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The chromatin landscape of neuronal plasticity

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Abstract

Examining the link between neural activity, transcriptional output, and synaptic function offers unique insights into how neurons adapt to changing environments and form memories. Epigenetic markers, such as DNA methylation and histone modifications, have been implicated in the formation of not only cellular memories such as cell fate, but also memories of experience at the organismal level. Here, we review recent advances in chromatin regulation that contribute to synaptic plasticity and drive adaptive behaviors through dynamic and precise regulation of transcription output in neurons. We discuss chromatin-associated proteins, histone variant proteins, the contribution of cis-regulatory elements and their interaction with histone modifications, and how these mechanisms are integrated into distinct behavior and environmental response paradigms.

Introduction

Dynamic regulation of transcription is a critical component of neuronal function. Transcription is regulated by many mechanisms in neurons, including through chromatin, the complex of DNA and histone proteins that package DNA into higher-order structures and control gene accessibility. The importance of chromatin in neuroscience is becoming increasingly appreciated, in both vertebrates and invertebrates, for its function in memory formation to its involvement in a wide range of behaviors (1–3). Here we review work on the role of chromatin in mature and healthy neurons from the last five years. Given the rapid growth of this field, we can address only a subset of this research, but aim to provide an overview of exciting new advances at the intersection of chromatin biology and neuroscience.

Reading, writing, and erasing the chromatin landscape of neurons

The N-terminal tails of core histones and the H1 linker histone are host to a striking number of post-translational modifications including acetylation, phosphorylation, methylation, and more. The classes of enzymes implicated in the deposition of histone modifications, termed ‘writers’, and the removal of modifications, termed ‘erasers’ are critical to these processes.

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Histone modifications regulate histone-DNA interactions and contacts between nucleosomes to facilitate selective unraveling or compaction of chromatin structure. In addition, these modifications interface with other proteins, termed ‘readers’, which can recruit additional factors that further modify chromatin and affect the transcriptional state of the cell. Together, the readers, writers, and erasers play important roles in the dynamic nature of chromatin and transcription regulation. In neurons, considerable recent work has illuminated how these proteins contribute to synaptic plasticity and memory formation.

Readers contain conserved domains such as bromodomains, chromodomains, and PHD domains. These proteins play a critical role in bridging neuronal activation, histone modifications, and transcriptional output that drives memory formation. Recent work demonstrated an important role for readers in regulation of AMPA-type glutamate receptors, the main excitatory receptor in neurons. L3mbtl1 is a polycomb group protein and recognizes mono- and dimethylated histone residues (4). L3mbtl1 is decreased upon neuronal activity and is required for AMPA receptor regulation in homeostatic downscaling, the process through which neurons modify their synapses to adjust to long-term changes in activity. Similarly, Brd4, a reader of acetylated lysines, regulates transcription of activity-dependent genes as well as genes encoding AMPA receptor subunits (5*, 6*). Small molecule inhibition of Brd4 results in impairments in memory consolidation and decreased seizure susceptibility, suggesting that Brd4-mediated transcription regulates neuronal firing.

Deposition of histone marks by ‘writers’ is another important epigenetic regulator of transcription, and considerable research in past decades has focused on the role of histone modifications in neuronal activity-dependent gene expression (7, 8). Exciting recent work has elegantly dissected the roles of acetyltransferases and methyltransferases in distinct memory processes. Kmt2a is H3K4 methyltransferase whose loss in the prefrontal cortex in mice impairs working memory and leads to increased anxiety (9). Conditional knockout of Kmt2a (10**) and the related histone methyltransferase Kmt2b (11) in the hippocampus both result in decreased activity-dependent gene expression. Interestingly, these enzymes regulate distinct memory processes, as Kmt2a deficient mice show deficits in working memory, and Kmt2b mice exhibit impairments in object recognition memory. Further, they affect H3K4 trimethylation at distinct genomic regions, and loss of Kmt2a and Kmt2b lead to unique gene expression patterns (10**).

