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Review article

MicroRNA: Small RNA mediators of the brains genomic response to environmental stress

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ABSTRACT

The developmental processes that establish the synaptic architecture of the brain while retaining capacity for activity-dependent remodeling, are complex and involve a combination of genetic and epigenetic influences. Dysregulation of these processes can lead to problems with neural circuitry which manifest in humans as a range of neurodevelopmental syndromes, such as schizophrenia, bipolar disorder and fragile X mental retardation. Recent studies suggest that prenatal, postnatal and intergenerational environmental factors play an important role in the aetiology of stress-related psychopathology. A number of these disorders have been shown to display epigenetic changes in the postmortem brain that reflect early life experience. These changes affect the regulation of gene expression though chromatin remodeling (transcriptional) and post-transcriptional influences, especially small noncoding microRNA (miRNA). These dynamic and influential molecules appear to play an important function in both brain development and its adaption to stress. In this review, we examine the role of miRNA in mediating the brain's response to both prenatal and postnatal environmental perturbations and explore how stress- induced alterations in miRNA expression can regulate the stress response *via* modulation of the immune system. Given the close relationship between environmental stress, miRNA, and brain development/function, we assert that miRNA hold a significant position at the molecular crossroads between neural development and adaptations to environmental stress. A greater understanding of the dynamics that mediate an individual's predisposition to stress-induced neuropathology has major human health benefits and is an important area of research.

Contents

Abbreviations: miRNA, microRNA; DGCR8, DiGeorge syndrome critical region gene 8; Ago, Argonaut; RISC, RNA- Induced Silencing Complex; MRE, miRNA recognition element; poly I:C, polyinosinic-polycytidylic acid; INF-α, Interferon alpha; PFC, prefrontal cortex; THC, Δ^9tetrahydrocannabinol; CB_1, cannabinoid receptor; DA, dopamine; endocannabinoid, endogenous cannabinoid; eCB, endocannabinoid; AEA, anandamide; $GABA_A$, gamma-aminobutyric acid A; MIA, maternal immune activation; EC, entorhinal cortex; GD, gestational day; GCs, glucocorticoids; FAS, Fetal Alcohol Syndrome; HPA, hypothalamic-pituitary-adrenal; NMDA, N-methyl-D-aspartate; PND, post-natal day; MEF2, Myocte Enhancer Factor 2; MHCI, Major histocompatibility complex class I; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; TLR, toll-like receptor; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TNF- α, tumour-necrosis factor-alpha; nAChRs, nicotinic acetylcholine receptors; CHRNA7, α7 nAChR subunit; ACh, acetylcholine; AChE, acetylcholinesterase; mPFC, medial prefrontal cortex; PVN, paraventricular hypothalamus; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; GR, glucocorticoid receptor; BDNF, brain-derived neurotrophic factor; IPA, Ingenuity Pathway Analysis; GATHER, Gene Annotation Tool to Help Explain Relationships; WNT, Wingless/int.

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1. Introduction

The adult brain is an incredibly complex organ comprising many different cells types with an astonishing capability for intercellular connectivity. This is utilized to generate even more complicated networks with the capacity to integrate neural input through synapses and synaptic plasticity to form, maintain and modify circuits. These circuits provide the neural basis for sensation, cognition, memory and motivation. The organisation of this assembly at the molecular level is no less complex and involves many layers of gene regulation. At the transcriptional level there is a myriad of epigenetic influences on chromatin structure including DNA methylation and histone modifications that modify the synthesis of RNA. This however, is just the beginning of mRNA's journey that will take it from the nucleus out into the cytoplasm to a discrete site of translation or interaction point. The intracellular traffic and fate of RNA is highly organized by ribonucleoprotein complexes and small non-coding RNAs. As relative newcomers on this scene, miRNAs are small non-coding RNAs (~22 nucleotides) that post- transcriptionally modulate gene expression by either repressing translation or inducing degradation of mRNA. MiRNAs are abundant in the human brain and display a diverse range of regulatory functions in the central nervous system (CNS). One role emerging for miRNAs is in the cellular response to stress. These molecules and their extensive gene networks provide a mechanism to both drive important developmental initiatives and maintain system homeostasis. This later feature, in particular, comes to the fore at times of environmental adversity and may be modifying the system dynamics to provide the most appropriate conditions to buffer against cellular crisis.

The activation of the stress response by the CNS is necessary to maintain health and homeostasis, however, there are also consequences as these mechanisms can induce significant changes in neural structure and function that lead to the development of a broad range of psychopathology. One of the manifestations of this response is stress-induced neuronal atrophy (dendritic retraction) in key brain regions implicated in "depressive illness" (Christian et al., 2011; Cook and Wellman, 2004). Environmental stressors may be physiological, such as through exposure to toxins, pathogens, or nutrient deprivation; or psychological, occurring when we face a situation deemed to exceed our potential for coping. Both types of stress produce physiological and psychological responses, such as elevated blood pressure, elevated corticosteroids and deficits in sustained attention (reviewed by Evans and Cohen, 1987).

In particular, exposure to environmental stressors can bring about changes in expression of genes involved in the modulation of miRNA expression, as well as changes in expression of miRNA involved in the development and function of the CNS (Conaco et al., 2006; Uchida et al., 2010; Wiesen and Tomasi, 2009). This may be reflected in changes to the brain observed following stress exposure such as region-specific increases in microglia (Tynan et al., 2010); microglial and glutamatergic pyramidal neuron activation (Hinwood et al., 2011a,b; Tynan et al., 2010); dendritic retraction (Brown et al., 2005; Christian et al., 2011; Cook and Wellman, 2004; Martin and Wellman, 2011) and cognitive deficits (Hinwood et al., 2011a,b; Wei et al., 2007). Indeed, changes in miRNA expression levels are linked to neurodegeneration (reviewed by Nelson et al. (2008)), with recent evidence supporting a role for the dysregulation of miRNA expression in psychiatric and neurological disorders (Beveridge and Cairns, 2012; Geaghan and Cairns, 2014; Miller and Wahlestedt, 2010).

2. MiRNA biogenesis and function

MiRNA biogenesis is a two-compartment process (Fig. 1) beginning in the nucleus, with the transcription of primary (pri-) miRNAs by RNA polymerase II (pol II). The pri-miRNAs are 5′ capped and poly-adenylated, can be several kilobases long and may comprise of one (monocistronic) or several (polycistronic) miRNA precursors (Lee et al., 2002). The stem- loop (hairpin) structure is recognized by DGCR8 (DiGeorge syndrome critical region gene 8), which then docks with the RNase-III enzyme Drosha to form what is known as the Microprocessor complex (Gregory et al., 2006). Upon guidance by DGCR8, Drosha cleaves the stems to release the precursor (pre-) miRNA, hairpins of ~70 nucleotides with a two-nucleotide overhang at the 3′ end and 3′ hydroxyl and 5′ phosphate groups (Han et al., 2004; Lee et al., 2003, 2002). Pre-miRNAs are transferred to the cytoplasm by exportin-5 where they are further cleaved by Dicer, another RNase-III family member, to yield the mature, double-stranded duplex (~18-25 nucleotides), consisting of the antisense, or guide strand (miRNA) and a sense, or passenger strand (Lee et al., 2002; Yi et al., 2003). The guide strand becomes integrated with proteins from the Argonaut (Ago) family to form the RNA-Induced Silencing Complex, or RISC (Gregory et al., 2005; Preall et al., 2006; Siomi and Siomi, 2009). As either strand can be incorporated into the RISC, miRNA derived from the 5′ arm or 3′ arm of the precursor are denoted by a -5p or -3p postscript respectively (Alexiou et al., 2010). The miRNA 'activated' RISC then

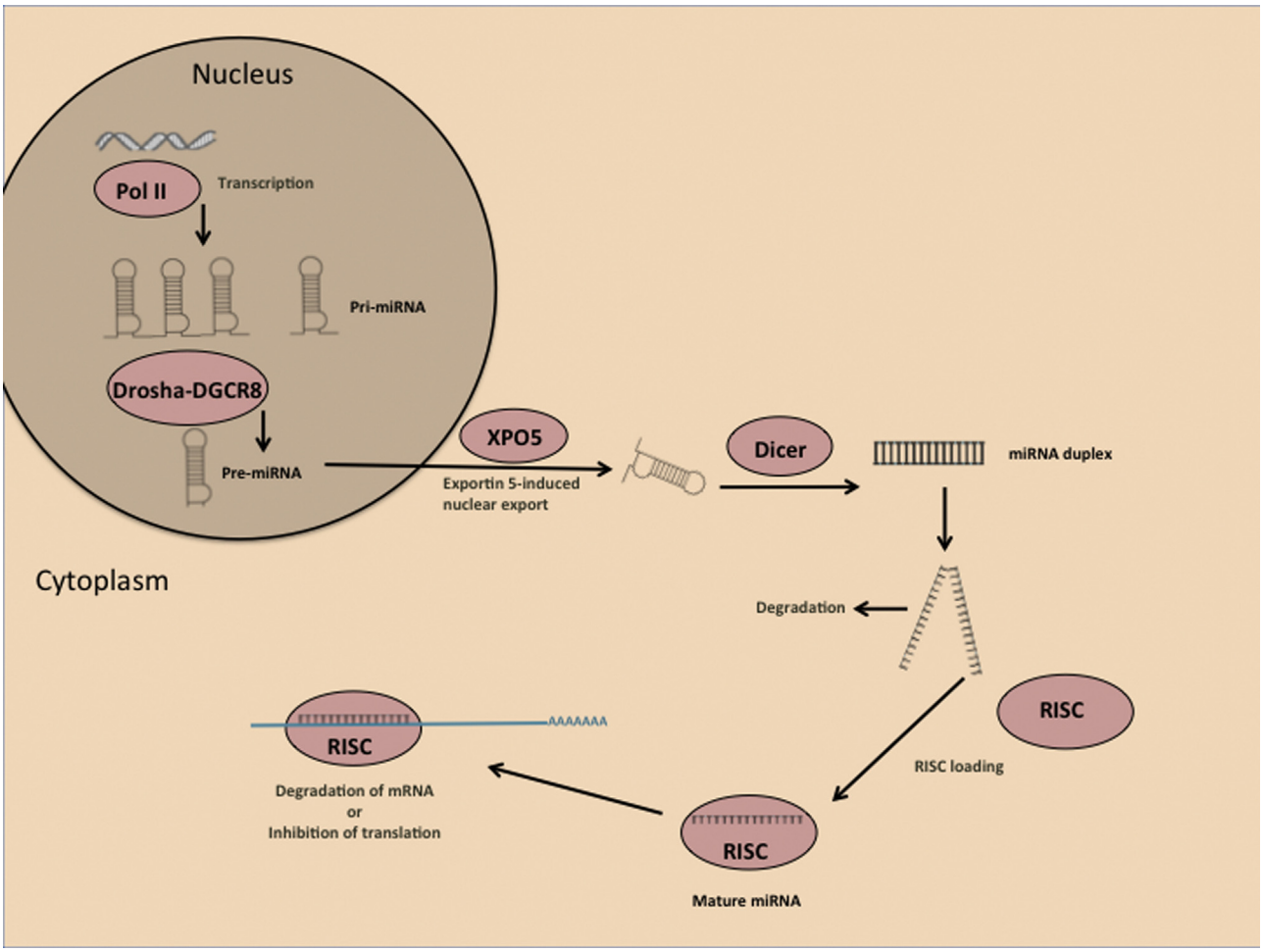

Fig. 1. MicroRNA biogenesis In the nucleus, pri-miRNAs are transcribed by RNA polymerase II (Pol II), and may comprise of one (monocistronic) or several (polycistronic) 5′ capped and poly-adenylated miRNA precursors (hairpin loop structures). Following transcription, the pri-miRNA stem-loop structure is cleaved by the DROSHA-DGCR8 microprocessor complex to release the pre-miRNA, which is then transferred to the cytoplasm by exportin 5 (XPO5). The pre-miRNA is then cleaved by Dicer to yield the mature, double-stranded miRNA duplex. Following degradation of the passenger strand, the guide strand is incorporated into the miRNA-containing RNA-induced silencing complex. Abbreviations: miRISC, miRNA-containing RNA-induced silencing complex; NPC, nuclear pore complex; pri-miRNA, primary transcript miRNA; pre-miRNA, precursor miRNA.

interacts *via* Watson-Crick pairing with the 3′-untranslated region (UTR) of target mRNAs primarily through its 5′ seed region (positions 2–8). miRISC binding to the target's miRNA recognition element (MRE) leads to destabilisation and degradation in the cytoplasmic processing bodies, or translational repression (inhibition of protein synthesis) in other cytoplasmic sites and ribonucleoprotein granules (Goldie and Cairns, 2012). Although rare in animals, perfectly matched target sequences are destroyed directly through AGO2 mediated cleavage.

