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MicroRNA dysregulation in psychiatric disease

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Abstract

MicroRNAs (miRNAs) are small regulatory RNAs that individually regulate up to several hundred genes, and collectively may regulate as much as two-thirds of the transcriptome. Recent evidence supports a role for miRNA dysregulation in psychiatric and neurological disorders, including schizophrenia, bipolar disorder, and autism. Small changes in miRNA expression can fine-tune the expression of multiple genes within a biological network, suggesting that miRNA dysregulation may underlie many of the molecular changes observed in psychiatric disease, and that therapeutic regulation of miRNA levels may represent a novel treatment option.

Keywords

MicroRNA; schizophrenia; bipolar disorder; NMDA; miR-132

Introduction

Psychiatric disorders, including schizophrenia and bipolar disorder, are highly heritable, yet also highly resistant to genetic dissection. The results of recent genome-wide association studies indicate that most cases of psychiatric illness are the result of hundreds or thousands of common genetic variants acting in concert to produce a neuropsychiatric phenotype. Such heterogeneity will continue to confound the development of novel drug therapies in the absence of new approaches that address the complex gene networks dysregulated in disease. We suggest that studying microRNA function in psychiatric disease may represent a road forward: dysregulation of miRNA expression may account for some of the neurodevelopmental aspects of psychiatric disorders and the difficulty in identifying individual causative genes, while targeting a single miRNA for therapeutic purposes offers the ability to fine-tune the expression of entire gene networks. In the following review, we summarize the current state of the genetics of psychiatric disease and the basic biology of miRNAs and miRNA function in the nervous system. We then focus on evidence suggestive of miRNA dysregulation in psychiatric disease.

Genetics of psychiatric disorders: the “missing heritability” problem

Psychiatric disorders, including schizophrenia, bipolar disorder, and depression, are a major burden on both patients and society. On an annual basis, approximately 25% of adults in the US will suffer from a major psychiatric illness; of these, schizophrenia and bipolar disorder, the most psychologically and economically disabling of the disorders, account for 1.1 and 2.5%

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of cases, respectively (Kessler et al., 2005b; WHO, 2004). Both disorders are associated with a poor quality of life and reduced life-span, yet both lack effective treatments. Although lithium and certain anticonvulsants help many bipolar patients, the treatments cause significant side effects that often lead to patient non-compliance (Thase, 2007). Schizophrenia is even more difficult to treat: neither the efficacy nor the side effect profile of pharmaceutical treatments for schizophrenia has improved substantially since the introduction of antipsychotics in the 1950s (Lieberman et al., 2005; Miller et al., 2008). While drug therapy can suppress the positive symptoms associated with schizophrenia, the less florid, but equally disabling, negative symptoms are often treatment-resistant (Kapur and Remington, 2001; Tandon et al., 2008).

For both schizophrenia and bipolar disorder, development of new drug therapies is hindered by a lack of understanding of the biological underpinnings of the illnesses. Despite heritability estimates as high as 80% (Cardno and Gottesman, 2000; McGuffin et al., 2003), complex psychiatric diseases have been resistant to genetic dissection (Williams et al., 2009). Traditional genetic approaches, such as quantitative trait locus (QTL) studies, have linked more than 7,000 genetic polymorphisms to schizophrenia (Allen et al., 2008), but the majority of these studies have not been replicated in separate populations, or have produced loci that are too large for candidate gene identification. The loci that have been most clearly linked to psychiatric disorders, including 1q21, 8p, and 13q, have yet to yield candidate genes that have been definitively associated with schizophrenia (Bertram, 2008; Craddock et al., 2005; Porteous, 2008). Candidate gene analysis has likewise had limited success: there is clear molecular evidence supporting altered glutamate and dopamine (DA) signaling in schizophrenia-like symptoms, but genetic studies have often failed to associate mutations in key genes in these pathways with disease risk (Owen et al., 2004). For example, a recent meta-analysis of 118 schizophrenia QTL studies found that associations with the dopamine, glutamate, and GABA receptor genes did not meet genome-wide significance (Allen et al., 2008).

To date, the most striking advances in the genetics of schizophrenia have resulted from small family-based studies of rare diseases that include schizophrenia/psychosis as a phenotype. Family-based linkage studies attempt to identify risk loci by looking for co-segregation of a genomic locus with disease in multiple families or a single large pedigree. This was the method used to identify the Disrupted-in-Schizophrenia-1 (DISC1) locus, which was originally identified in a Scottish pedigree with a high rate of schizophrenia, bipolar disorder, and psychosis (St Clair et al., 1990). The Scottish family carries a balanced translocation (1;11) (q42.1; q14.3) that results in the truncation of the DISC1 gene. Subsequent work has shown that DISC1 plays a major role in human hippocampal structure and function, cerebral cortex development, and fetal and adult neurogenesis (Duan et al., 2007; Kamiya et al., 2005; Schurov et al., 2004). Binding partners of DISC1, including NDEL1 and PDE4B, have also been shown to be altered in some schizophrenic patients, suggesting that the DISC1 pathway may play a central role in schizophrenia in a subset of the population (Tomppo et al., 2009). However, it is important to note that DISC1 mutations are not found in the majority of patients: therefore, although DISC1 is highly penetrant in a subset of patients and may provide important insight into the neurobiology of schizophrenia, it is not a general risk factor (Sanders et al., 2008).