The importance of methyltransferase activity in neurons is also demonstrated by the polycomb repressive complex 2 (PRC2). PRC2 catalyzes H3K27 methylation to repress gene expression and is required to maintain neuronal function and survival in the adult brain (12). Acetyltransferases such as KAT2a in the brain also affects specific memory processes, and KAT5 is implicated in hippocampal memory enhancement (13, 14).

Removal of methyl and acetyl marks by ‘erasers’ is a critical mechanism to gate the appropriate transcription of plasticity genes. Erasers are often regulated in concert with writers to facilitate a highly dynamic chromatin state in response to neuronal stimulation. Neuron-specific alternative splicing of Lysine-Specific Demethylase 1 (LSD1) results in the neuroLSD1 isoform (also called LSD1n). While LSD1 mainly exhibits H3K9 demethylation, neuroLSD1 functions more as a H4K20 demethylase (15*). This altered

demethylation profile regulates activity-dependent gene expression including genes required for learning and memory. Loss of neuroLSD1 results in spatial learning deficiencies and changes in stress responses (discussed later).

The histone deacetylases (HDACs) are generally described as suppressors of gene transcription and memory formation (7), and recent work has added new mechanistic insights into how blocking HDACs leads to memory enhancement. In a fear-induced learning model, HDAC3 inhibits memory by forming a complex with CREB to suppress transcription of activity-regulated genes implicated in synaptic plasticity (14). Upon fear training, HDAC3 is exchanged for the KAT5 acetyltransferase, which acetylates histones at the *Fgf1b* promoter, and promotes learning. HDAC3 has also been implicated in regulating synaptic plasticity in the primary auditory cortex during reward learning (16). However, histone tails are not the only substrates for HDACs which also deacetylate critical synaptic proteins, producing memory deficits in knockout animals (17, 18). The cytoplasmic and synaptic activities of HDACs underlie the importance of careful dissection of mechanism without bias towards well-studied histone functions.

While transcription regulation of synaptic function has been explored, in only some cases is it clear how the synapse signals to chromatin through specific kinases or signaling cascades (5, 19). It will be intriguing to further investigate how neuronal activity results in altered activity or expression of histone-associated proteins. Together, these exciting studies illuminate the carefully orchestrated interplay between histone readers, writers, and erasers and their important links to synaptic function and memory formation (Fig. 1). This recent work also demonstrates the remarkable degree to which closely related histone-modifying enzymes regulate distinct transcriptional programs in an activity-dependent manner to allow the brain to perform complex tasks such as memory formation.

Histone variants in modulating neuronal plasticity

In addition to regulation by post-translational modifications, histone proteins themselves can also come in different ‘flavors’ called histone variants. These variants are encoded by separate genes and have distinct amino acid sequences from their canonical counterparts. Differences range from a few scattered amino acids to large-scale changes that modify the charge of critical regions of the histone. Unlike most histone proteins, several of these variants do not require cell replication to be incorporated into chromatin so are potentially highly important in postmitotic cells like neurons. Recent work has demonstrated that histone variants play a particularly critical role in the brain and are closely linked to transcriptional changes underlying learning and memory.

Histone variants H3.3, H2A.Z, and H2BE contribute to various aspects of neuronal function, from neuronal development to neuronal cell death (Fig. 2). One of the first histone variants studied in the brain was H2BE, a variant of the H2B histone (20). H2BE is expressed in the mouse olfactory bulb in neurons that receive low levels of input. Unlike much of the brain, the olfactory system uses cell turnover to continually adapt to new environments through a process controlled in part by H2BE-mediated cell death. While this extraordinary

mechanism may be specific to the unique neurons of the olfactory system, this work sparked the wider study of histone variants throughout the brain.

