Neuropharmacology 80 (2014) 103–114

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

What's wrong with epigenetics in Huntington's disease?

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ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form
16 October 2013
Accepted 21 October 2013
Available online 31 October 2013

Keywords:
Polyglutamine
Histone
Post-translational modification
KAT
HDAC
DNA methylation
Amelioration

ABSTRACT

Huntington's disease (HD) can be considered the paradigm of epigenetic dysregulation in neurodegenerative disorders. In this review, we attempted to compile the evidence that indicates, on the one hand, that several epigenetic marks (histone acetylation, methylation, ubiquitylation, phosphorylation and DNA modifications) are altered in multiple models and in postmortem patient samples, and on the other hand, that pharmacological treatments aimed to reverse such alterations have beneficial effects on HD phenotypic and biochemical traits. However, the working hypotheses regarding the biological significance of epigenetic dysregulation in this disease and the mechanisms of action of the tested ameliorative strategies need to be refined. Understanding the complexity of the epigenetics in HD will provide useful insights to examine the role of epigenetic dysregulation in other neuropathologies, such as Alzheimer's or Parkinson's diseases.

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

1. Introduction

The relevance of epigenetics in human disease has been extended from the field of cancer research to several diverse conditions, including a vast variety of neuropathologies, as reviewed in articles of this Special Issue and elsewhere (Day and Sweatt, 2012; Jakovcevski and Akbarian, 2012). Huntington's disease (HD) is the most common polyglutamine (polyQ) disorder and has emerged as a prototypical paradigm of epigenetic dysregulation in a neurodegenerative condition. Pioneering work in HD and other polyQ disorders at the beginning of the last decade suggested a relevant role of epigenetics in neuronal malfunction and cell loss, and proposed for the first time a corrective strategy based on epigenetics in neurodegeneration. These seminal results were soon translated to more common neurodegenerative disorders like Alzheimer's disease, leading to the general hypothesis of epigenetic imbalance as an important feature in neurodegeneration. Nonetheless, our knowledge of the primary cause of HD makes the proposal of general principles more feasible compared to other pathologies of uncertain origin.

HD is inherited in a fully penetrant, autosomal-dominant manner, with a prevalence of 5–10 cases per 100,000 worldwide (Bates et al., 2004). Onset commonly occurs around the 30s and 40s, although juvenile cases have been documented. Classical HD is characterized by personality changes, weight loss, cognitive disorders and motor impairment, including the hallmark feature of chorea (involuntary jerky movements of the face and limbs), and gait abnormalities. The disease lasts 15 years on average, until the death of the patient. Currently, HD has no effective therapy. A prominent morphological feature is a marked degeneration in medium spiny GABAergic neurons of the striatum, although several neuronal types and brain areas become more affected as its pathology progresses (Bates et al., 2004). In all cases, HD is caused by an aberrant expansion of the trinucleotide sequence CAG (>36) in a polymorphic region encoding a polyQ stretch located in the N-terminus of the huntingtin (Htt) protein (see Fig. 1 for a scheme of the primary sequence). This mutation causes two types of effects (Zuccato et al., 2010): 1) depletion of the normal Htt, which plays roles in endocytosis and vesicle trafficking, among others, and this can compromise its prosurvival and synaptic functions; and 2) the formation of a misfolded mutant Htt (mHtt) that can affect the activities of several components of multiple cellular processes. mHtt is cleaved and forms intracellular aggregates in the cell nucleus, cytoplasm, neurites and terminals, which constitutes a universal hallmark of HD despite the controversial role of these aggregates in the pathogenesis of the disease. Whether soluble or aggregated, aberrant interaction of mHtt with transcription factors and chromatin-remodeling proteins is the primary basis of the

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http://dx.doi.org/10.1016/j.neuropharm.2013.10.025

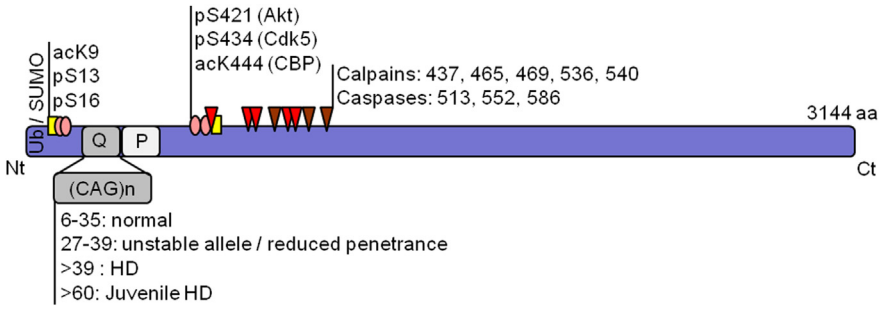

Fig. 1. Scheme of the human huntingtin. Polyglutamine (Q) and polyproline (P) tracts are indicated, in addition to the polymorphic range of CAG repeats found in human population. Cleavage sites and post-translational modifications are also shown, together with the residue number: Ub/SUMO, ubiquitylation/SUMOylation; yellow square, acetylation; pink oval, phosphorylation; red and brown triangles, calpain and caspase cleavage sites, respectively. Nt and Ct, amino- and carboxy-termini, respectively.

prominent transcriptional dysregulation observed in several HD models and in patients, which can occur in presymptomatic stages and in peripheral samples (Cha, 2007; Seredenina and Luthi-Carter, 2012).