Similarly, genome-wide analysis of copy number variation (CNV) has identified a subset of psychiatric disease cases linked to CNV burden (ISC, 2008; Need et al., 2009; Walsh et al., 2008; Xu et al., 2008; Zhang et al., 2009). Several groups have suggested that schizophrenia-associated CNVs preferentially disrupt genes that may be involved in nervous system function (Walsh et al., 2008; Wilson et al., 2006) Although the increased CNV burden in schizophrenia and other neuropsychiatric disorders has been replicated in multiple populations, CNVs are believed to account for only a small minority of cases. Furthermore, many of the CNVs

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represent *de novo* or rare ("private") genomic rearrangements, and therefore cannot account for the significant heritability of schizophrenia (Conrad et al., 2009).

It is estimated that less than 10% of psychiatric illness are caused by rare, highly penetrant genes, such as DISC1, or by genomic rearrangements resulting in copy number variation (CNV), suggesting that the majority of cases are the result of the interaction of many genes, each with a small effect—the common variant/low penetrance model (Conrad et al., 2009; Purcell et al., 2009) (Figure 1). Genome-wide associations studies (GWAS), which use high-density single nucleotide polymorphism (SNP) genotyping to link phenotypes to underlying haplotypes, have been successfully applied to complex, presumably polygenic disorders such as breast cancer and obesity, but have had limited success when applied to psychiatric disorders. To date, approximately 10 GWAS studies have been directed at schizophrenia and/or bipolar disorder, the largest of which include 8,000 cases and 19,000 controls (Kirov et al., 2008; Need et al., 2009; O'Donovan et al., 2008; Purcell et al., 2009; Shi et al., 2009; Shifman et al., 2008; Stefansson et al., 2009; Sullivan et al., 2008). Although several of these studies are of sufficient power to detect loci carrying a relative risk of approximately 1%, only two genes, ZNF804A (O'Donovan et al., 2008) and ANK3 (Ferreira et al., 2008), have been linked to schizophrenia or bipolar disorder at a significant level. Statistical analysis of the most recent GWAS results suggests that both schizophrenia and bipolar disorder are highly polygenic, with hundreds, or possibly thousands, of common SNPs contributing to a large percentage of disease liability (Purcell et al., 2009).

The failure of genetic association studies to shed significant light on the genetics of psychiatric disease has been termed the problem of "missing heritability" (Manolio et al., 2009; Purcell et al., 2009). Several potential hurdles may ultimately limit the success of genetic studies, including genetic and phenotypic heterogeneity, epistatic gene interactions, and the role that the environment plays in the development and expression of psychiatric illness (Burmeister, 1999; Burmeister et al., 2008). On a practical basis, however, it is not necessary to identify all causative genes in order to develop effective treatments: in this case, the rare variant and CNV models of psychiatric disease may be most instructive. The recent associations between genomic structural variants with schizophrenia, bipolar disorder, and autism indicate that there may be many biological pathways that, when disrupted, lead to affective and cognitive disorders; in this sense, schizophrenia and bipolar disorder may not be individual diseases, but rather phenotypes of altered neuronal development (Guilmatre et al., 2009).

This hypothesis is supported by a number of lines of evidence, particularly for schizophrenia. First, the genes that have been most clearly associated with schizophrenia are genes involved in neuronal development. DISC1 and its binding partners regulate hippocampal gray matter volume, neurite outgrowth, dendritic arborization, and neuronal migration and maturation (Callicott et al., 2005; Millar et al., 2007). Two other risk genes, NRG1 and ERBB4, interact to regulate neuronal migration, axon myelination, and synapse formation (Buonanno et al., 2008; Mei and Xiong, 2008). Second, the symptoms of psychiatric illness have a developmental trajectory that parallels the maturation of the brain. The timing of peak disease risk for all psychiatric disorders overlaps with the substantial cortical dendritic pruning that occurs during adolescence (Feinberg, 1982; Kessler et al., 2005a), and, although there are clear prodromal signs for some disorders, outright symptoms such as psychosis are rare during childhood (Borgmann-Winter et al., 2006; Paus et al., 2008). Finally, a number of studies have found significant structural differences between schizophrenic and control brains, including decreased cortical neuron spine density, enlarged lateral ventricle size, and decreased hippocampal and cortical volume (Fatemi and Folsom, 2009; Schultz and Andreasen, 1999).

The association of CNVs and genes involved in neurodevelopment with schizophrenia also has important implications for therapeutic treatments. If there are multiple biological pathways

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that can lead to psychiatric disease, with any single cause being relatively rare in the population, useful therapies must have a broad effect. Currently available antipsychotics reduce psychosis via activity at the D2 receptor, but also act non-specifically on almost all the catecholaminergic and monoaminergic systems of the brain (Carpenter and Koenig, 2008). These drugs not only have poor efficacy and serious side effects, but also fail to address what may be the underlying genetic and molecular causes of psychiatric disease (Gogos, 2007). In contrast, microRNAs, which have the ability to regulate a large network of protein coding targets, may prove a more promising therapeutic avenue.