Exciting new research has explored the role of H2A.Z, a variant of H2A, in neuronal function and in regulation of activity-dependent gene expression. H2A.Z is actively exchanged with other histones in chromatin in response to learning paradigms. Intriguingly, knockdown of H2A.Z promotes stronger fear conditioning suggesting that H2A.Z restrains memory formation in the brain (21**), while brain-specific knockout early in development impairs neurogenesis and memory formation (22). As animals age, H2A.Z accumulates in the brain (21**), similar to other histone variants (24**). However, in both young and old mice, H2A.Z is evicted from genes during learning, though the genes regulated by H2A.Z change with aging (23). As an added layer of complexity, two different genes encode distinct versions of H2A.Z and these ‘hypervariants’ also appear to regulate different subsets of genes (25).

H2A.Z is deposited at the promoters of activity-dependent genes by the nucleosome remodeling and deacetylase (NuRD) complex (26**). Knockdown of one component of this complex, Chd4, decreases deposition of H2A.Z at specific genes, promotes their expression, and blocks dendritic pruning. This results in increased responsivity of neurons to sensorimotor inputs causing procedural learning deficits. The link between decreased H2A.Z deposition and increased recruitment of neurons that respond to specific stimuli could explain how H2A.Z loss could also lead to enhanced memory formation in other tests (21**). H2A.Z deposition is also regulated by the Tip60- p400 complex and inhibition of this complex also improves memory formation (27).

Similar to H2A.Z deposition, H2A.Z eviction is likely a highly regulated and activity-dependent process (21**) though is less well studied in neurons. However, monoubiquitination of histone H2B blocks access to the H2A.Z evictor INO80 at inducible enhancers in HEK293- T cells (28). Such a mechanism could apply to inducible genes in neurons as well.

The histone variant H3.3 is also incorporated into chromatin in response to increased neuronal activity (24**). H3.3 is incorporated throughout gene bodies while H2A.Z is primarily at promoters and H3.3 appears to function in a manner opposite to H2A.Z. Knockdown of H3.3 in postmitotic neurons decreased activity-dependent gene induction and caused deficits in learning and memory. More recently, this work has been extended to show that depression in humans and chronic stress in rodents can affect H3.3 levels (29).

Research on H2BE, H3.3 and H2A.Z has demonstrated that our environment and experiences control not just histone modifications but also the makeup of nucleosomes in our neurons. It is particularly intriguing to consider how these variants may work together to regulate gene expression. The opposing effects on gene expression of H3.3 and H2A.Z, particularly in response to neuronal activity, suggest a model in which neurons make use of multiple variants to balance their response to neuronal activity. Also intriguing is whether more replication-independent histones remain to be discovered. Whether other specific cell

types or brain regions also have unusual histone variants like H2BE that allow neurons to perform their unique functions has yet to be seen.

Interplay of chromatin and neuronal activity-dependent enhancers

Enhancers are short (100–500 bp) regions in the genome that act as regulatory elements and recruit sequence-specific transcription factors (TFs). The binding of TFs to the correct enhancer is crucial in allowing any given cell type, such as neurons, to precisely activate cell type-specific genes at the right time and in response to the right signaling pathways (30). However, for a given enhancer to be activated, nucleosomes may need to be evicted or moved (31). Active enhancers are also marked by specific histone modifications on the surrounding nucleosomes, particularly H3K27ac and H3K4me1 (32).

A subset of enhancers control stimulus-dependent genes. In neurons, these genes, termed Immediate Early Genes (IEGs), are rapidly transcribed in response to neuronal activity and are critical for numerous neuronal functions (33). Such enhancers are marked by dynamic regulation of H3K27ac (34, 35) making this mark particularly important in ensuring that IEGs are activated as animals learn and store information. In addition, enhancer regions themselves are actually transcribed in the process of recruitment of TFs and polymerase, generating a class of RNAs termed enhancer RNAs (eRNAs) (36). eRNAs can then affect transcription through mechanisms such as regulating chromatin looping (37). The process of inducible acetylation, TF recruitment, eviction of nucleosomes, and eRNA transcription are all critical points of regulation in neuronal gene induction.

