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Regulatory RNAs in Brain Function and Disorders

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Abstract

Regulatory RNAs are being increasingly investigated in neurons, and important roles in brain function have been revealed. Regulatory RNAs are non-protein-coding RNAs (npcRNAs) that comprise a heterogeneous group of molecules, varying in size and mechanism of action. Regulatory RNAs often exert post-transcriptional control of gene expression, resulting in gene silencing or gene expression stimulation. Here, we review evidence that regulatory RNAs are implicated in neuronal development, differentiation, and plasticity. We will also discuss npcRNA dysregulation that may be involved in pathological states of the brain such as neurodevelopmental disorders, neurodegeneration, and epilepsy.

Keywords

Regulatory RNA; non-protein-coding RNA; neurons; brain disorders

1. Introduction

A large body of studies indicates that, in addition to protein coding RNAs (mRNAs), ribosomal RNAs and transfer RNAs, other RNA molecules – generally referred to as non-protein-coding (npc) RNAs – participate in the regulation of a variety of cellular processes (Carninci et al., 2005; Costa, 2007; Erdmann et al., 2001; Kapranov et al., 2007; Mattick and Makunin, 2006; Mattick, 2009; Ponting et al., 2009; Satterlee et al., 2007). Since their discovery in the late sixties and early seventies, the number of identified npcRNAs has increased substantially and, for some of them, evidence of regulatory functions has emerged. In this review, we will first provide a brief introduction on the classification of npcRNAs and will then focus on npcRNAs that have documented regulatory functions in physiological and diseased states in the brain. We refer to these regulatory RNAs as ‘non-protein-coding’ – rather than ‘non-coding’ – RNAs to emphasize that these RNAs carry codes, even if they do not encode specific amino acidic sequences (Brosius and Tiedge, 2004).

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Regulatory RNAs have been classified into three relatively distinct groups on the basis of their length: microRNAs (miRNAs) and small interfering RNAs (siRNAs), ranging from 18 to 25 nucleotides; small RNAs with a length of 50-300 nucleotides; and medium, large, and macro RNAs with transcript lengths reaching 100,000 nucleotides (Costa, 2005; Costa, 2007; Eddy, 2001; Shamovsky and Nudler, 2006).

The use of biocomputational analysis, followed by biochemical validation, has contributed significantly to the identification of regulatory RNAs, especially those expressed at low levels (Griffiths-Jones, 2007; Voss et al., 2009; Yoon and De Micheli, 2005a; Yoon and De Micheli, 2005b). For example, the sequence and structure of several regulatory RNAs in yeast have been identified through comparative genomics coupled to thermodynamic stability analysis, and the function of these RNAs has subsequently been experimentally verified (Kavanaugh and Dietrich, 2009). In the human genome, 79 miRNAs regulatory modules – defined as groups of miRNAs and target genes cooperating in post-transcriptional gene regulation – have been identified by computational and experimental approaches (Tran et al., 2008; Yoon and De Micheli, 2005a).

RNA folding/unfolding and secondary structure formation are hierarchical processes as secondary structure determines tertiary structure formation (Onoa and Tinoco, 2004). Since the tertiary structure defines the function of a molecule, computational studies of the regulatory RNA's three-dimensional structure, folding dynamics predictions (Ding et al., 2008b; Frellsen et al., 2009; Mathews and Turner, 2006; Sharma et al., 2008), and analysis of secondary and tertiary structure conservation (Abraham et al., 2008; Xu et al., 2007) can provide insights into their putative functions.

Regulatory RNAs that control the expression of genes located in close proximity are called cis-acting regulatory RNAs, whereas those that act on distant target genes are called transacting regulatory RNAs. Cis-acting regulatory RNAs constitute a growing class of long and macro RNAs that regulate expression of flanking genes (Koerner et al., 2009; Latos and Barlow, 2009). These RNAs show monoallelic expression (i.e. they originate from paternal or maternal allele) and are involved in the epigenetic regulation of chromatin (Kloc et al., 2008; Royo and Cavaille, 2008). A prototypical cis-acting RNA is Xist (Pauler et al., 2007; Wutz and Gribnau, 2007), a large (17 kb long) npcRNA that is located on, and expressed from, the inactive X chromosome. Xist ensures dosage compensation of the X-linked genes in mammals (Brown et al., 1992).

