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Brain Plasticity, Signal Transduction and Epigenesis: a Missing Link Revealed

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Abstract

Báez-Saldaña A, Fetter-Pruneda I, Fuentes-Farías AL, Granados-Rojas L, Gutiérrez-Ospina G, Martínez-Méndez R, Meléndez-Herrera E, Mendoza-Torreblanca J, Sandoval-Velasco M. Brain Plasticity, Signal Transduction and Epigenesis: a Missing Link Revealed. Annu Rev Biomed Sci 2009;11:T114-T122. It has been long thought that the brain reorganizes itself in response to environmental needs. Sensory experiences coded in action potentials are the mean by which information on the surroundings is introduced into neuronal networks. The information approaching the brain in the form of electrochemical codes must then be translated in biochemical, epigenetic and genetic ones. Only until recently we have begun understanding the underpinning of such informational transformations and how this process is expressed as neuronal plastic responses. Central for our comprehension of this matter is the finding that signals transduction cascades can modify gene expression by remodeling the chromatin through epigenetic mechanisms. Hence, chromatin remodeling seems to be the process by which experiences are "imprinted"

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in the genome leading to differential gene expression and brain plasticity. In this review, we briefly comment on this possibility.

Keywords: signal transduction pathways, epigenetic mechanisms, chromatin remodeling, gene expression, neuronal plasticity

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1. Introduction

The single most significant property of the brain, and indeed of the entire nervous system, is its ability to re-organize itself constantly throughout life. Given the biological and medical importance of the so called neural plasticity, an impressive effort has been made for over a century to understand the mechanisms that underlie this property. The central premise derived from the research program on brain plasticity sustains that plastic brain responses occur as the result of the interaction of the organism's neuronal networks with the environment. In this scenario, environmental information is transformed by sensory channels and pathways into neuronal electrical codes that in turn are used by the nervous tissue to shape and re-shape its circuits thus presumably adapting their configuration to the daily environmental requirements. Additional information that modulates the process of brain plasticity comes from endocrine codes that are also generated after the organism has interacted with the environment. In this last scenario, sensory information codes are used by the brain to organize endocrine responses. In spite of the prevalence of this influential view, the precise mechanisms by which "experiences" are translated into activity/hormonally-driven neuronal morpho-functional change were a matter of debate until recently. Fortunately, nowadays, this issue has begun to be unraveled by research showing links between external stimuli, physiological signaling, signal transduction pathways, chromatin remodeling and differential gene expression. In this review, we will comment and discuss evidence that supports that experiences are indeed coded by combinatorial processes that involve the translation of them into neuro-endocrine codes that are, in turn, transformed into metabolic and genetic ones following the activation or inactivation of signal transduction pathways, whose intermediaries have the ability to induce chromatin remodeling. The review does not intend to be an extensive one because the list of intracellular messengers that mediate chromatin reorganization and hence differential gene expression after sensory transduction and under plasticity conditions is still growing. We just seek to propitiate in the reader a reflection on the importance of epigenetics in the process of the organism's interpretation of environmental contexts.

2. The Plasticity of the Brain: Definition, General Mechanisms and Significance

Plasticity in biological systems may be conceived as an organism's fundamental property that provides it with the ability to reorganize its body's structure and function as a result of the interactions with the environment. The phenotypic variations observed after a plastic response had taken place must then be viewed as the expression of the body's interpretation of the information derived from such interactions. Even though plasticity is a body's property, nowhere in the organism this property has been explored so thoroughly than in the nervous system. Indeed, plastic responses in the brain have

inspired for over a century a wealth of carefully crafted studies aimed at describing their phenomenology and unveiling their physiological, cellular, molecular and genetic mechanisms.

In general, it is believed that environmental information "trapped" by sensory organs is coded in patterns of neuronal electrical activity that will promote competitive interactions among neurons (reviewed in Penn & Shatz, 1999). Such competition will end leading to neuronal plastic responses. It is now recognized that, at the cellular level, neuronal plastic responses feature among other processes the counterbalance of excitatory and inhibitory transmission, the selective growth or pruning of dendrites and axons, the preferential generation or elimination of synapses, the facilitation or depression of neuronal transmission and the increment or decrement of neuronal metabolic rates (reviewed in Buonomano & Merzenich, 1998). At the molecular level, events such as the shift in neurotrophic factor availability, the modulation of the process of activation or inactivation of neurotransmitter ionotropic or metabotropic receptors, neurotransmitter and neuromodulator release and uptake, the molecular constitution of receptors and the mobility of synaptic elements greatly influence the progress and outcome of neuronal plastic responses (Bruel-Jungerman *et al*., 2007). From a genetic stand point, studies have portrayed the diversity of gene expression patterns that frame short-and long-term plastic responses in distinct brain regions when subjected to different environmental conditions (e.g., Cotman & Berchtold, 2002).