Both *in vivo* and *in vitro* stress models provide evidence for the altered expression of miRNA biogenesis genes in response to stress. Protein levels of dicer were reduced following *in vitro* culturing with the ds-RNA viral mimic polyinosinic-polycytidylic acid (poly I:C) and Interferon alpha (INF-α) (Wiesen and Tomasi, 2009). Similarly, animal models of stress have demonstrated a decrease in protein levels of the transcription factor REST (Repressor element-1 silencing transcription factor) (Conaco et al., 2006; Uchida et al., 2010), responsible for regulating the expression both pre- and mature neural miRNA involved in prominent neuronal functions such as brain development and plasticity (Conaco et al., 2006; Uchida et al., 2010). Conversely, mice housed under environmental enrichment conditions demonstrated increased levels of Dicer and Ago2 combined with reduced anxiety-like behavior (Durairaj and Koilmani, 2014). Stress resilient mice have also been shown to display β-catenin-associated Dicer upregulation (Dias et al., 2014).

MiRNAs are abundant in the human brain, having many diverse and important roles in the development and function of the CNS, including: neurogenesis (Maiorano and Mallamaci, 2009), migration, differentiation/specification, (Sempere et al., 2004), regulation of morphogenesis (Giraldez et al., 2005), axonogenesis, synaptogenesis dendritic spine development (Schratt et al., 2006) and myelination (Dugas et al., 2010). There are over 1800 human miRNAs listed in the miRNA database (miRBase Release 21.0) and collectively miRNA may regulate at least two-thirds of the transcriptome. By affecting gene regulation, miRNAs are likely to be involved in most biological processes, with small changes in miRNA expression being able to fine-tune the expression of multiple genes within a biological network.

While the majority of miRNA sequences are conserved, a large percentage of known miRNA are unique to primates, with many unique to humans. These miRNA are thought to play a significant role in evolution and phenotypic variation between species. For these more recently emerged miRNA, the lack of sequence conservation for these molecules and their recognition sites in the 3′UTR of target genes, beyond primates, means there are significant implications for studies using non-primate animal

models. Where this is the case, it becomes more of a necessity to use bioinformatics, cell model systems and perhaps in some circumstance primate models.

3. MiRNA and the stress response

When stress occurs, these small but influential molecules are ideally positioned to optimize stress responses through dynamic modulation of gene expression *via* rapid and reversible responses. However, regulation of the stress response requires a concerted effort by numerous miRNA, including miRNA clusters and families, and although initially a protective mechanism, stress-induced alterations in miRNA expression are linked to neurodegeneration and the pathogenesis of neurodegenerative diseases.

The complexity of miRNA function requires identification of the many genes that each miRNA targets and an understanding of the context-specific factors that determine when and how these genes are regulated. miRNA are able to regulate target genes directly through interactions with both conserved and non-conserved target recognition elements, which can lead to both a decrease and increase in transcript abundance (Carroll et al., 2013, 2012). The complexity of regulatory mechanisms involved in target recognition makes elucidation of the actual impact of individual miRNAs very difficult. In addition, there are other factors that can affect an individual's response to stress. For example, copy number variations (CNVs) are associated with altered expression of multiple genes and pathways and impact on miRNA-mediated post-transcription regulatory networks, leading to an individual difference in disease susceptibility (reviewed (Persengiev et al., 2013)). Likewise, single-nucleotide polymorphism (SNP) interference with miRNA functions affects the expression of corresponding targets, modifies brain functions and induces a risk of disease. A recent study demonstrated that SNPs in miRNA-binding regions of AChE could lead to alterations in downstream effects, increasing inherited risks of anxiety and hypertension. Carriers of the rs17228616 SNP minor allele, which impairs the primate-specific regulation of AChE by miR- 608, show 60% higher brain AChE activity compared with carriers of the major allele (Hanin et al., 2014).

In addition, other factors such as ethnicity (Huang et al., 2011), gender and age (Ziats and Rennert, 2013), can all influence miRNA levels and therefore and individuals response to stress. Sex- biased differences in microRNA expression have been found to influence disease pathogenesis (Sharma and Eghbali, 2014) and miRNA profiling has shown significant alterations in the expression levels of miRNA during aging. One of the most consistently observed declines encountered during aging is stress attenuation: the robustness of the response to stress is diminished in aged animals. Therefore, the expression of miRNA needs to be balanced at the proper threshold levels, allowing the avoidance of stress attenuation (reviewed (Liang et al., 2009; Persengiev et al., 2013)). It is therefore highly likely that all of these factors would have a prominent role in an individual's response to stress.

Furthermore, due to the complexity of miRNA–target interactions, miRNA can affect an individual's response to stress and consequently their risk of inherited disease and disorders that may occur due to an aberrant stress response. Therefore, the importance of genome information to human health and wellbeing cannot be undervalued. Importantly, not only can miRNA be used as biomarkers of disease, they are also now being recognized as a promising therapeutic tool (Campbell and Booth, 2014; Gebert et al., 2014; Scott et al., 2015), with the potential to yield a novel class of therapeutics.

4. MiRNA expression associated with acute stress

miRNAs are ideally positioned to coordinate the genomic response to stress. These molecules have the ability to ensure adaptation to environmental perturbations *via* rapid and reversible responses. Emerging evidence in a number of model systems show that miRNA are involved in the stress response (Supplementary Table 1), with stress-induced modulation of miRNA expression and changes in target gene expression affecting cytokine production, receptor density, inflammation, neurotransmission and plasticity. Additionally, exposure to environmental stressors has been demonstrated to modulate the expression of both miRNA and their biogenic machinery (Leung and Sharp, 2010; Meerson et al., 2010; Mor et al., 2011; Uchida et al., 2008; Vasudevan et al., 2007; Wiesen and Tomasi, 2009), capable of inducing long-lasting behavioral adaption. This is supported by evidence suggesting that miRNA modify experience-dependent neuronal plasticity, through both short-term changes in neural transmission and gene regulation, and long-term changes that lead to structural modifications.

4.1. Psychological stress

Stress-induced alterations in miRNA expression can be region-specific (Babenko et al., 2012; Rinaldi et al., 2010), with exposure to stress affecting neural activity in different brain areas. For example, let-7a, miR-9 and miR-26a/b had increased expression in the frontal cortex, but not the hippocampus, of 10–12 week-old male mice following acute restraint stress (Rinaldi et al., 2010). Similarly, using a chronic stress/recovery paradigm, Babenko et al. (2012) found that exposure of adult male rats to two weeks of mild restraint stress significantly downregulated miR-709 in the cerebellum but not in the hippocampus or prefrontal cortex (PFC). Alterations in expression of miR-709 in the cerebellum were resistant to two-week long recovery from stress, however, in the hippocampus and PFC, its expression was upregulated after two weeks of recovery.

It is possible that changes in miRNA expression upon exposure to environmental stressors may lead to altered neuronal morphology and problems with neural circuitry. In a study by Meerson et al. (2010), adult male rats subjected to both acute and chronic immobilisation stress showed altered expression of numerous miRNAs in two stress-responsive regions of the rat brain, the hippocampal CA1 region and the central nucleus of the amygdala. These miRNA have established brain or stress-related functions, including miR-134, miR-17-5p and miR-124, involved in the regulation of dendritic spine development and control of neuronal development and differentiation (Beveridge et al., 2009; Schratt et al., 2006; Yu et al., 2008), and miR-1, miR-132 and miR-182, shown previously to be associated with stress (Shaked et al., 2009; Simon et al., 2009). Importantly, miR-182 has been demonstrated to regulate amygdala-dependent memory formation (Griggs et al., 2013), while the miR-134 observation is especially noteworthy as this molecule has a prominent role in synaptic plasticity and long-term memory formation (Gao et al., 2010) and has altered expression in schizophrenia (Gardiner et al., 2012; Santarelli et al., 2011).

These animal models evoke emotional states related to fear and anxiety, inducing anxiogenic-like effects in animals similar to those observed in humans, with studies suggesting that this may contribute fundamentally to the development and pathogenesis of several psychiatric disorders, including mood disorders, schizophrenia, and anxiety. For a detailed review on animal stress models, see (Campos et al., 2013).

4.2. Physiological stress

4.2.1. Environmental pathogens

Exposure to environmental pathogens such as bacterial and viral infections can alter miRNA expression, prompting an immune response. Bacterial infections can induce the release of inflammatory cytokines and the production of corticosteroids (glucocorticoids (GC)) from the hypothalamic- pituitary-adrenal (HPA) axis, while viral infections can elevate systemic GC levels (Belkaya et al., 2011). Murine glial cells cultured with the bacterial endotoxin lipopolysaccharide (LPS) showed altered expression of miR-351, miR-298, miR-146, miR-147 and miR-155 (Mor et al., 2011; Ponomarev et al., 2010). These miRNA are involved in neuronal differentiation (Cheng et al., 2009; Maiorano and Mallamaci, 2009; Yu et al., 2008) and in the regulation of inflammatory pathways (Liu et al., 2009; O'Connell et al., 2007; Sonkoly et al., 2008; Taganov et al., 2006). Altered expression of these miRNA are associated with neuropsychiatric disorders, including schizophrenia (Gardiner et al., 2012; Hebert et al., 2008; Lee et al., 2011; Lehmann et al., 2012; Lukiw et al., 2008; Schipper et al., 2007). Similarly, mice exposed to Japanese encephalitis virus (JEV), a single-stranded, positive-sense RNA virus that causes Japanese encephalitis, displayed a time-dependent increase in miR-155 expression. Correspondingly, expression of miR-155 was also increased in JEV-infected human brain samples when compared to the uninfected control (Thounaojam et al., 2014).

