Neuropharmacology 80 (2014) 95–102

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue?

Andre Fischer [a,b]

[a] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Grisebachstr. 5, 37077 Göttingen, Germany
[b] Research Group for Epigenetic Mechansims of Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE) Göttingen, Grisebachstr. 5, 37077 Göttingen, Germany

ARTICLE INFO

Article history:
Received 16 October 2013
Received in revised form
20 January 2014
Accepted 21 January 2014
Available online 31 January 2014

Keywords:
Histone-acetylation
Alzheimer
Gene-expression
Memomry
HDAC inhibitors

ABSTRACT

Alzheimer' s disease (AD) is the most common form of dementia causing an increasing emotional and economical burden to our societies. Although much progress has been made regarding the molecular mechanisms that underlie AD pathogenesis effective therapies are not available yet. The emerging field of neuroepigenetics has provided evidence that de-regulation of epigenetic processes play a role in AD. In this article we will critically review the primary research data that led to the hypothesis that targeting histone-modifying enzymes could be used to treat AD pathogenesis and address the question if the field is ready to translate such findings into clinical application.

This article is part of the Special Issue entitled 'Neuroepigenetic Disorders'.

1. Introduction

An universal finding across species is that the consolidation of long-term memories requires differential gene-expression (Davis and LR, 1984) (Kandel, 2001) (Barco et al., 2008). The precise gene-expression programs that underlie memory function and the mechanisms that orchestrate these programs during memory consolidation are however poorly understood. In turn de-regulation of gene-expression programs is observed in neurodegenerative diseases including Alzheimer's disease (AD) (Lu et al., 2004) (Caldeira et al., 2013) suggesting that these processes are mechanistically linked. In addition to the activity of transcription factors there is now mounting evidence that epigenetic mechanisms play an important role in memory formation under physiological and pathological conditions (Sananbenesi and Fischer, 2009) (Fischer et al., 2010) (Day and Sweatt, 2011). The term epigenetics has been introduced by Conrad Waddington to describe heritable changes of a phenotype that do not depend on altered DNA-sequence (Holliday, 1994). It is now more generally used to describe processes – including the orchestration of gene-expression programs in post-mitotic neurons – that are mediated via epigenetic processes (Stilling and Fischer, 2011). Epigenetic processes can be divided into 3 major categories: (1) Histone-modifications (2) DNA methylation and the more recently discovered DNA-hydroxymethylation and (3) non-coding RNAs. Such processes appear to play a critical role for transforming the variable combinations of genetic and environmental factors into long-term adaptive changes in gene-expression. Thus, epigenetic mechanisms are key regulatory processes that mediate genome–environment interactions (GxE).

Histones are highly conserved basic proteins that act as building blocks of the nucleosome, the fundamental unit of chromatin. The nucleosome is an octamer consisting of two molecules of each core histone (H) H2A, H2B, H3, and H4 around which is wrapped 147 bp of DNA. Histones contain a flexible N-terminus that protrudes from the surface of the nucleosome and is often named the "histone tail." Histone tails are subjected to multiple posttranslational modifications of which lysine acetylation and lysine methylations are the most common forms (Fischer et al., 2010). Acetylation of histones is regulated by the counteracting activity of Histone-acetyltransferases (HATs) and histone-deacetylases (HDACs). The same principle holds true for other histone-modifications such as methylation which is regulated by Histone-methyltransferases (HMTs) and Histone-demethylases (HDMs). The variable pattern of histone-modifications is believed to build a code, the so called "histone-code" that marks genes to be either active or inactive.

E-mail address: afische2@gwdg.de.

0028-3908/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropharm.2014.01.038

Methylation of DNA at the C-5 atom of cytosine is the best studies epigenetic mechanism and is generally associated with gene silencing. It is mediated by DNA-methlytransferases and often occurs in Cytosin-Guanin rich regions of the genome (CpG islands). A number of studies show that DNA-methylation in brain tissue can be very dynamic and is regulated by environmental stimuli (Day and Sweatt, 2011). More recently it has been discovered that Cytosine can be hydroxymethylated which occurs predominantly in brain tissue, is mediated by the TET proteins and compromises a novel mechanism of gene-regulation (Tan and Shi, 2012) While DNA-methylation is generally linked to gene-repression, the role of DNA-hyroxymethylation is less clear and in the most simple explanation DNA-hydroxymethylation can be viewed simply as a step of DNA-demethylation (Tan and Shi, 2012).

Finally, there is emerging evidence that non-coding RNAs orchestrate changes in gene-expression and protein production and also play a role during memory consolidation and contribute to the pathogenesis of neurodegenerative diseases (Schonrock et al., 2010) (Zovoilis et al., 2011) (Im and Kenny, 2012). Until recently it was assumed that gene-regulatory programs are orchestrated by regulatory proteins. Due to new sequencing technologies we know now that cells produce a wide range of non-coding RNAs (ncRNAs) with regulatory functions. The best studied group of non-coding RNAs are the so called micro RNAs (miRs). Micro RNAs are 19–22 nt long non-coding RNAs that are key regulators of protein homeostasis (Im and Kenny, 2012). MiRs are expressed as precursors that are further processed and eventually loaded to the RNA silencing (RISC) complex that catalyzes miR-mediated gene-silencing or inhibition of protein translation. Notably, one miR can target multiple mRNAs and in turn one mRNA can be targeted by more than one mIR, giving rise a complex regulatory network of gene-expression and protein homeostasis.

