BRAIN RESEARCH 1476 (2012) 203–210

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Review

NF-κB and epigenetic mechanisms as integrative regulators of brain resilience to anoxic stress

Ilenia Sarnico[a,1], *Caterina Branca*[a,1], *Annamaria Lanzillotta*[a], *Vanessa Porrini*[a], *Marina Benarese*[a], *Pier Franco Spano*[a,b], *Marina Pizzi*[a,b,*]

[a]*Department of Biomedical Sciences & Biotechnologies, University of Brescia and Istituto Nazionale di Neuroscienze, Italy*
[b]*IRCCS San Camillo Hospital, Venice, Italy*

ARTICLE INFO

Article history:
Accepted 9 April 2012
Available online 17 April 2012

Keywords:
NF-κB
OGD
Preconditioning
RelA acetylation
Epigenetic
Resveratrol

ABSTRACT

Brain cells display an amazing ability to respond to several different types of environmental stimuli and integrate this response physiologically. Some of these responses can outlive the original stimulus by days, weeks or even longer. Long-lasting changes in both physiological and pathological conditions occurring in response to external stimuli are almost always mediated by changes in gene expression. To effect these changes, cells have developed an impressive repertoire of signaling systems designed to modulate the activity of numerous transcription factors and epigenetic mechanisms affecting the chromatin structure. Since its initial characterization in the nervous system, NF-κB has shown to respond to multiple signals and elicit pleiotropic activities suggesting that it may play a pivotal role in integration of different types of information within the brain. Ample evidence demonstrates that NF-κB factors are engaged in and necessary for neuronal development and synaptic plasticity, but they also regulate brain response to environmental noxae. By focusing on the complexity of NF-κB transcriptional activity in neuronal cell death, it emerged that the composition of NF-κB active dimers finely tunes the neuronal vulnerability to brain ischemia. Even though we are only beginning to understand the contribution of distinct NF-κB family members to the regulation of gene transcription in the brain, an additional level of regulation of NF-κB activity has emerged as operated by the epigenetic mechanisms modulating histone acetylation. We will discuss NF-κB and epigenetic mechanisms as integrative regulators of brain resilience to anoxic stress and useful drug targets for restoration of brain function.

This article is part of a Special Issue entitled: Brain Integration.

* *Corresponding author at:* Division of Pharmacology, Department of Biomedical Sciences & Biotechnologies, Viale Europa, 11, 25123 Brescia, Italy. Fax: +39 030 3717529.
E-mail address: pizzi@med.unibs.it (M. Pizzi).

Abbreviations: CBP, p300/CREB-binding protein; HAT, histone acetyltransferase; HDAC, histone deacetylase; K310, lysine 310; MCAO, middle cerebral artery occlusion; NF-κB, nuclear factor kappa B; OGD, oxygen glucose deprivation; SIRT1, sirtuin 1

[1] These authors contributed equally.

0006-8993/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2012.04.013

Contents

1. Introduction

Epigenetics is a rapidly expanding field that focuses on stable and heritable changes in gene expression that are not accompanied by changes in DNA sequence. Different definitions of epigenetics have been claimed since Waddington (1942) first coined the term in the 1940s. Nowadays the most agreed is the following: the structural adaptation of chromosomal regions so as to register signals or perpetuate altered activity states (Bird, 2007). Epigenetic machinery represents the effector of stable chromatin modifications during cell division and development, but it also represents the molecular interface mediating gene–environmental interactions during critical periods throughout the lifecycle (Fagiolini et al., 2009; Mehler, 2008). Several mechanisms contribute to the epigenetic regulation of transcriptional activity, such as DNA methylation (Laird, 2010), post translational modifications of histone proteins (Heintzman et al., 2009; Wang et al., 2008), nucleosome repositioning (Kerppola, 2009), expression of microRNA and non-coding RNAs (Guttman et al., 2009), and RNA and DNA editing (Mattick, 2009). DNA and histone modifications can affect transcription in two different ways. One is through direct alteration of the chromatin packing to open or close the DNA polymer and control the access of DNA-binding proteins such as transcription factors. The other is through alteration of the nucleosome surface to promote the association of chromatin binding proteins. It explains why the differentiated cells in a multicellular organism express only the genes that are necessary for their own activity (Berger, 2007) and require mutually reinforcing mechanisms permitting heritable patterns of gene silencing. Mutations in genes that affect global epigenetic profiles can give rise to human diseases (Egger et al., 2004). Recent studies have shed some light on the relationship between epigenetic alterations and central nervous system (CNS) disorders (De Sario, 2009; Urdinguio et al., 2009). Although CNS disorders are characterized by epigenetic persistence of an altered chromatin state, it has emerged that most of the histone modifications are reversible and can be affected by drugs. Thus, a comprehensive understanding of epigenetic mechanisms, their interactions and alterations in health and disease, has become a priority in biomedical research.

Neurodegenerative disorders create a tremendous burden on aging societies, due to their destructive nature, the number of affected individuals and the health care costs. Developing innovative therapies for neurodegenerative diseases represents a great chance to reduce disability, improve the quality of life and decrease national direct and indirect health-related costs. For this purpose, investigations on factors affecting neuronal vulnerability or resilience are considered a top priority of translational research in neurology nowadays. Among the age-related neurodegenerative disorders, the post-ischemic brain injury represents the first cause of long term disability and the second cause of death in the western world, but at the present time there is a stunning lack of efficacious treatments. Understanding the cellular and molecular machineries underlying the pathogenesis of such a devastating disorder will facilitate the development of strategies to limit brain damage and facilitate the recovery. The cellular and molecular mechanisms activated in brain ischemia are complex and not completely clarified. The involvement of the nuclear factor kappa B (NF-κB) pathway in triggering inflammatory and neurodegenerative processes has been well established, but the tools to finely dissect detrimental from beneficial NF-κB activation are still limited (Mattson and Meffert, 2006; Ridder and Schwaninger, 2009).

2. NF-κB in CNS

In CNS NF-κB acts as regulator of growth, differentiation, and adaptive responses to extracellular signals (Kaltschmidt et al., 1993; O′Neill and Kaltschmidt, 1997; West et al., 2002). However, NF-κB activation is also involved in the pathophysiology of neurological diseases associated with neurodegeneration (Clemens et al., 1997; O′Neill and Kaltschmidt, 1997; Schneider et al., 1999), where a dual role of NF-κB as regulator of apoptosis has been demonstrated and widely discussed (Grilli et al., 1996; Kaltschmidt et al., 1999; Mattson and Camandola, 2001; Pizzi and Spano, 2006; Qin et al., 1999; Yu et al., 1999).

Several studies focused on the expression and regulation of NF-κB transcription factor in the nervous system as a pleiotropic regulator of target genes controlling physiological function. Different members of the NF-κB family have been identified in mammalian cells, these include p65 (RelA), RelB, c-Rel, p50/p105 (NF-κB1), and p52/p100 (NF-κB2). Among the members of the NF-κB family, only RelA, c-Rel and RelB are able to activate the transcription of target genes. The transcriptional capacity of p50 and p52, which are initially synthesized as large precursors called p105 and p100, depends on dimerization with RelA, c-Rel or RelB (Dejardin, 2006; Siebenlist et al., 1994). In the absence of stimuli, these factors are present as homo- and