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TARGETING EPIGENETICS TO ACHIEVE THERAPEUTIC SELECTIVITY IN DISORDERS OF THE CENTRAL NERVOUS SYSTEM

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SUMMARY

Targeting epigenetics may offer the potential for achieving therapeutic selectivity in disorders of the central nervous system, by simultaneously modulating the expression of multiple genes involved in disease mechanisms. Histone acetylation, regulated by histone acetyltransferases and deacetylases, affects chromatin condensation and gene transcription. DNA methylation is also involved in histone modification. Methylation of CpG islands in promoter regions is associated with gene silencing. The development and functions of the human central nervous system are largely shaped by postnatal experiences, indicating that both genetic and epigenetic information are indispensable. The epigenetic regulatory mechanisms in the central nervous system have recently been object of intense research. As a result, mutations of epigenetic modulator genes have been implicated in several neurodegenerative and psychiatric disorders. This article reviews some common disorders, such as Alzheimer's disease, mood disorders and Attention Deficit Hyperactivity Disorder, where epigenetic mechanisms may offer potential targets for experimental therapeutics.

Introduction

Achieving therapeutic selectivity is a key objective in drug discovery and development. In pharmacology, the term "selectivity" refers to the ability of a drug to discriminate between related targets (e.g., receptors or enzymes), showing a higher binding affinity for one subtype or isoform. Pharmacological selectivity should be assessed by screening in pure systems (e.g., cell lines transfected with one receptor subtype at a time) and eventually in complex systems, including wild type *in vivo* and genetically altered models [1]. In pharmacology, the term "specificity" refers not only to the ability of a drug to identify a receptor of interest, but also to its potential for discriminating between negative and positive interactions, i.e., the drug should bind the receptor with appropriate affinity, and have a low or no cross-reactivity with other receptors [1]. In medicine, however, the term "therapeutic selectivity" often incorporates the meaning of "specificity". Achieving therapeutic selectivity requires precise target modulation. The study of selective interaction may gain insight from *in silico* analysis and subsequent *in vitro* testing [2]; however, *in vivo* the selectivity can be thwarted by the compensatory mechanisms operating in complex biological systems. Overcoming this compensation often requires high drug doses that can induce unwanted, off-target effects. Pharmacological synergism, that has been known and exploited in therapeutics for a long time, has recently been proposed as a means to increase therapeutic selectivity [3]. Synergistic drug combinations are usually more specific to particular cellular contexts than single agents. In line with this view, we

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have performed *in vitro* research in the past on the vasodilatory synergism between two drugs, dantrolene and nimodipine, that inhibit vascular smooth muscle contraction through distinct, but functionally sequential mechanisms [4]. Such drug combination could result effective when administered to patients with vasospasm of cerebral arteries following subarachnoid hemorrhage. The context-specificity of synergistic combinations creates many opportunities for achieving therapeutically relevant selectivity, and enables improved control of complex biological systems. The so-called "pleiotropic" agents, that exert multiple actions, may achieve therapeutic selectivity because they simultaneously target several processes involved in the mechanism of a disease [5, 6]. Such agents include isoflavones and antioxidants in specific therapeutic contexts [7, 8]. It is worth noting that the mammalian cellular epigenome is modulated by phytochemical phenolic antioxidants, with implications in human diseases [9]. Epigenetic modulation is, in fact, considered a potential novel technique for achieving therapeutic selectivity by simultaneously modulating the expression of a panoply of genes involved in a disease mechanism. Epigenetics is the study of the changes in gene expression or cellular phenotype caused by mechanisms that do not involve a change in the nucleotide sequence. Examples of such modifications include DNA methylation and histone modification. Gene expression can be controlled through the action of repressor proteins that attach to the silencer regions of the DNA. These changes may remain through the cell's life span, and may also endure through multiple cell divisions. The best example of epigenetic changes is the process of cellular differentiation. Histone acetylation is the main histone modification that has been considered as a potential drug target. Histone acetylation is dynamically regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs neutralize the positive charge on lysine residues, thereby inhibiting their electrostatic interaction with the negatively charged phosphate backbone of DNA, and allowing chromatin to adopt a more relaxed structure and recruit the transcriptional machinery; HDACs reverse lysine acetylation, restore the positive charge of histones and locally stabilize chromatin architecture [10]. Thus, the level of histone acetylation dramatically affects chromatin condensation and gene transcription. DNA methylation is also involved in histone modification. Methylation of CpG islands in promoter regions is associated with gene silencing and is highly interactive with histone acetylation and the other histone-modifying mechanisms [10]. The development and functions of human CNS are largely shaped by postnatal experiences, indicating that both genetic and epigenetic information are indispensable. The epigenetic regulatory mechanisms in the central nervous system have recently been object of intense research. As a result, mutations of epigenetic modulator genes have been implicated in several neurodegenerative and psychiatric disorders. Here we look at a few examples of common CNS disorders, in which epigenetic mechanisms have gained enough attention to become potential targets for experimental therapeutics.