4.2.2. Cellular stressors

MiRNA levels have also been shown to be regulated by a variety of cellular stressors such as oxidative stress, hypoxia, cold stress, and nutrient deprivation (Hudder and Novak, 2008). For example, hypoxic-ischemic brain injury in rats significantly altered the expression of miRNA, including mir-429, mir-200b, and mir-182 (Cui and Yang, 2013) and significantly decreased miR-30a in mouse cortical neurons (Wang et al., 2015). Glucose deprivation in human glioblastoma cells led to a marked reduction in miR-451 levels. Down-stream effects included the phosphorylation and activation of AMPK and MARKs, leading to reduced cell proliferation; stress responses leading to adaptation and cell survival; and increased cell migration (Godlewski et al., 2010).

Sangiao-Alvarellos et al. (2014) demonstrated changes in hypothalamic miRNA expression profiles in rats reared with a high-fat diet (HFD), and caloric restriction (CR) during 3 months after weaning. A HFD increased the expression of let-7a, mir-9, mir-30b, mir-100a, and mir-145 while CR increased the expression of mir-29a, mir-30e, mir-323-3p, and mir-374-5p, and decreased the expression of mir-200a, mir-200b, and mir-200c. Furthermore, mir-132, mir-218, and mir-539 showed increased expression with either HFD or CR. Interestingly, they found a prominent effect on miRNA families in response to nutritional challenge, including the mir-30 family, the mir-200 family and the let-7 family.

4.2.3. Environmental chemicals

In humans, exposure to environmental chemicals is well known to increase risks for various diseases and induce alterations in the expression of many miRNA (Hou et al., 2011). These effects are also observed in in vitro and animal models. For example, human astroglial cells exposed to combined iron plus aluminum-sulfate significantly upregulated miRNA-125b and miRNA-146a expression, as well as reactive oxygen species (ROS) abundance and NF-κB-DNA binding (Pogue et al., 2013). In the mouse brain, exposure to hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), a common environmental contaminant, altered the expression of more than 100 miRNAs, including: let-7; miR-10b; miR-125a,b; miR-128; miR-146b; miR-15a; miR-16, miR- 181a,b,d; miR-183; miR-191; miR-195; miR-199a; miR-200a,b,c; miR-218; miR-222; miR-26b; and miR-98 (Zhang and Pan, 2009). Let-7 and mir-98 are involved in neuronal differentiation (Beveridge et al., 2009; Roush and Slack, 2008) and associated with the inflammatory response (Garbuzov and Tatar, 2010); miR-146 is involved in the immune response (Sonkoly et al., 2008; Meerson et al., 2010); miR-15 has a role in neural processes and is associates with schizophrenia (Beveridge et al., 2010) while miRs-200a, -200b and -200c have prominent neuronal functions and are associated with the pathogenesis of psychiatric disorders. Similarly, lead, another widespread heavy metal contaminant in the environment, is a significant neurotoxicant with exposure leading to altered neuronal development and cognitive deficits including learning and memory. Lead exposure has also recently been associated with schizophrenia (Guilarte et al., 2012). Specifically, male rats exposed to lead for eight weeks in their drinking water displayed impairments in spatial memory and altered hippocampal miRNA expression. These miRNA included miR-204, miR-211, miR-448, miR-449a, miR-494, miR-34b, and miR-34c, with pathway analysis predicting these miRNA to be highly associated with neural injury and neurodegeration, axon and synapse function, and neural development and regeneration (An et al., 2014).

4.2.4. Drugs of abuse

Substance abuse is widespread with around 15% of the population using illicit drugs (Australian Institute of Health and Welfare 2011, 2011). Exposure to drugs of abuse (such as cannabis, cocaine, heroin and amphetamines) can lead to altered synaptic plasticity and subsequent changes in behavior and psychological function, such as learning and memory. This may occur through alterations in miRNA, for example, dynamic changes in miRNA expression were observed in rat hippocampus following repeated cocaine exposure and subsequent abstinence from cocaine treatment, including miR-133b, miR-134, miR-181c, miR-191, miR-22, miR-26b, miR-382, miR-409-3p and miR-504 (Chen et al., 2013). MiR-134 has a role in cholinergic neurotransmission (Meerson et al., 2010), dendritic spine development (Schratt et al., 2006) and hippocampal synaptic plasticity, long-term memory formation (Gao et al., 2010). Similarly, rat primary hippocampal neuron cultures and mouse hippocampi treated with the synthetic opioid fentanyl resulted in the downregulation of miR-190 with possible down-stream effects on neurogenesis and neuropathology (Zheng et al., 2010).

Exposure to cannabinoid compounds, particularly during adolescence, can induce long lasting changes in in both cognitive and emotional behaviors (Pope et al., 2003; Trezza et al., 2012). Cannabis exposure in healthy individuals is associated with: decreased adult hippocampal neurogenesis; increased stress responsivity (Lee et al., 2014); altered white matter microstructure (Baker et al., 2013; Bava et al., 2009); increased dopamine neurotransmission (Bossong et al., 2009); increased plasma cortisol levels and impaired working memory (D'souza et al., 2004); and increased risk for psychotic disorder (Boucher et al., 2010; D'souza et al., 2004; Henquet et al., 2005; Long et al., 2010; Moore et al., 2007). In our recent study (Hollins et al., 2014) we showed that rats exposed to the synthetic cannabinoid HU210 during early adolescence displayed altered miRNA expression during late adolescence (miR-23a-5p, miR-98, miR-340-3p, miR-374, miR-300 -5p, miR-382-3p and miR-499). MiR-23 has been associated with autism spectrum disorders (Geaghan and Cairns, 2014), miRs-23a and -98 play a role in stress- induced Fas/FasL-mediated apoptosis, critical to the development and homeostasis of the immune system (Singh et al., 2012; Wang et al., 2011a,b), and miR-340 is involved in pro-inflammatory immune responses (Guerau-de-Arellano et al., 2012). It is possible that the miRNA response to exogenous cannabinoid exposure may work to suppress stress-induced inflammation by exerting immunosuppressive effects *via* miRNA regulation of inflammatory targets (D'Addario

et al., 2013). Interestingly, when administered following in utero infection, the number of miRNAs with altered expression was increased, suggesting that an interaction of environmental insults may enhance the miRNA response to stress (see Section 5.2).

5. MiRNA expression associated with prenatal stress

The developing brain is highly plastic and particularly sensitive to environmental insults (reviewed (Dudley et al., 2011; Rice and Barone, 2000)). Exposure to environmental stressors during this critical period is known to lead to altered neurodevelopmental processes resulting in differences in the adult brain, such as altered neuronal morphology and problems with neural circuitry, that may manifest as neuropsychiatric disorders (Dorph-Petersen et al., 2007; Jakob and Beckmann, 1986; Schultz et al., 2011). Epidemiological research suggests an association between gestational stress and increased vulnerability in offspring to stress-related psychopathological conditions (Khashan et al., 2008; Malaspina et al., 2008). This includes nutrient deprivation, particularly deficiency in folate and vitamins A and D; oxidative stress through smoking; preterm birth or obstetric complications; recreational drug exposure or fetal alcohol syndrome; in utero infection; and psychosocial stress experienced by the mother and associated GC exposure. Environment-genome interactions, therefore, are vital in understanding how environmental risk factors can influence the genome and subsequent neurodevelopmental processes.

Development of the mammalian brain is a highly controlled process (Rice and Barone, 2000) requiring precise temporal and spatial regulation of gene expression (Abramova et al., 2005; Stead et al., 2006). By regulating mRNAs post- transcriptional fate, miRNA play a significant role in organising complex patterns of gene activity. These small RNA molecules display distinct expression profiles (Miska et al., 2004; Smirnova et al., 2005; Smith et al., 2010), and exhibit both temporal and spatial specificity that help to curate and buffer transcriptional output during development (Kapsimali et al., 2007; Krichevsky et al., 2003; Miska et al., 2004; Mukhopadhyay et al., 2011). Recent evidence suggests that these molecules are both responsive and susceptible to developmentally significant environmental insults.

5.1. Maternal anxiety

There is increasing evidence that maternal anxiety is a key risk factor for neurodevelopmental disorders. Complex interactions between the maternal environment and the developing fetus can result in alterations in prenatal programing associated with psychiatric disorders such as schizophrenia. Stressful life events that induce maternal anxiety, such as unwanted pregnancy, death of a spouse or relative, war or natural disaster, are associated with poorer memory and attention skills (Plamondon et al., 2014) as well as an increased risk of schizophrenia in the offspring (reviewed (Brown, 2011)). Correspondingly, there is vast experimental evidence in animal models that maternal stress can induce permanent alterations in fetal neurodevelopment and subsequent offspring behavior (reviewed (Huizink et al., 2004; Ulupinar, 2009)). These changes in offspring can persist into young adulthood and include: altered microglial development, microglial differentiation and number (Gómez-González and Escobar, 2010); impaired hippocampal neurogenesis (Fujioka et al., 2006); impaired hippocampal-dependent spatial memory and hippocampal NMDA receptor-mediated synaptic plasticity (Son et al., 2006); impaired HPA axis activity (Barbazanges et al., 1996); altered HPA axis stress responsiveness and anxious behavior (Brunton and Russell, 2010); and altered responses to stressful situations (Fride et al., 1986)

Recently, Zucchi et al. (2013) (carried out experiments in an animal model which suggested miRNA expression is altered in offspring following maternal exposure to psychological stress. Two stressors, restraint of the body and forced swimming, were applied to pregnant rats daily from gestational days 12–18, and miRNA expression examined in whole brain of newborn offspring. A total of 336 miRNA were identified as differentially expressed in response to gestational stress, including the upregulation of miR-103, miR-323, miR-98, miR-219 and the downregulation of miR-145 as well as genes involved in development, axonal guidance and neuropathology. Interestingly, miR-323 and miR-98 are associated with the inflammatory response while miR-145 is a marker of the inflammatory disorder multiple sclerosis (Guerau-de-Arellano et al., 2012) and is associated with bipolar disorder (Kim et al., 2010). The miR-219 observation is particularly interesting as this molecule is elevated in schizophrenia (Beveridge et al., 2010) and has been demonstrated to target genes associated with both schizophrenia and bipolar disorder including synaptotagmin V, netrin, and serine hydroxymethyltransferase (Coyle, 2009). This miRNA has also been shown to modulate excitatory synaptic plasticity through N-methyl-D-aspartate (NMDA) glutamate receptors (Kocerha et al., 2009; Wibrand et al., 2010), with a disruption of NMDA receptor signaling demonstrated to reduce levels of miR-219, inducing aberrant behavior in mice (Kocerha et al., 2009). Interestingly, the NMDA-hypofunction model of schizophrenia suggests that the disorder is associated with a loss of NMDA receptors (Kehrer et al., 2008). A substantial decrease in NMDA receptor subunits in synapses of the hippocampus, along with significant reductions in NMDA receptor-mediated long-term potentiation, has been observed in maternally stressed offspring in adulthood. Furthermore, both spatial learning and memory were found to be significantly impaired (Son et al., 2006). Together, these observations suggest that maternal stress may modify the expression of miR-219 in offspring, and thus alter neurodevelopmental plasticity, inducing neurobehavioral dysfunction and possibly neuropsychosis.