Recent work has shed light on how these processes are interconnected and converge in neurons to allow for highly specific transcriptional responses to synaptic activity. The enhancers regulating the IEG *Fos* can distinguish between different types of neuronal stimuli as seen by distinct patters of eRNA synthesis at different *Fos* enhancers (38*). This could allow for different stimuli to recruit TFs and chromatin-regulating proteins to distinct enhancer regions. Different durations of neuronal activity also result in different patterns of IEG activation with the most rapidly induced genes having the most open chromatin state indicated by various histone marks around gene promoters (39*). IEGs Fos and Jun are TFs that, once induced, can recruit BAF remodeling complexes to establish open chromatin domains (40). Interestingly, enhancer regions that recruit these TFs differ markedly between mouse strains implying that DNA sequence heterogeneity could affect chromatin remodeling in IEG activation. Enhancers can also counteract large heterochromatin domains to allow neurons to activate a single olfactory receptor gene in the midst of large regions of silenced genes (41). Taken together, these findings begin to hint at the complexity involved in the transcriptional response to any given neuronal stimuli, at least some of which is highly influenced by interplay of enhancers and the surrounding chromatin (Fig. 3).

The influence of the environment on neuronal chromatin

The external environment and experiences of an organism are tightly linked to chromatin state and modulation of neuronal transcription. Because most neurons persist for the full lifetime of an animal, this connection also raises the questions of whether our environment

can have enduring effects on the chromatin landscape (Fig. 4). Recent elegant work demonstrated that the level of gene expression early in life has lasting consequences for gene expression in the adult brain (42). This research focused on DNA methylation but similar effects could occur as a result of histone modifications, particularly those that are more stable.

One such external influence that has long-term consequences for the epigenome of neurons is stress. In particular, early life stress causes lasting transcriptional changes and leads to future behavioral changes such as increased susceptibility to depression (43). Newly uncovered mechanisms demonstrate how chromatin is involved in the response to stress. Histone demethylase LSD1, described above, as well as its neuronal-specific splicing isoform neuroLSD1, are induced by social stress and function as corepressors of IEGs (44*). Mice lacking neuroLSD1 show altered histone methylation and acetylation and have a low-anxiety phenotype. In addition, HDAC2 is required for the resilience to chronic stress observed in TRPV1 knockout mouse (45). Modifying histones at key genes can also induce behavioral changes in response to stress. Using zinc finger proteins to modify H3 acetylation at the *Cdk5* locus promotes resilience in response to social stress (46) demonstrating that the chromatin landscape at individual genes can dictate whether specific experiences have long-lasting adverse consequences. These exciting studies provide examples of how chromatin-associated proteins can link past experiences to future transcriptional output.

In addition to stress, external substances we are exposed to throughout our lives have clear effects on our chromatin landscape. Drugs of abuse have long been known to modulate the epigenome and new work has expanded on our knowledge of such mechanisms (47). Histone deacetylase HDAC5 (48), histone dimethyltransferase G9a (49), and many other histone modifiers and histone readers (50) have been implicated in the response to drugs. Alcohol also alters HDAC expression, resulting in enhanced vulnerability to subsequent exposure to cocaine (50). Less well-studied modifications such as histone arginine methylation are also linked to addiction (52) suggesting that more mechanisms tying chromatin to the drugs of abuse have yet to be discovered.

Our diet and metabolism also play an important role in regulating chromatin and many chemical modifications deposited on histones are generated from metabolites (53–56). For example, the metabolic enzyme acetyl-CoA synthetase 2 (ACSS2) generates acetyl-CoA for histone acetylation. Recently, exciting work found that ACSS2 binds near memory-related genes providing local generation of acetyl-CoA (57**). Loss of ACSS2 impairs the activation of these genes and the formation of long-term memory. Other recent work demonstrated that metabolites generated during digestion that modify histones and are also expressed at very high levels in the brain (58). Together, these findings hint at the possibility that our diet may affect our neuronal epigenome by changing the availability of key metabolites needed to modify histones and regulate key neuronal genes.