MicroRNA biogenesis and function

MicroRNAs, first identified less than two decades ago, are one of several classes of small RNAs found only in eukaryotes (Lai, 2002). Initially, the pri-miR sequence is transcribed in a PolII-dependent manner into a double-stranded RNA hairpin with a stem-loop structure (Kim, 2005). As miRs are often found clustered in the same genomic locus, a pri-miR may contain sequences for several different miRNAs (Bartel, 2004). Following transcription, the RNase III endonuclease Drosha, in conjunction with DGCR8 (in mammals) or *pasha* (in *D. melanogaster*), excises the stem-loop, resulting in the pre-miR, which is exported from the nucleus by Exportin 5 (Carthew and Sontheimer, 2009). In the cytoplasm, the proteins Dicer and TRBP cleave the terminal loop, producing a ~22 nt single-stranded mature miRNA (Denli et al., 2004). This process produces both a major (abundant) miRNA and a minor (less abundant) form; the major form is the guide strand used to specify the interaction between the target mRNA and the silencing complex, while the minor form, known as the miRNA* form, is generally discarded and degraded (Bartel, 2004; Carthew and Sontheimer, 2009).

RNA silencing occurs within the RNA-induced silencing complex (RISC), a ribonucleoprotein complex composed of the miRNA, the target mRNA, Dicer, and the Argonaute proteins (AGO1-4 in mammals) (Carthew and Sontheimer, 2009). RISCs may also include proteins such as FMRP, the protein encoded by the FMR1 gene, and GW182, a component of cytoplasmic structures known as P bodies (Eulalio et al., 2008). The sequence of the miRNA specifies the target mRNA sequence via perfect Watson-Crick base-pairing between nucleotides 2-8 (the seed region) of the miRNA and a complementary site in the 3′ UTR of the target mRNA. The degree of complementarity between miRNA and mRNA dictates the method of RNA inhibition: perfect complementarity results in AGO-mediated cleavage of the target mRNA, while mismatches result in translational repression, a reversible process that may allow cells to store mRNAs in preparation for rapid translation (Bartel, 2009). MiRNAs may also regulate pre-mRNA processing, mRNA structure, and mRNA-protein interactions (Filipowicz et al., 2008). As a single miRNA transcript can catalyze multiple rounds of RNA cleavage, miRNA levels must be tightly regulated (Flynt and Lai, 2008; Kosik, 2006).

MiRNA target prediction is still in its infancy, but several rules for prediction have been identified. First, there must be perfect complementarity between the miRNA seed region and a region within the mRNA 3′ UTR, and the miRNA-mRNA interaction must be thermodynamically permissive (Ameres et al., 2007; Lai, 2002; Lewis et al., 2003). As any 7-nucleotide sequence is likely to appear thousands of times within a genome, the most accurate prediction algorithms require evolutionary conservation of 3′ UTR sites across eukaryotic genomes. Following these rules, each miRNA is predicted to have an average of 400 protein-coding targets, suggesting that 50-60% of the genome is subject to RNA inhibition (Brennecke et al., 2005; Friedman et al., 2009). However, there are multiple factors that can affect which mRNAs are subject to regulation, and the strength of the inhibition. Chief among these is selective avoidance: mRNAs that contain non-conserved 3′ UTR binding sites are generally not expressed in the same cell or tissue as their cognate miRNA. The UTR context of the miRNA binding site, the number of miRNA binding sites within a single 3′ UTR, mRNA

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polyadenylation, and alternative splicing also regulate miRNA-mRNA interactions (Bartel, 2009).

Several studies have measured proteome-wide changes following miRNA manipulation. Selbach and colleagues found that, as predicted by the number of conserved 3′ UTR binding sites, overexpression of a single miRNA results in the repression of hundreds of proteins, a change that can, for the majority of targets, also be measured at the RNA level by microarray. However, the repressive effect was generally 30-40%, and almost never exceeded 4-fold downregulation (Selbach et al., 2008). Similarly, Baek and colleagues found that overexpression or knockdown of a single miRNA downregulated or upregulated, respectively, hundreds of genes at both the mRNA and protein level (Baek et al., 2008).

Function of miRNAs in the nervous system

As might be expected from the proteome-wide studies, a single microRNA can have widespread effects on the molecular identity of an individual cell. Co-expression of specific miRNAs thus results in cell type-specific regulation of a battery of protein-coding genes in a manner that allows cells to establish and maintain tissue identity. This was clearly demonstrated by Lim and colleagues, who over-expressed either miR-1, a heart- and skeletal muscle-enriched miRNA, or miR-124, a brain-enriched miR, in HeLa cells (Lim et al., 2005). Upregulation of miR-1 resulted in the down-regulation of 96 genes that are normally expressed at a very low level in mature heart tissue, while upregulation of miR-124 repressed the expression of almost 200 genes that are normally expressed at low levels in the brain versus all other tissues (Lim et al., 2005). Within the nervous system, miR-124a and miR-9 regulate neuronal precursor fate by regulating glial versus neuronal patterns of gene expression and alternative splicing (Krichevsky et al., 2006). The expression of miR-124 is restricted to differentiating and mature neurons by the transcriptional repressor RE1 silencing transcription factor (REST); in the absence of REST, miR-124 inhibits a large number of non-neuronal genes, including the splicing factor PTBP1, the absence of which leads to the establishment of alternative splicing patterns specific to neurons (Conaco et al., 2006; Makeyev et al., 2007; Visvanathan et al., 2007).

RNAi has been shown to play a crucial role in neural development and patterning. Disruption of *dicer* during zebrafish development results in abnormal neurulation (Giraldez et al., 2005); although *Dicer* mouse mutants arrest prior to neurulation (Bernstein et al., 2003), selective deletion of *Dicer* in the developing mouse neocortex results in increased neuronal apoptosis and severe cortical hypotrophy (De Pietri Tonelli et al., 2008). In C. elegans, the left-right asymmetry of chemosensory ASE neurons is established by two miRNAs, *lsy-6* and miR-273. In the left ASE, the transcription factor *die-1* induces expression of *lsy-6*, which represses the homeobox gene *cog-1*; in the right ASE, miR-273 targets *die-1* for inhibition, effectively repressing *lsy-6* expression (Chang et al., 2004; Johnston et al., 2005).

