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RNA binding proteins, neural development and the addictions

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Abstract

Transcriptional and post-transcriptional regulation of gene expression defines the neurobiological mechanisms that bridge genetic and environmental risk factors with neurobehavioral dysfunction underlying the addictions. More than 1000 genes in the eukaryotic genome code for multifunctional RNA binding proteins (RBPs) that can regulate all levels of RNA biogenesis. More than 50% of these RBPs are expressed in the brain where they regulate alternative splicing, transport, localization, stability, and translation of RNAs during development and adulthood. RBP dysfunction can exert global effects on their targetomes that underlie neurodegenerative disorders such as Alzheimer's and Parkinson's disease as well as neurodevelopmental disorders, including autism and schizophrenia. Here, we consider the evidence that RBPs influence key molecular targets, neurodevelopment, synaptic plasticity, and neurobehavioral dysfunction underlying the addictions. Increasingly well-powered genome-wide association studies in humans and mammalian model organisms combined with ever more precise transcriptomic and proteomic approaches will continue to uncover novel and possibly selective roles for RBPs in the addictions. Key challenges include identifying the biological functions of the dynamic RBP targetomes from specific cell types throughout subcellular space (e.g., the nuclear spliceome versus the synaptic translatome) and time and manipulating RBP programs through post-transcriptional modifications to prevent or reverse aberrant neurodevelopment and plasticity underlying the addictions.

Introduction

RNA binding proteins (RBPs) bind both RNAs and proteins to regulate all aspects of mRNA biogenesis and metabolism, "from the cradle (transcription) to the grave (decay)" (Doyle & Kiebler, 2012). RBPs bind and package specific pre-mRNAs and proteins into unique and highly dynamic ribonucleoprotein (RNP) complexes to regulate splicing, editing, polyadenylation, nuclear export, localization, translation, and stability (Glisovic et al., 2008). More than 1000 mammalian genes code for RBPs and 20% of all protein products represent RBPs (Gerstberger, Hafner & Tuschl, 2014), reflecting the extensive splicing and diversity of RBP function. RBPs possess modular RNA binding motifs that cooperatively determine target specificity as well as auxiliary domains that mediate protein-protein interactions and post-translational modifications that can modify RNA binding, transport, and localization of RBPs (Glisovic et al., 2008). Importantly, post-translational modification of RBP signaling is potentially a useful strategy to prevent and treat a variety of disease states (Wang et al., 2009; Kim et al., 2014).

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Dozens of RBPs have established roles in neurodevelopment and synaptic plasticity (Doxakis, 2014) and a large literature documents the contribution of RBPs to neurodegenerative disorders (Romano & Buratti, 2013) and neurodevelopmental disorders such as autism and schizophrenia (Bill et al., 2013; Fernandez, Rajan & Bagni, 2013). However, much less is known regarding RBPs and neuropsychiatric disorders such as the addictions. There are several reasons to suspect that RBPs play a crucial role in the addictions. First, alternative splicing – one of the key nuclear functions of RBPs – is highly prevalent within the CNS and is associated with several psychiatric disorders (Glatt et al., 2011). Human genome-wide association studies (GWAS) have yet to uncover statistically significant associations between RBPs and the addictions; however, several genome-wide significant intronic variants for psychiatric disorders have been identified within RBP targets that affect RBP binding and splicing (Glatt et al., 2011). Second, several RBPs play a critical role in neurodevelopment and thus, could mediate transcriptomic programs that are activated following encounter with stressors during critical developmental periods and increase risk for the addictions (Andersen & Teicher, 2009). Third, drug-induced synaptic plasticity is an important component throughout all stages of addiction and dozens of RBPs have been identified that exhibit cytoplasmic function in transporting, localizing, and translating mRNAs in synaptic plasticity (Thomas et al., 2014; Tolino, Kohrmann & Kiebler, 2012).

Considering the addictions as neuropsychiatric disorders that have a neurodevelopmental component

Genetic and fluctuating environmental risk factors affect neurodevelopment and the later neurobiological responses to external stimuli (van Loo & Martens, 2007). The addictions are gene x environment disorders that require drug exposure to manifest. Both genetic and environmental risk factors likely interact to affect neurodevelopment and neuropharmacological sensitivity to reinforcing stimuli, including drugs and associated cues (Leyton & Vezina, 2014; Andersen & Teicher, 2009). Severe childhood adversity is a key environmental risk factor that greatly increases susceptibility to the addictions (Kendler et al., 2000) and early life stress causes structural changes that affect mesolimbic reward function, including reduced hippocampal and prefrontal cortical development that may heighten dopamine release in the nucleus accumbens (Andersen & Teicher, 2009). We posit that a subset of RBPs orchestrate neurodevelopmental plasticity induced by environmental risk factors that increases susceptibility to the addictions. The mesocorticolimbic dopaminergic circuitry is involved in reward/aversion processing and positive/negative reinforcement learning in the addictions and includes midbrain dopaminergic neuron projections from the ventral tegmental area to the medial prefrontal cortex and nucleus accumbens and glutamatergic projections from the prefrontal cortex to the nucleus accumbens (Volman et al., 2013). Mesocorticolimbic dysfunction is common in numerous neurodevelopmental and neuropsychiatric disorders, especially the addictions (Dichter, Damiano & Allen, 2012). Understanding the potential contribution of RBPs in mesocorticolimbic development, environmental risk factor-induced plasticity, and drug-induced plasticity could improve our understanding of the heritable basis of addictive disorders, especially within the context of gene x environment (G x E) interactions (Wermter et al., 2010).

As an example of a hypothesized role for RBPs in G x E interactions in neurodevelopment and plasticity underlying psychiatric traits, a genetic variant in the gene coding for brain-derived neurotrophic factor (BDNF; the Val66/Met allele) that decreases activity-dependent secretion of BDNF is associated with phenotypic variation in psychiatric endophenotypes (e.g., fear/aversion learning) during childhood versus adolescence (Casey et al., 2009). Furthermore, individuals carrying the Val66/Met BDNF variant that also underwent early childhood adversity (institutionalization) showed a decrease in cortical volume, an increase in amygdala volume, an increase in behavioral anxiety, and an increase in cortisol stress response (Casey et al., 2009). Accumulating evidence indicates that RBPs can regulate translation of BDNF (Allen et al., 2013; Vanevski & Xu, 2015) and that an increase in BDNF signaling can increase translation and synaptic localization of RBPs (Castren et al., 2002). In this review, we summarize recent examples of RBPs that affect primary molecular targets and cellular, neurodevelopmental, and neurobehavioral function relevant to the addictions. We begin by discussing examples that contain the most direct experimental and circumstantial evidence that draws a link to the addictions (FMRP, hnRNPs). Toward the end, we discuss those RBPs for which there is less, yet accumulating evidence (RBFOX and CELF proteins). Finally, we include a section on RNA editing and the addictions, as this exciting new area of research comprises distinct molecular mechanisms from the remainder of the review. Because multiple RBPs frequently coordinate in large RNP complexes to coordinate post-transcriptional regulation of mRNAs, we have attempted to draw links between various discussed RBPs and their families whenever relevant, while keeping in mind that it would be beyond the scope of the review to document all possible connections between the large number of RBPs that are discussed.

FMRP

Fragile X mental retardation protein (FMRP) is a polyribosome-associated neuronal RBP that targets and translationally represses mRNAs associated with synaptic plasticity and has been implicated in autism, affective disorders, ADHD, bipolar disorder, schizophrenia and the addictions (Fernandez, Rajan & Bagni, 2013; Smith et al., 2014). FMRP is expressed throughout neurodevelopment and is necessary for proper differentiation, migration, axon formation, refinement and stabilization, synapse formation and circuit wiring of neocortical layers (Till, 2010). FMRP inhibits ribosomal translocation of mRNAs that is relieved following activity-dependent signaling to permit cytoskeletal remodeling that underlies synaptic plasticity (Darnell et al., 2011; Darnell & Klann, 2013). The N-terminal region contains two Tudor domains that bind noncoding RNAs followed by a nuclear localization signal NLS. The middle of the protein contains two hnRNP K homolology (KH) domains that further specify RNA and protein interactions. The C-terminal region contains a nuclear export signal followed by an RGG box that directly binds to mRNA targets (Fernandez, Rajan & Bagni, 2013).