The reorganization of neuronal networks is not a "purely neuronal" event. It is accompanied by dramatic shifts in glial, immune and vascular arrangements, as well as by changes in the molecular make up of the neural extracellular matrix. Long- and short-distance interactions mediated by endocrine and paracrine messengers released by "non-neural" organs are also involved. All of these "inner" factors are also important sources of environmental information that will not be treated in the present discussion for the sake of clarity and shortness.

Based on the preceding paragraphs, it is clear that over the years we have learned a great deal on the details of the mechanisms that underlie brain plastic responses at different levels of the organism's structural and physiological organization. What is still missing and hence remains as a challenging quest in the field is the elucidation of the processes that bridge, across organization levels, the mechanisms that configure brain plastic responses. To fill this gap is necessary to fully comprehend how brain plastic responses are integrated in the context of the organism as a whole, thus providing an adequate framework to value such responses instead of simply assuming it based upon inferences moved by "adaptationists" perspectives. This last argument is explicitly stated because it is generally believed that plastic responses have an inherent adaptive nature. However, mounting evidence shows that this is not always true since maladaptive plastic responses may occur in a variety of situations (e.g., the phantom limb). Hence, the adaptive value of the brain's plastic responses may be absolutely circumstantial or context-dependent, and it might reflect the need of neurons to survive at any cost even if this means to establish or retain misplaced, non-optimal connections.

3. The Neuronal Code: Transforming Experiences into Meaningful Neuronal Information

Organisms interact with the environment through sensory organs. Such interactions give rise to sensation or sensory experiences that convey information on the physical and chemical attributes of the environmental stimuli to the brain. To make experiences useful for the brain to generate perceptions and behavior, however, sensory receptors and pathways must "write" experiences in an intelligible language. Electrical activity is the universal language among neurons. It then follows that the attributes of the environmental stimuli must be transformed into electrical activity before reaching the brain; hence experiences are encased in the electrical activity of neurons.

Neuronal activity, whether spontaneous or evoked, has been long recognized as a highly pervasive factor that influences plastic responses in the brain. This is not surprising because shifts in the neuronal electrical activity are frequently associated with the remodeling of dendrites, axons and synaptic fields (Penn & Shatz, 1999). The question that arises from these observations is where does the informational value (i.e., the code) of neuronal electrical activity lie in? Is the total amount, the relative levels and/or the patterns of activity what features the information that might be used later to instruct neuronal change?

We believe that neurophysiologists have convincingly shown that words in the neuronal language that translate attributes of the environmental stimuli emerge from combining the amplitude, frequency and spatial organization of each neuron's electrical activity; for instance, neurons encode the intensity of the stimulus in their firing rate (reviewed in Romo & Salinas, 2001 and Caporale & Dan, 2008). The way the parameters of neuronal activity are combined to generate bio-information depends on many features such as: the nature and attributes of stimulus applied, the neurons' metabolic status and their history of activation, the neurons' phenotype (including biophysical properties), their synaptic partners, the interaction between them and the degree of convergence and relative strength of their various subsets of excitatory and inhibitory connections by the time of stimulation, among others. A level of complexity is added when spontaneous activity across neuronal assembles is considered; the capacity of neuronal circuits to process incoming information may be facilitated or hindered by self generated patterns of activation (Gray, 1994). In sum, the physical and chemical attributes of environmental stimuli are encased in neuronal electrical codes that are somehow translated into morphological and physiological changes.

Neuronal electrical activity, however, is not the complete story behind neuronal codes. A large percentage of the neuronal communication is set up to occur, at least in the mature brain, through chemical synapses. So, for electrical codes (i.e., experiences) to be passed on to the next synaptic relay they have to be ciphered in the release of neurotransmitters and neuromodulators from the excited nerve terminal. To the best of our knowledge, whether the pattern of neurotransmitter release faithfully replicates that of the electrical activity that elicits it is unclear. Our guess, however, is that it does. What is indeed known is that different frequencies may preferentially facilitate or depress the release of neurotransmitters alone or of neurotransmitters and neuromodulators together (Feldman, 2009). In any event, it is this transformation of the electrical codes into the chemical ones what makes experiences available to the genome of a given neuron.