5.2. Maternal immune activation

It is not well understood how maternal infection produces abnormalities in offspring, however recent studies suggest that it may be the maternal response to infection that plays a large role in determining the responses of the offspring (Bronson et al., 2011; Fatemi et al., 2011; Smith et al., 2007). Experimental evidence in animal models indicates that following stress, the maternal immune response, or maternal immune activation (MIA), results in increased plasma corticosterone levels in pregnant dams. This, along with increased maternal cytokine levels, are predicted to mediate both the behavioral and transcriptional changes in offspring following maternal infection and play a causal role in the development of neuropathological conditions (Fatemi et al., 2011; Smith et al., 2007). Evidence in animal models indicates that maternal infection can induce long-lasting abnormalities in the offspring including: impaired neuronal differentiation and hippocampal neurogenesis (Cui et al., 2009; Meyer et al., 2006); impairments in hippocampal synaptic function, hippocampal synaptic protein expression and short- and long-term plasticity (Oh-Nishi et al., 2010); altered neural gene expression (Fatemi et al., 2011; Smith et al., 2007); altered expression of genes involved in the maturation of midbrain DA neurons and modulated fetal dopaminergic development (Meyer et al., 2008). In addition, infection in utero can lead to: increased vulnerability to stress in adulthood (Fride et al., 1986); changes in offspring response to drugs acting on dopaminergic and glutamatergic neurotransmitter systems (Vorhees et al., 2015, 2012); increase the risk for relapse to drug dependence (Richtand et al., 2012); and abnormalities in

offspring behaviors similar to those seen in subjects with schizophrenia (Smith et al., 2007; Wischhof et al., 2014; Wolff and Bilkey, 2010, 2008).

Not surprisingly, MIA has been documented to be strongly associated with an increased risk of offspring developing schizophrenia (Brown and Derkits, 2010; Brown, 2012; Ellman et al., 2010). However, studies suggest that multiple factors are likely to be involved in the aetiology of neuropsychiatric disorders, where early developmental disturbances enhance susceptibility to neurological disorders, and the activation or amplification of symptoms occur only after a pathological response to a secondary factor (Bayer et al., 1999; Maynard et al., 2001). To further understand the role of miRNA in this process, we recently examined the effects of MIA alone, and in combination with, adolescent cannabis exposure on miRNA expression in the rat entorhinal cortex (EC) (Hollins et al., 2014). Pregnant rats received an intravenous injection of poly I:C or vehicle on gestational day (GD) 15 and beginning post-natal day (PND) 35, select male offspring were treated daily with the synthetic cannabinoid HU210, or vehicle, for 14 days. MiRNA expression was examined at late adolescence (PND 55). We found that prenatal poly I:C caused significant alterations in miRNA expression in the left hemisphere of the EC, an effect that was strengthened by exposure to HU210 during adolescence, with 72 miRNA found to have significantly altered expression levels ($p < 0.05$). A large subgroup consisting of 20 miRNA was identified as being transcribed from a single imprinted locus within the Dlk1-Dio3 domain in a cluster of differentially expressed miRNAs on chromosome 6q32 (human 14q32/mouse 12qF1). It is possible that because of their involvement in brain development and dendritic re-modeling, these miRNAs may be involved in an adaptive response, altering neural circuitry associated with environmental stressors. The role of miRNA clusters in the stress response is discussed in further detail in Section 8.

5.3. Fetal alcohol syndrome

Heavy alcohol consumption during pregnancy can result in the development of Fetal Alcohol Syndrome (FAS), characterized by a range of physical and mental defects in the fetus. The main effect of FAS is permanent and irreversible damage to the CNS, in particular, neuronal damage and structural abnormalities in the brain. Phenotypes commonly associated with FAS include poor growth, facial defects, cognitive impairment and behavioral problems. Recent studies show a role for miRNA in the fetal response to alcohol in utero. Using a murine model, Wang et al. (2009) determined that prenatal ethanol exposure significantly altered expression of miRNA in fetal brain, including the upregulation of miR-10a, miR-10b, miR-9, miR-145, miR-30a-3p and miR-152, and downregulation of miR-200a, miR-496, miR-296, miR-30e-5p, miR-362, miR-339, miR-29c and miR-154. In addition, they observed that ethanol treatment also caused birth defects such as intrauterine growth retardation, craniofacial dysmorphology and brain abnormality, with offspring demonstrating intellectual disabilities. Using a similar model, Laufer et al. (2013) demonstrated global changes in miRNA expression in the adult brain of offspring in response to both voluntary chronic ethanol exposure and binge injections. In addition, the miRNAs that were affected were specific to the developmental timing of alcohol treatment. Interestingly, a large proportion were part of large miRNA clusters encoded within three brain-specific imprinted regions of the mouse genome. These clusters, Snrpn- Ube3a (Human 15q11–q13/Murine 7qC) and Dlk1-Dio3 (Human 14q32/Rat 6q32/Murine 12qF1) and rodent specific Sfmbt2 (Murine 2qA1) are associated with processes involved in neuronal plasticity and several neurodevelopmental disorders. The Dlk1-Dio3 locus in particular is discussed in further detail in Section 8.

5.4. Transgenerational effects of stress modulated by miRNA

While significant offspring abnormalities are evident following maternal stress, it is now evident that these effects may be passed on to future generations. For example, exposure in utero to the pesticide vinclozolin induces distinct transgenerational changes in the brain transcriptome of F3 generation male animals that correlated with alterations in behavior. Altered genes were found to be relevant to behavior and neuropsychiatric disorders (Skinner et al., 2008), suggesting a transgenerational role for miRNA in regulating the genome. Indeed, this was shown to be the case in a recent study by Yao et al. (2014), who provided evidence of transgenerational epigenetic inheritance. In the study, pregnant rats were stressed daily from GD 12 to GD 18 (a period thought to cover a large extent of the human second trimester) by restraint and forced swimming. Delayed developmental milestones were observed in the F1 generation offspring, with an even stronger impact in subsequent F2 and F3 generations. The multi-generational stress was found to induce drastic changes in neural miRNA of the F2 generation. The altered miRNA, miR-23b, miR-96, miR-141, miR-182, miR-183, miR-200a, miR-200b, miR-200c, miR-429 and miR-451, have prominent neuronal functions and are associated with the pathogenesis of psychiatric disorders. In particular, miR-182 has been demonstrated to regulate amygdala-dependent memory formation (Griggs et al., 2013). In addition, the expression of genes targeted by these miRNA was also altered, including transcription regulators and mediators of neuropsychiatric disorders. These changes were accompanied by reduced gestational length, an increase in blood glucose levels and delayed behavioral development. Strikingly, it was the F3 offspring of transgenerationally stressed mothers that exhibited the greatest impact of prenatal stress, displaying low body weight, reduced growth trajectories and delayed behavioral development. These findings suggest a genuine role for the epigenetic inheritance for the stress response through transgenerational programing of the female germline.

Importantly, a recent study has shown that it is not only maternal stress that can affect offspring. In a study by Rodgers et al. (2013), male mice were exposed to six weeks of chronic variable stress before breeding. Offspring of the paternally stressed mice exhibited a significantly blunted HPA stress axis response and global gene pattern changes in transcription. Gene set enrichment analyses identified increased expression of GC-responsive genes within the PVN of the hypothalamus, consistent with altered offspring stress responsivity. To uncover potential epigenetic mechanisms of transmission, they examined miRNA expression in the paternal sperm and identified nine miRNA as significantly increased (miRs-29c, -30a, -30c, -32, -193-5p, -204, -375, -532-3p, -698). These miRNA are predicted to target DNMT3a, a DNA methyltransferase that is required for genome-wide de novo methylation and is essential for the establishment of DNA methylation patterns during development. In a follow-up study to confirm causality of these miRNA changes in offspring neurodevelopmental programing, these nine miRNA in the sire's sperm were identified as a potential mechanism of epigenetic transmission. Specifically, following micro- injections of these nine miRNA into single-cell zygotes, both male and female offspring mounted a significantly blunted corticosterone response to an acute restraint stress as adults (Rodgers et al., 2015). Together, these findings indicate that environmental factors, such as prenatal stress, can cause transgenerational transmission of miRNA that modify epigenetic profiles and offspring behavior associated with

neuropathologies and may provide a functional link to adult- onset complex psychiatric and neurological disease pathogenesis.

6. MiRNA regulation of the stress response *via* the immune system

While numerous studies demonstrate stress-induced dysregulation of miRNA expression, understanding the role miRNAs play in the regulation of stress- induced neuronal plasticity is of paramount importance. MiRNAs are involved in the regulation of innate immune responses (Sonkoly et al., 2008) and emerging evidence now indicates a role for miRNA in regulating stress-induced responses *via* the immune system. Dysregulation of the immune system represents an important vulnerability factor for psychosis, with inflammation a recognized precursor for neuropathology (reviewed (Bergink et al., 2014)). In the mammalian brain, activation of the inflammatory response system primarily occurs due to the activation of glial cells (astrocytes and microglia) (Tyagi et al., 2010a). Astrocytes are the most abundant glial cells in the CNS, providing support by maintaining homeostasis and by regulating neuronal signaling, survival and synaptic plasticity (Mor et al., 2011). Microglia, macrophage-like cells resident within the CNS, sense changes in the brain's microenvironment and accordingly act as the predominant form of active immune defence. In response to inflammatory or other pathological conditions, astrocytes and microglia leave their quiescent state and become activated, releasing pro-inflammatory cytokines to activate immune cells throughout the brain (Monji et al., 2009; Mor et al., 2011). In fact, acute psychological stress has long been known to stimulate production of a plethora of cytokines (Kaufer and Soreq, 1999).

Glial cells play an important role in modulating the stress response (Röhl et al., 2010), with exposure to stress demonstrated to induce microglial activation (Hinwood et al., 2011a,b; Tynan et al., 2010) and region-specific increases in microglial number (Tynan et al., 2010). Gestational stress in animal models results in offspring with accelerated microglial development, enhanced microglial differentiation and increased microglial number in the post-natal brain (Gómez-González and Escobar, 2010).

Microglial activation is a recognized precursor of pathology in the CNS (reviewed (Carson et al., 2007)) and neuroinflammation is associated with both neurological and neurodegenerative diseases (Doorduin et al., 2009; Halleskog et al., 2011; Willard et al., 1999). During gestation/early life, the activation of microglia by infection or other environmental stressors can adversely affect processes central for normal neuronal development, thereby setting the stage for vulnerability for later psychotic disorders (reviewed (Bergink et al., 2014; Meyer, 2011)). Later life exposure to an environmental stressor could further activate microglia, leading to functional abnormalities in neuronal circuitry and psychosis. In addition, alterations in both the neural and immune systems play a role in the pathophysiology of chronic pain, which has cognitive, emotional and behavioral components. As miRNAs regulate immune and neuronal processes, it is highly likely that they too are involved, as specific miRNAs have been associated with pathological pain in rodent pain models. Evidence also suggests that miRNA may also have a role in the response to pain, and to the responsiveness and tolerance to medications (reviewed (Kress et al., 2013)).