Signaling by several different receptor types modulate FMRP activity, including mGluRs, AMPA, GABA, NMDA, TrkB, dopamine, and cannabinoid receptors (Fernandez, Rajan & Bagni, 2013). Accordingly, FMRP targets hundreds of neurodevelopmental and neuroplasticity proteins involved in cytoskeletal remodeling; many of these targets have been associated with the addictions, including mGluR1, mGluR5, PSD-95, CYFIP1/2, GABA-A

receptor subunits, NR2A/2B NMDA receptor subunits, Homer1, neuroligins, CREB binding protein and D1 dopamine receptor-coupled GRK2 (Wang et al., 2008; Darnell & Klann, 2013). FMRP also targets elongation factor-1 and −2 (EF-1, EF-2), argonaute 1/2 (Ago1/2), and Dicer which are ubiquitously involved in protein translation and miRNA processing, respectively (Darnell & Klann, 2013). Thus, FMRP can also exert widespread, indirect regulation of the translatome.

With regard to drugs of abuse, deletion of FMRP perturbs midbrain dopaminergic neuron development, amphetamine-induced dopamine release in the striatum and prefrontal cortex, psychostimulant-induced locomotor activity, stereotypy, and drug reward (Fish et al., 2013; Fulks et al., 2010). FMRP deletion also disrupts cocaine-induced neurobehavioral plasticity in the nucleus accumbens, including decreased locomotor sensitization, enhanced stereotypy, perturbed dendritic morphology, changes in AMPA/NMDA receptor ratios and glutamatergic transmission, and reduced cocaine reward that is associated with increased mGluR5 activation (Smith et al., 2014). In prefrontal cortical neurons, D1 dopamine receptor activation is sufficient to induce FMRP phosphorylation and synthesis of synaptic proteins involved in glutamate receptor trafficking and plasticity (Wang et al., 2008; Wang, Kim & Zhuo, 2010). In another example that indirectly implicates FMRP in the addictions, cytoplasmic FMRP-interacting protein 1 (CYFIP1) inhibits elf4E–mediated cap-dependent mRNA translation of proteins involved in actin cytoskeleton remodeling and dendritic spine maturation (De Rubeis et al., 2013; Napoli et al., 2008) and mutations in the closely related *Cyfip2* gene in mice modulates psychostimulant-induced locomotor activity and sensitization, dendritic morphology, and AMPA receptor neurotransmission (Kumar et al., 2013). In addition to an mGluR5 mechanisms underlying neurobehavioral dysfunction in the absence of FMRP (Smith et al., 2014; Bear, Huber & Warren, 2004), neuronal activity and BDNF/TrkB signaling can regulate expression of FMRP in the hippocampus (Castren et al., 2002) and FMRP deletion perturbs both BDNF and TrkB spatiotemporal expression and signaling in neurodevelopment and neuroplasticity (Castren & Castren, 2014). Thus, both BDNF/TrkB and mGluR5 signaling could converge on FMRP mechanisms of psychostimulant neurobehavioral plasticity (Smith et al., 2014; Kumar et al., 2013).

Because FMRP deletion increases protein translation and disrupts structural and synaptic plasticity induced by glutamate receptor signaling (e.g., mGluR-LTD), an important question is whether or not fine tuning glutamatergic signaling by the use of pharmaceuticals targeting NMDA receptors and mGluR can improve the outcome of neurodevelopmental and neuropsychiatric disorders associated with FMRP dysfunction (Michalon et al., 2012; Bear, Huber & Warren, 2004), including the addictions (Cleva et al., 2010). FMRP also undergoes post-translational modifications, including mGluR-mediated dephosphorylation and relief from translational repression as well as mTOR-mediated dephosphorylation by protein phosphatase 2A (PP2A) and re-establishment of translational repression via PP2A suppression (Narayanan et al., 2008; Ceman et al., 2003), presenting additional opportunities for perturbing FMRP mechanisms of neurodevelopmental and neuropsychiatric dysfunction.

hnRNPs

Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a large and diverse group of nucleoplasmic-localized multifunctional RBPs that form RNP complexes and can regulate splicing, export, localization, translation, and stability (Han, Tang & Smith, 2010; Dreyfuss, Kim & Kataoka, 2002). Rapidly accumulating studies are identifying new contributions of hnRNPs to neurodevelopment (Sinnamon et al., 2012; Liu & Szaro, 2011) and synaptic plasticity (Zhang, Neubert & Jordan, 2012; Leal, Afonso & Duarte, 2014; Folci et al., 2014; Sinnamon & Czaplinski, 2011). hnRNPs contain highly conserved, modular RNA recognition motifs (RRMs) that determine sequence binding specificity and affinity and intevening regions that localize and permit generalized and specific roles in post-transcriptional processing. The hnRNPs were originally classified based on their coimmunopurification in RNA complexes with monoclonal antibodies against the founding member hnRNP C, thus identifying hnRNP A-U (Dreyfuss et al., 1993). Although hnRNPs can be highly similar in protein structure and function, their nomenclature is not consistent with their sequence homology, suggesting independent evolution and expansion of several RRMs. As examples, some hnRNPs share greater sequence similarity with other RBP classes such as hnRNP A1 versus ELAVL4/CELF1 or hnRNP C versus the SR protein transformer-2β (Tra2β) (Tang et al., 2012). Furthermore, other hnRNPs such as E/K, I/L, U, I (PTBP-1), and hnRNP F/H contain separate, quasi-RRMs that do not share sequence homology with canonical RRMs of hnRNPs (Tang et al., 2012). Thus, discussing hnRNPs as a separate class is somewhat arbitrary but for ease of reference, here we will discuss addiction-relevant RBPs that have been named hnRNPs and in the immediately following sections, we will discuss hnRNPs that have alias names.

The mu opioid receptor (MOR) is a primary molecular target for the addictive properties of opioids and other drugs of abuse (Contet, Kieffer & Befort, 2004) and undergoes alternative splicing by hnRNP H1 binding to the intronic AGGG sequence and recruiting hnRNP A1, A2B1, AB, C, H3, and U which results in exclusion of exon 2 and decreased expression of *Oprm1* (mu opioid receptor; MOR) (Xu et al., 2014). The MOR intronic SNP rs9479757 decreased binding of hnRNP H1, resulting in exon 2 skipping and increased MOR expression that was associated with increased severity of heroin dependence (Xu et al., 2014). hnRNP H1 and hnRNP F can also post-transcriptionally regulate MOR expression by repressing translation at the 5’ UTR (Song et al., 2012), providing a second level of MOR regulation by hnRNP H1.

We used fine-scale gene mapping with interval-specific congenic mouse lines to identify a 206 kb region on chromosome 11 containing *Hnrnph1* (the gene coding for hnRNP H1) and *Rufy1* that was necessary for reduced sensitivity methamphetamine-induced locomotor activity. Replicate mouse lines harboring transcription activator-like effector nucleases (TALENs)-induced frameshift deletions in *Hnrnph1* recapitulated the QTL phenotype, thus identifying *Hnrnph1* as the quantitative trait gene (Yazdani et al., 2015). Inheritance of this caused a decrease in expression of *Bdnf, Elavl2, Elavl4*, and *Nurr1* (nuclear receptor related 1 protein) (Yazdani et al., 2015), a transcription factor that is crucial for the development and function of midbrain dopaminergic neurons (Campos-Melo et al., 2013). hnRNP H1 (along with hnRNP A1, K, and M) has been shown to be co-regulated with *Nurr1* expression across

neuronal cell lines (Johnson et al., 2011) and a recent review of proteomic studies of neuronal and brain expression with drugs of abuse identified psychostimulant- and opioid-induced changes in hnRNP H2 and A1 expression that could regulate gene networks enriched for protein modification/degradation, synaptic/neuronal function, transmission, and signaling (Wang, Yuan & Li, 2011). We are currently evaluating the potential role of *Hnrnph1* in the rewarding and reinforcing properties of psychostimulants and opioids and changes in the transcriptome and spliceome associated with *Hnrnph1* dysfunction.

