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Review article

The role of active DNA demethylation and Tet enzyme function in memory formation and cocaine action

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ABSTRACT

Active DNA modification is a major epigenetic mechanism that regulates gene expression in an experience-dependent manner, which is thought to establish stable changes in neuronal function and behavior. Recent discoveries regarding the Ten eleven translocation (Tet1-3) family of DNA hydroxylases have provided a new avenue for the study of active DNA demethylation, and may thus help to advance our understanding of how dynamic DNA modifications lead to long-lasting changes in brain regions underlying learning and memory, as well as drug-seeking and propensity for relapse following abstinence. Drug addiction is a complex, relapsing disorder in which compulsive drug-seeking behavior can persist despite aversive consequences. Therefore, understanding the molecular mechanisms that underlie the onset and persistence of drug addiction, as well as the pronounced propensity for relapse observed in addicts, is necessary for the development of selective treatments and therapies. In this mini-review, we provide an overview of the involvement of active DNA demethylation with an emphasis on the Tet family of enzymes and 5-hydroxymethylcytosine (5-hmC) in learning and memory, as well as in drug-seeking behavior. Memory and addiction share overlapping molecular, cellular, and circuit functions allowing research in one area to inform the other. Current discrepancies and directions for future studies focusing on the dynamic interplay between DNA methylation and demethylation, and how they orchestrate gene expression required for neuronal plasticity underlying memory formation, are discussed.

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1. Introduction

It is now generally accepted that gene expression is required for long-lasting forms of neuronal plasticity, cognition, and memory. Furthermore, as in many other fields, the role of epigenetics in regulating gene expression is redefining how we think about normal dynamic transcriptional events and, more importantly, how the epigenome serves as a signal transduction platform that encodes past experience, integrates current experience, and can establish forms of molecular and cellular memory that poise cell function for future action. Here, we focus on the modification of deoxyribonucleic acid (DNA), with an emphasis on the role of the ten–eleven

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translocation (Tet) family of dioxygenases involved in active DNA demethylation. For many years, as major advances have been made in the understanding of the nature of DNA methylation in neuronal function, a major question has troubled the field of epigenetics: if DNA methylation is dynamic, where are the DNA demethylases? The discovery of the Tet family enzymes and their role in active DNA demethylation is a critical step in addressing this issue, providing new insight into the complexity and power of the epigenome in action. In this mini-review, we discuss the convergent and contrasting findings surrounding the role of DNA modification and Tet-dependent mechanisms in learning and memory, as well as what little is currently known with respect to these epigenetic mechanisms in cocaine action in the brain, drug-seeking behavior, and relapse following extended periods of abstinence. The mini-review is focused on memory and addiction because the molecular and cellular mechanisms thought to underlie the acquisition and ultimately the persistent compulsive aspects of drug use are hypothesized to also serve long-term associative memory function and reward-related learning processes (e.g., [1–4]).

2. Dynamic DNA modification, active DNA demethylation and the Tet family of DNA dioxygenases

DNA methylation is a covalent modification that governs gene expression through a number of mechanisms, including the binding of transcription factors [5], the recruitment of methylated DNA-binding proteins and chromatin-modifying proteins leading to changes in chromatin states [6], as well as the regulation of alternative splicing, nucleosome repositioning, and retrotransposon activity [7]. Although DNA methylation was once thought to be an inherently stable mark that is not capable of rapid changes, recent findings show that DNA undergoes rapid methylation and demethylation in the adult brain. For example, DNA methylation via the accumulation of 5-methylcytosine (5-mC) is dynamically regulated in an activity-dependent manner by the same intracellular signaling cascades that are necessary for memory formation (e.g., [8,9]). More recently, there has been significant interest in understanding the interplay between DNA methylation/demethylation mechanisms involving 5-mC and 5-hydroxymethylcytosine (5-hmC).

There are three DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) that have enzymatic activity in mammals, with DNMT1 and DNMT3a being the most active in neurons [10–12]. The addition of a methyl group from SAM (*S*-adenosyl-L-methionine) to cytosine is catalyzed by these DNMTs, resulting in 5-mC ([10]; Fig. 1). 5-mC was originally thought to act as a stable transcriptional silencer [13], but it was recently discovered that 5-mC levels are rapidly and reversibly changed at memory and synaptic plasticity-associated genes, suggesting active DNA demethylation as a result of neuronal activity [14–17]. While DNA methylation at 5-cytosine residues as well as the DNMT enzymes that are responsible for this process have been reasonably well characterized [12,18], the opposing mechanism of active DNA demethylation in differentiated neurons is only beginning to be understood. One key mechanism in DNA demethylation involves the Tet-family of methylcytosine dioxygenases. This family consists of TET1, TET2, and TET3, which participate in the conversion of 5-mC to 5-hmC [15,19]. 5-hmC is enriched within gene bodies, promoters, and transcription factor binding regions, where it may influence gene expression [20,21]. Recent findings suggest that 5-hmC not only serves as a DNA demethylation intermediate, but also functions as a stable epigenetic mark in its own right [20,21]. Its abundance and dynamic nature have therefore led to significant excitement regarding Tet enzymes and 5-hmC as this mechanism may lead to new insight into neuronal plasticity and long-term changes in behaviors related to memory and even drugs of abuse.