Alzheimer's disease (AD) (Table 1)

Studies of late-onset AD in twins support the notion that risk factors may affect AD pathophysiology through epigenetic mechanisms [11]. HDAC2, but not HDAC1, is known as a negative regulator of memory [12]. Cognitive function in AD may be affected by an epigenetic blockade of gene transcription. A recent study suggests that this blockade is mediated by HDAC2 in patients with AD, and potentially reversible in mouse models of neurodegeneration [13]. Non-specific pan-HDAC inhibitors, including valproic acid, trichostatin A, sodium 4-phenylbutyrate and vorinostat have been shown to possess neuroprotective properties *in vitro*, as well as reinstating memory and reversing learning deficits in AD mouse models, but it is still unclear whether they act through A*β* clearance, rather than primarily through HDAC inhibition. Environmental influences during brain development inhibit DNA-methyltransferases (DNMT), thus hypomethylating promoters of genes associated with AD, such as the beta-amyloid precursor protein (APP). This early life imprint is sustained and triggers increase in APP and amyloid β (Aβ) later in life. Furthermore, some AD-associated genes are overexpressed later in life, while others are repressed, suggesting that these early life perturbations result in hypomethylation as well as hypermethylation of genes. The

hypermethylated genes are prone to Aβ-enhanced oxidative DNA damage, since methylcytosines restrict repair of adjacent hydroxyguanosines [14]. APP is a gene potentially controlled by methylation [15], given that the APP promoter region has a high GC content (72%) and shows tissue-specific and brain region-specific methylation patterns [16]. The methylation status of DNA extracted from the parietal cortex of post-mortem brains shows decreasing amounts of methylcytosine within the APP promoter with increasing age (a known risk factor for AD) [17-20]. Higher levels of inter-individual variation in genes that participate in methylation homeostasis (methylene tetrahydrofolate reductase, MTHFR; DNMT1) have been observed in AD patients compared to healthy control individuals; this factor may contribute to AD predisposition [21]. Immunoreactivity for methylcytosine, DNMT1 and components of the methylation co-repressor complex have been found to be decreased in AD patients, consistent with the view that loss of APP promoter methylation plays a role in AD [22]. Folate and vitamin B12 are required to generate methionine from homocysteine. Elevated homocysteine levels in AD patients are associated with folate and vitamin B12 deficiency [23, 24]. Folate deficiency and elevated homocysteine impair DNA repair mechanisms in hippocampal neurons in APP mutant mice, sensitizing them to oxidative damage induced by Aβ [25]; furthermore, oxidative stress is increased in the brains of APOE4 mice and it can be suppressed by administering additional folate [26]. Folate deficiency can also arise from MTHFR polymorphisms, considered another risk factor for AD [27]. The resulting elevated homocysteine levels and corresponding decrease in *S*-adenosyl methionine in AD [28] may decrease APP promoter methylation and augment the increased expression of APP. Based on these premises, administration of high-dose supplements of folate, vitamin B12 and vitamin B6 have been tested in AD, but so far the results have not been encouraging despite the decrease in homocysteine levels in treated patients [29, 30]. The exact role of MTHFR remains controversial since the analysis of its polymorphisms has not produced statistically significant correlation with AD so far.