4. Signal Transduction and Epigenetic Chromatin Remodeling: a Missing Link Revealed

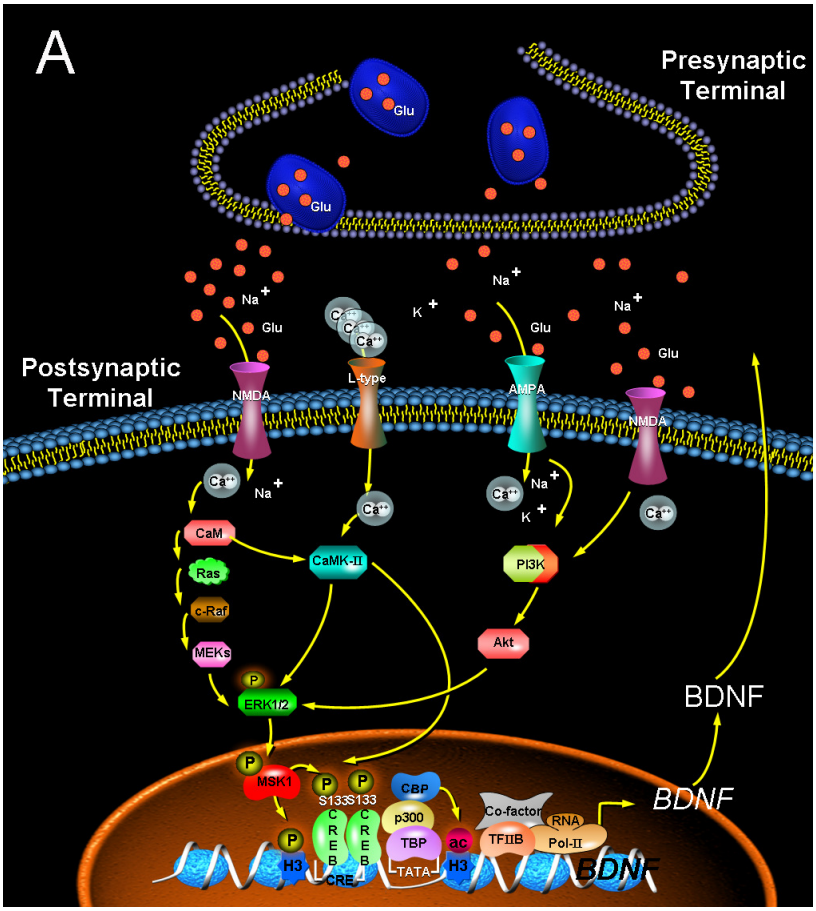
How neurochemical codes carrying sensory experiences are translated into neuronal morpho-functional change has been a long debated issue in the neurosciences. Fortunately, hints on how this might occur have begun to be published in the recent years. At the core of this integrative process lays the activation/inactivation of different sorts of receptors and associated signal transduction cascades following the release of neuromessengers. The other core element of the molecular process that integrates experiences in the genome is the remodeling of chromatin through epigenetic mechanisms. Interestingly, recent evidence has shown that both processes crosstalk through enzymatic intermediaries that, after being rendered active or inactive, not only modify the metabolic state of neurons that later primes their ulterior responses to stimuli, but also control the differential packing of chromatin and thus gene expression and protein synthesis. For the first time, the articulation of both processes allow us to envision mechanisms by which "nurture" could readily "imprint" experiences on gene expression, molecular memories and epigenetic inheritance that undoubtedly influence the ways neuronal plasticity is built up throughout each organism's life.

In the following paragraph, we will provide a wonderful example of a daily live activity that enhances the availability of a molecular messenger released by neurons upon stimulation that, after activating its receptor and associated signal transduction cascades, induces chromatin remodeling under a variety of neuronal plasticity settings. This example is used just to illustrate our call.

4.1. Exercise, BDNF, epigenesis and plasticity: an illustration

Regular exercise is commonly associated with brain reorganization. Accordingly, physical activity increases neurogenesis, angiogenesis and the elaboration of new neuronal connections in brain at different ages (Neeper *et al*., 1995; Oliff *et al*., 1998; Vaynman *et al*., 2004). Also, cognitive deterioration in the elderly slows down if exercise is practiced on regular bases (Oliff et *al.*, 1998). Physical activity, however, is not the only way to influence brain plastic responses throughout life. Executing frequently simple or complex cognitive tasks such as learning new tricks, memorizing new

