Activity-dependent Gene Regulation: How Do Synapses Talk to the Nucleus and Fine-tune Neuronal Outputs?

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MAJOR CONTRIBUTIONS


MAIN TOPICS

Stability and plasticity of a neuronal circuit: requirement for activity-dependent gene expression to sustain a long-term adaptive response in input-output relationship
Activity-regulated neuronal transcription factors: what are they?
CREB as a transcriptional regulator
Control of CREB activity by regulated phosphorylation at residue Ser-133

SUMMARY
A large number of molecular mechanisms contribute to ensuring that the neuronal transcriptome can be adapted in function of the various kinds of external and internal events that the neuronal network is exposed to. In recent years, activity-induced gene expression/protein synthesis has received much attention as a potential mechanism likely to play a significant role in synaptic plasticity and long-term memory formation. The involved regulatory processes are intrinsically complex, and we still lack a detailed understanding of how specific neuronal nuclear factors are activated and modulated in concert to give rise to reliable and reproducible gene induction. In this chapter, we will consider the regulation of one of the most studied neuronal nuclear factor, the transcription factor CREB (Ca\(^{2+}/cAMP\)-response element-binding protein).

CREB structure is conserved from mollusk to rodents, and neuronal CREB mediates long-lasting forms of synaptic plasticity. Its activation was shown to be essential for higher brain functions such as learning and memory in many species. CREB usually resides in the nucleus, and is tightly bound to CRE loci, thus being ideally suited to rapidly convert cellular signaling into transcription. A large number of neuronal signaling pathways (e.g. Ca\(^{2+}/CaM/CaMKK/CaMKIV, cAMP/ PKA, Ras/MAPK, CaN/PPI) are employed and converge onto the regulation of the phosphorylation state of CREB Ser-133, consistent with its presumed importance in many adaptive biological processes, including long-term neuronal plasticity and survival. The amount of information storage available in the neuronal network will soon saturate quickly, however, without built-in mechanism for reversibility and regulated extinction/erasure of plasticity. Resolving all these problems will be of an immense clinical value when addressing cases involving aberrant persistence of pain sensation or posttraumatic stress disorder.

INTRODUCTION
In order to execute a higher cognitive task in response to external and internal stimuli, the brain needs to compute an output, based upon a barrage of input information that it receives from the outside world. As our brain is able to successfully compute a correct answer above par on a continuous basis, it has been speculated that there must a particular mechanism for online storage of data about the input-output relationship of the events that have received attention (and not been neglected) from our brain. Furthermore, it is also believed that "useful" information can be consolidated within a neuronal network, thereby perhaps allowing the brain to store experience as a memory and become smarter. Such external stimuli-dependent changes in the brain have been proposed to be acquired by using mechanisms of synaptic plasticity. According to the synaptic plasticity and memory hypothesis, as defined by Richard Morris and colleagues, "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed". In recent years, both activity-induced gene expression/protein synthesis and activity-induced changes in neuronal morphology have received much attention as potential mechanisms likely to play a significant role in synaptic plasticity and long-term memory formation. Experiments in hippocampal pyramidal excitatory neurons have shown that robust electrical activity can induce a large number of Ca\(^{2+}\)-dependent gene expression events. A crystal-clear picture of the molecular events following synaptic Ca\(^{2+}\) entry still remains missing, however, in part because the repertoire of activity-dependent transcription factors is not fully understood. Indeed, the mechanisms for their activation and their physiological significance have been elucidated for only a few of them, such as the Ca\(^{2+}/cAMP\)-response element-binding protein (CREB) or the nuclear factor of activated T-cells (NFAT). In this review, we shall overview some of the key signaling events by which the Ca\(^{2+}/CREB/CREB-binding