The products of amyloidogenic APP processing, such as APP-CTs, produced from β- and γ-secretases, may interact with pathways that increase histone acetylation [31, 32]. The use of HAT inhibitors may therefore be proposed for the treatment of AD. In fact, the risk of developing AD has been shown to be significantly reduced in populations that consume large quantities of curcumin, a HAT inhibitor that interferes with the formation of amyloid plaques [33-36]. Developmental exposure of neonates to lead (Pb) causes a delayed overexpression of APP and increases Aβ load [37, 38], associated with a reduction in DNA methyltransferase activity [38]. Therefore, certain early life events, including exposure to heavy metals or other toxic substances, seem to predispose individuals to epigenetic dysregulation and the devel-

Epigenetic target	Drug treatment	Tested species
Histone deacetylases (Histone deacetylase 2)	**valproic acid trichostatin A sodium 4-phenylbutyrate vorinostat**	**mouse**
Histone acetyltransferase	**curcumin**	**mouse, human**
DNA-methyltransferases (DNA (cytosine-5)-1 Methyltransferase)	**folate vitamin B12**	**human**
Methylene tetrahydrofolate reductase	**folate, vitamin B12 vitamin B6**	**human**

Table 1. Potential epigenetic targets in Alzheimer's Disease

opment of AD in later life.
The causal involvement of epigenetic mechanisms in AD, if confirmed, will not only provide novel targets for drug discovery, but may also help to understand the failure of clinical trials of disease-modifying drugs, despite their proven efficacy in Aβ clearing [39]. According to this view, if the epigenetic blockade is set off before the clinical onset of AD, reducing Aβ generation and deposition alone may not suffice to rescue cognitive function [40].

Mood disorders (Table 2)
Epigenetic events that alter chromatin structure to regulate gene expression programs have been associated with depression-related behavior, antidepressant action, and resistance to depression, or 'resilience', in animal models, with increasing evidence for similar mechanisms occurring in postmortem brains of depressed human patients. Very recently, it was shown that antidepressant-like effects involve epigenetic modifications associated with changes in HDAC expression in mice, with increased expression of HDAC2, HDAC3 or HDAC5 [41]. In parallel with genome-wide association studies to identify sequence variations influencing susceptibility to major depressive disorder, the search for epigenetic marks, such as DNA methylation, which can be influenced by environment, is also ongoing. Recently, a genome-wide scan of DNA methylation has been carried out in postmortem frontal cortex samples from patients with major depressive disorder [42]. By Comprehensive High-throughput Arrays for Relative Methylation, 224 candidate regions with DNA methylation differences >10% have been identified. These regions are highly enriched with neuronal growth and development genes, and one of them may change acetylcholinesterase in neuronal membranes and increase cholinergic transmission [42]. Impaired neuronal plasticity is increasingly viewed as crucial in depression. Mechanisms proposed to be responsible for neuronal atrophy include glucocorticoid and glutamate toxicity for both glial cells and neurons [77], decreased neurotrophic factor expression [43, 44] and decreased neuroplasticity. Impaired neurogenesis has been reported in subjects with depression-like symptoms [45-47], whereas diverse antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and tricyclic antidepressants, increase neurotrophic factor expression [44] and, in the long term, neurogenesis in the mammalian hippocampal dentate gyrus [48]. Epigenetic regulation is implicated in the first stages of adult neurogenesis, by promoting the maintenance of the self-renewal potential of adult neural stem cells. Trithorax and polycomb proteins are chromatin modifier complexes that, respectively, activate or silence the targeted loci, maintaining such transcriptional state for several cell divisions [49-51]. Furthermore, the PcG zinc-finger protein Bmi1 has been identified as an epigenetic regulator, promoting H3K27 methylation and repressing the expression of the cyclin-dependent kinase inhibitor gene p16; as a consequence, the proliferative rate of adult neural stem cells is maintained [52,53]. Methyl-CpG binding protein 1 may also be involved, because mice deficient in this protein show reduced neurogenesis that correlates with cognitive im-