Controlling neuroinflammation is considered a promising approach to treat neurodegenerative disorders, therefore, understanding the role of miRNA in regulating stress-induced inflammatory responses could have significant therapeutical benefits. In this section we will discuss the role of miRNA in modulating the stress response *via* three key mechanisms: TLR signaling; the cholinergic anti-inflammatory pathway; and the HPA axis. Both TLR signaling and the cholinergic anti-inflammatory pathway regulate the innate immune response (innate immunity), while the HPA axis controls reactions to the immune system and the response to stress.

6.1. TLR signaling

Activation of both microglia and astrocytes in response to foreign pathogens occurs *via* TLR signaling (Jack et al., 2005). TLRs are key pattern recognition receptors that facilitate a tailored response to environmental signals, enabling direct modulation of the immune response (Jack et al., 2005; Olson and Miller, 2004). Although innate immunity in the CNS depends primarily on the function of glial cells, especially astrocytes and microglia, there is strong evidence to suggest TLRs are also expressed on neurons, having dynamic expression levels influenced by various mediators. TLR activation leads to the induction of proinflammatory cytokines and activation of MAPK family members involved in gene transcription. In addition to its role in modulating immune responses, TLR signaling is thought to have an important role in neurogenesis, with accumulating evidence indicating a role in tissue development, cellular migration, differentiation, and repair processes (reviewed (Trudler et al., 2010)).

Over activation of TLRs has been linked to neurodegeneration and the pathogenesis of neurodegenerative diseases (Kielian, 2006; Trudler et al., 2010), therefore, this signaling pathway must be tightly regulated to maintain homoeostasis. MiRNA most likely play an important role in achieving this critical balance between immunity and pathological tissue damage. Indeed, let-7 has recently been identified as a strong activator of TLR signaling in microglia and neurons, with TLR activation by this miRNA inducing dose- and time-dependent neuronal cell death (Lehmann et al., 2012). Expression levels of several members of the let-7 family (let-7a, -7c, -7f and miR-98) have been observed following both prenatal and postnatal exposure to stress (Supplementary Table 1). In addition, a number of studies using a variety of stress paradigms have shown both temporal and spatial regulation of the TLR-induced miR-9 in the brain. This miRNA is increased: in fetal mouse brain following in utero ethanol exposure (Wang et al., 2009); in the whole brain of newborn rats following gestational stress; in the frontal cortex of ten-week old mice following acute restraint stress (Rinaldi et al., 2010); and in the medial prefrontal cortex of ten-week old rats following chronic restraint stress (Uchida et al., 2010). However, in adult rats, miR-9 expression was found to decrease in the amygdala and hippocampus following both acute and chronic restraint stress (Meerson et al., 2010).

Similarly, astrocytes cultured *in vitro* with the LPS and the cytokine interferon-gamma (IFN-γ) increased their expression of known TLR-induced miRNAs, miRs-146, -147 and -155 (Mor et al., 2011). These miRNA are demonstrated to negatively regulate the activation of inflammatory pathways by regulating TLR signaling and the ensuing cytokine response (Liu et al., 2009; O'Connell et al., 2007; Sonkoly et al., 2008; Taganov et al., 2006). In the same study, the mouse and rat-specific miRs-351 and -298, predicted to be involved in the regulation of genes involved in the tumour-necrosis factor-alpha (TNF-α) signaling pathway and the increased secretion of IL-6, had their expression downregulated (Mor et al., 2011). Expression levels of miR-298 were also decreased in the amygdala of an animal model of chronic immobilisation stress (Meerson et al., 2010).

Microglia activated by culturing *in vitro* with LPS and IFN-γ downregulated expression of miR-124, an abundant, brain-specific miRNA normally highly expressed by microglia (Ponomarev et al., 2010). This miRNA has a role in neuronal differentiation during both CNS development and adult neurogenesis (Cheng et al., 2009; Maiorano and Mallamaci, 2009; Yu et al., 2008). Altered expression

of these miRNA are associated with Alzheimer's disease (Hebert et al., 2008; Lehmann et al., 2012; Lukiw et al., 2008; Schipper et al., 2007), Huntington's disease (Lee et al., 2011) and schizophrenia (Gardiner et al., 2012). Together, these findings support the possibility of stress-induced chronic or sustained inflammatory responses inducing long-lasting alterations in miRNA expression leading to altered neuronal development.

6.2. The cholinergic anti-inflammatory pathway

Studies suggest that miRNA regulation plays a critical role in balancing cholinergic neurotransmission (Nadorp and Soreq, 2014). In the CNS, the cholinergic anti-inflammatory pathway can regulate the innate immune response, providing a braking effect by inhibiting the production of proinflammatory cytokines *via* signaling through nicotinic acetylcholine receptors (nAChRs). Interestingly, current research indicates cholinergic modulation of microglial activation through the α7 nAChR subunit (CHRNA7) expressed on microglia (Shytle et al., 2004), with the inhibition of proinflammatory cytokine production *via* signaling through CHRNA7 demonstrated to protect the brain against inflammation-induced tissue damage (Pavlov et al., 2009; Rosas-Ballina and Tracey, 2009; Tyagi et al., 2010b; Wang et al., 2003).

Innervation of the cholinergic system increases cholinergic activity, releasing acetylcholine (ACh), the principal neurotransmitter of brain cholinergic neurons, into the synaptic cleft where it binds to nAChRs on the post-synaptic membrane (Pavlov et al., 2009; Rosas-Ballina and Tracey, 2009; Tyagi et al., 2010b; Wang et al., 2003). Following the use of restraint stress, miR-1 was demonstrated to be upregulated in both the amygdala and hippocampus of adult male rats (Meerson et al., 2010). This miRNA has been shown to regulate nAChR subunit abundance as well as the expression of the transcription factor MEF-2, resulting in altered pre-synaptic ACh secretion (Simon et al., 2009). Intriguingly, MEF-2 has been shown previously to regulate the miRNA cluster imprinted on chromosome 14q32 (see also Section 8 below) (Fiore et al., 2009) and was recently shown to be directly modulated by MIA *via* major histocompatibility class I molecules, resulting in reduced cortical synapse density in offspring (Elmer et al., 2013). MEF-2 isoforms have been shown to regulate multiple aspects of synaptic development (Flavell et al., 2008) indicating a role for MEF-2 modulation of miRNA expression in modulating neuronal plasticity in response to stress.

Cholinergic neurotransmission is terminated *via* the hydrolyzation of ACh by acetylcholinesterase (AChE) (Pavlov et al., 2009; Rosas-Ballina and Tracey, 2009; Salpeter, 1967; Wang et al., 2003). In the mammalian brain, acute psychological stress induces hyperexcitation of cholinergic neurotransmission and rapid, long lasting increases in AChE gene expression. Several studies have confirmed that both the transcriptional activation and activity of AChE are altered under stress conditions, with experimental evidence supporting the notion that miRNA play a role in this process. Specifically, miR-134 and miR-183 were upregulated under conditions of acute immobilisation stress in both the amygdala and hippocampus of adult male rats, while under conditions of chronic immobilisation stress, miR-134 expression was downregulated in both brain regions and miR-183 expression remained unchanged (Meerson et al., 2010). Both miRNA were demonstrated to modulate the expression of the serine/arginine-rich splicing factor 2 (SFRS2) (Meerson et al., 2010), a pre-mRNA splicing factor that regulates the stress-induced alternative splicing of AChE mRNA in neurons (Soreq and Seidman, 2001). Following stress exposure, SFRS2 mediates long-term alternative splicing of AChE gene expression, affecting the local regulation of cholinergic neurotransmission (Meshorer et al., 2005).

The study by Meerson et al. (2010) also found increased levels of hippocampal miR-132 following chronic immobilisation stress. This miRNA has been demonstrated to directly regulate AChE activity (Meerson et al., 2010; Shaked et al., 2009) and to have significantly increased expression levels following exposure to a variety of stress paradigms. For example, Shaltiel et al. (2012) demonstrated significantly increased hippocampal miR- 132 expression levels in mice that were accompanied by a reduction in hippocampal AChE following both exposure to predator scent and foot-shock stress. Uchida et al. (2010) demonstrated that following early maternal separation, exposure of eight-week old rats to two weeks of chronic restraint stress significantly increased expression levels of both pre-miR-132 and mature miR-132 in the medial prefrontal cortex (mPFC), and that expression of miR-132 remained upregulated in the adult rat.

Collectively, these studies suggest a role for miRNA in the stress-induced regulation of the cholinergic response *via* modulation of AChE activity. Indeed, studies suggest that stress exposure can alter body–brain signaling through cell-mediated ACh hydrolysis, leading to changes in miRNA expression and a decrease in the levels of AChE, potentiating ACh signaling, and exacerbating anxiety (Meshorer and Soreq, 2006; Shaltiel et al., 2012; Soreq, 2015). As AChE has been demonstrated to enhance neurite growth and synapse development (Sternfeld et al., 1998), not surprisingly, AChE imbalances are associated with neuropathology and neurological disease (Meshorer and Soreq, 2006; Soreq and Seidman, 2001). Indeed, miR-134 has been demonstrated to regulate hippocampal synaptic plasticity, long-term memory formation (Gao et al., 2010) and dendritic spine development (Schratt et al., 2006) while miR-132 has been shown to regulate dendritic maturation, neurogenesis (Magill et al., 2010; Wayman et al., 2008) and synapse formation (Luikart et al., 2011). Overexpression of miR-132, as seen in these studies, has been demonstrated to induce an anti- inflammatory molecular expression (Luikart et al., 2011), to increase dendritic spine density and is associated with neuronal developmental abnormalities (Hansen et al., 2010). It is conceivable that stress-induced alterations in cholinergic activity *via* miRNA activity may result in chronic inflammation, leading to the cognitive impairments associated with neuropsychiatric disorders as cholinergic innervation has been demonstrated to influence spatial learning (Fish et al., 2004). Chronic neuroinflammation can have cytotoxic effects on cholinergic cells within the CNS (Willard et al., 1999) with cholinergic mechanisms thought to underlie the progressive neurodeterioration characteristic of several neurodegenerative disorders (Kaufer and Soreq, 1999).

Neuroinflammatory modulation of the cholinergic system is also thought to be a major factor in the pathophysiology of epilepsy. Unprovoked seizures affect more than 50 million people worldwide. Rodent models of epilepsy have demonstrated an association between cholinergic dysfunction and epilepsy, including upregulation of AChE, which was linked to an enhanced immune response and facilitation of the epileptogenic process (Gnatek et al., 2012). Emerging evidence suggests a role for miRNA in this process, with experimental models demonstrating a unique miRNA signature in whole blood that differed from trauma, stroke and haemorrhage, including up-regulation of miR-21, miR-34a, miR-132, miR-146a, miR-155, miR-199a and miR-375. In particular, miR-132 regulates AChE activity (Meerson et al., 2010; Shaked et al., 2009), while miR-146a has been shown to regulate expression of toll-like receptors (TLRs) and cytokine pathways (Sonkoly et al., 2008) (reviewed (Jimenez-Mateos and Henshall, 2013) and (Henshall, 2014)).

Given the potential significance of miRNA in mediating the brains response to inflammation through the ACh system, it is important to reflect on the conservation of this interaction, with a

recent study finding that many of the miRNAs that are predicted to target genes involved in ACh synthesis and degradation were primate-specific (Nadorp and Soreq, 2014). As discussed in Section 2, this could have significant implications for studies using animal models as well as for their potential to yield a novel class of therapeutics.

