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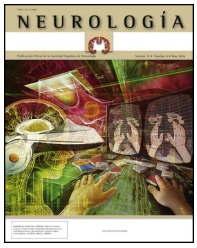

REVIEW ARTICLE

Epigenetic mechanisms in the development of memory and their involvement in certain neurological diseases☆

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Abstract
Introduction: Today, scientists accept that the central nervous system of an adult possesses considerable morphological and functional flexibility, allowing it to perform structural remodelling processes even after the individual is fully developed and mature. In addition to the vast number of genes participating in the development of memory, different known epigenetic mechanisms are involved in normal and pathological modifications to neurons and therefore also affect the mechanisms of memory development.
Development: This study entailed a systematic review of biomedical article databases in search of genetic and epigenetic factors that participate in synaptic function and memory.
Conclusions: The activation of gene expression in response to external stimuli also occurs in differentiated nerve cells. Neural activity induces specific forms of synaptic plasticity that permit the creation and storage of long-term memory. Epigenetic mechanisms play a key role in synaptic modification processes and in the creation and development of memory. Changes in these mechanisms result in the cognitive and memory impairment seen in neurodegenerative diseases (Alzheimer disease, Huntington disease) and in neurodevelopmental disorders (Rett syndrome, fragile x, and schizophrenia). Nevertheless, results obtained from different models are promising and point to potential treatments for some of these diseases.

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PALABRAS CLAVE
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Mecanismos epigenéticos en el desarrollo de la memoria y su implicación en algunas enfermedades neurológicas

Resumen
Introducción: Hoy en día se acepta que el sistema nervioso central adulto posee una enorme flexibilidad morfofuncional que le permite realizar procesos de remodelación estructural aún después de haber alcanzado su desarrollo y maduración. Además del enorme número de genes que participan en el desarrollo de la memoria, los diferentes mecanismos epigenéticos conocidos también han sido involucrados en procesos de modificación neuronal normal y patológica y, por ende, en los mecanismos de desarrollo de la memoria.
Desarrollo: Este trabajo fue llevado a cabo a través de una sistemática revisión de las bases de datos de publicaciones biomédicas sobre los aspectos genéticos y epigenéticos que participan en la función sináptica y la memoria.
Conclusiones: La activación de la expresión génica, en respuesta a estímulos extrínsecos, ocurre también en células nerviosas diferenciadas. La actividad neuronal induce formas específicas de plasticidad sináptica que permiten la formación y almacenamiento de la memoria a largo plazo. Los mecanismos epigenéticos tienen un papel crucial en los procesos de modificación sináptica y en la formación y desarrollo de la memoria. Alteraciones en estos mecanismos producen déficit cognitivo y de memoria en padecimientos neurodegenerativos (enfermedad de Alzheimer y Huntington) así como en trastornos del desarrollo neurológico (síndrome de Rett, x-frágil y esquizofrenia). Los resultados obtenidos en diferentes modelos muestran, sin embargo, un escenario promisorio con tratamientos potenciales para algunos de estos padecimientos.

Introduction

For some time, it was believed that the adult mammalian brain was an organ unable to maintain structural remodelling processes once its developmental stages were complete. This concept was thought to apply to all structures in the nervous system, and especially to synapses. But these concepts have been revised drastically in recent years, to such an extent that the flexibility of neuronal shape and function in the adult brain is now widely accepted. Neurons and synapses are subject to many types of structural and functional plasticity, and this results in profound changes in inner cerebral structures. These changes adapt to and are mainly generated by neuronal activity patterns, which in turn are stimulated by sensory experience from both internal and external sources.[1]

Recent discoveries in developmental biology show that activation of gene expression in response to extracellular signals, such as growth factors, also occurs in differentiated postmitotic cells. Transcriptional activation in mature cells may be induced by different extrinsic stimuli, including some of the factors that activate transcription during embryonic and fetal development. More specifically, research has shown that neurons may modify the expression of a group of genes in response to depolarisation stimuli; this finding led to the hypothesis that gene activity may be affected by normal synaptic activity.

The observation that neuronal activity induces both adaptive neuronal changes and changes in gene expression patterns suggests that this sequence of events is the source of specific forms of neuronal, and especially synaptic, plasticity. It has also been shown that the same genes that are stimulated by synaptic activity are at work during brain development; this suggests that plasticity, throughout all stages of brain development, uses similar molecular mechanisms and machinery (Table 1).[2]

More recently, scientists demonstrated that gene expression underlying synaptic and neuronal activity is largely regulated by epigenetic mechanisms of the same type as those occurring in embryonic or fetal development. The evidence suggests that epigenetic modifications within the CNS, crucial for behavioural adaptation in the short and long term, are the result of a variety of environmental stimuli. Activation or silencing of these genes, determined by epigenetic mechanisms, seems to constitute an important regulator of synaptic potential and memory.

This study aims to present an updated systematic review of the epigenetic mechanisms related to synaptic function and memory, and of the epigenetic changes involved in memory disorders, whether they are caused by neurodevelopmental anomalies or by neurodegenerative disease.

Epigenetic mechanisms

'Epigenetics' was coined by Waddington to refer to the array of hereditary processes that regulate gene expression without altering the DNA nucleotide sequence.[3] At this date, research has uncovered 3 mechanisms that participate extensively in gene regulation: (1) histone modification, (2) DNA methylation, and (3) non-coding ribonucleic acids