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Review

Epigenetic mechanisms of neuroplasticity and the implications for stroke recovery

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ABSTRACT

Ischemic stroke is a devastating brain injury and an important cause of neurologic disability worldwide and across the lifespan. Despite the physical, social, and economic burdens of this disease there is only a single approved medicine for the treatment of acute stroke, and its use is unfortunately limited to the small fraction of patients presenting within the narrow therapeutic window. Following stroke, there is a period of plasticity involving cell genesis, axon growth, and synaptic modulation that is essential to spontaneous recovery. Treatments focusing on neuroprotection and enhancing recovery have been the focus of intense preclinical studies, but translation of these treatments into clinical use has been disappointing thus far. The important role of epigenetic mechanisms in disease states is becoming increasingly apparent, including in ischemic stroke. These regulators of gene expression are poised to be critical mediators of recovery following stroke. In this review we discuss evidence for the role of epigenetics in neuroplasticity and the implications for stroke recovery.

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Introduction

Stroke is one of the leading causes of neurologic morbidity and mortality worldwide. United States data estimate the annual incidence of stroke in adults at nearly 800,000, with a corresponding economic burden surpassing $35 billion (Go et al., 2014). While more common in the elderly, stroke afflicts people across the entire age span including infants and children and thus represents an important cause of neurologic disability in the pediatric population as well. The past two decades have witnessed the advent of dedicated stroke centers, along with the widespread use of thrombolytic treatment. These advances have substantially improved our management of acute stroke, but little success has been realized in developing therapies that provide true neuroprotection and enhanced recovery. Recognizing the burden of stroke-related disability in our population and limitations of our ability to provide hyperacute therapies such as t-PA due to narrow therapeutic time windows, the development of neurorestorative therapies without such restrictive uses is imperative.

Epigenetics refers to changes in gene expression that are not based on mutation of the underlying DNA sequence (Ma et al., 2010). Epigenetic changes are generally considered to be long lasting and heritable through successive cell generations, but recent evidence also suggests the potential for previously unappreciated dynamic changes under certain conditions (Felling et al., 2012). Although the field of epigenetics is now well established, interest in the epigenetic mechanisms involved in stroke pathophysiology has only recently gained traction. Our understanding of the epigenetics of neural plasticity has been substantially informed by the study of learning and memory (Levenson and Sweatt, 2005). Using this knowledge as a basis to better understand the structural and functional changes that occur following stroke could provide innovative approaches to stroke recovery and rehabilitation because motor learning is a critical component of this process (Krakauer, 2006). The primary epigenetic mechanisms often considered involve DNA methylation, histone modifications including methylation and acetylation, and posttranscriptional mechanisms of regulation through small, noncoding RNAs. Recent reviews support the emerging interest in the relevance of this field to stroke pathophysiology, but these largely focus on the injury process (Qureshi and Mehler, 2010a,b, 2011). In this review we discuss the available evidence supporting epigenetic mechanisms of neuroplasticity, with emphasis on implications for stroke recovery. This is an emerging domain with the potential to offer important insight into the biology of regeneration and recovery after stroke.

A critical period of injury-induced plasticity

Stroke recovery is an incredibly complex process and therefore any discussion of underlying mechanisms requires a good framework. Most clinical measures of recovery focus on the ability to accomplish various tasks essential to everyday life. In this sense, recovery can be achieved a number of ways, the most efficient of which is arguably compensatory adaptation, or learning to accomplish the task in a different way. For instance, if I have suffered a left middle cerebral artery stroke and can no longer reach for an object with my right hand, the easiest way to obtain the desired object is to reach instead with my left hand. Much of today's clinical focus concentrates on such means of compensatory adaptation. This does not reflect any degree of real neurologic recovery, and the holy grail of brain recovery research is the true restoration of function to the injured brain. Stroke patients do exhibit a spectrum of true recovery, but this is frequently far too limited. Understanding the mechanisms underlying this spontaneous recovery is an essential prerequisite to augmenting it.

There is tremendous evidence that the majority of spontaneous recovery occurs within a defined period of time after stroke. A large study of the natural history of stroke demonstrated that patients reached their maximal improvement by 3 months regardless of the initial severity of their symptoms (Jorgensen et al., 1999). Additionally, animal models indicate that early initiation of rehabilitative therapies within the first days after stroke leads to better functional outcomes (Krakauer et al., 2012). Despite significant challenges in studying similar effects in human stroke patients, clinical studies have also demonstrated trends toward beneficial effects of early rehabilitation (Cifu and Stewart, 1999). Some have drawn comparisons between this early recovery phase after stroke and the critical periods of plasticity that occur during development (Nahmani and Turrigiano, 2014). This leads to 2 important concepts: 1. Interventions designed to truly target reduced neurologic impairment after stroke need to be implemented within this critical period; and 2. Understanding the molecular and cellular characteristics that define critical period may allow a similar window of opportunity to be recreated long after a stroke occurs.

What characteristics of the early post-stroke time period are so critical to the recovery process? The immediate post-stroke epoch can be conceptualized as a period of enhanced plasticity, in many ways resembling the time of neurodevelopment (Cramer and Chopp, 2000). This enhanced plasticity includes the generation of new cells and blood vessels, sprouting and growth of new axons, and modulation of new and existing synapses (Carmichael, 2006). How the mature brain can suddenly launch into a period of renewed growth and development remains largely mysterious. The possibility that key components in epigenetic regulation stand poised to mediate this process in response to injury is a promising concept. In this review we highlight epigenetic mechanisms that altered in the aftermath of stroke and are known to have important functions in neuroplasticity (Table 1).

Global epigenetic changes following stroke

Before discussing the roles of epigenetics specific to recovery, summarized in Table 1, we would like to introduce the global epigenetic changes induced by stroke and briefly mention the evidence that these may generally be involved in stroke physiology. These include some roles in neuroprotection and preconditioning, two processes that are certainly important to outcomes after stroke although not directly related to repair processes which by definition require injury to have occurred first. While the general mechanisms of epigenetic regulation are beyond the scope of this review, we do provide a brief introduction to each and refer the reader to excellent reviews of these topics for further detailed discussions.

DNA methylation

The methylation of cytosine residues was first observed by Johnson and Coghill (1925) but not implicated in the regulation of gene expression until posited by Holliday and Pugh (1975). The methylation of cytosine-guanine (CpG) dinucleotides by a family of methyltransferase enzymes (DNMTs 1–4) has since been well characterized (Goll and Bestor, 2005). The role of this DNA modification within CpG-rich islands near 5′ promoter sites has long been appreciated as an effective means of gene silencing (Bird, 1986), but more recently scientists have expanded the classical view of DNA methylation. The role of intragenic methylation, which in fact comprises most of the methylated residues under homeostatic conditions, has garnered significant attention (Maunakea et al., 2010). Furthermore CpG dinucleotides may not be the exclusive site of methylation in the mammalian genome as previously thought (Ramsahoye et al., 2000), at least in neurons (Xie et al., 2012; Lister et al., 2013; Guo et al., 2014). Evidence of active demethylation of DNA has also called into question the stability of this epigenetic mark (Ma et al., 2009a; Guo et al., 2011a). These recent advances demonstrate the evolving nature of our understanding of DNA methylation.

Following stroke the level of global DNA methylation increases significantly in the infarcted tissue compared to the contralateral hemisphere (Endres et al., 2000). Interestingly, this occurred without measurable changes in DNMT protein or enzymatic activity. While the authors suggest that this may have been due to the technical limitations of the assays used, it may also reflect the complexity and regional