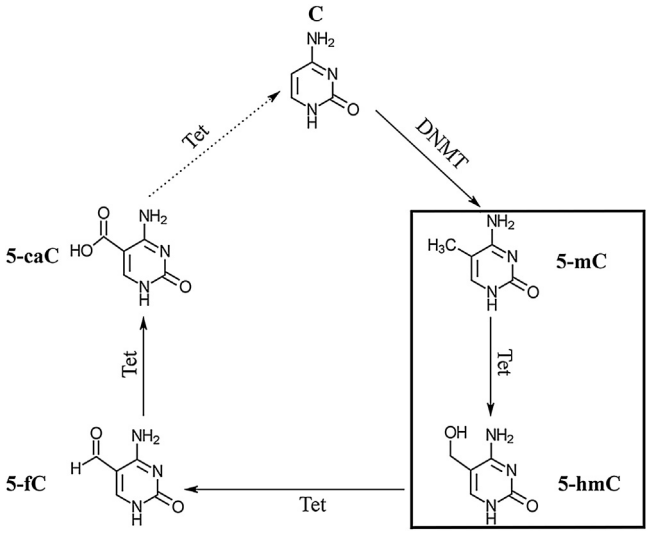

Fig. 1. Schematic representation of the DNA methylation/demethylation pathway. Boxed reaction is the demethylation step on which we focus this review. *C*, cytosine; *5-mC*, 5-methylcytosine; *5-hmC*, 5-hydroxymethylcytosine; *5-fC*, 5-formylcytosine; *5-caC*, 5-carboxylcytosine; *DNMT*, DNA methyltransferase; *Tet*; Ten-eleven translocation enzyme. (see also [53,54]).

The Tet enzymes also mediate the conversion of 5-hmC to 5-formylcytosine (5-fC), and 5-carboxylcytosine (5-caC; [15,22]; Fig. 1). 5-fC and 5-caC base modifications serve as DNA demethylation intermediates subject to deamination, glycosylase-dependent excision and repair, resulting in a reversion to unmodified cytosine [23,24]. Recently, it was discovered that 5-fC can be a stable epigenetic mark [25], and can have functionally relevant effects on gene expression independent of demethylation through direct effects on DNA structure [26]. Although little is known about the functional roles of 5-fC and 5-caC [27,28] in learning and memory, what has been learned about 5-mC and 5-hmC has ignited the field by providing new insight into the mechanisms that regulate expression of genes required for neuronal plasticity and long-term changes in behavior (reviewed below), suggesting that it is critically important to also investigate the role of these base modifications as well as others, including 5-fC and 5-caC.

As one might predict, Tet enzyme activity can affect global levels of both 5-mC and 5-hmC. For example, Tet1 manipulation by viral expression of wild-type TET1 significantly decreases 5-mC levels, with a concurrent increase in 5-hmC levels in area CA1 [29] and the dentate gyrus of the hippocampus [14]. Conversely, expression of a catalytically inactive mutant TET1 in these regions produces the opposite effect [14,29]. Thus, these studies demonstrate the role of TET1 activity in actively regulating global levels of 5-mC/5-hmC in the adult hippocampus. With regard to other Tet family members, TET3-deficient zygotes from conditional knockout mice exhibit a failure to convert 5-mC into 5-hmC and levels of 5-mC remain relatively constant [30], whereas TET2 mutations lead to decreased 5-hmC levels in myeloid leukemia [31,32]. These examples of studies examining the role of Tet enzymes highlight the importance of their function in regulating the dynamic interplay between 5-mC and 5-hmC.

The Tet enzymes are highly expressed in the brain, with TET3 being the most abundantly expressed in the cerebellum, cortex, and hippocampus as compared to TET1 and TET2 [33]. Importantly, these are key regions involved in the acquisition and extinction of memory and, as described below, the functional relevance of their activity in the adult brain has recently been characterized with respect to learning and memory.

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