MiRNAs continue to play a major role in nervous system function during adulthood. A number of studies have linked miRNAs to both basic biology, such as synaptic plasticity and circadian regulation, and to disease-associated pathologies including Parkinson's disease and Tourette's Syndrome. Perhaps best-known is the role of miR-134, a regulator of activity-dependent RNA translation in dendritic spines. Local protein synthesis in dendrites was first identified in the 1980s, and later shown to be necessary for BDNF-induced changes in dendritic plasticity (Sutton and Schuman, 2006). Under static conditions, miR-134 binds to and inhibits the translation of LIMK1, a regulator of synaptic morphogenesis; BDNF signaling rapidly inhibits the effect of miR-134, allowing LIMK1 to be translated (Schratt et al., 2006). The brain-enriched miR-132 also regulates dendritic outgrowth via interactions with Rho family GTPase-activating protein p250GAP. MiR-132 transcription is induced by activity-dependent CREB

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signaling, resulting in translational inhibition of p250GAP, de-inhibition of Rac family GTPases, and a subsequent increase in dendritic size and branching (Wayman et al., 2008) (Figure 2).

MiR-132 also plays a role in circadian rhythms, along with the brain-enriched miR-219. Both miRNAs are expressed in the suprachiasmatic nucleus (SCN), where they mediate separate aspects of the circadian pacemaker. MiR-219 is transcriptionally induced by the core circadian proteins CLOCK and BMAL and regulates phase length, whereas miR-132 transcription is induced by light-dependent activation of CREB and regulates light-induced phase-shifting (Cheng et al., 2007). In addition, miR-132 regulates neuronal excitability by potentiating the depolarizing effects of glutamate and NMDA, while miR-219 has the opposite effect (Cheng et al., 2007), suggesting that these miRNAs have a broader, as yet unknown role in regulating neuronal activity.

The widespread expression and activity of miRNAs in the brain suggest that they may be major players in neurological disorders. Indeed, two separate groups have associated global depletion of brain miRNA via selective deletion of *Dicer* with dopaminergic behaviors and Parkinson's-like symptoms. Deletion of *Dicer* in dopamine neurons results in the progressive loss of dopamine neurons and expression of Parkinson's-like behaviors, including reduced locomotion and increased immobility (Kim et al., 2007). Loss of *Dicer* in dopamine-receptive neurons also produces both behavioral changes, such as ataxia, and neuronal defects, such as reduced neuronal size and astrogliosis (Cuellar et al., 2008). As at least one miRNA, miR-133b, is significantly downregulated in midbrain tissue from Parkinson's disease patient samples, it is possible that miRNA dysregulation regulates some aspects of Parkinson's disease (Kim et al., 2007).

MicroRNAs have been suggested to play a role in several other neurological disorders. FMR1, the gene responsible for Fragile X mental retardation, encodes the protein FMRP, which is present in synapses and is part of the RISC complex that includes Dicer, miRNAs, and target mRNAs. Loss of FMRP impairs the function of RISC-mediated gene silencing, resulting in altered synaptic development (Jin et al., 2004). Some cases of Tourette's syndrome may also be caused by miRNA dysregulation: mutations in the miR-189 binding site in the 3′ UTR of SLITRK1, a protein involved in neurite outgrowth, have been associated with Tourette's syndrome in a small number of patients (Abelson et al., 2005). Finally, multiple studies have also suggested a link between miRNA dysregulation, including miR-29a/b-1, miR-106, and miR-9, and Alzheimer's Disease, although the specific molecular mechanisms remain unknown (Hebert and De Strooper, 2009).

MiRNAs in psychiatric disease

The ability of miRNAs to have a broad effect on gene expression and functional pathways has important implications for psychiatric disease. Schizophrenia and bipolar disorder, which are now believed to represent different aspects of a clinical continuum, are characterized by dysregulation of multiple signaling pathways. For example, all currently available antipsychotics preferentially block neurotransmission at the dopamine D2 receptor (D2R), but may also affect signaling at as many as 10 other types of receptors, including the serotonergic, adrenergic, muscarinic, and histaminergic receptors (Meltzer and Huang, 2008). The action of antipsychotics at the D2R has led to the hypothesis that dopaminergic signaling is dysregulated in the schizophrenic brain, with the prefrontal areas exhibiting DA hypoactivity and the subcortical areas exhibiting DA hyperactivity (Alves Fda et al., 2008; Stone et al., 2007). This hypothesis is supported by a number of human and animal studies that have focused on the role of dopamine transmission (Schultz and Andreasen, 1999; Zhuang et al., 2001). However, dopamine antagonists do not treat negative symptoms of schizophrenia, nor do dopamine

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agonists fully recapitulate the spectrum of schizophrenic symptoms, suggesting that altered dopamine function represents only one aspect of schizophrenia.