The group of trans-acting regulatory RNAs includes miRNAs (Kocerha et al., 2009b; Kosik, 2006; Krichevsky et al., 2006). In *C. elegans*, the miRNA lin-4 negatively regulates the level of LIN-14 protein which controls postembryonic development (Lee et al., 1993; Lee and Ambros, 2001). Lin-4 is thus classified as small temporal RNA. Subsequently, more temporal RNAs, such as let-7, have been identified (Eddy, 2001).

Further work on miRNAs has led to the identification, in 58 species, of about 5000 loci, which transcripts are processed into almost 6000 mature miRNA sequences. (Gardner et al., 2009; Griffiths-Jones et al., 2008). miRNAs are involved in many processes such as development and differentiation, apoptosis, tumorigenesis, and brain functions. In this review, we will primarily focus on small and large npcRNAs involved in brain function and disorders. Neuronal functions of miRNAs have been reviewed elsewhere (Eacker et al., 2009; Fineberg et al., 2009; Schratt, 2009) and therefore will not be extensively discussed here.

2. Regulatory RNAs in brain

Recent studies have begun to reveal neuronal functions of regulatory RNAs (Cao et al., 2006; Chang et al., 2009; Mehler and Mattick, 2006; Mehler and Mattick, 2007; Pollard et al., 2006; Satterlee et al., 2007). Several hundreds of miRNAs have been implicated in brain development (Amaral and Mattick, 2008; Krichevsky et al., 2003), neurodevelopmental disorders (Amaral and Mattick, 2008; Chang et al., 2009), and long-term memory storage (Mercer et al., 2008a).

In situ hybridization data on protein-coding transcripts in developing and adult brain (Lein et al., 2007) were also screened for npcRNAs (Mercer et al., 2008b). Expression levels of mRNAs in brain were higher compared to those of regulatory RNAs, but regulatory RNA expression levels in different brain regions were more heterogeneous. These data suggest that many of the 849 npcRNAs identified are specifically associated with brain regions, cell types, and subcellular compartments (Mercer et al., 2008b), and that they may play roles in various nervous system disorders (Bilen et al., 2006a; Bilen et al., 2006b; Mehler and Mattick, 2007; Weinberg and Wood, 2009).

2.1. Regulatory RNAs and gene expression silencing

Post-transcriptional regulation mediated by miRNAs usually results in gene silencing. A miRNA typically targets a specific mRNA and through RNA/RNA interaction either degrades the mRNA or interferes with the translational machinery, and consequently reduces synthesis of the cognate protein (Chekulaeva and Filipowicz, 2009; Valencia-Sanchez et al., 2006).

A brain-relevant example is the suggested role of miRNAs in regulating schizophrenia risk genes (Perkins et al., 2005; Perkins et al., 2007). In drug-induced schizophrenic mice, expression of miRNA-219, a brain-specific RNA in humans and rodents, is strongly reduced, and such reduction can be prevented with antipsychotic treatments (Cheng et al., 2007; Kocerha et al., 2009a; Lukiw, 2007). miRNA-219 regulates expression of CaMKII γ in cortical cells in in vitro experiments, and it modulates expression of CaMKII γ protein levels in the prefrontal cortex, suggesting a role in NMDA receptor-mediated signaling cascades associated with neurobehavioral functions (Kocerha et al., 2009a).

2.2. Regulatory RNAs and gene expression stimulation

Recent work has suggested additional mechanisms of gene expression regulation involving regulatory RNAs. These RNAs enhance transcriptional and post-transcriptional activity (e.g. by increasing target mRNA stability), rather than silencing the target gene. Their function is mediated either through RNA/RNA interactions or through RNA/protein interactions.

Kohtz and colleagues identified a developmentally regulated 2.7 kb-long npcRNA, named Evf-1, that is expressed in embryonic dorsal and ventral telencephalon (Kohtz et al., 1998; Kohtz and Fishell, 2004). The Evf-1 gene is located upstream of the Dlx-6 gene, whose expression pattern it closely resembles. In vertebrates, the family of Dlx comprises six homeodomain transcription factors (Dlx-1 to 6), with critical roles in neuronal differentiation and migration and in epilepsy (Acampora et al., 1999; Anderson et al., 1997; Cobos et al., 2005). Embedded in one of the highly conserved intergenic regions of Dlx-5/6 resides Evf-2 RNA, a 3.8 kb-long npcRNA, a splice variant of Evf-1 (Feng et al., 2006). The authors showed that Evf-2 RNA forms a complex with the Dlx-2 protein. It has been proposed that this complex, interacting with an intergenic enhancing sequence situated between the Dlx-5 and Dlx-6 genes, increases transcriptional activity (Feng et al., 2006).