Hnrnph1 is highly and ubiquitously expressed throughout the mouse brain (Lein et al., 2007). It contains three quasi-RRMs that mediate binding to poly-(G) tracts to either enhance or silence splicing (Han, Tang & Smith, 2010). hnRNP H protein is primarily localized to the nucleus in primary rat cortical neurons and depolarization via KCl application increased the intensity of nuclear immunocytochemical staining (Fig. 1), suggesting activity-dependent nuclear function that is consistent with its role in alternative splicing and polyadenylation (Katz et al., 2010). Nevertheless, hnRNP H1 also contains three, intervening glycine-rich domains and the central domain contains a NLS that permits bidirectional transport between the nucleus and cytoplasm (Van Dusen et al., 2010). These modular glycine-rich domains are also necessary for regulation of splicing (Wang et al., 2012) and likely mediate interaction with other proteins, including complexing and cooperating with hnRNP A1, RBFOX2, and hnRNP F to enhance the suppress exon inclusion (Mauger, Lin & Garcia-Blanco, 2008; Fisette et al., 2010). hnRNP H1 can also cooperate with hnRNP I (see PCBP-1 below) to form a a splicer enhancer complex in neurons (Chou et al., 1999).

To summarize, increasing evidence indicates that hnRNPs such as hnRNP H1 may be involved in establishing multiple addictions. The role of hnRNP H1 in activity-dependent synaptic plasticity is not known although intriguingly, *Hnrnph1* was identified as one of the most significantly upregulated transcripts in transcriptome analysis of cortical brain tissue following experimental traumatic brain injury (Kobori, Clifton & Dash, 2002) which could indicate a role in regenerative plasticity. Available evidence from our laboratory indicates that neuronal stimulation induces an increase in hnRNP H staining that is localized to the nucleus (Fig. 1), suggesting that the contribution of hnRNP H1 to neuroplasticity is either indirect (e.g., via nuclear splicing or nuclear polyadenylation of synaptic targets) or that dendritic localization of hnRNP H requires signaling through specific receptors. We are currently testing the latter hypothesis in the context of the addictions by treating neurons with dopamine receptor agonists and examining changes in hnRNP H staining. Because hnRNP H1 can undergo several post-translational modifications such as phosphorylation, methylation, and sumoylation (Chaudhury, Chander & Howe, 2010), there is potential to fine tune hnRNP H1 signaling to prevent or normalize plasticity associated with the addictions.

PCBPs (including hnRNP K)

Polycytosine-binding proteins (PCBPs) 1–4 (hnRNP E1-E4) and hnRNP K, bind with high affinity to poly(C) DNA and RNA sequences to regulate transcription and post-transcriptional processing via three, modular hnRNP K homolology (KH) RNA binding

domains (Han, Tang & Smith, 2010). PCBPs also contain an intervening sequence between the second and third KH domains with nuclear localization signals (PCBP1 and 2) or an hnRNP K-specific nuclear shuttling domain to permit bidirectional transport. hnRNP K also has a SH-3 (KI) binding domain and both hnRNP K and PCBP4 contain an NLS in the third KH domain (Choi et al., 2009). hnRNP K, PCBP1, and PCBP2 are located primarily in the nucleus whereas PCBP3 and 4 are located primarily in the cytoplasm (Chaudhury, Chander & Howe, 2010).

In neurodevelopment, PCBPs regulate axonogenesis (Thyagarajan & Szaro, 2004) and corticogenesis (Pilaz & Silver, 2015). PCBP1–3 are expressed in the adrenal medulla, midbrain and locus coeruleus, respectively where they bind the 3’ UTR of tyrosine hydroxylase (TH, the enzyme necessary for synthesis of dopamine and norepinephrine) in the cytoplasm to increase stability and protein translation (Boschi et al., 2015; Czyzyk-Krzeska & Beresh, 1996). In addition to regulating catecholamine synthesis, hnRNP K, PCBP1, and PCBP2 can all bind to the MOR promoter to activate MOR transcription whereas PCBP3 acts as a transcriptional repressor (Choi et al., 2008; Choi et al., 2007; Choi et al., 2009).

hnRNP K interacts with ELAVL2 to control neuronal differentiation (Yano, Okano & Okano, 2005) and regulates axonogenesis via post-transcriptional interaction with genes involved in neurodevelopment, transport, localization, and cytoskeleton, including GAP-43 (Liu & Szaro, 2011; Liu, Gervasi & Szaro, 2008). hnRNP K exhibits early developmental expression in several components of the mesocorticolimbic circuitry and subsequently a more restricted expression to the hippocampus (Blanchette, Fuentes Medel & Gardner, 2006). hnRNP K can bind to the TH promoter to activate transcription (Banerjee et al., 2014) and co-localizes with TH in the ventral midbrain. Thus, hnRNP K could regulate catecholamine synthesis during midbrain dopaminergic neuron development, maintenance, and synaptic plasticity in adulthood (Folci et al., 2014). hnRNPK also binds to the polyadenylation sequence within the 3’UTR of the serotonin transporter (SERT), a primary molecular target for cocaine reward (Sora et al., 2001), to increase SERT protein levels by preventing miR-16-mediated inhibition of translation (Yoon et al., 2013). In addition to its link to catecholamines and monoamines, hnRNP K can bind to the MOR promoter and to the promoter of the beta-2 subunit of the neuronal nicotinic acetylcholine receptor to activate transcription (Choi et al., 2008; Du, Melnikova & Gardner, 1998). Finally, morphine can stimulate hnRNP K translation in multiple brain regions independent from transcription (Lee et al., 2014).

To summarize, PCBPs and hnRNP K are associated with neurodevelopment, catecholaminergic, monoaminergic, and opioidergic, and cholinergic signaling and thus, are prime suspects in regulating neurotransmitter signaling underlying the addictions. Importantly, post-translational modifications can also significantly impact cell function of PCBPs. A notable example is ERK-induced phosphorylation of hnRNP K which translocates hnRNP K to the cytoplasm where it can then bind to the 3’ UTR of mRNAs to regulate protein translation (Habelhah et al., 2001). Therefore, therapeutic modulation of hnRNP K signaling could be a future treatment avenue in the addictions.

PTBPs (including PTBP-1; a.k.a. hnRNP I)

Polypyrimidine tract-binding protein (PTBPs) bind to both intronic and exonic polypyrimidine tract sequences to repress exon inclusion. PTBPs contain four RRMs, a nuclear localization signal and a nuclear export signal in the N-terminus that permit alternative splicing, shuttling, polyadenylation, transport, localization, stabilization, and translation (Romanelli, Diani & Lievens, 2013; Keppetipola et al., 2012). RRM-1 and RRM2 are separated by flexible linkers that permit independent conformations whereas RRM-3 and −4 form a globular structure and binds to nearby, intervening pyrimidine tracts to induce RNA looping (Romanelli, Diani & Lievens, 2013). Alternatively spliced isoforms of PTBP1 can contain longer intervening domains or isoforms that lack RRM-1 and −2, thus diversifying PTBP targets and function within the context of an RNP complex. Splicing repression by PTBP can depend on its proximity to the splice site, its antagonism by other RBP splicing co-factors such as CELF proteins (Spellman et al., 2005; Gromak et al., 2003) and neuro-oncological ventral antigen1 (Nova1) (Polydorides et al., 2000), and its interaction with co-repressors such as the Raver proteins (Henneberg et al., 2010). In addition to splicing, PTBP1 can bind directly to 3’ UTRs to regulate cleavage in polyadenylation, 3’ UTR exon inclusion, and mRNA stability (Sawicka et al., 2008). Finally, PTBPs interact with PCBPs act at the internal ribosomal entry site (IRES) to initiate translation (Bushell et al., 2006).

During neurodevelopment, reciprocal changes in PTBP1 and 2 expression coordinate differential splicing of PSD-95 to control the timing of neuronal differentiation (Zheng et al., 2012). PTBP1 is expressed in neural progenitors and decreases during differentiation and is restricted to glia during adulthood. In contrast, expression of the gene paralog PTBP2 increases during neuronal differentiation, decreases during cortical maturation, and shows moderate neuronal expression during adulthood (Keppetipola et al., 2012). Notably, PTBP1 inhibits the expression of PSD-95 in neural progenitors whereby it represses the inclusion of a coding exon which results in nonsense-mediated decay and delays excitatory synapse stabilization and maturation (Zheng et al., 2012; Keppetipola et al., 2012). A similar mechanism is used by PTBPs to inhibit their own expression (Boutz et al., 2007). PTBP2 is essential for postnatal survival and genome-wide RNA target analysis of the developing mouse brain revealed that PTBP2 inhibits a splicing program involved in neuronal cell cycle, proliferation, actin cytoskeleton, and neuronal differentiation (Licatalosi et al., 2012).