Glutamatergic signaling, primarily via the NMDA receptor (NMDAR), has also been implicated in schizophrenia. The NMDAR antagonists phencyclidine (PCP) and MK-801 induce psychosis and cognitive impairment in normal human subjects, and NMDA receptor levels are reduced in schizophrenic patients (Pilowsky et al., 2006). Mouse models with hypoactive NMDAR function similarly exhibit hyperlocomotion, stereotypic movements, and deficits in cognitive and neurosensory function and social interaction (Enomoto et al., 2007). Many of these mouse models also exhibit reduced inhibitory GABAergic transmission. Importantly, NMDAR hypofunction recapitulates aspects of both positive and negative symptoms of schizophrenia. Recent experiments indicate that bipolar disorder shares many of the same genetic risk factors as schizophrenia, and is therefore likely to share many of the same molecular mechanisms (Potash and Bienvenu, 2009; Purcell et al., 2009).

The involvement of multiple signaling pathways in psychiatric disease complicates both the investigation of the underlying biological causes and efforts to develop effective therapies. Furthermore, it is likely that drugs that target a single receptor or signaling pathway are likely to be unsuccessful. Focusing on the role of miRNAs in psychiatric disease may both explain dysregulation of multiple pathways and offer a path to novel therapies that can target entire gene networks.

Several studies have directly looked at miRNA dysregulation in schizophrenia, although the results are somewhat conflicting (Table 1). Perkins and colleagues examined the expression of 264 miRNAs in prefrontal cortex (Brodmann's Area 9) from a group of 15 schizophrenic or schizoaffective patients and 21 control samples, and identified 16 differentially regulated miRNAs, 15 of which were down-regulated in schizophrenia (Perkins et al., 2007). Of these, miR-26b, miR-30b, miR-29b, and miR-106b showed the greatest fold change, although all fold changes were less than 2-fold. Interestingly, for several of the differentially-expressed miRNAs, the ratio of mature miRNA to pri-miRNA was lower in schizophrenia, suggesting a disruption in miRNA biogenesis in schizophrenia.

A second group has also observed miRNA dysregulation and altered miRNA biogenesis in schizophrenic brain tissue. In 2 separate studies evaluating the expression of 262 (Beveridge et al., 2008) or 322 (Beveridge et al., 2009) miRNAs in superior temporal gyrus (STG) and dorsolateral prefrontal cortex (DL-PFC) from schizophrenia and control samples, Beveridge and colleagues observed schizophrenia-associated upregulation of a very large number of miRNAs: 21% of expressed miRNAs in the STG and 9.5% of expressed miRs in the DL-PFC. Upregulated miRNAs included miR-181b, miR-219, and members of the miR-15 family; surprisingly, of the 81 dysregulated miRNAs, only 4 were upregulated in both the STG and DL-PFC (miR-128a, miR-16, miR-20a, and miR-338). Four miRNAs, including miR-24, miR-26b, miR-29c, and miR-7, overlapped with the set of significantly changed miRNAs from the Perkins study; in the Perkins study, all four miRNAs were downregulated, while in the Beveridge study all were upregulated. Changes in miRNA biogenesis were also contrary to those in the Perkins study: Beveridge and colleagues found that the pool of ~22-nt RNAs and levels of the miRNA processing enzymes Dicer and DGCR8 were significantly upregulated in schizophrenia, suggestive of a global increase in miRNA biogenesis.

Further studies in larger, separate populations will be necessary to reconcile the contradictory human data. However, there is strong experimental support for altered miRNA biogenesis in at least one subset of schizophrenic patients. Hemizygous deletions of the 22q11.2 locus in humans result in deficits in attention, learning, executive function, and emotional behavior, and account for up to 2% of all cases of schizophrenia (Karayiorgou et al., 1995). Stark and

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colleagues produced a mouse model hemizygous for a deletion of a 1.3 Mb region syntenic to 22q11.2 and observed a number of schizophrenia-like phenotypes (increased hyperactivity, poor pre-pulse inhibition, and reduced dendritic spine density), upregulation of pri-miRNA levels, and downregulation of mature miRNA levels in the brain (Stark et al., 2008). Contained within both the 22q11.2 region and the deleted murine locus is DGCR8, the absence of which results in a bottleneck in the processing of pre-miRNAs to mature miRNAs. Deletion of *Dgcr8* alone was also sufficient to produce a number schizophrenia-like behaviors in mice.

Several groups have produced data associating specific miRNAs with schizophrenia. Hansen and colleagues genotyped SNPs near or within 28 brain-expressed miRNAs in three case/control populations of European ancestry, and found that minor alleles in miR-206 and miR-198 were over- or under-represented, respectively, in schizophrenia (Hansen et al., 2007). Feng and colleagues sequenced 59 X-linked SNPs in a small case/control population and found an increase in private, ultra-rare mutations of the pri- or mature miRNA sequences in schizophrenia (Feng et al., 2009). Zhu and colleagues used bioinformatics to identify the miRNAs that target the largest number of schizophrenia-associated genes, and found that two miRNAs, miR-566 and miR-346, target more schizophrenia-associated genes than would be expected by chance. Furthermore, miR-346 is located within an intron of GRID1, a glutamate receptor subunit gene that is downregulated in schizophrenia (Zhu et al., 2009). Finally, 6 miRNAs, including miR-124 and miR-383, are located with the 8p21-23 locus, a CNV “hot spot” linked to schizophrenia and autism (Tabares-Seisdedos and Rubenstein, 2009).

