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Chromatin remodeling: a new landscape to treat harmful alcohol-use disorders

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Addiction

Excessive use of alcohol is the second most detrimental neuropsychiatric disorder that results in multiple somatic diseases [1]. Specifically, the WHO reported in 2011 that 4% of deaths worldwide are related to misuse of alcohol [1]. However, the mechanisms that underlie harmful alcohol consumption are still not well understood, and thus available medications for alcohol-use disorders are limited. Current medications used to reduce craving and prevent relapse show a long-term efficacy in only 20–30% of patients [2]. The difficulty in treating alcohol-use disorders stems from the fact that they are influenced by complex interactions between genetic and environmental factors (familial, social and stress) [2]. Thus, there is a great need to identify new and more efficient drugs that overcome these complexities.

Modifications in gene expression are important features responsible for the long-term neuroadaptations caused by excessive alcohol use [3]. Epigenetic mechanisms, such as chromatin remodeling, change the level of gene expression without affecting DNA integrity [4]. Chromatin consists of a DNA molecule wrapped around an octamer of H2A, H2B, H3 and H4 histone proteins. The chromatin structure is flexible and can be remodeled by post-

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translational modifications, such as the addition or removal of an acetyl or methyl group on both histones and DNA [4]. Specifically, histone acetylation, catalyzed by histone acetyltransferase, promotes chromatin relaxation, which allows transcriptional machinery to reach gene promoters. By contrast, histone deacetylation, catalyzed by histone deacetylases (HDAC), leads to chromatin condensation and the repression of transcription [4]. Conversely, DNA methyltransferases (DNMT) catalyze DNA methylation on specific cytosine–guanine dinucleotide domains (CpG islands) within gene promoters, generating docking sites for protein complexes that promote chromatin condensation at the promoter to repress gene transcription [5,6].

Studies conducted over the past few years suggest that alcohol intake results in modifications of the mechanisms regulating chromatin remodeling [7–14]. We, and others, generated data indicating that excessive alcohol drinking in rodents is associated with low levels of histone acetylation [7–9]. Specifically, we recently demonstrated that rodents with a history of excessive alcohol drinking exhibit low levels of histone H4 acetylation in the nucleus accumbens [7], a key brain region in the reward circuitry [15], which plays a central role in the expression of the behavioral phenotypes associated with alcohol intake [2]. Similarly, another recent study revealed that rats selectively bred for their propensity to drink high levels of alcohol display low levels of histone H3 acetylation in the amygdala, a brain region that has a role in craving and relapse of alcohol drinking [16], as compared with rats selectively bred for low levels of drinking [8]. Interestingly, 24 h of deprivation following chronic access to alcohol also promotes a reduction in the level of histone H3 and H4 acetylation in the amygdala of rats compared with naive animals [9]. Similarly, we have observed that DNA methylation is also altered by alcohol intake [7,10]. We found that excessive alcohol drinking leads to an increase in the protein level of DNMT1, the enzyme responsible for DNA methylation, in the nucleus accumbens of mice [7]. Barker *et al.* demonstrated that alcohol consumption induces a brain region-specific DNA methylation pattern of the serotonin receptor (Htr3a) promoter compared with naive animals [10]. Interestingly, clinical studies suggest that alcoholics exhibit alterations in the level of DNA methylation. A post-mortem study showed a reduction in DNA methylation and DNMT1 levels in the amygdala and the superior frontal cortex [11]. However, several studies found an increase in DNA methylation on promoters of various genes in patients that suffered from alcohol addiction as compared with healthy subjects [12–14]. These data, together with the rodent data, put forward the possibility that low histone acetylation and/or hypermethylation of the DNA may be responsible for the neuroadaptations that result in excessive alcohol drinking and craving.

Thus, developing therapeutics targeting chromatin-remodeling mechanisms offer a new strategy to treat alcohol use and abuse disorders. In a recent study, we showed that drugs targeting chromatin remodeling, particularly those that promote chromatin relaxation and gene expression, could be used to regulate alcohol drinking and craving [7]. We used a model of excessive alcohol drinking in mice in which animals experience repeated periods of binge drinking and abstinence similar to those of human alcoholics [17]. We showed that systemic administration of DNMT (5-azacitidine) and HDAC inhibitors (SAHA, trichostatin A, MS-275) reduced excessive drinking of alcohol in mice [7]. Operant self-administration

in rats assesses the level of motivation to drink alcohol. In this procedure, rats are asked to accomplish a task (pressing several times on a lever) to obtain one aliquot (100 μ l) of alcohol; thus, the amount of work required to obtain alcohol is correlated with the motivation to consume alcohol. To measure alcohol seeking, after being trained to self-administer alcohol, rats go through an extinction session in which pressing on the lever no longer results in alcohol delivery. In this context, perseverance/obsession in pressing the lever previously associated with alcohol delivery is correlated with the level of alcohol seeking in rats [18]. We demonstrated that the systematic administration of an HDAC inhibitor (SAHA) reduced both the motivation to consume and to seek alcohol in rats [7]. Together our data indicate that agents that reduce chromatin condensation have the potential to be developed into medications to treat harmful excessive alcohol drinking [7]. Furthermore, it is well known that alcohol abusers report high levels of craving (seeking) for alcohol, and that this phenomena leads to the development of persistence in alcohol drinking that makes it extremely difficult to stop drinking and/or maintain abstinence [2]. The finding that the HDAC inhibitor SAHA produces a specific inhibition of alcohol seeking [7] is therefore of particular interest. In addition, we found that DNMT and HDAC inhibitors did not change the levels of drinking and seeking of other rewarding solutions, such as saccharin and sucrose [7], indicating that these drugs have a specific effect on alcohol and do not affect the general propensity to consume other rewarding substances. This finding is particularly important from a therapeutic perspective as current US FDA-approved medications used to treat alcoholism, such as naltrexone and acamprosate, also reduce water and sucrose intake [19,20], which likely explains compliance issues associated with these two drugs [21].

Several of the DNMT and HDAC inhibitors that we chose for our studies have been already approved by the FDA or are currently in clinical trials. SAHA (Zoninza[®]) and 5-azaC (Vidaza[®]) are two FDA-approved drugs that have been used as therapeutic agents for the treatment of several types of cancers [22–25,101]. In addition, MS-275 (entinostat) is in Phase II clinical trials [101]. Furthermore, reports indicate that 5-azaC, SAHA and MS-275 also show a potential anti-depressant use [26–28]. Therefore, the fact that most of those drugs are FDA-approved opens the possibility to conduct clinical trials in alcohol abusers in the near future.

There are different possibilities to explain the beneficial effect of DNMT and HDAC inhibitors on excessive alcohol drinking. The chromatin decondensation promoted by the inhibitors may lead to the increased expression of endogenous factors in the brain that protect against alcohol drinking, such as BDNF and GDNF [3]. It is also plausible that DNMT and HDAC inhibitors promote the expression of genes that are negative regulators of alcohol-responsive genes or signaling pathways. Further studies are needed to have a better understanding of how DNMT and HDAC inhibitors, and by extension chromatin decondensation, reduce excessive alcohol drinking.

In summary, chromatin-remodeling mechanisms represent a new landscape for the development of strategies to treat excessive alcohol drinking. The lack of a specific target for alcohol in the brain makes treatment strategies that target the general chromatin structure

of particular interest, and drugs promoting chromatin decondensation may potentially be used as a therapeutic strategy to treat alcohol-use disorders.

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