With regard to dopamine receptors and the addictions, the short and long splice forms of the D2 dopamine receptor (D2L and D2S) are highly conserved and have different signaling properties and physiological function (Picetti et al., 1997) that have been associated with the addictions (Smith et al., 2002; Levran et al., 2015). Both PTBP1 and Nova1 promote exon 6 inclusion whereas hnRNP M inhibits exon 6 inclusion, thus bi-directionally regulating D2L versus D2S expression (Sasabe, Futai & Ishiura, 2011; Park et al., 2011). Overexpression of PTBP1 *in vitro* was associated with a decrease in transcription of ΔfosB, a stable splice variant of the transcription factor fosB that accumulates in the nucleus accumbens following chronic administration of drugs of abuse and is associated with sustained drug-induced synaptic plasticity (Alibhai et al., 2007; Nestler, Barrot & Self, 2001). Thus, perhaps post-translationally modifying PTBP1, e.g., via phosphorylation and cytoplasmic translocation

(Xie et al., 2003), could modulate ΔfosB-mediated neuroplasticity associated with the addictions.

ELAVL

The neuronal-specific mammalian embryonic lethal, abnormal vision-like (ELAVL)2, 3, and 4 RBPs are an RBP family based on homology to ELAV protein in *Drosophila* (Robinow et al., 1988) and regulate the transport, stabilization, localization and translation of mRNAs. They contain three RRMs that mediate binding to intronic targets for splicing as well as binding to highly conserved AU-rich element (ARE) sequences of 3'UTR targets to regulate stability (Colombrita, Silani & Ratti, 2013), including Nova1 (Ratti et al., 2008). ELAVL4 can also enhance cap-dependent translation via structural unwinding of 5' UTRs (Fukao et al., 2009). ELAVL RBPs contribute to all stages of neuronal differentiation, maintenance, synaptogenesis, and activity-dependent synaptic plasticity (Perrone-Bizzozero & Bolognani, 2002). The localization of ELAVL RBPs in the neocortex and hippocampus (Okano & Darnell, 1997) suggest potential involvement in neurodevelopmental and neuroanatomical risk for the addictions (Andersen & Teicher, 2009). RBP target analysis of ELAVL of mouse forebrain tissue identified a spliceome enriched for axonal and synaptic cytoskeleton dynamics and 3'UTR-regulated genes involved in amino acid synthesis. Of note, ELAVL regulates the splicing and half-life of glutaminase, indicating an essential role in excitatory neurotransmission (Ince-Dunn et al., 2012).

Acute cocaine treatment caused a decrease in whole brain FMRP expression and an increase in ELAVL expression that was associated with an increase in expression of genes enriched for dendritic synaptic plasticity (Tiruchinapalli, Caron & Keene, 2008). Combining repeated cocaine administration with swim stress increased ELAVL4 phosphorylation and translation in the hippocampus as well as expression of its canonical cytoskeletal target, Growth Associated Protein (GAP)-43 (Pascale et al., 2011), which could contribute to structural plasticity and drug associative learning (Bolognani et al., 2007). Importantly, ELAVL4 selectively binds to the unique ARE sequence of the long 3' UTR but not the short 3' UTR of BDNF mRNA to increase BDNF stability and activity-dependent translation (Allen et al., 2013). The increase in BDNF translation is mediated by PKC-induced phosphorylation of ELAVL4 which disinhibits 3'UTR-mediated translational repression of the long 3'UTR BDNF mRNA in hippocampal neuronal dendrites (Vanevski & Xu, 2015). Selective regulation of the long 3' UTR of BDNF is important because it is responsible for activity-dependent neuronal translation of BDNF (Lau et al., 2010) and synaptic maturation in the dendrites (An et al., 2008). Psychostimulant administration increases the expression of BDNF (Russo et al., 2009) and in turn, BDNF can regulate neuronal expression of FMRP and synaptic protein translation (Castren & Castren, 2014). Thus, an ELAVL-mediated increase in activity-dependent translation of BDNF and other mRNA targets may work in parallel with FMRP to induce neurobehavioral plasticity in response to drugs of abuse (Smith et al., 2014). Interestingly, an increase in BDNF expression may serve as a biomarker for severity of psychostimulant addiction and vulnerability to relapse in recently abstinent individuals (Sinha, 2011).

ZBP1

Zipcode Binding Protein-1 (ZBP1) is a cytoplasmic protein that shuttles between the nucleus and cytoplasm via its NES and NLS sequence. ZBP2 is a second, homologous RBP that is localized to the nucleus and cooperates with ZBP1 to shuttle beta-actin mRNA into the cytoplasm (Gu et al., 2002; Pan et al., 2007). ZBPs share significant homology with PCBPs and contain two RRMs and four KH-type RNA binding motifs. KH3 and KH4 domains of ZBP1 form a pseudodimer that recognizes a 54 nucleotide zipcode sequence on the 3' UTR of beta-actin mRNA for transport and translation in dendrites (Doyle & Kiebler, 2012; Gu et al., 2002; Huttelmaier et al., 2005; Ross et al., 1997; Farina et al., 2003).

ZBP1 represses beta-actin translation in the cytoplasm that is relieved upon Src phosphorylation at Tyr396 (Huttelmaier et al., 2005). Both BDNF and netrin-1 stimulate phosphorylation of ZBP1 at Tyr396 and increased protein synthesis of beta actin in a model of axon guidance in cortical neurons (Sasaki et al., 2010; Welshhans & Bassell, 2011). Neurodevelopmental studies demonstrate ZBP1 transport and localization of beta-actin in synaptogenesis of dendritic filopodia (Eom et al., 2003) and neurotrophin-induced growth cone motility (Zhang et al., 2001). Furthermore, ZBP1 is necessary for NMDA receptor-dependent targeting of beta-actin mRNA to the hippocampal dendrites (Tiruchinapalli et al., 2003) as well as dendritic arborization induced by Src-induced ZBP1 phosphorylation and relief of translational repression (Perycz et al., 2011). In addition to dendritic plasticity, axonal regeneration in severed sensory neurons involves ZBP1-mediated transport of both beta-actin and GAP-43 mRNAs to localize protein synthesis and increase axonal growth and branching, respectively (Donnelly et al., 2011; Donnelly et al., 2013).

Similar to ELAVL-associated increased expression of GAP-43 following *in vivo* administration of cocaine and stress (Pascale et al., 2011), *in vivo* axonal injury induced an increased in expression of GAP-43 that interacts with ELAVL4 as well as ZBP1 in a complex to induce axonal outgrowth and branching (Yoo et al., 2013). It was recently shown that although both ZBP1 and ELAVL4 interact with beta-actin, ELAVL4 binds specifically to the ARE sequence in the 3' UTR whereas ZBP1 requires a specific secondary structure (Kim et al., 2015) that could permit their ability to form a EVAL/ZBP complex in neuroplasticity underlying axonal regeneration and possibly cocaine neuroplasticity. In further support of a link between ZBP1 and cocaine, transgenic, ectopic expression of ZBP1 in the striatum during adulthood blocked cocaine-induced conditioned place preference that was rescued by eliminating ZBP1 expression. Direct, experimental target analysis identified nearly 200 transcripts involved in synaptic plasticity that could be responsible for the effect of ZBP1 on cocaine reward, including the scaffolding gene *Homer1* that negatively regulates cocaine reward (Szumlinski et al., 2004) as well as cadherins, transcription factors, kinases, ion channels, and Ras members (Lapidus et al., 2012). Interestingly, we previously identified both a behavioral QTL and a *cis*-acting eQTL from striatal tissue on chromosome 11 for *Igf2bp1* (insulin growth factor 2 mRNA binding protein 1; the gene coding for ZBP1 protein) that was causally associated with reduced methamphetamine-induced locomotor activity and increased *Igf2bp1* expression. In light of the recent ZBP1 findings discussed above, *Igf2bp1* could represent a quantitative trait gene underlying methamphetamine stimulant sensitivity (Bryant et al., 2012).

An intriguing possibility is that native ZBP1 expression could be re-awakened in the mature brain following chronic exposure to drugs of abuse and regulate a neurodevelopmental program that underlies certain addictions such as cocaine (Dong & Nestler, 2014). Furthermore, based on the combined evidence described above, ZBP1 could promote BDNF-mediated structural recovery of damaged catecholaminergic and monoaminergic axons following administration of neurotoxic drugs such as methamphetamine and MDMA (Adori et al., 2010; Ares-Santos et al., 2014).