The specific molecular mechanisms through which altered miRNA activity may cause psychiatric phenotypes are still poorly understood. Recently, our group found that miR-219 mediates the behavioral effects of MK-801 treatment in mice (Kocerha et al., 2009). Acute, but not chronic, MK-801 treatment decreased levels of miR-219 in the prefrontal cortex, and inhibition of miR-219 prevented MK-801-induced hyperlocomotion and stereotypies. One of the targets of miR-219 is CAMK2G, a member of the calcium/calmodulin-dependent protein kinase family involved in NMDA signaling. When combined with data showing that miR-219 attenuates NMDA-induced neuronal depolarization (Cheng et al., 2007), these results indicate that miR-219 may inhibit NMDA signaling at the level of both the receptor and second messenger signaling. Upregulation of miR-219 in DL-PFC from schizophrenic patients, as observed by Beveridge and colleagues (Beveridge et al., 2009), is therefore consistent with the NMDAR hypoactivity hypothesis of schizophrenia.

BDNF is another major player in schizophrenia, bipolar disorder, and depression. In addition to inhibiting the effects of miR-134 on *Limk1*, described above, BDNF is itself the target of several miRNAs. Mellios and colleagues identified 2 miRNAs, miR-30a and miR-195, that are expressed in human prefrontal cortex, directly target the BDNF 3′ UTR, and reduce BDNF expression (Mellios et al., 2008). BDNF is indirectly regulated by miR-132: CREB-induced transcription of miR-132 results in a decrease of MECP2, the protein involved in Rett syndrome, and a subsequent decrease in BDNF due to de-repression of REST (Abuhatzira et al., 2007; Klein et al., 2007). CREB expression has been shown to be reduced in schizophrenia, suggesting that miR-132 expression may also be reduced (Yuan et al., 2009). Our lab has recently observed a significant reduction in miR-132 levels in prefrontal cortex from schizophrenic and bipolar patients (unpublished data); because miR-132 potentiates NMDAR depolarization (Cheng et al., 2007), reduced expression of miR-132 in schizophrenia, like up-regulation of miR-219, would also be consistent with NMDAR hypofunction in schizophrenia (Figure 3). The mechanism of the interaction between the NMDAR and miRNAs is still unknown: it is not clear whether miRNAs directly regulate receptor subunit activity and availability, or instead act on key members of the NMDAR signaling pathway.

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MiRNAs may also mediate some of the effects of psychiatric drug therapies. Zhou and colleagues found that *in vitro* lithium and valproic acid treatment differentially regulated 37 and 31 miRNAs, respectively, with 8 miRNAs in common (Zhou et al., 2009). Several of the miRNA target genes, including GRM7, DPP10, and THRB, are potential genetic risk factors for bipolar disorder. Similarly Chen and colleagues examined miRNA expression in lymphoblastoid cell lines derived from bipolar disorder patients or unaffected siblings, and identified alterations in expression of several miRNAs following lithium treatment (Chen et al., 2009). In rats, treatment with the antipsychotic haloperidol upregulates 3 miRNAs, miR-199a, miR-128a, and miR-128b (Perkins et al., 2007). All three miRNAs have been shown to be upregulated in brain tissue from schizophrenia patients (Beveridge et al., 2009), although it is unclear whether the upregulation is central to schizophrenia or a result of antipsychotic treatment.

Conclusion

Individual miRNAs regulate several hundred proteins in tandem, with a few targets downregulated greatly and many other targets downregulated to a lesser extent. The ability of miRNAs to fine-tune the activity of entire biological pathways may underlie some of the difficulties associated with linking psychiatric disorders to specific causative genes. A more complete picture of the miRNAs that are dysregulated in psychiatric illness may improve our understanding of the molecular mechanisms underlying neuropsychiatric phenotypes, and, due to their tuning effect on large numbers of proteins, miRNAs may ultimately represent a new therapeutic target for psychiatric disease.

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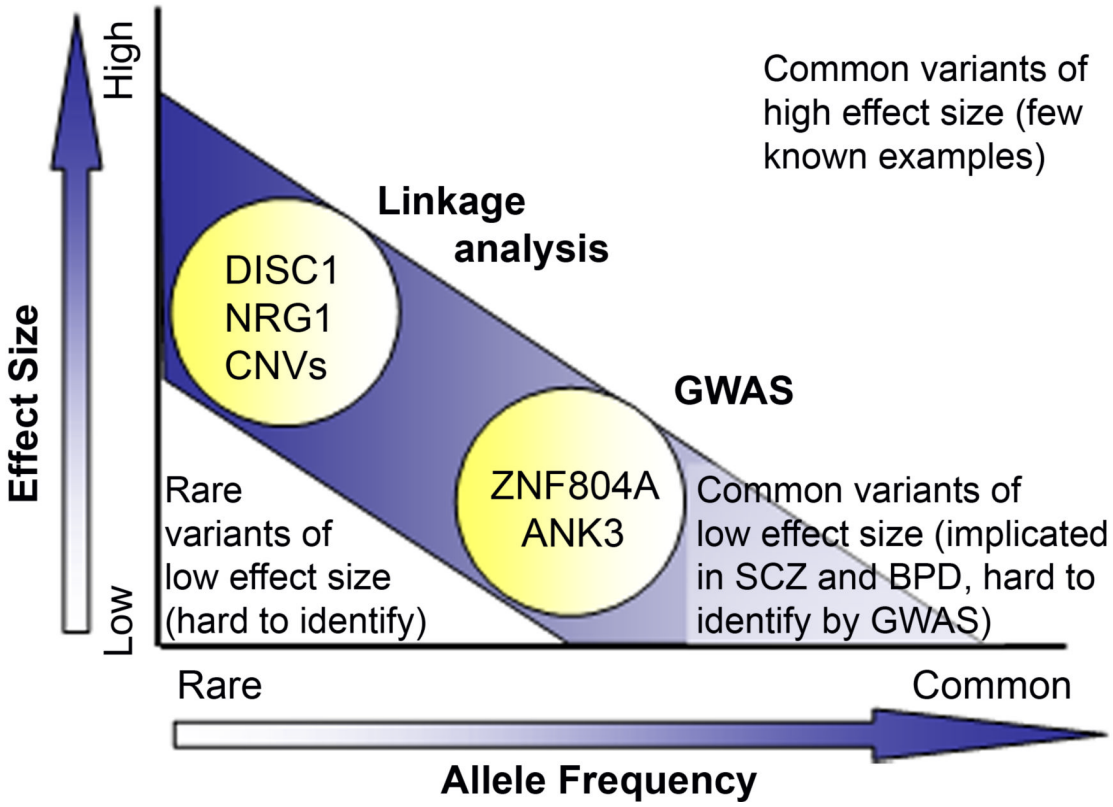