More recently, the same group has shown that in mice lacking an exon resulting in the absence of *Evf-2* RNA, the number of GABAergic interneurons in the dentate gyrus and in the hippocampal CA1 and CA3 regions is reduced by 40-65% during early postnatal stages (Bond et al., 2009). The number of GABAergic interneurons recovers in adult mice, but reduced synaptic inhibition persists, suggesting that GABA-dependent connectivity in adult brain is modulated by the regulatory RNA *Evf-2*.

Another example of post-transcriptional regulation by an npcRNA has been reported in Alzheimer's disease (AD). A regulatory antisense RNA directed against *BACE1* (β -site amyloid precursor protein-cleaving enzyme) mRNA, encoding a vertebrate specific p-secretase, is elevated by six-fold in AD patients (Faghihi et al., 2008; St George-Hyslop and Haass, 2008). The *BACE1* antisense transcript (*BACE1-AS*), a conserved circa 2-kb long RNA, is located on the positive strand of chromosome 11, and on the opposite strand of the *BACE1* locus with which it shares a 104-nucleotide complementarity. *BACE1-AS* positively regulates *BACE1* mRNA by increasing its stability: knock-down of *BACE1-AS* results in a reduction of *BACE1* mRNA and consequently of protein abundance in vitro (Faghihi et al., 2008). Cell stressors implicated in AD pathogenesis (e.g. hyperthermia, high glucose) increase *BACE1-AS* and *BACE1* protein, thereby facilitating the "amyloid cascade" (Faghihi et al., 2008).

2.3. Non-protein-coding repeat expansions

Non-protein-coding CTG or CGG expansions, located in an untranslated region of a gene, may result in gain or change of function of an RNA (Daughters et al., 2009; Dick et al., 2006; Ranum and Cooper, 2006). Three notable examples are spinocerebellar ataxia type 8 (SCA8), fragile X tremor ataxia syndrome (FXTAS), and myotonic dystrophy (DM) (Brouwer et al., 2008; Daughters et al., 2009; Ranum and Cooper, 2006).

SCA8 is a progressive degenerative disease (Soong and Paulson, 2007) with a neurodegeneration pattern distinct from other ataxias (Ito et al., 2006). SCA8 ataxia is caused by expansion of CTG repeats that are transcribed as part of SCA8 RNA (Koob et al., 1999; Nemes et al., 2000). SCA8 RNA is expressed primarily in brain but is not translated. The SCA8 transcript is an antisense RNA overlapping with the sense strand of the actin-binding protein *KLHL1* gene (Nemes et al., 2000). It has been proposed that neurodegeneration in SCA8 ataxia is caused either by abnormal interaction of SCA8 RNA with RNA binding proteins or by altered SCA8 RNA-mediated regulation of *KLHL1* expression (Chen et al., 2008; Mutsuddi et al., 2004; Nemes et al., 2000).

RNA gain-of-function has also been reported in FXTAS. Patients with high number of non-protein-coding CGG expansions in the 5' UTR region of the *FMR1* gene display progressive tremor, ataxia, brain atrophy, and cognitive decline (Greco et al., 2002; Hagerman and Hagerman, 2004; Hagerman et al., 2001). Intranuclear inclusions have been observed in neuronal and astrocytic cells in the cerebral cortex (Greco et al., 2002). In FXTAS, the number of CGG repeats in the 5' UTR of human *FMR1* mRNA ranges from 55 to 200, and the severity of symptoms correlates with increasing repeat number (Leehey et al., 2008). The RNA toxicity hypothesis has been supported by recent work with a mouse model in which 98 CGG triplets contained in the 5' UTR of murine *Fmr1* mRNA are expressed (Hashem et al., 2009). In this model, CGG repeats give rise to the formation of intranuclear inclusions in Purkinje neurons, probably as a result of interaction of the repeats with RNA binding proteins. In post-mortem brain tissues of FXTAS patients, hnRNP A2/B1 and Pura have been identified in intranuclear inclusions (Iwahashi et al., 2006; Jin et al., 2007).