RBFOX1 (A2BP1)

RBFOX (RNA binding protein, fox-1 homolog) proteins are neuronal splicing factors that promote both exon inclusion and skipping that depends on the position of the canonical UGCAUG binding motif near the exon (Underwood et al., 2005; Zhang et al., 2008). RBFOX proteins contain a highly conserved, identical RRM that is responsible for binding RNAs and less conserved regions in the N-terminus and NLS-containing C-terminus that also dictate splicing of RBFOX proteins themselves and other proteins which can govern subcellular localization and increase the functional diversity of these RBPs (Kuroyanagi, 2009).

Genome-wide target analysis of RBFOX2 in human embryonic stem cells identified several RBP splicing factors as targets, including hnRNP A2/B1, H1, H2, and PTBP (Yeo et al., 2009)., which emphasizes the high degree of network connectivity in genomic coordination of RBP splicing (Huelga et al., 2012). Enrichment analysis of the predicted RBFOX spliceome revealed sets of genes involved in neuromuscular, cytoskeleton, ion channel, and phosphorylation functions (Zhang et al., 2008). Experimental identification of direct RBFOX targets in the mouse brain identified intronic splicing targets and 3’ UTR targets that could regulate alternative polyadenylation and mRNA stability. RBFOX targets were enriched for cytoskeleton anchoring, scaffolding and signaling, and neuronal projections. Increased expression of RBFOX1 and RBFOX3 and decreased expression of RBFOX2 were associated with a change in the RBFOX spliceome programs from E17 to adulthood (Weyn-Vanhentenryck et al., 2014).

RBFOX1 is a neurodevelopmental splicing RBP whose dysfunction is associated with autism, intellectual disability, attention deficit hyperactive disorder, bipolar disorder, and schizophrenia (Bill et al., 2013; Fogel et al., 2012). CNS-specific knockout of *Rbfox1* in mice resulted in enhanced hippocampal neuronal excitability and susceptibility to seizures, demonstrating a role for RBFOX1 in neuronal excitation and synaptic transmission (Gehman et al., 2011). RBFOX1 is expressed throughout development in the mouse and human basal forebrain, neocortex, and hippocampus (Hammock & Levitt, 2011; Fogel et al., 2012). Spliceome and transcriptome analysis of differentiated primary human neural progenitor cells following RBFOX1 knockdown identified parallel networks of transcription factors, splicing factors, and synaptic proteins involved in neurogenesis, neurodevelopment, maintenance, cytoskeletal organization and cell adhesion, projection, proliferation, and synapse function. Notably, differential splicing was observed for several genes coding for RBPs, including *HNRNPD, HNRNPA1, ELAVL2*, and *HNRNPH1* (Fogel et al., 2012) which in turn, was associated with a perturbation in their predicted splicing programs based

on their RNA binding motifs. For example, 205 of the total 996 alternative splicing events that were identified following RBFOX1 knockdown contained the binding site for hnRNP H1, suggesting that RBFOX1 regulates the splicing of *HNRNPH1* (Fogel et al., 2012). Conversely, hnRNP H1 regulates the splicing activity of *RBFOX1/2* by interacting with the C-terminal domain (Sun et al., 2012). In addition to splicing *HNRNPH1*, RBFOX2 can form a complex with hnRNP H1 and F to silence splicing of other genes (Mauger, Lin & Garcia-Blanco, 2008). Thus, hnRNP H1 and RBFOX proteins could coordinate splicing in affecting methamphetamine stimulant behavior (Yazdani et al., 2015) and heroin addiction (Xu et al., 2014).

Recent, direct evidence implicating RBFOX in the nucleus accumbens in the addictions comes from a genome-wide trancriptomic and epigenomic study of chronic cocaine administration in mice that identified a translocation of RBFOX1 to the nucleus which was associated with an increase in splicing events that coincided with the location of histone modifications. Furthermore, site-specific Cre-mediated knockdown in the nucleus accumbens of floxed RBFOX1 mice blocked cocaine reward (Feng et al., 2014), which together suggests that that RBFOX1 coordinates an adaptive splicing program underlying cocaine dependence. Interestingly, RBFOX1 variants have been nominally associated with nicotine dependence, alcohol dependence, and cocaine reward and regulate the splicing of cell adhesion molecule genes in dopaminergic neurons that are associated with neurodevelopmental connectivity, plasticity, and genetic variation underlying the addictions (Zhong et al., 2015).

CELF4 and CELF6

CELF (CUG-BP, ELAV-like factor) is a family of highly expressed multifunctional RBPs in the brain that have both nuclear splicing and cytoplasmic functions in RNA processing. CELF and ELAV can cooperatively promote splicing in mammalian neurons and a recent study in *C. elegans* indicates that they co-regulate overlapping and distinct splicing networks to determine cholinergic versus GABAergic neuronal cell type (Norris et al., 2014). CELF RBPs bind to pyrimidine-rich sequences and compete with PTBPs to activate splicing (Spellman et al., 2005; Gromak et al., 2003). Notably, the high sequence similarity between hnRNP A1 versus CELF1 suggests shared functions (Tang et al., 2012). CELF RBPs contain highly conserved RNA recognition motifs (RRM)-1 and −2 at the N-terminus and a third RRM at the C-terminus (Dasgupta & Ladd, 2012). RRM-1 and −2 are separated from RRM-3 by a non-conserved divergent linker domain that differentiates CELF1–2 from CELF 3–6 in determining RNA-protein and protein-protein interactions in forming target-specific RNP complexes (Gallo & Spickett, 2010; Dasgupta & Ladd, 2012). The RRMs contain RNP motifs that typically bind to introns, 3’ UTRs, and 5’ UTRs of mRNAs to regulate splicing, poly(A)-specific ribonuclease recruitment and deadenylation [e.g., with c-fos (Moraes, Wilusz & Wilusz, 2006)], polyadenylation, mRNA stability and translation (Dasgupta & Ladd, 2012). Both the divergent domain and C-terminus contain the signals that determine nuclear versus cytosolic localization of CELF1 and CELF2 (Ladd & Cooper, 2004; Fujimura, Kano & Murata, 2008). Importantly, CELF proteins contain multiple phosphorylation sites that regulate protein and RNA interactions to influence protein stability, localization and translation of CELF targets (Dasgupta & Ladd, 2012).

CELF RBPs are linked to several neurological and neurodegenerative disorders, as well as neurodevelopmental and neuropsychiatric disorders, including social communication problems in autism (CELF4, CELF6), epilepsy (CELF4), bipolar disorder (CELF5), and schizophrenia (CELF5) (Ladd, 2013; Welter et al., 2014; Dougherty et al., 2013). Recent evidence implicates both CELF4 and CELF6 in the addictions. CELF4 is a brain-specific isoform that is expressed throughout development and is highly expressed in the hippocampus, amygdala, and cortex. CELF4 loss of function in mice causes seizures (Yang et al., 2007) and a functional deficit in excitatory synaptic transmission in cortical and hippocampal neurons (Wagnon et al., 2011). The complex seizure phenotype implicates a role for CELF4 in corticothalamic development (Wagnon et al., 2011). RNA target analysis of CELF4 in cortical and hippocampal tissue identified several 3' UTR-targeted mRNAs involved in synaptic transmission (Wagnon et al., 2012). Of potential relevance to the addictions, genetic variation in *CELF4* showed a nominal association ($P = 3–5 \times 10^{-6}$) with the subjective amphetamine response (Hart et al., 2012) and has been linked to hyperphagia-related obesity (Comuzzie et al., 2012; Halgren et al., 2012).

Translational profiling of ribosome-bound mRNAs from mouse serotonergic neurons combined with analysis of human genetic variants identified *CELF6* as a candidate gene associated with autism. *Celf6* knockouts exhibit reduced brain serotonin, deficits in ultrasonic vocalizations in neonatal pups, and behavioral resistance to change (Dougherty et al., 2013). CELF6 is expressed in both the nucleus and cytoplasm throughout development and exhibits localized expression in monoaminergic and catecholaminergic cells in the basal forebrain, ventral tegmental area, substantia nigra, raphe nuclei, and locus coeruleus (Maloney, Khangura & Dougherty, 2015). Thus, *Celf6* could influence neurodevelopment and function of the mesocorticolimbic reward circuitry. In support, *Celf6* knockouts show a disruption of conditioned cocaine reward (Dougherty, 2015). *CELF6* can promote both exon inclusion and skipping (Ladd et al., 2004). It will be important to determine the direct nuclear and cytoplasmic targets of *CELF6* which will provide insight into the subcellular mechanisms of behavioral and psychiatric dysfunction.

