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Emerging Epigenetic Therapies in Neuroscience: Focus on Bromodomain-Containing Drug Targets

Failure to appropriately control gene expression is a salient feature of most human diseases. Therefore, the field of epigenetic therapeutics has rapidly grown into one of the most active areas of drug discovery. This is fueled by the

fact that there exist hundreds of so-called druggable (by small molecules) epigenetic targets, many of which affect the state of chromatin and therefore gene expression. The result of this type of drug action, exemplified here by bromodomain inhibitors, is typically an alteration of the expression of a number of genes (up- as well as down-regulation). While some genes are more susceptible to this type of regulation, there is marked context dependency that represents both a challenge and an opportunity to drug hunters.

The bromodomain module, a critical component of epigenetic regulation, selectively recognizes acetylated lysine residues present in both histone and non-histone proteins. In human cells, there exist 46 proteins that contain bromodomain(s). The dysregulation of these so-called protein reader functions, and the genes that they control downstream, have been implicated in the development of a variety of diseases, making them attractive targets for drug discovery. It has been known for about a decade that small molecules are capable of binding to a bromodomain and the number of reported inhibitors has expanded dramatically in the past few years. The profound and broad pharmacology of bromodomain inhibition, especially that associated with targeting the so-called BET subfamily of bromodomains (BRD2, BRD3, BRD4, and BRDT), has led to the progression of a number of small molecules into the clinic for liquid as well as solid tumors. However, these BET bromodomain inhibitors may also have utility for non-malignant diseases of the nervous system.

BET bromodomain inhibitors can influence the differentiation and maturation of a variety of cell types. Indeed, anti-cancer effects, mediated primarily by modulation of BRD4, have been the main driver of drug discovery thus far. For example, strong inhibitor efficacy can be observed in models of glioblastoma, which has stimulated the discovery of novel ligands with high brain exposure (Pastori *et al*, 2015). Moreover, much interest has been placed on immunomodulatory activi-

ties including altered expression of a number of cytokines. Indeed, BET bromodomain inhibitors hold promise to be used for the treatment of brain disorders characterized by neuroinflammation, including Alzheimer's disease (Magistri *et al*, 2016).

Like other epigenetic modulators, BET bromodomains could conceivably be employed to correct single gene disorders. An example thereof is the hexanucleotide repeat expansion residing within the C9ORF72 gene, representing the most common known cause of amyotrophic lateral sclerosis (ALS). Indeed, BET bromodomain inhibitors increase the expression of C9ORF72 mRNA and pre-mRNA and may therefore compensate for haploinsufficiency without increasing the production of toxic RNA and protein products (Zeier *et al*, 2015).

Moreover, epigenetic phenomena have often implicated in memory as well as addiction. Korb *et al*, 2015 demonstrated that BRD4 provides a critical link between neuronal activation and the transcriptional responses that occur during memory formation.

In recent studies, we observed that BRD4 is elevated in the nucleus accumbens and recruited to promoter regions of addiction-related genes following repeated cocaine administration, and that inhibition of BRD4 attenuates transcriptional and behavioral responses to cocaine (Sartor *et al*, 2015). Thus, it is possible that bromodomain inhibitors may have therapeutic utility in the treatment of cocaine and perhaps other addictions.

Importantly, it must be noted that epigenetic drug will affect the expression of a number of genes and that the undesired effects can arise as a consequence (eg, Sullivan *et al*, 2015). However, it is reasonable to assume that the most critical period for putative adverse effects would occur early in development.

In conclusion, a variety of epigenetic drug candidates—mostly thanks to efforts in the cancer field—have recently become available to the field of neuroscience. This offers a tremendous opportunity that must be seized. This brief piece has focused on BET

bromodomain inhibitors that display interesting effects. However, these are still early days and additional studies are still needed.

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REM Sleep on It!

Upon discovery, rapid-eye-movement sleep (REMs) was met with curiosity regarding its function due to its

association with dreaming and the seemingly paradoxical occurrence of 'wake-like' eye and brain activity during sleeping behavior. Six decades later, a substantial body of evidence linking REMs to memory formation has been described (Rasch and Born, 2013). In humans, increased REM amounts have been reported following procedural memory tasks, as well as declarative memory tasks incorporating complex or emotionally relevant material. Furthermore, depriving REMs after learning of such tasks produced memory deficits. Similar findings have been described in rodents using tasks such as the Morris water maze and active or passive avoidance (Abel *et al*, 2013).

Despite the cumulative body of evidence, the debate surrounding the role of REMs in memory formation has persisted for some time (Rasch and Born, 2013; Siegel, 2001). This has been due to the difficulty in experimentally isolating REMs, which occurs in multiple episodes of varying (seconds to minutes) duration throughout sleep interposed by periods of non-REMs (NREMs). Thus, traditional pharmacological techniques are not temporally precise enough to selectively target REMs. Additionally, as REMs is an integral component of mammalian sleep, selective REM deprivation inevitably results in physiological changes, such as increased metabolic hormone levels, making interpretation of data obtained difficult. Correlative approaches avoid these issues but cannot prove a direct relationship (Rasch and Born, 2013).

To overcome these caveats, we took advantage of the temporally precise control of specific neural circuits enabled by the use of optogenetic techniques. Our approach was to target a population of GABAergic neurons within the medial septum of mice (MS^{GABA}) implicated in memory formation, yet not associated with the regulation of sleep itself. We therefore optogenetically silenced MS^{GABA} neurons specifically during REMs in the period immediately following learning of either a spatial novel object place recognition test ($n = 6$ mice) or standard fear conditioning paradigm ($n = 8$

mice). Critically, the occurrence of REMs during MS^{GABA} silencing was undisturbed as hallmark features of REMs—defined in the context of our experiments as a combination of sustained behavioral quiescence, muscle atonia, and absence of NREMs—and restful wakefulness-associated slow (1–4 Hz) EEG oscillatory activity—were indifferent from unsilenced control mice (Boyce *et al*, 2016). The following day mice in the test group demonstrated impaired spatial and fear-conditioned contextual memory. REMs was a critical factor as optical silencing of MS^{GABA} neurons for similar durations non-specifically during NREMs and wakefulness had no effect on cognition, although this result does not preclude involvement of NREMs in memory formation as well. Indeed, the non-specific MS^{GABA} inhibition occurring during NREMs did not influence the NREMs-associated neural activity patterns implicated in memory formation, including hippocampal sharp-wave ripples and neocortical spindles (Rasch and Born, 2013; Boyce *et al*, 2016).

Our study directly demonstrated for the first time that the activity of a specific population of neurons (MS^{GABA}) selectively during REMs is required for normal memory formation. However, a precise mechanistic understanding of how REMs helps consolidate spatial and contextual memories requires further work. The ~7 Hz theta EEG rhythm that occurs in rodents during REMs has been implicated in the processing of spatial information at the neuronal level (Rasch and Born, 2013). Therefore, considering we found that a significant decrease in theta power accompanied MS^{GABA} silencing selectively during REMs following learning in the test group (Boyce *et al*, 2016), it is possible that our experiments disrupted normal physiological processing of spatial information at the level of individual place cells, or perhaps that of more structured neuronal assemblies (Malvache *et al*, 2016). It is also possible that our optogenetic manipulation perturbed neural homeostasis during REMs (Grosmark *et al*, 2012; Tononi and Cirelli, 2014; but see Hengen *et al*, 2016). Fully investigating