This paper provides an excellent example of gene-environment interactions leading to impaired function that mimics one of the phenotypic markers for schizophrenia.

Experimental results implicate deficits in GABA and/or glutamate in schizophrenia but they also continue to focus on the important contribution of dopamine. If dopaminergic neurotransmission is overactive in schizophrenia, how can this abnormality lead to the phenotypic changes seen in the disease? It is well know that dopamine is involved in reward-related incentive learning (Beninger, 1983; Miller *et al.*, 1990; Berridge and Robinson, 1998). Beninger (1983; Beninger and Hahn, 1983) suggested that the positive symptoms of schizophrenia might be understood as resulting from excessive incentive learning, an idea recently discussed by Kapur (2003). According to this idea, dopamine-mediated incentive learning leads to a broadening of the range of stimuli that acquire incentive value, an increased ability to elicit approach and other responses. The affected individual's interpretation of this expanded range of apparently important stimuli is manifested as delusional thought. Once antipsychotic treatment is begun, delusional thought gradually resolves as inappropriate incentive learning gradually extinguishes (Beninger, 1983). Thus, hyperactivity of the dopamine system can be seen as leading to some of the symptoms of schizophrenia.

SIGNALING MOLECULES IN COGNITION

Beninger and Gerdjikov (2004) review the role of signaling molecules in reward-related incentive learning. There is extensive evidence implicating signaling pathways in learning (e.g., Kandel, 2001) and it appears that many of the signaling molecules that have been shown to play a critical role in learning in relatively simple systems such as *Aplysia* (Kandel, 2001), *Drosophila* (Waddell and Quinn, 2001) or *Caenorhabditis elegans* (Rankin, 2002) also play a role in incentive learning in mammals. Among the signaling molecules that have been implicated in incentive learning are cyclic adenosine monophosphate-dependent

protein kinase (PKA), protein kinase C, mitogen-activated protein kinases and a number of related molecules. The largest number of studies has looked at PKA.

PKA in several structures including the basolateral amygdala, nucleus accumbens and prefrontal cortex has been implicated in incentive learning. Most studies have focused on the nucleus accumbens. A range of incentive learning tasks has been studied including conditioned approach, lever pressing for food, stimulant self-administration and conditioned reward, place conditioning to amphetamine or cocaine or conditioned activity to amphetamine. In almost every case, inhibition of PKA in the nucleus accumbens has led to impaired learning of the task. However, also in almost every case, inhibition of PKA during tests of expression of the task after learning has taken place had no effect. Results strongly implicated PKA in acquisition but not expression of incentive learning (Beninger and Gerdjikov, 2004).

Results of experiments examining the role of signaling molecules in reward-related incentive learning have led to a complex synaptic model for how this learning might take place in the nucleus accumbens or striatum. First proposed by Wickens (1990) and further elaborated by Sutton and Beninger (1999) and Kelley and Berridge (2002), this model proposes that dopamine produces incentive learning by modifying glutamatergic synapses formed by cortical efferents making contact with dendritic spines of medium spiny striatal cells. One of the steps in the dynamic interaction between dopaminergic and glutamatergic synapses common to medium spiny neuron dendrites involves the activation of PKA. Results suggest that PKA plays a role in modifying glutamate synaptic effectiveness but once the modification has occurred, learning will be manifested even if PKA function is blocked. Future studies will continue to elaborate the signaling molecules that participate in incentive learning. Results will provide possible new targets for pharmacotherapy and will point to new candidate genes for schizophrenia.

SEARCH FOR GENE-ENVIRONMENT INTERPLAY

Genetic researchers seeking to identify genes associated with schizophrenia and other psychotic disorders have attempted to refine diagnostic classification and to identify endophenotypes in an effort to increase the reliability of results. Their efforts have been rewarded with the identification of a number of genes that appear to be reliably associated with subtypes of schizopsychotic illness. Many of these genes code for molecules that participate in neurodevelopment and/or neurotransmitter function. Neurotransmitter systems researchers have continued to probe the function of a number of neurotransmitters including GABA, glutamate and dopamine and signaling molecules in the control of behaviors thought in many cases to provide good models of some of the symptoms of schizophrenia. A variety of environmental factors such as stress also influences neurotransmitter system function. Results continue to unravel the interplay of genes and environment in the etiology of schizophrenia and other psychotic disorders.

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