6.3. The HPA axis

Emerging evidence suggests a role for cholinergic receptors and ACh in regulating the HPA axis (Bugajski et al., 2007), the principal neuroendocrine stress response system. In response to stress, parvocellular neurons of the paraventricular hypothalamus (PVN) increase secretion of corticotropin-releasing hormone (CRH; also known as CRF), which is released into portal vessels activating secretion of adrenocorticotrophic hormone (ACTH) from anterior pituitary cells. In turn, ACTH enters the circulation and stimulates the release of GCs, cortisol in humans and corticosterone in rodents, from the adrenal gland (Fig. 2). Interestingly, ACh has been shown to stimulate hypothalamic CRH secretion (Calogero et al., 1988), with stress being a critical trigger for the initiation of chronically elevated CRH levels in humans. Stressor-enhanced GC secretion, as part of the HPA axis response to stress, is a sign of health and promotes behavioral adaptation. Nonetheless, these signaling events must be tightly controlled in order to avoid an exaggerated stress response. In healthy individuals, exposure to a stressor elicits a negative-feedback regulation of the HPA axis involving the release of GCs (de Kloet et al., 2009), modulating a wide range of adaptations, including anxiety-like behaviors. However, dysregulation of the HPA axis has been associated with several psychiatric disorders such as depression, panic disorder, posttraumatic stress disorder and schizophrenia (Jansen et al., 2000; Ströhle and Holsboer, 2003).

Several studies have reported stress-induced alterations in miRNA expression levels affecting regulation of HPA axis activity. Following both acute and chronic stress exposure, Haramati et al. (2011) reported the upregulated expression of two members of the prominent stress-induced miR-34 family, miR-34a and miR-34c, in the amygdala of adult male mice. Additional *in vitro* studies demonstrated that miR-34c reduced the responsiveness of cells to CRH in neuronal cells endogenously expressing corticotropin releasing hormone receptor 1 (CRHR1). Additionally, miR-34c was found to regulate CRHR1 transcript, which has previously been demonstrated to modulate anxiety-like behavior (Heinrichs and Koob, 2004). In accordance with these observations, overexpression of miR-34c in the amygdala of adult male mice was demonstrated to induce anxiolytic properties which were more pronounced after a stressful event (Haramati et al., 2011). These findings are in line with evidence suggesting that many fundamental symptoms characteristic of depression are most likely mediated by CRH (Holsboer, 1998) and suggest a role for miR-34c in mediating stress-induced anxiety *via* HPA regulation. Alterations in mir-34 expression are also associated with Parkinson's disease (Miñones-Moyano et al., 2011) and schizophrenia (Kim et al., 2010) and increased hippocampal expression of miR-34c is suggested to play a role in memory impairment (Zovoilis et al., 2011).

The synthesis and release of CRH and ACTH are inhibited by GCs acting through two types of receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). These two receptors are part of a feedback loop that involves the activation and transporting of the CORT receptor complexes, ultimately affecting transcriptional outcome. Within the limbic system, MRs maintain stability and protect neural networks, control threshold/sensitivity of the stress response, activate glutamate release in the hippocampus

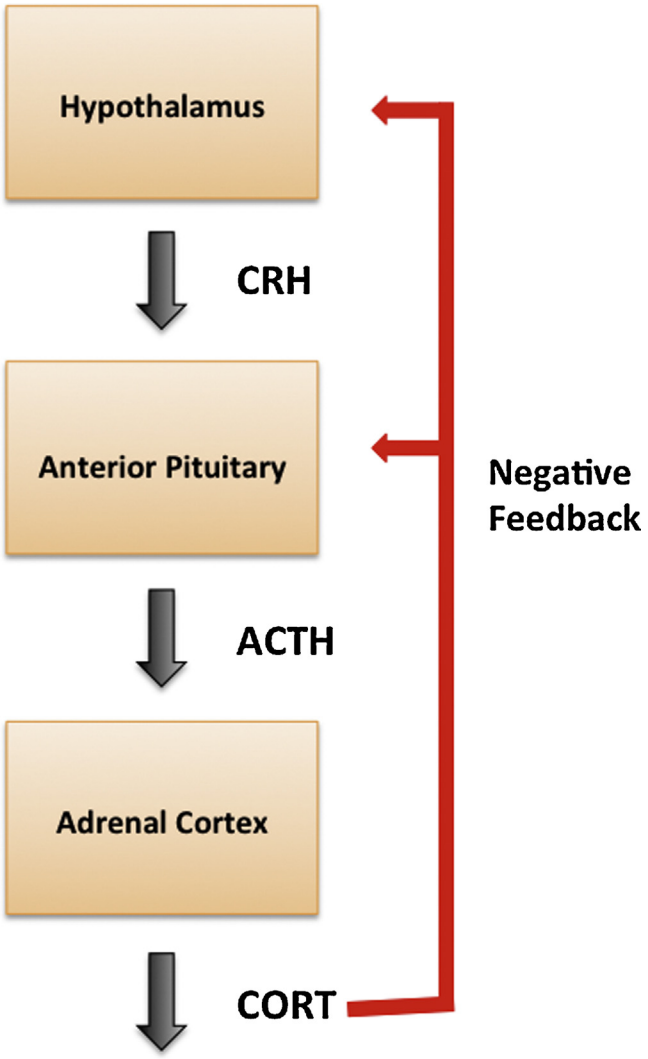

Fig. 2. Activation of the hypothalamic- pituitary-adrenal (HPA) axis Exposure to stress causes secretion of corticotropin-releasing hormone (CRH) by the hypothalamus; CRH release stimulates secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland where it acts on the adrenal gland to stimulate the release of glucocorticoid hormones (CORT). CORT then acts on the anterior pituitary and the hypothalamus in a negative feedback system.

and amplify the stress reaction (de Kloet et al., 2009). The GRs moderate hippocampal neuronal maturation and neurogenesis as well as acting as transcriptional regulators, inhibiting transcription of genes involved in the innate immune response (Fujioka et al., 2006). Importantly, the level of cellular GRs determines the cell's responsiveness to the circulating GCs (de Kloet et al., 2009), which are increased following stress exposure (Gómez-González and Escobar, 2010; Uchida et al., 2008). Recent studies indicate that miRNA play a role in this process with miR-124 and miR-18 demonstrated to post-transcriptionally regulate expression levels of GR protein in the brain (Uchida et al., 2008; Vreugdenhil et al., 2009). The expression of both miRNA is altered following stress exposure. Chronic early-life stress induced upregulated expression of miR-124 in the mPFC of 14-day-old rats, with upregulation persisting into adulthood (Uchida et al., 2010). However, in adult rats, expression of miR-124 is decreased in the amygdala following acute stress (foot-shock) (Mannironi et al., 2013), in the hippocampus following acute immobilisation stress (Meerson et al., 2010) and in whole brain

following exposure to ethanol in utero (Laufer et al., 2013). Both pre- and mature miR-18 expression levels were increased in the PVN of the hypothalamus in nine-week old rats following chronic restraint stress, accompanied by significantly reduced GR protein (Uchida et al., 2008). These findings suggest an early-response mechanism that persists into adulthood, whereby GR protein levels are decreased in response to early-life stress, reducing the cell's responsiveness to GCs. This response may protect the brain from neuropathology, as excess levels of GCs can induce dendritic retraction (Wellman, 2001) while blockade of GRs has been demonstrated to inhibit stress-induced dendritic retraction (Fujioka et al., 2006; Liu and Aghajanian, 2008; Vreugdenhil et al., 2009). GR activation has been demonstrated to suppress miR-132 expression resulting in a decrease in glutamate receptors and brain-derived neurotrophic factor (BDNF) (reviewed (Schouten et al., 2013)), associated with the survival of cholinergic synapses in the rat forebrain (Fish et al., 2004). Additionally, overexpression of miR-135a has been demonstrated to reduce the expression of MR by more than 60% using a luciferase assay in HeLa cells. Acute stress in adult mice significantly decreased the expression of miR-135a in the amygdala, which was accompanied by a three-fold increase in MR protein levels (Mannironi et al., 2013).

The interaction of GCs and CRH with their respective receptors during critical periods of brain maturation can alter the programing of the fetal HPA axis (Ulupinar, 2009), and stress-induced alterations in GC levels and GR/MR activity *via* miRNA regulation could be responsible for alterations in neuronal development and an increased susceptibility to later psychopathology. Indeed, maternal stress during pregnancy has been demonstrated to increase plasma GC levels in the fetus leading to a downregulation of fetal GR and MR, in turn, impairing the feedback regulation of the HPA axis in the offspring. Alterations in these stress hormones can affect both the morphology and function of limbic system structures in offspring leading to deficits in both mood and cognitive behaviors (reviewed (Weinstock, 2005)).

7. Analysis of differentially expressed miRNA from a variety of stress paradigms

To gain further insight into how miRNA might exert their influence following stress exposure, miRNA differentially expressed in a variety of stress paradigms (Supplementary Table 1) were analyzed to identify putative target genes using the Ingenuity Pathway Analysis (IPA) Software Tool (Ingenuity Systems). These target genes were assessed for enrichment in gene ontology (GO) categories and involvement in biologic pathways using the Gene Annotation Tool to Help Explain Relationships (GATHER; available at http://gather.genome.duke.edu/) (Chang and Nevins, 2006) and IPA, which maps biomolecular networks based on known signaling pathways and known interactions with reliable data curation. Functional analysis confirmed that stress-induced alterations in miRNA expression could affect a multitude of biological systems. For example, these miRNA are highly predicted ($p < 0.0001$) to regulate genes involved in development, neurogenesis, cell proliferation, Wnt receptor signaling, neurophysiological process and the defence response (Supplementary Table 2). Additionally, functional analyses identified 35% of miRNA as likely to be involved in TLR signaling (Table 2). Pathway analyses of the target gene lists identified the MAPK signaling; oxidative phosphorylation; focal adhesion; adherens junction and Wingless/int (WNT) signaling pathways as being significantly ($p < 0.0001$) highly enriched (Table 3). In particular, the MAPK and WNT signaling pathways are involved in microglial function, cholinergic signaling and HPA axis function and are discussed below.

7.1. Stress-induced microRNA regulation of MAPK and WNT signaling pathways

Both MAPK and WNT signaling feature prominently in the regulation of microglial function (Koistinaho and Koistinaho, 2002), and play a role in regulating the stress response *via* both cholinergic signaling and initiation of the HPA axis. Recent studies in several neuronal models suggest both the WNT signaling and MAPK pathways play a crucial role in nicotinic cholinergic signaling (Tang et al., 1998), indicating a role in the stress response. Both pathways are involved in regulating the expression (Farías et al., 2007; Kim et al., 2013), translocation (Jensen et al., 2012) and function (Farías et al., 2007) of nAChRs during activity-dependent synaptic plasticity and the MAPK pathway is itself activated by nAChRs (reviewed (Dajas-Bailador and Wonnacott, 2004)). In microglial cells challenged with LPS, the neurotransmitter ACh is able to regulate TNF-α production *via* regulation of MAPKs phosphorylation (Shytle et al., 2004). This is most likely achieved through the binding of ACh to CHRNA7 on microglia and the subsequent inhibition of proinflammatory cytokine production (see Section 6.2). The nAChRs significantly contribute to multiple facets of brain function, including neuronal development, learning and memory; therefore dysregulation of this system could have deleterious effects on cognitive functioning.