Conclusion

The last several years of research into the role of chromatin in neurons has helped to advance our understanding of many critical mechanisms of transcriptional regulation in the

brain. In particular, the complex interplay of histone modifications, histone variants, enhancers, and environmental factors has emerged as an exciting new forefront in neuroscience. Yet much remains to be discovered and the next phase of research in this field promises to be at least as thrilling as these recent discoveries.

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Highlights

- Histone modifications are highly dynamic in the brain and drive changes in many behaviors including learning and memory.
- Chromatin-associated proteins that interact with and regulate histone modifications control expression of genes critical for synaptic function.
- Exchange and accumulation of specific histone variants affect neuronal function and survival.
- Enhancer elements are marked by histone modifications and regulate transcription of activity-dependent genes.
- Short and long-term changes to the neuronal epigenome by external influences from stress, drugs of abuse, and diet drive dynamic changes in gene expression and behavior.

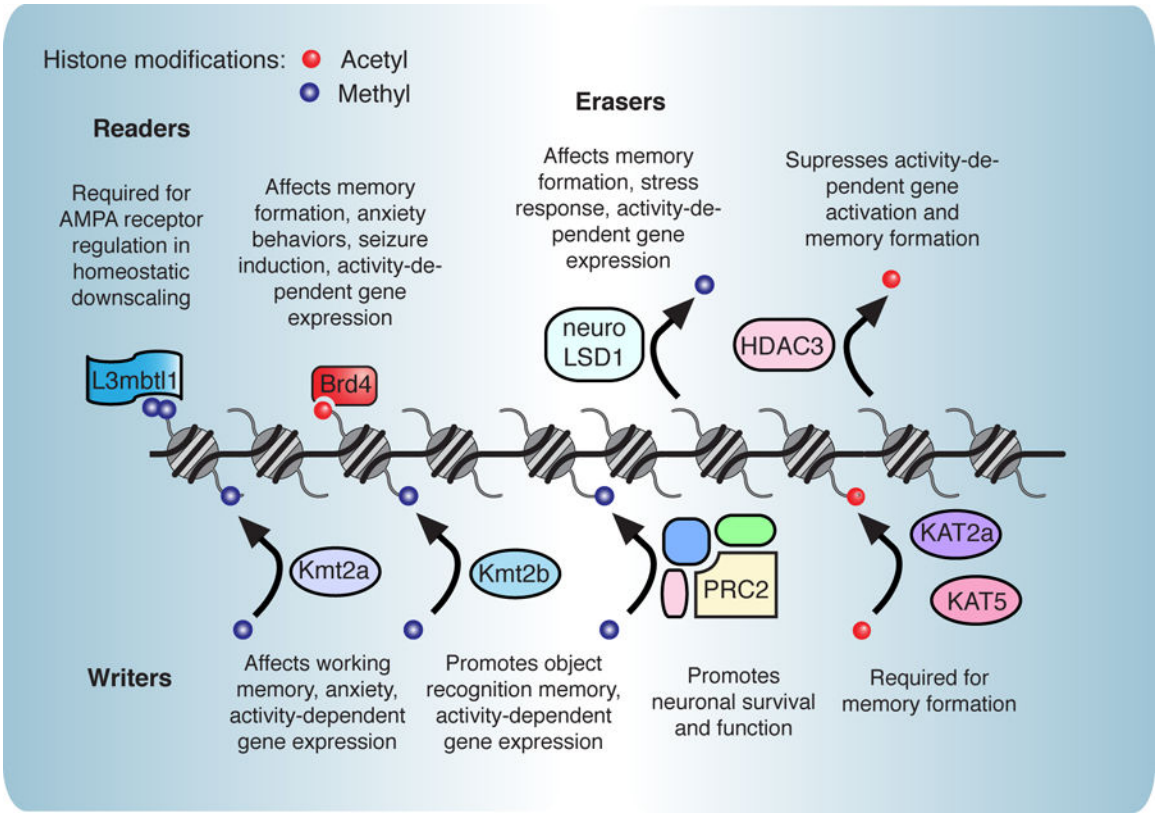

Figure 1. Chromatin-associated proteins in learning and memory formation.