Figure 1.

Probability of identifying psychiatric risk alleles by genetic analysis. Rare risk alleles with high penetrance, such as DISC1 and certain CNVs, including 22q11.2 microdeletions, can be identified using standard linkage analysis. Common variants that have an odds ratio of ~1.0 or higher, such as ZNF804A and ANK3, can be identified by GWAS. However, recent studies suggest that most cases of psychiatric disorders may be the result of many common variants, each with a very small effect size. These variants are undetectable by current genetic methods.

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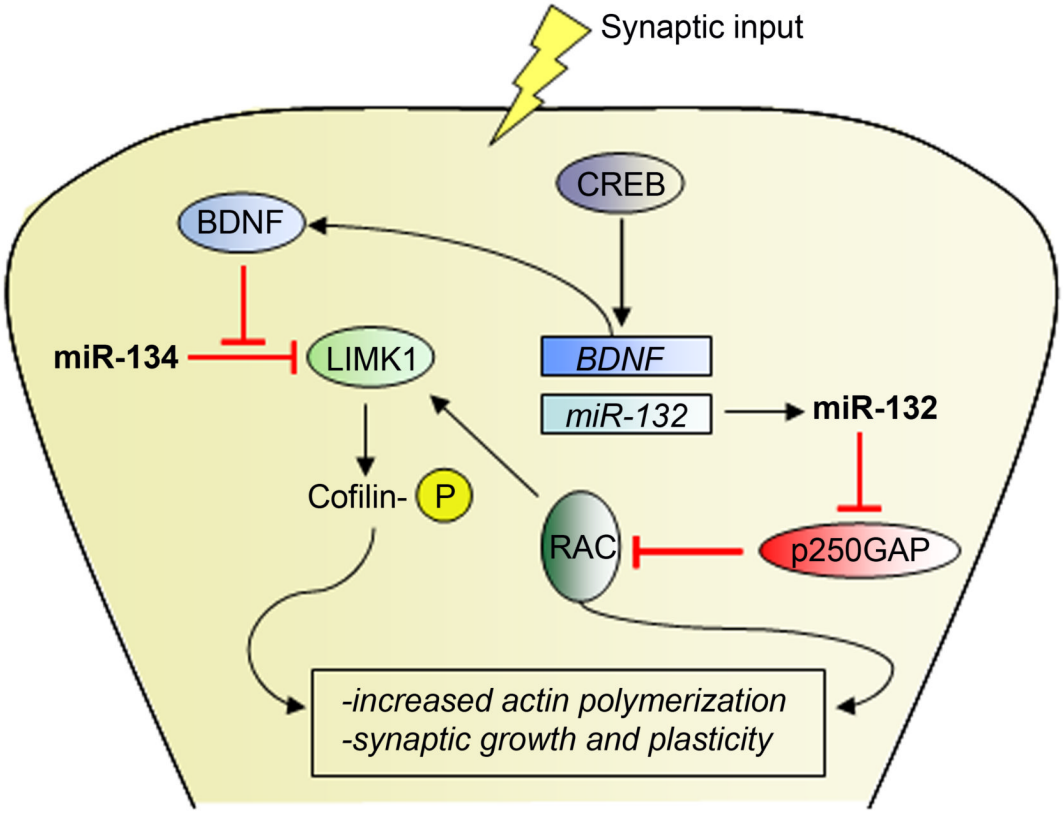

Figure 2.
Function of microRNAs at the synapse. Synaptic input co-regulates miR-132 and miR-134, producing changes in synaptic plasticity. MiR-132, transcription of which is induced by CREB signaling, targets p250GAP for translational inhibition, resulting in an increase in RAC signaling and subsequent increase in LIMK1 activity. MiR-134 function is inhibited by activity-induced BDNF signaling, resulting in de-inhibition of LIMK1.