DM is an inherited muscular dystrophy characterized by progressive atrophy of voluntary muscles (Batten and Gibb, 1909). Two types of DM, DM1 and DM2, share the same toxic RNA gain-of-function mechanism but involve two different genes. DM1 is caused by CTG repeat expansion in the 3' UTR of the myotonic dystrophy protein kinase (DMPK) gene (Brook et al., 1992; Fu et al., 1992), while in DM2, tetranucleotide CCTG expansions occur within intron 1 of the zinc finger 9 (ZNF9) gene (Liquori et al., 2001). Multiple molecular mechanisms have been proposed for DM1 (Cho and Tapscott, 2007; Kaliman and Llagostera, 2008). Repeat expansions in DMPK gene cause decreased expression at the mRNA and protein levels (Carango et al., 1993; Fu et al., 1993; Hofmann-Radvanyi et al., 1993). It is thought that CUG expansions in DMPK mRNA form stem-loop structures (Napierala and Krzyzosiak, 1997) which sequester CUG-binding proteins (CUG-BPs) such as muscleblind-like protein 1 (MBNL1) (Fardaei et al., 2001; Miller et al., 2000; Timchenko et al., 1996). These RNA-protein complexes, trapped in the nucleus, give rise to the ribonuclear foci observed in DM muscle fibers (Liquori et al., 2001; Miller et al., 2000; Wheeler et al., 2007). MBNL1 is homologous to the mbl proteins which in *Drosophila* are crucial for terminal differentiation of muscle cells and photoreceptors (Artero et al., 1998; Begemann et al., 1997). In a DM mouse model, loss of the MBNL1 gene results in muscle and eye abnormalities similar to DM phenotypes (Kanadia et al., 2003). In addition, the DM mouse model shows splicing dysregulation. Splicing abnormalities as well as sequestration of MBNL1, and other CUG-BPs, by CUG and CCUG repeat expansions seem to contribute to the onset of these disorders.

2.4. Regulatory RNAs and Imprinting

It is becoming increasingly clear that regulatory RNAs are key factors in heterochromatin formation, chromosomal dynamics, epigenetic modification, and genomic imprinting (Bernstein and Allis, 2005; Koerner et al., 2009; O'Neill, 2005; Royo and Cavaille, 2008). Screening of chromatin-state maps in four mouse cell types has revealed over 1,580 large intergenic non-coding RNAs (lincRNAs) (Guttman et al., 2009). These regulatory RNAs show 95% evolutionary conservation across mammals, suggesting that they are required for biological functions yet to be identified. The same approach carried out on 6 human cell types detected over 1,700 new loci encoding lincRNAs (Khalil et al., 2009). A few of these regulatory RNAs have also been found physically associated with chromatin-modifying complexes, for instance the polycomb repressive complex 2 which silences genes involved in development and differentiation, and CoREST, a repressor of neuronal genes (Khalil et al., 2009; Qureshi and Mehler, 2009).

Eighty imprinted genes have been identified in the mouse genome, and many of these are grouped in clusters on chromosome 7 (Barlow and Bartolomei, 2007; Pauler et al., 2007; Verona et al., 2003). Interestingly, the Prader-Willi/Angelman syndrome (PWS/AS) cluster is also located on chromosome 7. This region corresponds to the human 15q11-q13 imprinting domain. The Prader-Willi syndrome (PWS) and the Angelman syndrome (AS) are sister imprinting disorders characterized by neurological and developmental abnormalities, cognitive impairments, obsessive-compulsive symptoms, seizures, and ataxia (Cassidy et al., 2000). The PWS/AS region contains several imprinted genes that encode proteins and ncRNAs. In PWS patients, the paternal expression of the following genes is impaired: protein coding genes MKRN3, MAGEL2, NDN, SNURF – SNRPN, and C/D box small nucleolar RNA (snoRNA) genes (SNORDs) such as HBII-436 (SNORD107), HBII-13 (SNORD64), HBII-437 (SNORD108), HBII-438A (SNORD109A), HBII-85 (SNORD116), HBII-52 (SNORD115), and HBII-438B (SNORD109B) (Cavaille et al., 2000; Runte et al., 2001). In AS patients, maternal expression of the protein coding genes UBE3A and ATP10A is impaired (Herzing et al., 2001; Kishino et al., 1997; Matsuura et al., 1997; Meguro et al., 2001).