routes or practicing meditation renders the brain prone to shift its organization and gene expression. How could this happen? We did not know much on the mechanisms mediating the effects of physical or mental activity on brain plasticity until recently. It is now known that exercise increases the synthesis and availability of protein factors collectively known as neurotrophins in selective brain regions. An increment in the availability of, for instance, brain-derived neurotrophic factor (BDNF), may promote neuronal growth and morphological plasticity and enhance synaptic transmission fostering synaptic strengthening. In this context exercise, by means of excitatory glutamatergic transmission, would trigger BDNF mRNA expression following the activation of glutamate AMPA and NMDA receptors and the influx of Ca^{2+} through voltage-dependent L-type channels generally located in neuronal dendritic spines. Transcriptional activation of the BDNF gene is commonly regulated by a key transcription factor denominated cAMP response element-binding protein (CREB) in cooperation with the upstream stimulatory factor (Tabuchi *et al.*, 2002; Tabuchi, 2008). Once BDNF is released and bound to its tyrosine-kinase receptor B (TrkB), the receptor dimerizes and its intracytoplasmic domains may then phosphorylate each other at different tyrosine residues. The signal transduction cascades that are triggered following TrkB activation would depend upon the code of tyrosine residues that are phosphorylated at a given condition. Two BDNF associated signal transduction pathways may be of interest in the context of this section: the Ras-Map kinase and PLC-γ1 pathways (Fig. 1). Both activate extracellular signal regulated kinase 1/2 (ERK1/2) (May & Hill, 2008). This enzyme directly phosphorylates mitogen and stress- activated protein kinase 1 (MSK1) which in turn phosphorylates histone 3, a process that leads to chromatin remodeling and hence to differential gene expression (Rakhit *et al.*, 2005). Also, Ras-Map kinase pathway ends up activating the transcription factor CREB that interacts with the coactivator CREB-binding protein (CBP) which controls chromatin folding because it displays histone acetyl transferase activity (Kuo & Allis, 1998; Rakhit *et al*., 2005). In this way, exercising would leave its epigenetic mark on chromatin organization and thus on gene expression.