Numerous reader [4,5*,6*], writer [9,10**,11–14], and eraser [15*,16, 41] proteins have recently been implicated in neuronal function. In particular, these proteins regulate activity-dependent gene expression and key synaptic receptor genes. In addition, many have been implicated in various forms of synaptic plasticity and various types of learning and memory formation.

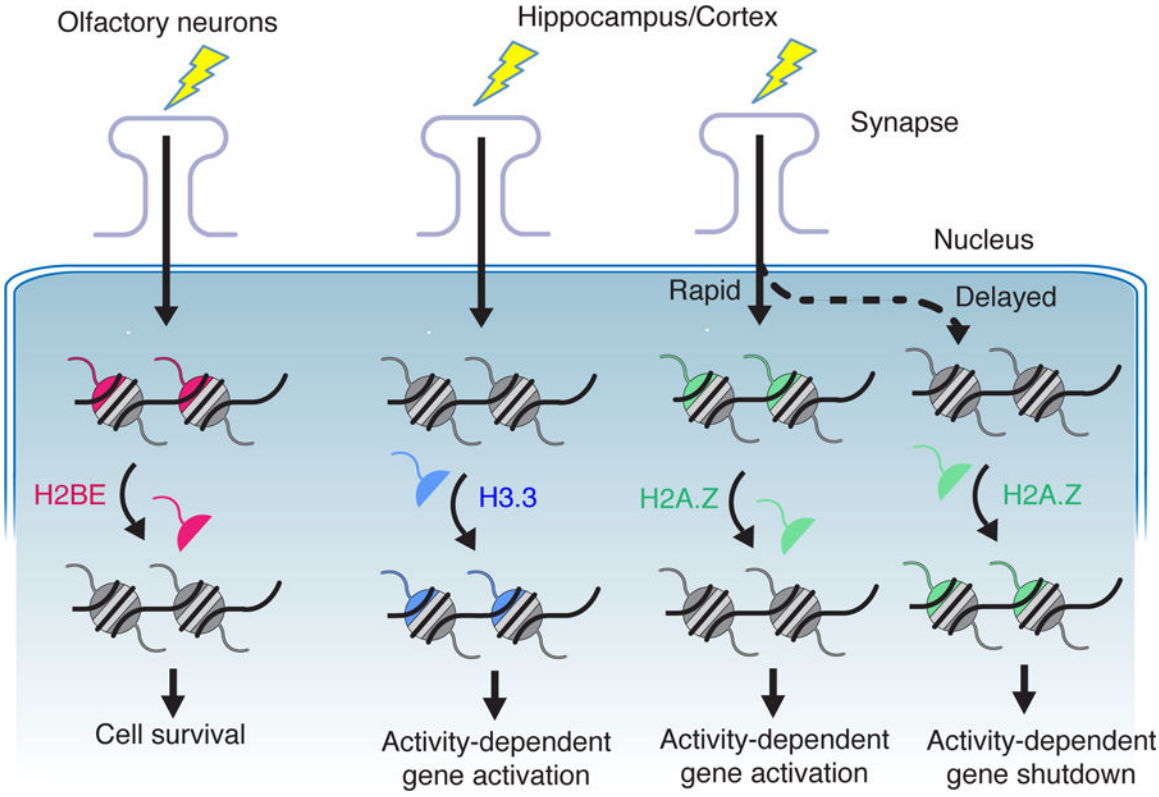

Figure 2. The role of histone variants in neurons.

The histone variants H2BE, H3.3 and H2A.Z are involved in various aspects of neuronal function. In olfactory epithelial neurons, the variant H2BE is expressed at low levels in active neurons and at high levels in inactive neurons and regulates cell survival [20]. The variants H3.3 and H2A.Z are expressed throughout the brain and have opposing effects on the neuronal response to activity. Increased activity results in greater expression of H3.3, which contributes to activity-dependent gene expression [24**, 29]. H2A.Z is initially evicted from chromatin in response to activity which promotes gene activation and later is deposited in chromatin to shut down gene expression [21**, 22, 23, 24**,25,26**,27].