ADAR1/2

RNA editing is yet another type of distinct and adaptive pre-mRNA processing mechanism that can increase proteome diversity to regulate neurodevelopment, plasticity, and human disease, including neurological and psychiatric disorders such as schizophrenia, bipolar disorder, and depression (Li & Church, 2013). Adenosine deaminase acting on RNA (ADAR)-1, 2, and 3 are nuclear, enzymatic RBPs that contain double-stranded RNA binding motifs and destabilize pre-mRNA to "edit" adenosine (A) nucleotides to guanosine-mimicking RNA inosine (I) nucleotides. A-I editing changes the complementary nucleotide to cytosine, thus modulating RNA base pairing and potentially splice site, transport, ribosome binding, translational efficiency, and amino acid sequence (Slotkin & Nishikura, 2013; Li & Church, 2013). Compared to extensive editing of noncoding RNA, re-coding of coding exons is rare in mammals and these sites are enriched for proteins involved in neuronal function, including neuronal excitability, vesicular release, and cytoskeleton architecture (Rosenthal, 2015). The expansion of RNA editing from rodents to non-human primates to humans suggests and important role in brain evolution and cognition (Li &

Church, 2013). Although the regulation of ADAR in RNA editing is poorly understood, it is relevant to note that FMRP interacts with ADAR in *Drosophila* to modulate enzymatic activity and editing of mRNA transcripts that affect synaptic morphology (Bhogal et al., 2011; Bassell, 2011). This observation highlights an additional function of FMRP and suggests that FMRP and ADAR could work together in neurodevelopment and neuroplasticity in the addictions.

ADAR-2 has an established role in editing of the GluA2 subunit of the AMPA receptor at Q/R site 607 which reduces calcium permeability (Geiger et al., 1995) and may protect against neuronal excitotoxicity *in vivo* (Higuchi et al., 2000). With regard to the addictions, cocaine abstinence and cocaine-primed reinstatement of self-administration in rats has been associated with decreased ADAR-2 expression and decreased GluA2 editing of the Q/R site in the nucleus accumbens shell. Overexpression of ADAR-2 prevented relapse and the concomitant increase in surface receptor expression of AMPAR (Schmidt et al., 2014). Thus, unedited AMPAR receptors are associated with a model of drug relapse that could be mitigated by restoration of surface edited AMPA receptors.

In addition to AMPA receptor editing, ADAR proteins also edit the 5-HT2C receptor [a promising drug target for treating addictive disorders (Higgins & Fletcher, 2015)] at five different sites within the second intracellular loop, yielding up to 24 brain region-specific isoforms that could alter pre-mRNA splicing, ligand affinity, ligand-induced g-protein signaling, ligand-induced blockade of constitutive activity, and brain region-specific functions, including modulation of dopamine release (Werry et al., 2008; Burns et al., 1997). Interestingly, rats categorized as high versus low novelty seeking (a trait that correlates with future drug use) show differences in 5-HT2C receptor editing in the mesocorticolimbic circuitry, in particular the nucleus accumbens shell that could affect dopamine transmission (Dracheva et al., 2009). An increase in alcohol drinking in different mouse strains was associated with an increase in anxiety as well as an increase in ADAR1/2 expression and 5-HT2C editing in the nucleus accumbens and dorsal raphe nucleus (Watanabe et al., 2014). Finally, chronic nicotine decreased editing of the 5-HT2C in the hippocampus that was associated with depressive-like behavior during nicotine withdrawal (Zaniewska et al., 2015; Zaniewska et al., 2010). Thus, differential 5-HT2C receptor editing could potentially predispose individuals to addiction risk as well as mediate the negative emotional states that support addictive behaviors.

An increase in 5-HT2C receptor editing is associated with hyperphagia and obesity in patients with Prader-Willi Syndrome and in mice expressing the fully edited 5-HT2C receptor (Kawahara et al., 2008). Furthermore, mice that differentially express the wild-type or catalytically inactive version of ADAR2 show hyperphagia and obesity (Singh et al., 2007) and increased preference for high fat food over running (Akubuiro et al., 2013). These physiological and behavioral changes indicate a food “addiction” propensity that is supported by increased mRNA expression of ADAR2, D1 and D2 dopamine receptors, MOR, 5-HT2C long and short splice variants in the hypothalamus as well as increased mRNA expression of D1 dopamine receptors in the striatum. PET imaging in mice using a tail vein injection of [^{18}F] flurodeoxyglucose indicated an increase in glucose metabolism in the mesolimbic reward circuitry, hypothalamus, and hippocampus. The combined

observations implicate hyperactive food-directed reward processing in ADAR2 transgenics (Akubuiro et al., 2013; Singh et al., 2011); however, direct evidence linking RNA editing to food or drug addictive behaviors is still lacking.

To summarize, changes in AMPA receptor and 5-HT receptor editing are associated with exposure to abused substances and could contribute to susceptibility and synaptic plasticity underlying the addictions. Future studies will likely involve the use of advanced genome editing approaches to directly test the causal, spatiotemporal role of re-coded proteins as well as non-coding RNAs in the brain in the establishment and maintenance of addictive behaviors.

Summary

This review highlights the diversity of RBP functions in regulating transcription, RNA metabolism, neurodevelopment and neuroplasticity relevant to the addictions (Figure 2). Although beyond the scope of this review, RBPs also interact with noncoding RNAs and there are several new and emerging RNA modifications that could be of relevance to the addictions (Satterlee et al., 2014). Identifying the key cell type-specific splice forms and unique functions of RBP splice variants and their alternatively spliced targets will be critical to yielding novel, biologically relevant discoveries in the addictions. Do a specific set of RBPs become recruited during environmental stress exposure or drug exposure that influence addiction risk? What are the transcriptomes, spliceomes and translatomes (King & Gerber, 2014) that these RBPs govern in response to risk exposure, drug exposure, and the interactive exposure to both? How do these programs change across neurodevelopment, across repeated drug exposure as addiction progress, and across recovery during abstinence? In addition to splicing, post-translational modifications of RBPs, including phosphorylation, ubiquitination, sumoylation, and methylation can further regulate the transport, stabilization, degradation, and binding of RBPs to their RNA targets and to other proteins (Chaudhury, Chander & Howe, 2010), thus adding additional layers of regulation in RBP function. This complexity may one day be harnessed to perturb RBP signaling in preventing and treating the addictions as has recently been demonstrated in other disease models (Kim et al., 2014; Wang et al., 2009).

We limited our discussion to RBPs where multiple lines of evidence implicate a potential importance in the addictions. However, additional RBPs are certainly going to be uncovered in the addictive process from neurodevelopment to drug-induced neuroplasticity. For instance, cytoplasmic polyadenylation element binding proteins (CPEBs) plays an important role in synaptic plasticity (Ivshina, Lasko & Richter, 2014). Second, the SR protein Tra2β can be spliced by the dopamine signaling molecule DARPP-32 (Benderska et al., 2010) and can promote splicing of RGS proteins (regulators of g-protein signaling) in response to morphine (Li et al., 2013; Traynor, 2010). Third, KH-type Nova proteins also regulate splicing of the D2 dopamine receptor and neocortical synaptic proteins involved in neurotransmitter release and signaling, receptor localization, synaptogenesis, axonogenesis, actin organization, cell adhesion, and extracellular matrix organization (Park et al., 2011; Ule et al., 2005).

The topic of RBPs and the addictions is clearly a wide open and promising field of research; understanding how these remarkable proteins coordinate splicing and translation during neurodevelopment and neuroplasticity promises to yield dividends in understanding and treating neuropsychiatric diseases.