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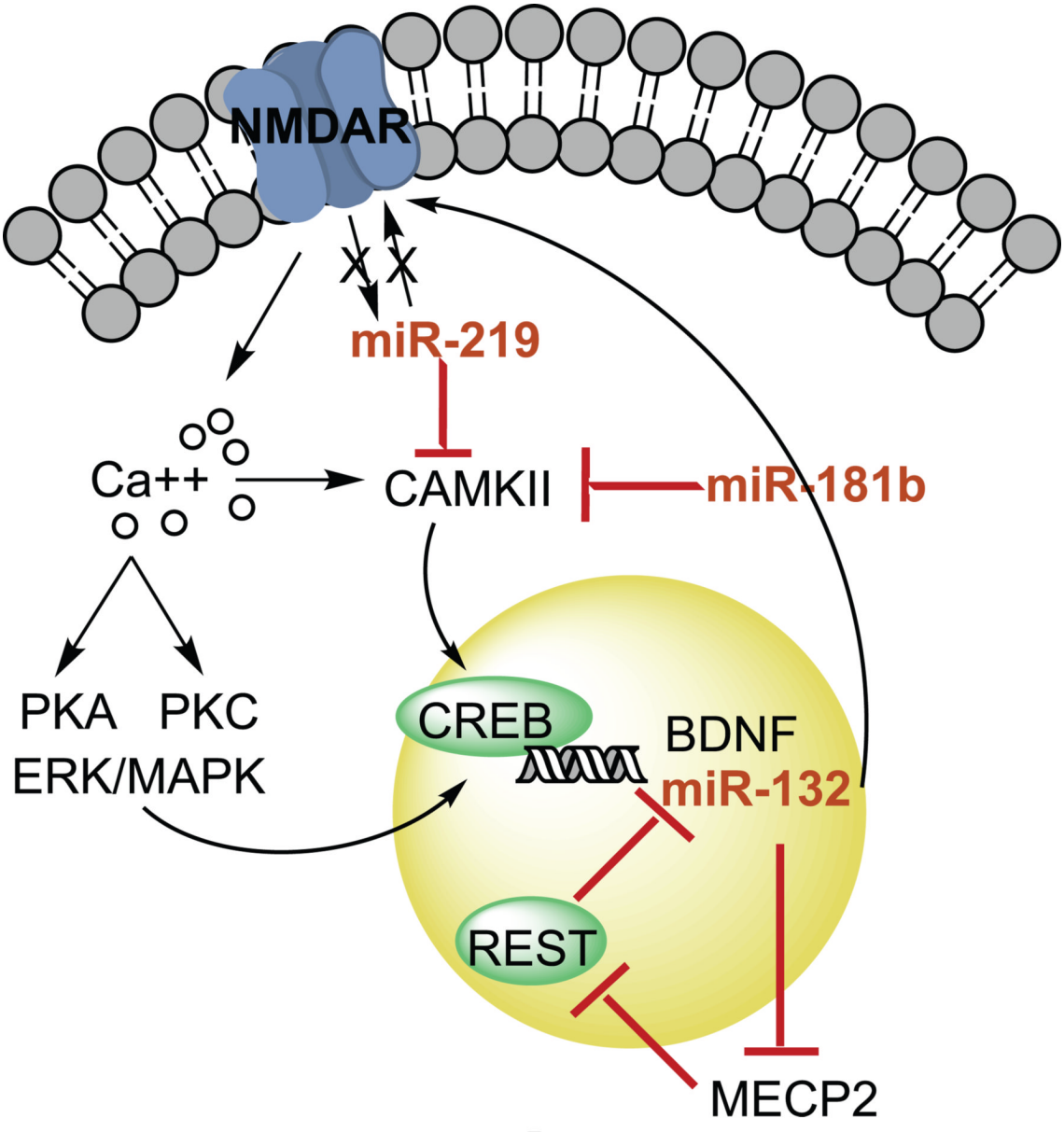

Figure 3.

Possible roles of miRNAs in signaling pathways associated with psychiatric disorders. MiR-132, miR-219, and miR-181b all regulate NMDA-induced calcium signaling pathways. NMDA signaling inhibits miR-219, resulting in disinhibition of CAMK2G, which is also a target of miR-181b. Both miR-219 and miR-181b are upregulated in schizophrenic tissue. NMDA signaling increases miR-132 levels; miR-132 potentiates NMDAR activity, but inhibits BDNF transcription by targeting MECP2, which targets the transcriptional repressor REST. Reduced NMDA function, as observed in schizophrenia, would result in reduced miR-132 levels in schizophrenia tissue.

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Table 1

MicroRNAs associated with psychiatric disease

miRNA	Validated target/Function	Reference
16 miRs dysregulated	Changed in DL-PFC from SCZ patients (microarray)	(Perkins et al., 2007)
let-7g, miR-181b	Changed in temporal gyrus from SCZ patients (microarray)	(Beveridge et al., 2008)
59 misR dysregulated	Changed in temporal gyrus from SCZ patients (microarray)	(Beveridge et al., 2009)
26 miRs dysregulated	Changed in DL-PFC from SCZ patients (microarray)	(Beveridge et al., 2009)
miR-124, 383, 320, 596, 597, 598	Located within chromosome 8 QTL for SCZ, autism	(Tabares-Seisdedos and Rubenstein, 2009)
5 X-linked miRs	Private mutations in SCZ patients	(Feng et al., 2009)
miR-346	Located in GRID2 intron, reduced in SCZ	(Zhu et al., 2009)
miR-34a	GRM7/reduced by both lithium and valproate treatment	(Zhou et al., 2009)
miR-221, 152, 152, 494	Changed in BPD lymphocytes after lithium treatment	(Chen et al., 2009)
miR-199a, 128a/b	Upregulated by haloperidol treatment in rats	(Perkins et al., 2007)
miR-195, miR-30a	BDNF regulation	(Mellios et al., 2008)
miR-96	HTR1B/aggressive behavior in humans	(Jensen et al., 2009)
miR-219	CAMK2G/reduced by MK-801 treatment in mice	(Kocerha et al., 2009)