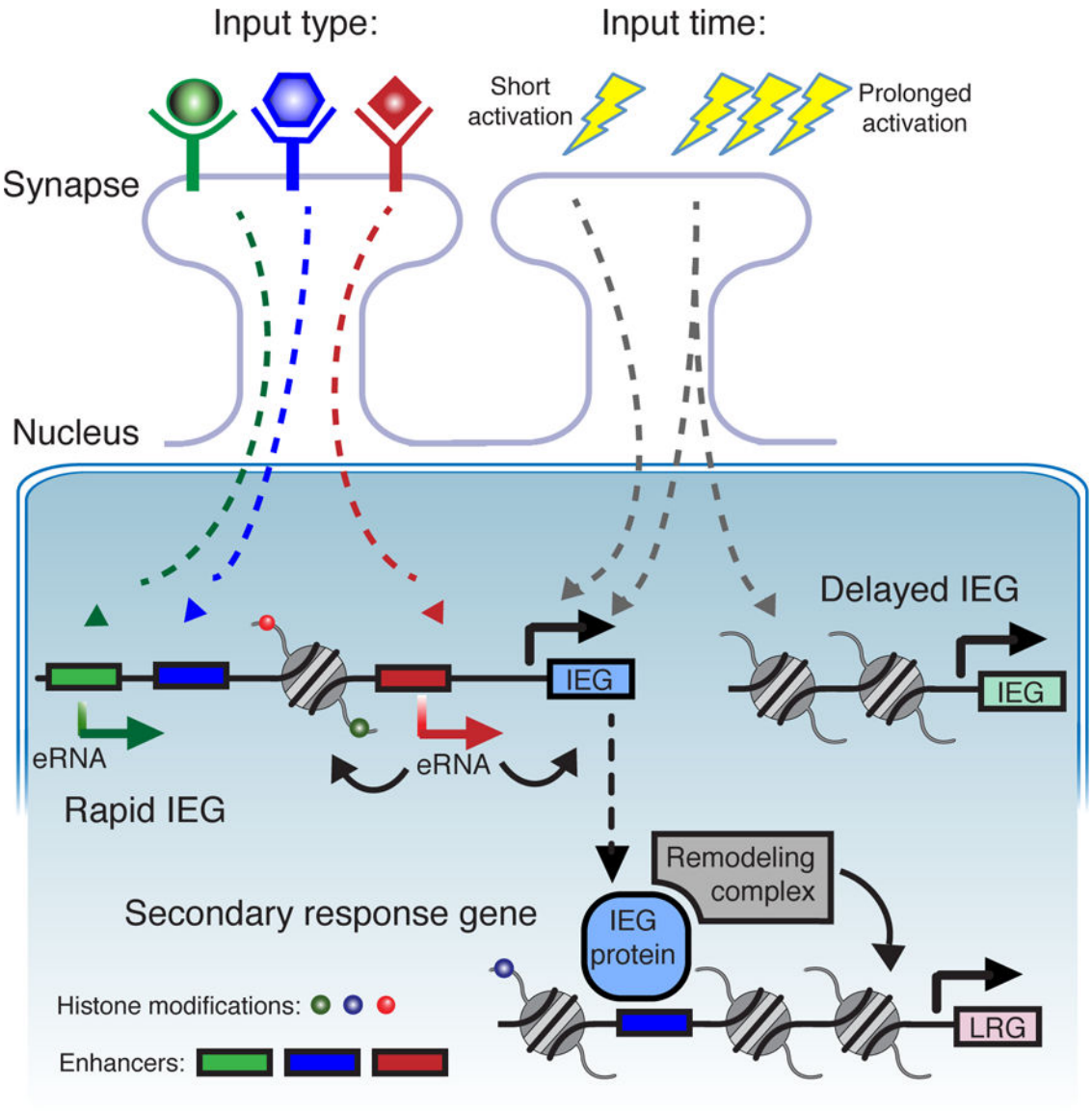

Figure 3. Chromatin and enhancers co-regulate activity-dependent gene activation in neurons.