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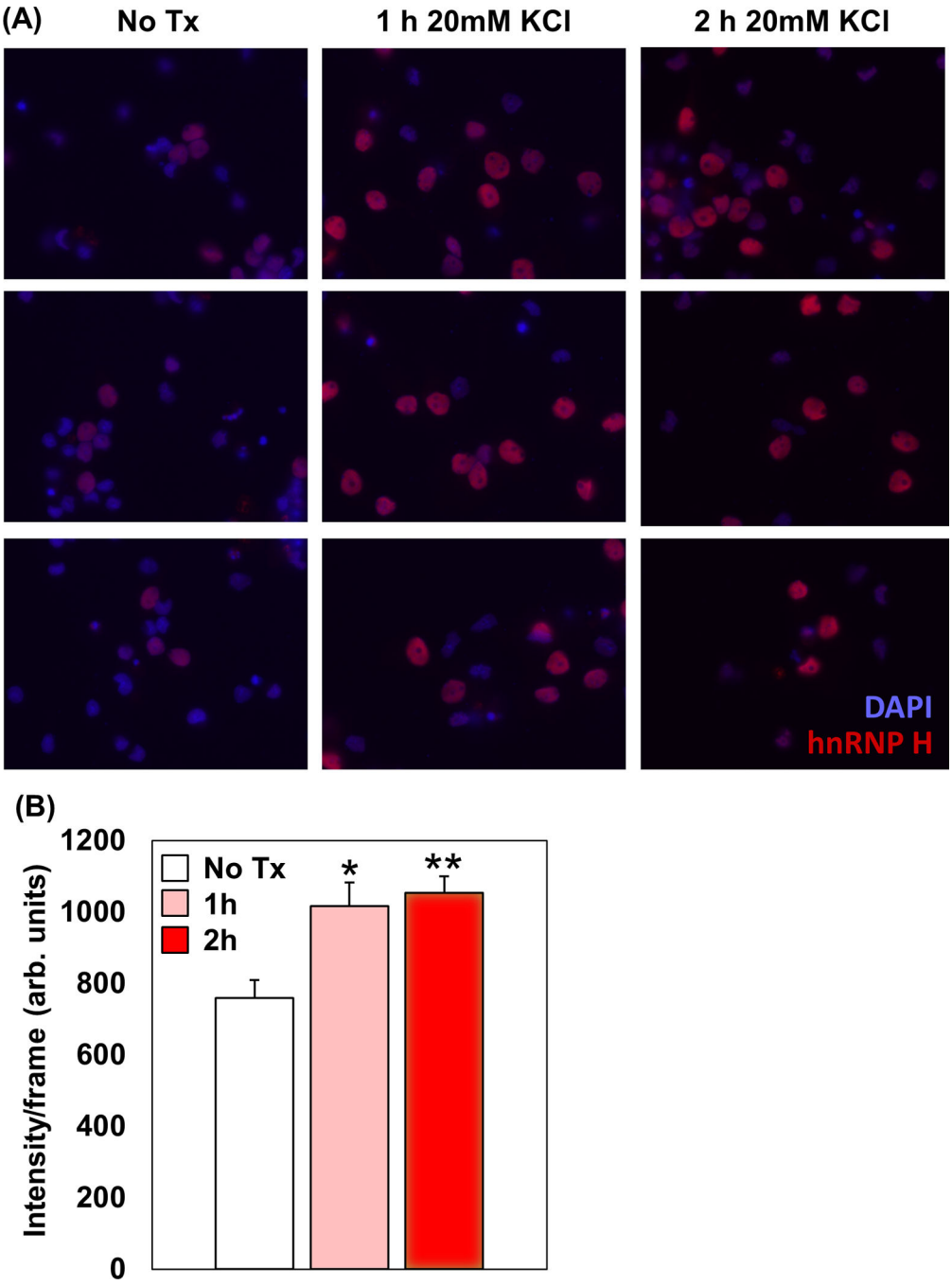

Figure 1. Immunocytochemical staining of hnRNP H in rat cortical neurons following KCl-induced depolarization

(A): Primary neocortical neurons were dissected from E18 Sprague-Dawley rat embryos (Charles River Laboratories). Dissociated neurons were cultured neurons for 1 week. For the control, no treatment (No Tx) group, 1 ml of conditioned media was replaced with 1 ml of neurobasal media. For the 1 h and 2 h Tx groups, 1 mL of conditioned media was replaced with 1ml of 20 mM KCl-enriched neurobasal media. Treated neurons were then washed, fixed, permeabilized, blocked, and incubated with primary hnRNP H antibody (1:500 Rabbit

polyclonal, Bethyl Labs) in 1% BSA overnight at 4° C. 12 h later, neurons were washed and incubated with an Alexa Fluor 594 antibody (1:500 Donkey anti-Rabbit, Life Technologies) in 1% BSA. Processed coverslips were then stained with DAPI (blue) and mounted onto glass slides. Images were collected using a Zeiss AxioObserver microscope under uniform settings for all three groups. 20 serial images (frames) were captured per condition and fluorescence was quantified using ImageJ under a uniform threshold range. Note both an increase in the number of H1 stained neurons following 1–2 h of KCl Tx as well as an increase in the fluorescent staining intensity after KCl treatment. **(B)**: Semi-quantification of fluorescence staining intensity. One-way ANOVA indicated a main effect of genotype ($F_{2,57} = 8.4$; $P = 0.0006$). *$P = 0.01$; **$P < 0.001$ (unpaired t-tests versus No Tx).

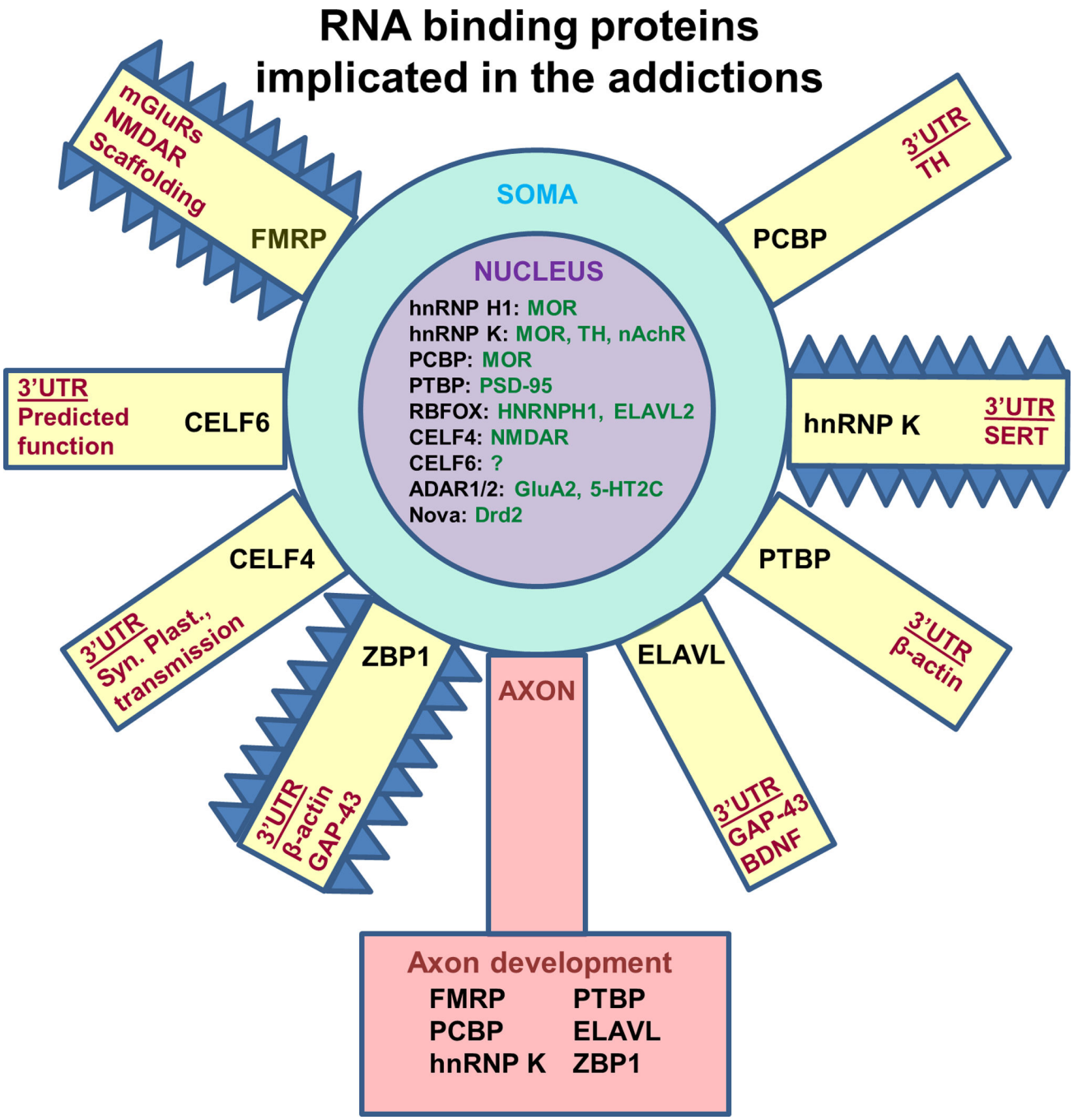

Figure 2. RNA binding proteins implicated in the addictions

Many RBPs have the capability to shuttle between the nucleus and cytoplasm to regulate all levels of RNA post-transcriptional processing. Here, we illustrate the location of action of the main examples that are discussed and some of their well-characterized targets. For the RBPs that are illustrated, we have also indicated whether not they contribute to axon development by listing them in the axon terminal (bottom). The yellow rectangles denote

dendrites. The blue spikes indicate an association with structural changes in dendritic morphology.