Imprinted expression of all these genes is controlled by the bipartite imprinting center (IC), located upstream of the SNURF – SNRPN promoter. The proximal part of the bipartite IC controls paternal expression of the PWS genes while the distal part controls maternal expression of the AS genes (for review see Kantor et al., 2006). It is generally believed that all PWS npcRNAs are processed from the extra long intron-containing U-UBE3A-AS RNA transcript, partially antisense to UBE3A, starting from the U-exons upstream of the SNURF – SNRPN gene and ending in the UBE3A gene (Runte et al., 2001). The UBE3A-AS npcRNA has been reported to negatively regulate expression of the UBE3A gene (Landers et al., 2005). Furthermore, the mature snoRNAs are processed from the introns of this long npcRNA. SNORD115 and SNORD116 are arranged in clusters of 47 and 29 copies, respectively, each interrupted by less conserved exons. The corresponding region on mouse chromosome 7 has a similar structure, except that the mouse has an additional paternally expressed protein coding gene *Frat3* and lacks orthologs of SNORD108, SNORD109A, and SNORD109B. The corresponding extra long RNA transcript in mouse is termed LNCAT (Le Meur et al., 2005). Several mouse models for PWS and AS have been generated. The UBE3A gene plays the chief role in the development of AS, which was confirmed by targeted elimination of *Ube3a* locus in a mouse model (Jiang et al., 1998), and whose loss decreases AMPA receptor expression at the synapses (Greer et al., 2010). The minimal critical region containing cluster of the HBII-85/SNORD116 snoRNA genes is responsible for PWS (de Smith et al., 2009; Ding et al., 2008a; Sahoo et al., 2008; Skryabin et al., 2007). However, other paternally expressed genes are likely to contribute to the phenotype (Kanber et al., 2009).

The second cluster of snoRNAs that is lacking in larger deletions of the PWS locus is HBII-52 (SNORD115) snoRNAs (Cavaille et al., 2000). HBII-52 snoRNAs harbor a guide sequence of 18 nucleotides that is complementary to the transcript encoding the serotonin receptor 2C. However, the modification status of the serotonin receptor 2C transcript is not significantly modulated by the snoRNA (Vitali et al., 2005). A suggested regulation of alternative splicing of the serotonin 2C receptor (Kishore and Stamm, 2006) was not observed in subsequent work (Doe et al., 2009). The question is raised whether the sequence complementarity may simply be fortuitous. Thus, a regulatory role of SNORD115 in serotonin receptor 2C expression remains to be substantiated even though it would fit well in the picture of PWS and other neurodevelopmental disorders. For example, duplication of chromosome 15q11-q13 (which contains the SNORD115 gene cluster among many other genes) is a chromosomal abnormality associated with autism (Bolton et al., 2004; Cook et al., 1997; Gillberg, 1998), a disorder characterized by verbal and nonverbal communication impairments (Consortium, 2001; Wassink and Piven, 2000). A transgenic mouse with duplication of the snoRNA cluster on chromosome 7, mirroring the duplication of human chromosome 15q11-q13, appears to show altered serotonin receptor 2C-mediated responses and autism-like phenotypes (Nakatani et al., 2009). Notably, a subgroup (~25%) of PWS patients have uniparental disomy (UPD) for maternal chromosome 15 (Fridman and Koiffmann, 2000), and they are likely to manifest autism spectrum disorder (ASD) behaviors, with an estimated comorbidity between 19-36.5% (Descheemaeker et al., 2006; Veltman et al., 2004).