There is also an established relationship between the stress-induced activation of the HPA axis and the MAPK and WNT signaling pathways. MAPK signaling can be initiated *via* stress-induced overexpression of CRH and subsequent activation of the CRHR1, resulting in decreased MAPK phosphorylation and increased GC secretion (Bonfiglio et al., 2011). GCs are proposed to markedly decrease proliferation and neuronal differentiation while promoting glial cell formation *via* the WNT signaling pathway (Moors et al., 2012). WNT signaling stimulation of microglia can induce activation of MAPK extracellular signaling which in turn mediates the WNT-induced transformation of microglia (Halleskog et al., 2012). In microglia, the powerful WNT signaling cascade initiates proinflammatory microglial transformation and accentuates pathogenic impact (Halleskog et al., 2011).

Importantly, along with it's role in neuronal maturation and plasticity, MAPK signaling is crucial for memory consolidation (Hebert and Dash, 2002; Samuels et al., 2008), therefore, alterations to this pathway may induce cognitive deficits, in particular memory impairments. In line with these findings, postmortem human studies show a disruption of the MAPK pathway in schizophrenia (Kyosseva et al., 1999). Accordingly, a series of human and animal studies suggest that antipsychotic dugs used in the treatment of psychiatric disorders such as schizophrenia may provide long-term benefits through their ability to regulate the MAPK signaling pathway with subsequent modulation of neuroplasticity (reviewed (Ishima et al., 2012; Molteni et al., 2009).

7.2. Stress-induced microRNA regulation of the endocannabinoid system

Analysis of the miRNA in Supplementary Table 1 identified 49 stress- induced miRNA that are predicted to target genes with biological roles in all aspects of endocannabinoid (eCB) signaling (Table 4). Throughout both pre- and post-natal life the eCB system is vital in brain organisation. During fetal development there is a functional eCB system in the CNS (in both humans and animal), with functional CB_1 receptors (PND 11-14 in rats and gestational week 19 in humans) at levels higher than those in the adult brain (Berrendero et al., 1998; Mato et al., 2003). In the brain, eCBs are neurotransmitters, acting as agonists for the CB_1 receptor. This receptor is thought to play an important role in modulating adult

hippocampal neurogenesis (Wolf et al., 2010) and in hypothalamic glutamate activity *via* retrograde eCB signaling (Di et al., 2003). The eCB system is a neuroactive lipid signaling system that functions to gate synaptic transmitter release and plays a functional role in sustaining a protective and healthy CNS microenvironment (Eljaschewitsch et al., 2006). In response to enhanced neuronal activity, eCBs are recruited by the nervous system where they suppress synaptic glutamate release (Di et al., 2003), playing an important role in mediating the brain's response to stress and modifying anxiety-like behaviors (Campos et al., 2010). The eCB system acts locally to affect multiple systems, with eCB signaling activated 'on demand', regulating the function of both the immune and nervous systems (Tanasescu et al., 2012).

7.2.1. Endocannabinoid signaling and the HPA axis

For example, eCB signaling through CB_1 receptors plays a vital role in the regulation of the HPA axis, an intricate system that exhibits both simple and complex means of regulation and exerts both rapid and delayed effects on neuronal function. Acute restraint stress has been demonstrated to induce activated GR-mediated increases in hippocampal eCB signaling, as well as eCB-dependent modulation of GABA release (Wang et al., 2012). In contrast, chronic stress leads to GC-activation of GRs and a functional downregulation of presynaptic CB_1 receptors within the PVN, resulting in impaired eCB signaling at GABA and glutamate synapses (Wamsteeker et al., 2010). In addition to these studies, there is a substantial body of research which suggest a biphasic relationship between stress and the eCB system, with eCB signaling regulating both the activation and termination of the HPA axis in response to stress (Hill et al., 2010). Increased eCB signaling during acute stress may help maintain homeostatic systems, however, the loss of eCB signaling following chronic stress exposure could contribute to the development of stress-related psychiatric disorders such as depression, panic disorder, posttraumatic stress disorder and schizophrenia (Jansen et al., 2000; Ströhle and Holsboer, 2003).

7.2.2. Endocannabinoid signaling and cholinergic neurotransmission

Similarly, eCBs may exert their influence through modulation of cholinergic neurotransmission. In the brain, the release of ACh is inhibited by eCBs and conversely, CB1 receptor blockade increases ACh release (Gifford and Ashby, 1996). Studies indicate that activation of muscarinic acetylcholine receptors (mAChRs) initiates the production and release of eCBs that bind to CB_1 receptors located on synaptic terminals (Alger et al., 2014; Rinaldo and Hansel, 2013). Acute exposure to the environmental toxins parathion and chlorpyrifos (organophosphorus insecticides) has been found to inhibit AChE as well as FAAH, the enzyme primarily responsible for metabolic degradation of AEA, leading to substantial increases in extracellular eCBs in the rat hippocampus (Liu et al., 2013). In addition, exposure to acute stress induces enhanced mAChR-mediated eCB mobilization and increased eCB hippocampal content (Wang et al., 2012).

Studies also suggest that the eCB system, *via* direct or indirect interaction with the cholinergic system, may be responsible for inducing deficits in spatial learning and memory (Robinson et al., 2010) and in the modulation of depression- related behavior (Krukslomka et al., 2015). A study by Goonawardena et al. (2010) found that administration of the synthetic cannabinoid WIN55,212-2 (WIN-2) induced significant deficits in short-term memory performance that was accompanied by a reduced firing rate in pyramidal neurons. After administering an AChE inhibitor, the memory deficits were reversed and the hippocampal firing rates normalized, demonstrating that WIN-2-induced deficits in memory performance are due to inhibited cholinergic activation within the hippocampus.

7.2.3. Endocannabinoid signaling and the immune response

Microglial cells express cannabinoid receptors (Waksman et al., 1999) and when activated can produce larger quantities of eCBs than neurons or astrocytes (Walter et al., 2003). Eljaschewitsch et al. (2006) found that activation of the eCB system during CNS inflammation induces a negative feedback loop in microglial cells to protect neurons from inflammatory damage. This feedback system acts *via* eCB receptor-mediated regulation of the anti-inflammatory protein dual specificity phosphatase 1 (DUSP1; also known as MKP-1) expression (Eljaschewitsch et al., 2006). This family of proteins are pivotal in the regulation of immune responses, with DUSP1 in particular having a central role in immune regulation (Liu et al., 2007) *via* a negative feedback effect that represses MAPK-mediated pro-inflammatory signaling pathways and cytokine secretion. DUSP1 is thought to play an important role in the human cellular response to environmental stress as well as in the negative regulation of cellular proliferation. Two miRNA, mi*R*-32 (Meerson et al., 2010) and let-7a (Meerson et al., 2010; Rinaldi et al., 2010), with observed expression changes following stress exposure (Supplementary Table 1), are predicted to regulate the expression of DUSP1. These findings suggest a role for miRNA in regulating stress responses and inflammation through eCB signaling *via* the HPA axis, the cholinergic anti-inflammatory pathway, microglia and the MAPK signaling pathway.

8. Coordinated miRNA activity in the stress response

Regulation of the stress response requires a concerted effort, demonstrated by recent evidence showing alterations in expression of miRNA clusters and family members. MiRNA clusters (Fig. 1) are generated as polycistronic primary transcripts (pri-miRNAs), functioning in combination to carry out their many roles (Lagos-Quintana et al., 2003; Lee et al., 2002). MiRNA with the same seed (position 2–8 from the 5′ end of the mature miRNA) are designated as belonging to a miRNA family, and usually perform similar, if not the same, functions. A recent study by Meerson et al. (2010) identified stress-induced changes in miRNA expression in the hippocampus and central amygdala of adult rats. Using a model of restraint stress, the study investigated the involvement of miRNA in regulating region-specific stress-induced changes in alternative splicing in adult male rats. However, closer examination of their data reveals stress-induced alterations in expression of many miRNA clusters and families (Table 1). Of particular interest are the miRNA in the miR-154 and miR-368 families, structurally associated by their genomic position on the long arm of chromosome 14 (14q32). Significantly, this locus is known as the DLK1-DIO3 region and is imprinted such that the associated miRNA cluster is expressed only from the maternal chromosome (Royo and Cavaillé, 2008). These miRNA are predicted to have an important role in brain function and development (Fiore et al., 2009; Kim et al., 2004; Manakov et al., 2009) and accordingly have

Table 1
miRNA clusters and families altered by stress.

Cluster/Family	miRNA
Cluster 1	miR-182, miR-183, miR-96
Cluster2	miR-134, miR-369, miR-381, miR-382, miR-410
Cluster 3	miR-15, miR-16
Cluster 4	miR-376a, miR376b, miR-376c, miR-381
miR-154 family	miR-323, miR-369, miR-381, miR-382, miR-410
miR-17 family	miR-17, miR-106b
miR-221 family	miR-221, miR-222
miR-368 family	miR-376a, miR-376b, miR-376c
let-7 family	let-7a-1, let-7c, let-7f-1, let-7f-2

Table shows miRNA clusters and families altered following restraint stress in adult male rats in a study by Meerson et al. (2010).

Table 2
Stress-induced miRNA regulation of TLR-signaling.