Epigenetic mechanisms can be classified into DNA modifications (methylation and hydroxymethylation), post-translational histone modifications (acetylation, methylation, phosphorylation, ubiquitylation, SUMOylation, ADP ribosylation, etc.) and exchange of histone variants (e.g., H1, H3.3, H2A.Z, H2A.X). More recently, certain non-coding RNA species have been considered as part of epigenetics as they can influence the chromatin (Kanduri, 2011). In the following sections, we will review the epigenetic alterations that have been documented for more than 10 years in both cellular and animal HD models (see Zuccato et al., 2010 for a description of HD models), together with tantalizing findings in postmortem human samples, and the examined upstream mechanisms that may lead to such alterations (Fig. 2). Next, we will summarize the ameliorative strategies that reverse epigenetic dysregulation and their accompanying beneficial effects at the behavioral and molecular levels. Finally, we will discuss the biological significance of these outcomes, as recent evidence challenges the classical view of the roles of epigenetics in regulating gene expression and in HD amelioration.

2. Altered epigenetics in Huntington's disease

2.1. Histone acetylation

Histone acetylation is the most studied epigenetic mark in cognition and neuropathology. It is associated with a relaxed chromatin conformation that facilitates the recruitment of transcription factors and the basal machinery to regulatory sequences in the DNA, and it is regulated by two opposing enzymatic activities: histone (or lysine) acetyltransferase (KAT) and histone deacetylase (HDAC) (Valor et al., 2013b). The first evidence of histone acetylation dysregulation in HD came from the observation that CREB-binding protein (CBP), which has KAT activity, was found in intracellular inclusions in *in vitro* preparations, animal model brains and postmortem tissue from patients (Kazantsev et al., 1999; Steffan et al., 2000; Nucifora et al., 2001), suggesting that depletion of soluble CBP may affect the transcriptional regulation of neuronal genes relevant to cell survival. In agreement with this view, overexpression experiments rescued the deficits in exogenous CBP/CREB-dependent transcription and the toxicity induced by mHtt in cell culture (Nucifora et al., 2001). In a parallel report, Steffan et al., 2001 discovered global hypoacetylation of histones H3 and H4 in stably transfected PC12 cells expressing mHtt.

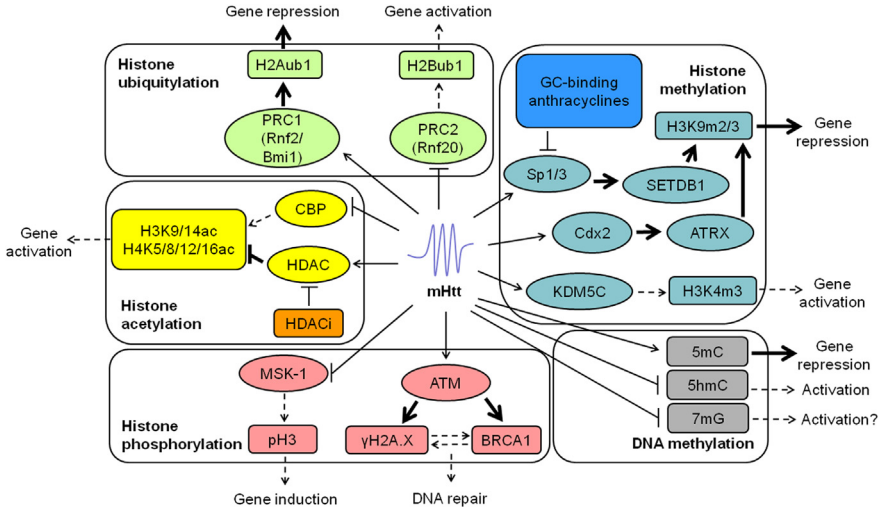

Fig. 2. Summary of the disrupted epigenetic mechanisms in HD and the tested ameliorative strategies. A gain-of-function effect is inferred because most of the HD models are based on transgenic or exogenous mHtt expression. Nonetheless, altered interactions between wt-Htt and chromatin-remodeling proteins are possible in HD (e.g., Htt-HDAC3). Actions by mHtt: regular arrow, activation; blunt end, inhibition. Resulting effects in the relationship between transcription factors and chromatin-remodeling proteins and their downstream targets and related processes are represented by dashed (reduced activity/effect) and thick arrows (enhanced activity/effect). No intermediate enzyme has been examined in altered DNA methylation. Ameliorative pharmacological compounds are also depicted. See main text for full acronyms description.