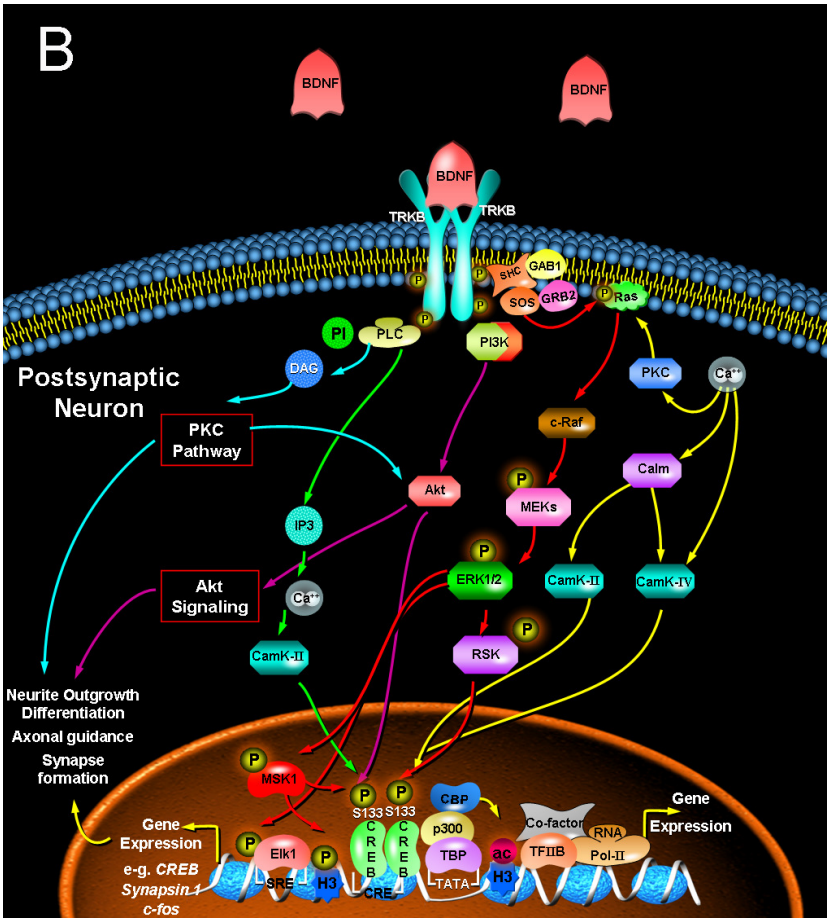


Figure 1. Translating sensory experience through signaling pathways and epigenetic chromatin remodeling. (A) Experience-dependent electrical codes elicit the release of glutamate from synaptic vesicles contained in the nerve terminal. The sequential activation of glutamate AMPA and NMDA receptors, followed by the opening of the L-type calcium channels, permits the entering of calcium that triggers multiple kinase signaling pathways that converge on to the extracellular signal regulated kinase 1/2 (ERK1/2). The activation of this enzyme leads to the phosphorylation of Mitogen- and Stress-activated protein Kinase 1 (MSK1) which in turn phosphorylates Cyclic AMP Response Element-Binding protein (CREB) and Histone H3 (Ser10). The binding of CREB with CREB Binding Protein (CBP) also induces the acetylation of histones 3 and 4. Phosphorylation and acetylation of histones remodel the chromatin facilitating BDNF expression, synthesis and release. (B) After being released, BDNF binds to TrkB receptors. This leads to auto - phosphorylation of tyrosin residues within the intracellular domains of the receptor, thus creating docking sites where adapting proteins such as SHC and FRS-2 bind. These complexes can in turn activate the Ras-Raf-ERK cascade and the phosphatidylinositol-3-OH kinase pathway. The docking of phospholipase C g (PLCg) to a separate site leads to the production of diacylglycerol (DAG) and inositol triphosphate (IP3). As a consequence Phosphokinase C (PKC) is activated and MEK is phosphorylated, a circumstance that leads to ERK1/2 phosphorylation. In addition, the IP3 induced release of calcium from the endoplasmic reticulum activates PKC-Ras and calcium/calmodulin-dependent kinase (CamK) pathways. Both ERK and CamK pathways end up phosphorylating CREB and MSK1, leading to differential gene expression following chromatin remodeling through a mechanism similar to that described in part A of the illustration. Adapted from SABiosciences Corporation (Frederick, MD, USA).

Other examples of brain plastic responses in which environmental factors, signal transduction pathways, chromatin remodeling and differential gene expression are bridged have been recently published. Depression (Tsankova *et al*., 2006), drug addiction (Kumar et al., 2005; Renthal & Nestler, 2008), alcoholism (Moonat *et al*., 2009), visual cortical plasticity (Putignano *et al*., 2007; Taniura *et al*., 2007) and learning and memory (Alarcon *et al*., 2004; Korzus *et al*., 2004; Levenson *et al*., 2004; Levenson & Sweatt, 2005; Miller & Sweatt, 2007; Taniura *et al*., 2007) are all conditions underlined by neural plasticity processes that entail chromatin remodeling through epigenetic mechanisms.

5. Coding Experiences in the Genome

Up to this point, we have briefly discussed how experiences are transformed into electrochemical codes. The information carried out by such codes is then translated, filtered and re coded by combining the activation or inactivation of diverse signal transduction cascades. It is this "combinatorial metabolic code" of experiences what is finally "imposed" on the genome through epigenetic mechanisms. The metabolic code must now be read, understood and translated by each cell into the epigenetic code that is "written" upon the chromatin by modifying its organization, essentially its degree of compactness and folding. The interpreter/writer's labor is consummated by the action of chromatin-modifying enzymes that are activated along signal transduction cascades. The modification of chromatin folding is achieved by attaching acetyl, phosphoryl, methyl, ubiquitin, sumo or ADP-rybosil groups to histones (Grunstein, 1997; *Cheung et al.*, 2000; Strahl & Allis, 2000; Allis *et al., 2007*; Kouzarides, 2007). In addition, DNA-modifying enzymes which methylate CpG dinucleotides in DNA also induce chromatin reorganization (Santos *et al*., 2005; MacDonald & Roskams, 2009). Other mechanisms reconfiguring chromatin involve adding histone variants (Sarma & Reinberg, 2005), ATP-dependent chromatin remodeling complexes (Johnson *et al.*, 2005; Yoo & Crabtree, 2009) and noncoding RNAs (Lippman & Martienssen, 2004; Bernstein & Allis, 2005; Allis *et al*., 2007).

6. Concluding Remarks and Future Directions

The nature-nurture debate has long confronted points of view that sustain that phenotypic features are either determined predominantly by genetic or by environmental factors, respectively (Oyama *et al*., 2001). We are now witnessing a renaissance of this debate but fortunately in a quite different context. The uncovering of enzymatic intermediaries linked to signal transduction pathways that are also capable of modifying histones or DNA, opens the possibility of envisioning mechanisms by which the information generated by the interaction between the organism and its surrounding environment could be translated into patterns of gene expression. Hence, an "interactionist" panorama is truly emerging.

In spite of the advances outlined above, there remain many other aspects on this topic that need to be addressed before reaching full understanding on how experiences are embossed in gene expression. From our point of view, how the cell makes sense of all of these metabolic codes going on simultaneously and constantly shifting in reflection of the ever changing incoming information in brief fractions of time is the most important of them. Disentangling this conundrum is not trivial and will surely require the development of supercomputer abilities put in the hands of a new generation of computer neuroscientists.

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