Table 1

RBPs associated with the addictions

RBP	Addiction-relevant targets	RNA function	Neurodevelopment neuroplastic function	Addiction-relevant circuitry	Addiction-associated result	References
ADAR1/2	5HT-2C receptor, AMPA receptor, GABA-A receptor	RNA editing, pri-miRNA binding and miRNA biogenesis	Neural differentiation and induction	Ubiquitous expression, hypothalamus, striatum, mesocorticolimbic circuitry, dorsal raphe nucleus, forebrain, cortex, hippocampus, diencephalon	Overeating, motivation to eat in a competing reward environment, novelty-induced locomotor activity, alcohol drinking, cocaine abstinence and seeking, nicotine withdrawal	(Satterlee et al., 2014; Akubuiro et al., 2013; Dracheva et al., 2009; Watanabe et al., 2014; Schmidt et al., 2014; Zaniewska et al., 2015)
CELF4	NMDA receptors, MAPT	Splicing, 3' UTR binding and mRNA stability, translation, localization	Neuronal differentiation and excitation, corticothalamic development, synaptic transmission and function, predicted synaptic plasticity	Ubiquitous expression, hippocampus, cortex	Amphetamine response in humans, hyperactivity, hyperphagia-associated obesity, food-related obsessions	(Hart et al., 2012; Halgren et al., 2012; Comuzzie et al., 2012)
CELF6	Serotonergic neurons, MAPT	Splice enhancement and repression	Expressed during neurodevelopment, beginning at E14	Basal forebrain, ventral tegmental area, locus coeruleus, prefrontal and hippocampal cortices, hypothalamus	Cocaine conditioned reward	(Dougherty, 2015; Dougherty et al., 2013; Maloney, Khangura & Dougherty, 2015)
ELAVL	cfos, BDNF, GAP-43, Nova1, GABA-A receptor, glycine alpha-2 receptor	Splicing, 3' UTR binding, translation, polyadenylation, stability, protein synthesis, transport	Neuronal differentiation, maintenance, maturation, axon growth, dendritogenesis, synaptic plasticity	Neocortex, hippocampus	Cocaine-induced changes in expression and phosphorylation	(Tiruchinapalli, Caron & Keene, 2008; Pascale et al., 2011)
FMRP	Cyfip1/2, AMPA receptor, mGluR1, mGluR5, ADAR, PSD-95, Homer1, CREB BP, GRK2	Transport, translational repression via stalling of ribosomal translocation, stability	Cell fate, progenitor maintenance, neurite, axonal and dendritic outgrowth Glutamate receptor trafficking, dendritic spine morphology	Mesocorticolimbic circuitry, hippocampus	Cocaine and amphetamine neurobehavioral plasticity, synaptic and structural plasticity	(Smith et al., 2014; Kumar et al., 2013; Pilaz & Silver, 2015; Fish et al., 2013; Fulks et al., 2010; Bhogal et al., 2011)

RBP	Addiction-relevant targets	RNA function	Neurodevelopment neuroplastic function	Addiction-relevant circuitry	Addiction-associated result	References
HNRNPA1	NMDA receptors	Splicing, spliceosome, translation, export, stability	Neurogenesis	Ubiquitous expression	Opioid and psychostimulant-induced changes in expression. Co-regulated with *Nurr1*.	(Wang, Yuan & Li, 2011; Johnson et al., 2011)
HNRNPH1	OPRM1, RBFOX, NMDA receptor, Per2	Splicing, regulation of splicing activity, polyadenylation and cleavage, 5' UTR translational suppression	Unknown	Ubiquitous Expression	Heroin addiction, MOR splicing, methamphetamine stimulant response, association with *Nurr1* expression	(Xu et al., 2014; Yazdani et al., 2015; Johnson et al., 2011; Song et al., 2012)
HNRNPH2		Splicing	Unknown	Low expression	Opioid and psychostimulant-induced change in expression	(Wang, Yuan & Li, 2011)
HNRNPK	TH, MOR, SERT, neuronal nicotinic acetylcholine receptor beta2	Transcription, silencing, splicing, 3'UTR binding and stability, translation	Hippocampal synaptic plasticity, dendritic spine morphology, filopodia formation, synapse maturation, axon development	Mesocorticolimbic circuitry, hippocampus, ventral midbrain	Activates TH and MOR transcription, promotes SERT translation, activates transcription of beta2 subunit of the neuronal nicotinic acetylcholine receptor	(Banerjee et al., 2014; Choi et al., 2008; Du, Melnikova & Gardner, 1998)
HNRNPM1	D2 dopamine receptor	Unknown	Unknown	Unknown	Splicing of D2 dopamine receptor	(Park et al., 2011)
Nova1/2	D2 dopamine receptor, GABA-A and GABA-B receptors, NMDA receptor, nicotinic acetylcholine receptor, GIRK2	Repression of splicing, polyadenylation	Synaptogenesis, neuronal migration of cortical and purkinje neurons, neuronal inhibition	Neocortex and midbrain (Nova1), hindbrain, motoneurons and ventral spinal cord (Nova2)	Splicing of D2 dopamine receptor	(Park et al., 2011)
PCBP 1–4 (HNRNPE1-4)	Tyrosine hydroxylase, MOR	Transcription, 3'UTR binding and stability, translational co-activation and repression	Corticogenesis, axonogenesis	TH-positive cells of the midbrain, locus coeruleus	Nicotine-induced changes in TH mRNA	(Boschi et al., 2015; Pilaz & Silver, 2015; Choi et al., 2007; Choi et al., 2008; Choi et al., 2009)

RBP	Addiction-relevant targets	RNA function	Neurodevelopment neuroplastic function	Addiction-relevant circuitry	Addiction-associated result	References
PTBP1-2 (HNRNPI)	D2 dopamine receptor, ΔfosB, PSD-95, PTBP, GABA-A receptor, Grip1, glycine receptor alpha2	Splicing, Polyadenylation , nonsense-mediated decay, transport, stability, translation initiation	Neuronal differentiation, synapse maturation and stability, plasticity	Cortex, hippocampus	D2 dopamine receptor splicing	(Sasabe, Futai & Ishiura, 2011)
RBFOX1 (A2BP1)	Cell adhesion molecules, HNRNPH1, PACAP receptor, GABA-A receptor, NMDA receptor, Grip1, Csnk1d, PTBP	Splicing, 3' UTR binding and stability, polyadenylation	Transmission, membrane excitability	Ubiquitous, basal forebrain, neocortex, hippocampus, nucleus accumbens	Cocaine conditioned reward, nicotine and alcohol dependence	(Fogel et al., 2012; Feng et al., 2014; Zhong et al., 2015)
Tra2β	RGS4, glutamate receptors	Splicing	Neuronal survival, differentiation, cortical neurogenesis	Locus coeruleus, cerebral cortex	Morphine-induced splicing of RGS4. DARPP-32 induces splicing of Tra2β	(Li et al., 2013; Benderska et al., 2010)
ZBP1	B-actin, GAP-43, Homer1, many other predicted targets	3' UTR binding and stability, translational repression, axonal mRNA transport and localization	Axon guidance, outgrowth and branching; dendritic development and morphology, hippocampal development and plasticity, corticogenesis, axonogenesis, synaptogenesis, regeneration	Ubiquitous expression, forebrain, hippocampus	Cocaine conditioned reward, methamphetamine stimulant response	(Lapidus et al., 2012; Bryant et al., 2012)