The distal region of the mouse chromosome 12 and on the human chromosome 14 contains an imprinting gene cluster, the *Dlk1-Dio3*-imprinted domain, that contains seven npcRNAs (Cavaille et al., 2002; Hagan et al., 2009). Deletion or epimutation in this cluster causes uniparental disomy for chromosome 14 (UPD14), a syndrome characterized by moderate to severe mental retardation (Kagami et al., 2005; Kagami et al., 2008). A gene identified in the *Dlk1-Dio3* cluster is an ortholog of the human gene *MEG3* (maternally expressed gene 3) and generates a polyadenylated npcRNA called *Gtl2* (da Rocha et al., 2008). Takahashi and colleagues suggests that *Gtl2* is a *cis*-acting element that plays a critical role in

embryonic development and neonatal growth by regulating the Dlk1-Dio3 domain (Takahashi et al., 2009). In addition, Hagan and coworkers suggest a regulatory mechanism on the Dlk1-Dio3 domain, mediated by 52 microRNAs that are embedded in introns of the seven npcRNA genes localized in the Dlk1-Dio3 cluster (Hagan et al., 2009). 80% of these microRNAs are also present in the human orthologous cluster whose loss may be associated with the UPD phenotype (Hagan et al., 2009).

Expression of the gene encoding the insulin-like growth-factor type-2 receptor (Igf2r) represents a well-studied example of regulation by imprinted npcRNAs in brain. The antisense transcript of the Igf2r gene is called Air (antisense Igf2r RNA) and is an imprinted, polyadenylated 108-kb npcRNA (Lyle et al., 2000). The Air promoter lies in the region 2 within the second intron of the Igf2r gene (Sleutels and Barlow, 2001). In non-neuronal somatic cells, imprinting of the Igf2r promoter in the paternal allele and imprinting of the Air promoter in the maternal allele result in expression of Igf2r from the maternal allele and expression of Air from the paternal one (Yamasaki et al., 2005). In contrast, in cultured neurons and in brain, Igf2r is expressed by both parental alleles (Hu et al., 1998; Yamasaki et al., 2005). Biallelic Igf2r expression occurs in the absence of Air expression in neurons, suggesting that Air is critical in Igf2r silencing and that npcRNAs may play a role in neuron-specific epigenetic modifications. Epigenetic mechanisms and chromatin remodeling have recently been discussed as processes important in brain function (Taniura et al., 2007), and more examples of regulatory RNAs involved in neuronal function are likely to be revealed in future work.

2.5. Other mRNA-like RNAs

Some of the npcRNAs mentioned above belong to the class of mRNA-like RNAs which are characterized by multiple spliced exons and by a poly(A) tail at the 3'-terminus; however, they lack an open reading frame (Erdmann et al., 2000; Szell et al., 2008). A further example of these class of npcRNAs is a transcript specifically expressed in brain, named Ntab (non-coding transcript abundantly expressed in brain) RNA (French et al., 2001). This RNA is expressed at high levels in the CA3 area and in the dentate gyrus of the hippocampus. Ntab RNA appears to be localized in dendrites, suggesting a possible role in synaptic activity or plasticity.

Human accelerated regions (HARs) are genome sequences that are conserved in vertebrates and that have been proposed to show a significant accelerated nucleotide substitution rate in humans (Pollard et al., 2006). In a comparative genome analysis, the 118 bp region HAR1 on chromosome 20 appeared as the fastest-evolving region in the human genome: 18 nucleotide substitutions have been estimated to have occurred in human HAR1 since the time of a human– chimpanzee ancestor, whereas for example only 4 nucleotide substitutions were observed between chimpanzee and mouse orthologous HAR1 sequences, and an average of 0.27 substitution was calculated among other amniotes (Pollard et al., 2006). HAR1 is part of the gene HAR1F, the transcript of which has been detected in human brain by in situ hybridization but not by Northern blot analysis (Pollard et al., 2006). Interestingly, the HAR1F transcript is likely an npcRNA, as suggested by analysis of its protein coding potential (Pollard et al., 2006). HAR1F is expressed in the developing human neocortex at critical stages of neuronal differentiation and migration (Pollard et al., 2006). A recent enzymatic and chemical analysis of the secondary structure of HAR1, the probable functional domain of HAR1F RNA, shows that just a few nucleotide substitutions cause the transition from the unstable hairpin structure found in chimpanzees to the cloverleaf-like structure observed in humans (Beniaminov et al., 2008). The distinct localization and structural characteristics of HAR1F RNA in humans suggest an important role of this npcRNA in brain, although its mechanism of action in neurons remains to be elucidated.