The combinatorial effects of enhancers and chromatin allow neurons to distinguish between different types of stimuli [38*] and different lengths of stimuli [39*]. Different signaling pathways activate different enhancers. This generates specific eRNAs [34] which in turn affect promoter activity and the surrounding chromatin. The most rapidly induced IEGs have more open chromatin with marks such as H3K27ac near gene promoters [34, 35]. The gene products of IEGs include transcription factors which can then regulate late response genes (LGRs) and recruit chromatin regulators and remodelers such as the BAF complex [40]. IEG, immediate early gene. eRNA, enhancer RNA.

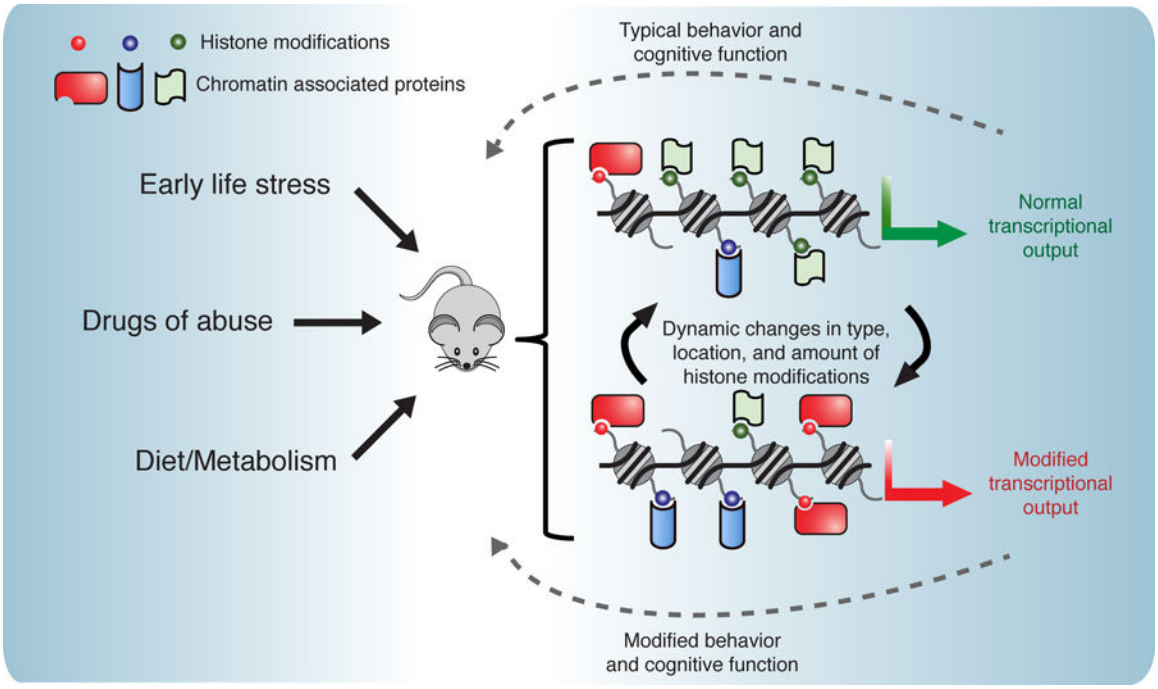

Figure 4. The effect of environment on neuronal chromatin.

The external environment and experience of an animal can have lasting effects on chromatin, leading to changes in transcriptional output and animal behavior. These external influences include exposure to drugs and alcohol [47–52], diet and metabolism [53–58], and adverse experiences such as social stressors [43–46]. Such influences can modify histones in numerous ways including the type of modification deposited on histones (such as acyl groups regulated by metabolic enzymes), the location of histone modifications, and the activity of the enzymes that deposit and remove modifications. These changes can in turn affect the transcriptional output and function of the neuron.