While the role of DNA-methylation and non-coding RNAs in brain plasticity and diseases has been discussed elsewhere (Day and Sweatt, 2011) (Delay et al., 2012) (Irier and Jin, 2012), the aim of this review is to critically review the evidence that histone-modifications play a role in Alzheimer's disease (AD).

AD is the most common form of dementia in the elderly. It arises on the pathological background of amyloid plaques, neurofibrillary tangles (NFT) and neuronal loss that eventually leads to severe dementia. About 2–5% of all AD patients suffer from familial AD that is characterized by an early onset (early onset AD, eoAD) and is explained by mutations in genes that regulated processes of the amyloid precursor protein (Haass and Selkoe, 2007). This correlates with the increase of soluble amyloid beta peptides and insoluble amyloid plaques. The common view is that specific amyloid beta peptides are toxic to nerve cells. Most of the currently used animal models and therapeutic approaches are based on eoAD. While there is convincing evidence for the role of amyloid beta in AD, all corresponding therapeutic approaches have failed in the clinic (Mangialasche et al., 2010). NFTs are intracellular aggregates of the microtubule binding protein Tau. Within such tangles Tau is often hyper-phosphorylated and the corresponding kinases are investigated as potential drug targets (Götz and Ittner, 2008). Mutations of the Tau protein have not been observed in AD patients. Instead Tau mutations cause frontotemporal dementia, a neurodegenerative disease that also causes dementia (Schneider and Mandelkow, 2008).

In contrast to eoAD, the more common form of AD is the so called late onset AD (loAD) or sporadic AD that affects 95–98% of all AD patients. LoAD patients also develop amyloid plaques, NTFs and dementia but at much older age. In fact aging is the most significant risk factor for loAD. Since life expectancies are increasing it is estimated that the number of individuals afflicted with loAD will double by the year 2025 causing a huge economical burden to our societies. Genome wide association studies (GWAS) have identified a number of genetic variants that correlate with loAD (Goate and Hardy, 2012). The most reproducible and significant variant is found for the apolipoportein E (ApoE). ApoE encodes a 299-amino acid glycoprotein that is highly expressed in the brain where it is mainly secreted by astrocytes but can also be produced by neurons. ApoE exists in 3 allelic variations, namely the isoforms ApoE2, ApoE3 and ApoE4 that differ at residues 112 and 158 which impacts on protein structure. Presence of the ApoE4 isoform dramatically increases the risk to develop loAD (Kim et al., 2009). Although the mechanisms by which ApoE4 increases the risk to develop AD are not entirely understood one possibility is altered clearance of amyloid beta peptides (Kim et al., 2009). Also other genes that were found to be associated with the risk to develop AD, such as CLU, ABCA7 od PICALM have been linked to amyloid beta processing (Tanzi, 2012).

Yet genetics alone do not explain the onset of loAD and it is now generally accepted that the variable combination of genetic and environmental risk drive loAD pathogenesis. A role of epigenetics in loAD pathogenesis is getting increasing attention since DNA-methylation, histone-modifications and the action of non-coding RNA are at the core of GxE interactions. An increasing body of literature investigates epigenetic changes linked to AD progression and first preclinical studies have demonstrated that epigenetic therapeutic strategies can reinstate cognitive function in disease models. In the following we will critically discuss the studies that try to provide evidence for a role of histone-modifications in AD pathogenesis and evaluate on this basis if targeting histone-modifying enzymes could indeed be a novel therapeutic strategy.

2. Histone-acetylation and HDAC inhibitors in AD

Already in 1979 it was found that acetylation of histones is altered when rats undergo memory consolidation (Schmitt and Matthies, 1979). Such studies were later confirmed showing that specific forms of learning correlate with increased HAT activity (Swank and Sweatt, 2001) and histone-acetylation (Levenson et al., 2004). Functional relevance was demonstrated via genetic models in which the activity of the HAT CREB binding protein (CBP) was reduced (Alarcon et al., 2004) (Korzus et al., 2004). Such mice showed impaired memory consolidation which could be rescued by administration of the HDAC inhibitor trichostatin A (TSA) (Alarcon et al., 2004). In line with this data, it was found that inhibiting histone-acetylation in the hippocampus can enhanced the consolidation of associative memories in rodents (Levenson et al., 2004). The therapeutic potential of HDAC inhibitors in AD was first tested in a mouse model that allowed inducible overexpression of the p25 protein (CK-p25 mice) (Fischer et al., 2005), a pathological subunit of the Cyclin-dependent kinase 5 (CDK5) that is de-regulated in human AD patients (Patrick et al., 1999). Inducible over-expression of p25 causes amyloid and tau pathology, severe neurodegeneration and memory impairment (Cruz et al., 2003) (Fischer et al., 2005) (Cruz et al., 2006). Intra-peritoneal (ip) administration of the HDAC inhibitor sodium butyrate for 4 weeks was able to reinstate learning behavior and restore retrieval of consolidated memories in CK-p25 mice that already suffered from severe AD pathology. This correlated with synaptogenesis and rewiring of the neuronal network suggest neuroprotective and neuroregenerative actions of HDAC inhibition (Fischer et al., 2007). A subsequent study employed a mouse model for amyloid deposition (APP/PS1 mice) and showed that acetylation of histone 4 was decreased in the hippocampus of APP/PS1 mice. Administration of the HDAC inhibitor trichostatin A (TSA) rescued the deficit in H4 acetylation and also increased associative memory formation in APP/PS1 mice (Francis et al., 2009). Similar findings were observed in other