2.6. BC RNAs

As discussed above, many of the regulatory functions of npcRNAs impact protein synthetic output through changes of mRNA stability or chromatin modifications. Other npcRNAs directly target the protein synthetic process by interacting with the translational machinery (Chekulaeva and Filipowicz, 2009). One example is the Brain-specific Cytoplasmic (BC) subtype of regulatory RNAs. BC1 RNA and the smaller BC2 transcript were identified in rodents, and both were found expressed almost exclusively in neurons (DeChiara and Brosius, 1987; Milner et al., 1984; Sutcliffe et al., 1982; Sutcliffe et al., 1984). BC1 RNA, and a human counterpart BC200 RNA, are located in somatodendritic domains (Tiedge et al., 1991; Tiedge et al., 1993). BC1 RNA is actively transported from somata to dendrites, in a process that is mediated by a cis-acting targeting element located in the 5'-most domain of the RNA (Muslimov et al., 1997). BC1 RNA inhibits formation of 48S initiation complexes through interaction with poly(A)-binding protein (PABP) and eukaryotic initiation factor 4 A (eIF4A) (Kondrashov et al., 2005; Wang et al., 2002; Wang et al., 2005). BC1 RNA, as well as BC200 RNA, blocks the ATP-dependent helicase activity of eIF4A, decoupling ATP hydrolysis from the mRNA unwinding (Lin et al., 2008).

More recently, physiological data have revealed a role of BC1 RNA in epileptogenesis (Zhong et al., 2009). Previous studies have shown that stimulation of group I metabotropic glutamate receptors (mGluRs) in hippocampal slices induces prolonged epileptiform discharges (Merlin and Wong, 1997; Merlin et al., 1998; Wong et al., 1999). Such epileptogenic induction requires activation of the mitogen-activated protein kinase kinase/extracellular regulated kinase (MEK-ERK) pathway (Zhao et al., 2004) and of protein synthesis (Merlin and Wong, 1997; Merlin et al., 1998; Wong et al., 1999). The prolonged epileptiform discharges result from group I mGluR-mediated induction of a voltage-dependent cationic current in hippocampal CA3 pyramidal cells that leads to hyperexcitability of the neuronal population (Bianchi et al., 2009; Chuang et al., 2000; Chuang et al., 2001). The group I mGluR-mediated epileptogenic process is triggered by application of the selective agonist 3,5-dihydroxyphenylglycine (DHPG), but not by synaptically released glutamate. Recent work suggests that group I mGluR-mediated epileptogenesis is normally prevented by BC1 RNA-mediated inhibitory control of translation (Fig. 1A) as in preparations from mice lacking BC1 RNA (BC1^{-/-}), synaptic stimulation of group I mGluRs does induce MEK-ERK- and protein synthesis-dependent epileptogenesis (Fig. 1B) (Zhong et al., 2009). BC1^{-/-} animals also show heightened susceptibility to epilepsy following auditory stimulation (audiogenic seizures). These audiogenic seizures are also suppressed by blockers of the group I mGluR–MEK-ERK–protein synthesis pathway.

Thus, the functional data show that BC1 RNA is a translational regulator of group I mGluR-mediated protein synthesis-dependent excitatory responses in the brain.

3. Concluding Remarks

Increasing evidence that diverse types of npcRNAs contribute to the regulation of gene expression in the nervous system suggests that these RNAs modulate neuronal functions. Abnormal expression or impaired binding properties of regulatory RNAs are associated with impaired brain function, suggesting a role of altered regulatory RNA functionality in brain disorders such as Alzheimer's disease, ataxias, and epilepsy. There is therefore reason to hope that future work in this area may lead to new diagnostic tools and therapeutic approaches.

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Fig. 1. BC1 RNA modulates group I mGluR-dependent excitability in the nervous system
(A) In wild type (WT) animals, BC1 RNA maintains an appropriate neuronal excitability tone at the synapse by inhibiting (red line) protein synthesis stimulated by the group I mGluR– MEK/ERK pathway (green arrows).
(B) Absence of BC1 RNA in BC1^{-/-} animals shifts the balance towards group I mGluR-stimulated protein synthesis and precipitates cellular hyperexcitability and epileptogenesis. mGluR, metabotropic glutamate receptor; MEK/ERK, mitogen-activated protein kinase kinase/extracellular signal-regulated kinase; PABP, poly(A) binding protein; eIF, eukaryotic initiation factor.