Gene Name	Description	Stress-induced differentially expressed miRNA										
CD14	CD14 molecule	miR-208										
CHUK	conserved helix-loop-helix ubiquitous kinase	let-7a	miR-146a	miR-23a								
ELK1	ELK1, member of ETS oncogene family	miR-186										
FOS	FBJ murine osteosarcoma viral oncogene homolog	miR-221	miR-29a									
IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	miR-15b										
IRAK1	interleukin-1 receptor-associated kinase 1	miR-146a	miR-134									
IRAK2	interleukin-1 receptor-associated kinase 2	miR-146a	miR-15b	miR-532-3p								
IRAK3	interleukin-1 receptor-associated kinase 3	miR-124										
IRAK4	interleukin-1 receptor-associated kinase 4	miR-106b										
JUN	jun proto-oncogene	miR-15b	miR-30a									
LBP	lipopolysaccharide binding protein	miR-146a										
MAP2K3	mitogen-activated protein kinase kinase 3	miR-19a	miR-21	miR-9	miR-96							
MAP2K4	mitogen-activated protein kinase kinase 4	miR-124	miR-137	miR-145	miR-15b	miR-22	miR-29a	miR-32				
MAP2K6	mitogen-activated protein kinase kinase 6	miR-29a										
MAP3K1	mitogen-activated protein kinase kinase 1, E3 ubiquitin protein ligase	let-7a	miR-124	miR-351	miR-137	miR-106b	miR-18a	miR-21	miR-23a	miR-26a	miR-30a	miR-9
MAP3K14	mitogen-activated protein kinase kinase 14	miR-137	miR-106b	miR-19a								
MAP4K4	mitogen-activated protein kinase kinase 4	let-7a	miR-145	miR-23a	miR-29a	miR-30a	miR-34c	miR-96				
MAPK1	mitogen-activated protein kinase 1	miR-124	miR-132	miR-15b	miR-106b	miR-186	miR-19a	miR-204	miR-26a	miR-410	miR-32	
MAPK11	mitogen-activated protein kinase 11	let-7a										
MAPK12	mitogen-activated protein kinase 12	miR-351										
MAPK13	mitogen-activated protein kinase 13	miR-34c										
MAPK14	mitogen-activated protein kinase 14	miR-124	miR-351	miR-19a	miR-22							
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	miR-9										
NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	miR-381										
PPARA	peroxisome proliferator-activated receptor alpha	let-7a	miR-124	miR-351	miR-106b	miR-19a	miR-21	miR-22	miR-9			
RELA	v-rel avian reticuloendotheliosis viral oncogene homolog A	miR-124										
TAB1	TGF-beta activated kinase 1/MAP3K7 binding protein 1	miR-134										
TAB2	TGF-beta activated kinase 1/MAP3K7 binding protein 2	let-7a										
TICAM2	toll-like receptor adaptor molecule 2	miR-186										
TLR1	toll-like receptor 1	miR-146a										
TLR10	toll-like receptor 10	miR-146a										
TLR4	toll-like receptor 4	let-7a	miR-145	miR-146a								
TLR5	toll-like receptor 5	miR-19a										
TLR6	toll-like receptor 6	miR-204	miR-382									
TLR8	toll-like receptor 8	miR-22										
TLR9	toll-like receptor 9	miR-146a										
TNFAIP3	tumour necrosis factor, alpha-induced protein 3	let-7a	miR-103	miR-351	miR-106b	miR-18a	miR-19a	miR-23a	miR-29a			
TOLLIP	toll interacting protein	miR-106b	miR-298									
TRAF4	TNF receptor-associated factor 4											

Table 2 (*Continued*)

Gene Name	Description	Stress-induced differentially expressed miRNA			
TRAF6	TNF receptor-associated factor 6, E3 ubiquitin protein ligase	miR-29a miR-124	miR-370 miR-351	miR-146a	miR-15b

Putative gene targets of differentially expressed miRNA in Supplementary Table 1 were identified using IPA. Table lists target genes identified by IPA as involved in TLR signaling.

Table 3
Putative pathways regulated by stress-induced miRNA.

KEGG Pathway	No. Genes	Bayes Factor	*p*-value
MAPK signaling pathway	179	21.38	<0.0001
Oxidative phosphorylation	31	18.65	<0.0001
Focal adhesion	170	18.05	<0.0001
Wnt signaling pathway	111	13.48	<0.0001
Adherens junction	64	11.99	<0.0001
Regulation of actin cytoskeleton	145	7.88	<0.0001
Tryptophan metabolism	27	7.17	<0.0001
Insulin signaling pathway	101	5.92	<0.0001

Table lists pathways identified by GATHER as significantly enriched in the putative miRNA target gene set based on Bayes factor >6 as recommended (Chang and Nevins 2006). Putative gene targets of differentially expressed miRNA in Supplementary Table 1 were identified using IPA.

been implicated in bipolar disorder (Cichon et al., 2001; Segurado et al., 2003), anxiety (Middeldorp et al., 2008) and fetal alcohol syndrome (Laufer et al., 2013). We have recently shown that this region is associated with MIA (Hollins et al., 2014) and is altered in peripheral blood mononuclear cells (PBMCs) from individuals with schizophrenia (Gardiner et al., 2012). This very large miRNA cluster evolved relatively recently emerging in eutherian mammals. Interestingly, expression of the long non-coding precursor RNA derivative of these miRNA is also highly sensitive to synaptic activity and displays coordinated upregulation in response to neural excitation by modulation of the calcium activated Myocte Enhancer Factor 2 (MEF2) transcription factor (Fiore et al., 2009). This suggests that the resident miRNAs are important for synaptic function. It is therefore quite significant that the MEF2C member of this family has been shown to be genetically associated with schizophrenia in the latest genome wide association study (Ripke et al., 2014). MEF2C has also been implicated in inflammation responses through activity-dependent Major histocompatibility complex class I (MHCI) signaling, leading to changes in synapse density in cortical neurons (Elmer et al., 2013).

Also of interest are the let-7 and mir-17 families involved in the regulation of development and neuronal differentiation (Beveridge et al., 2009; Roush and Slack, 2008). In addition, let-7 family members play a conserved role in mediating the inflammatory response through inhibition of the proinflammatory cytokine interleukin-6 (IL-6) (Garbuzov and Tatar, 2010), while the miR-17 family is involved in the regulation of the mitogen-activated protein kinase (MAPK) signaling pathway (Beveridge et al., 2009; Wu et al., 2012), a pathway known to be dysregulated in schizophrenia (Kyosseva et al., 1999). Alterations in expression of these miRNA could lead to alterations in neuronal processes as well as the increased secretion of proinflammatory cytokines, possibly *via* toll-like receptor (TLR) signaling (see Section 6.1), leading to subsequent neuropathology.

A similar study by Haramati et al. (2011) found members of the miR-15 family (miRs-15a, -15b) and the miR-34 family (miRs-34a, -34c) were significantly upregulated in the central amygdala of adult male mice following restraint stress. The miR-15 family regulate the expression of genes involved in cell division, metabolism and the stress response (Finnerty et al., 2010) and are associated with Alzheimer's Disease (Hébert et al., 2010; Wang et al., 2011a,b) and schizophrenia (Beveridge et al., 2010). Similarly, members of the miR-34 family target mRNAs important in cell cycle progression and cell survival, the innate immune response (O'Connell et al., 2010), and are associated with both Huntington's Disease (Gaughwin et al., 2011) and Alzheimer's Disease (Schipper et al., 2007). Certainly, miRNA families most likely play a key role in moderating the central stress response within different brain regions *via* the regulation of genes mediating both the behavioral and physiological changes required to restore homeostasis. However, although initially a protective mechanism, stress-induced alterations in miRNA expression could have deleterious effects on the mammalian brain.

9. Conclusions and perspectives

In this review we have drawn on the current evidence to support a physiological role for miRNAs in regulating the central stress response. However, as this is a relatively new field of investigation, it is likely that further evidence will emerge confirming the role of miRNA in stress-mediated functions as well as stress-induced neuropathological conditions. Multiple studies have shown that miRNA expression is altered following exposure to both pre- and post-natal environmental stressors. These alterations can be accompanied by morphological, physiological and behavioral abnormalities. MiRNA functions in stress responses involve numerous feedback systems and signaling pathways. These stress-mediated functions can lead to changes in neural structure, circuits, plasticity and cognition, manifesting as neurodevelopmental or neurodegenerative disorders. Remarkably, some studies suggest that the responses to these experiences induced by changes in miRNA are transmitted between generations, with significant transgenerational alteration of miRNA expression and neurobehavioral sequelae in the F3 generation. As the majority of studies investigate the effects of acute stress or maternal stress, it is highly likely that the potential outcomes are more detrimental and wide reaching than what is currently known. While the molecular mechanisms underlying miRNA-mediated responses remain unclear, the available data suggest a crucial role for miRNA in the response to environmental stress. Further investigation to elucidate these mechanisms is required in order to understand the causal relationship between miRNA regulation of the stress response and neuropathology. With mounting evidence that miRNA serve as biomarkers of disease, continuing research in this area may lead to novel miRNA-based therapies for the prevention and/or treatment of neurodevelopmental and neuropathological disorders.

Translational research which seek to further understand the role of miRNA in the brains response to stress, particularly in human subjects or primate models, will provide a clear platform for the stress related miRNA biomarkers and therapeutic strategies that can modulate miRNA biogenesis and function. Despite the significant problems in delivering nucleic acid based drugs,

Table 4
Stress-induced miRNA regulation of the endocannabinoid system.

MiRNA	Target endocannabinoid mRNA
let-7a	Napepld, Trpa1
let-7c	Napepld, Trpa1
let-7f	Napepld, Trpa1
miR-9	Drd2, Ptgs2, Ptpn22
miR-15a	Napepld
miR-15b	Napepld
miR-17	Cnr1, Mgll, Napepld
miR-18a	Grm1, Naaa
miR-19a	Cnr1, Grm1, Napepld, Ppara
miR-22	Daglb, Grm5, Gpr55, Trpv4
miR-23a	Cnr1, Grm5, Trpa1
miR-26a	Cnr1, Napepld, Ptgs2
miR-26b	Cnr1, Napepld, Ptgs2
miR-29a	Abhd4, Cnr1, Nat1
miR-30a	Cnr1, Dagla, Grm3, Grm5, Trpa1
miR-32	Faah2, Grm1, Ptpn22
miR-34c-5p	Gpr55, Pparg, Trpv4
miR-96	Grm1, Grm5, Pparg, Trpa1
miR-106b	Cnr1, Mgll, Napepld
miR-124	Napepld, Trpv1, Trpv4
miR-132	Cnr1, Faah2, Grm3, Grm5, Ptgs2
miR-134	Cnr1, Mgll
miR-138	Faah2
miR-146a	Ptgs2, Cnr1
miR-148a	Mgll, Ptgs2
miR-155	Napepld, Ptpn22
miR-182	Abhd4, Grm1, Grm4, Grm5, Mgll, Pparg, Trpa1
miR-183	Grm1, Dagla, Ptgs2, Ptpn22
miR-186	Faah2, Grm5, Napepld, Ptpn22, Trpa1, Trpv1
miR-190	Grm5, Ptpn22
miR-193a-3p	Ptpn22
miR-193b	Ptpn22
miR-202	Ptgs2, Trpa1
miR-208a	Faah2
miR-208b	Faah2
miR-212	Cnr1, Faah2, Grm3, Grm5, Ptgs2
miR-216b	Cnr1, Grm1, Grm5, Trpa1
miR-221	Cnr1, Grm1
miR-222	Cnr1, Grm1
miR-330-5p	Drd2
miR-361-5p	Grm1, Grm5, Pparg, Ptpn22
miR-370	Grm4
miR-376a	Grm3, Napepld
miR-376b	Grm3, Napepld
miR-381	Cnr1, Grm1, Grm3, Grm5, Ptgs2
miR-382	Cnr1, Grm1, Nat2, Napepld
miR-410	Cnr1, Grm1, Grm2, Nat1, Ptgs2
miR-422a	Trpv4
miR-424	Napepld

Putative gene targets of differentially expressed miRNA in Supplementary Table 1 were identified using IPA. Table lists target genes identified by IPA as involved in TLR signaling.

particularly to the brain, there are a number of groups that are exploring the potential for gene-delivered miRNA and miRNA antagonists for more specific interventions to this system. There have also been significant advances in the production and delivery of synthetic miRNA and miRNA antagonists that are modified by cell membrane penetrating peptides and other moieties. Other formulations using synthetic encapsulating lipid vesicles and even biological vesicles, such as exosomes, can be engineered with tropism for neural tissue that can facilitate the delivery of its gene regulating cargo through the blood brain barrier (Alvarez-Erviti et al., 2011). While the challenges of small molecule and nucleic acid based approaches to miRNA therapeutics are significant, these remain important new and influential targets for therapeutic manipulation of the neural stress responses.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pneurobio.2016.06.005.

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