Epigenetic target	Drug treatment	Tested species
Histone deacetylases	sodium butyrate	mouse
(Histone deacetylase 2)	valproic acid	
(Histone deacetylase 3)	trichostatin A	
(Histone deacetylase 5)	imipramine	
	MS-275	
(Histone deacetylase 6)	NCT-14b	
	sirtinol	
	amitriptylin	(*in vitro*)
Histone 3	L-acetylcarnitine	mouse

Table 2. Potential epigenetic targets in mood disorders

pairments in spatial memory [54]. It is worth to note that these epigenetic regulators operate together with several other epigenetic protein regulators, such as DNA methyltransferases, HATs, HDACs, and histone methyltransferases, that will actively participate in further regulatory steps of the neurogenic process. These steps may constitute, in the near future, novel druggable targets for depressive disorders.

Attention deficit, hyperactivity disorder (ADHD) (Table 3)

This is a common neurobehavioral disorder, characterized by hyperactivity, impulsivity, and deficit in attention and cognition, affecting as much as 5-10 % of school aged children in United States. Although the biological bases of ADHD remain partly unknown, increasing evidence suggests that ADHD is associated with a dysfunction of catecholaminergic (i.e. dopamine and norepinephrine) systems [55]. ADHD is a familial and highly heritable disorder. Several candidate genes involved in neurotransmission have been identified; however, simple genetic association has proven insufficient to explain the spectrum of ADHD, suggesting that for the most part, ADHD is not caused by single common genetic variants. Advances in genotyping, enabling investigation at the level of the genome, have led to the discovery of rare structural variants suggesting that ADHD is a genomic disorder, with potentially thousands of variants, and common neuronal pathways disrupted by numerous rare variants result in similar ADHD phenotypes. Heritability studies in humans also indicate the importance of epigenetic factors, and animal studies are deciphering some of the processes that confer risk during gestation and throughout the post-natal period. Prenatal exposure to some agents toxic to the CNS, such as trimethyltin chloride, are considered as putative experimental model of ADHD, because the animals exposed *in utero* display, in adulthood,ADHD symptoms that are sensitive to ADHD drug treatments [56]. In lymphoblastoid cells from patients with fragile X syndrome, valproic acid causes a modest reactivation of FMR1 transcription and increases levels of histone acetylation, confirming the histone hyperacetylation effect. *In vivo*, valproic acid, an HDAC inhibitor, improves the adaptive behavior, due to a significant reduction in hyperactivity of ADHD symptoms in patients with fragile X syndrome [57]. More recently, a study in a Noonan syndrome-like phenotype, that includes attention deficit hyperactivity disorder, has demonstrated that H3 acetylation is important for neural, craniofacial and skeletal morphogenesis, mainly due to its ability to specifically regulate the MAPK signaling pathway [58]. These reports suggest that epigenetics may be involved in ADHD, but the evidence available today is still insufficient for proposing new specific druggable targets.

Concluding remarks

The three examples mentioned above show that epigenetics are involved in a range of CNS disorders. However, it is still unclear whether or not individual components of the epigenome can be successfully targeted with pharmacological interventions. Current HDAC inhibi-tors were initially studied and used in neoplastic diseases, such as haematological malignancies [10]. Vorinostat and romidepsin were first approved for the treat-ment of cutaneous T cell lymphoma, but the potential therapeutic utility of HDAC inhibitors for non-oncology indications requires more stringent safety profiles. Key safety issues include the long-term effects on stem cells and germ cells. In general, currently available drugs targeting the epigenetic players

Epigenetic target	Drug treatment	Tested species
Histone acetyltransferase	garcinol anacardic acid	(human, *ex vivo*)
Histone deacetylases	valproic acid	

Table 3. Potential epigenetic targets for Attention Deficit Hyperactivity Disorder (ADHD) symptoms, occurring in fragile X syndrome

lack selectivity and/or specificity, which may increase the risk of off-target responses. Future studies using class- and subtype-specific HDAC inhibitors and/or modifiers of histone methylation and phosphorylation may provide greater specificity of action and better therapeutic outcomes with improved tolerability.

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