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Review

The divergence–convergence model of acquired neuroprotection

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ARTICLE INFO

Article history:
Available online 10 October 2012

Keywords:
Calcium signaling
Gene transcription
Apoptosis
Programmed cell death
Synapse to nucleus communication
Gene network

ABSTRACT

It is commonly known that mental activity helps to maintain a healthy brain. Recent research has unraveled the underlying molecular mechanisms that explain why an active brain lives longer. These mechanisms involve the activation of a comprehensive transcriptional program that is triggered by enhanced synaptic activity and renders neurons resistant to harmful conditions. Functionally, this state of acquired neuroprotection may be achieved mainly via one mechanism, which is the stabilization of mitochondria. In this review we propose a model that describes the signaling network that links synaptic activity to neuroprotection. We suggest that the divergent-convergent architecture of this signaling network ensures both robust and reliable as well as persistent activation of the neuroprotective machinery.

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1. Introduction

It has been known since ancient times that physical exercise helps to maintain a healthy body. Recently, it has been increasingly acknowledged that this holds true for the brain as well, i.e. physical activity directly promotes cognitive function and brain health by mechanisms that include the induction of neurotrophins such as BDNF and IGF-1, increased angiogenesis and neurogenesis (for review see Lista and Sorrentino, 2010; van Praag, 2009). Common wisdom tells

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0925-4773/$ - see front matter
http://dx.doi.org/10.1016/j.mod.2012.09.008

us, however, that not only physical activity, but also mental exercise helps to maintain a healthy brain. Research over the last two decades has confirmed this notion and has unraveled the molecular mechanisms that explain why an active brain lives longer. In this review we briefly summarize this research. First, we define the concept of acquired neuroprotection. We then describe the underlying mechanisms that couple synaptic activity to enhanced robustness of neuronal cells. Finally, we propose a model that integrates our current knowledge of acquired neuroprotection and provides a mechanistic framework for future studies.

2. The concept of acquired neuroprotection

Neurons depend on synaptic activity for their survival. First evidence for this phenomenon came from denervation experiments in sensory systems. For example, lesioning of the olfactory bulb leads to transneuronal degeneration of pyramidal neurons in the piriform cortex (Heimer and Kalil, 1978). Similarly, in the auditory system, ablation of the cochlea or transection of the eighth nerve causes neuronal cell death in the cochlear nucleus or nucleus magnocellularis in mammals or chick, respectively (Born and Rubel, 1985; Powell and Erulkar, 1962). Silencing neurons by injection of tetrodotoxin into the auditory nerve mimics the effect of cochlea ablation (Born and Rubel, 1988). This indicates that denervated neurons die because of a lack of afferent activity. Blockade of synaptic transmission in a variety of peripheral and central neuronal cell types both *in vivo* and *in vitro* further demonstrated the requirement for synaptic activity for the survival of developing neurons (Catsicas et al., 1992; Fishbein and Segal, 2007; Lipton, 1986; Maderdrut et al., 1988). Several studies have shown that ongoing synaptic activity promotes neuronal survival by a mechanism that involves *N*-methyl-D-aspartate (NMDA)-type ionotropic glutamate receptors, calcium influx into neurons, and activation of PI3K/Akt signaling (Collins et al., 1991; Heck et al., 2008; Hegarty et al., 1997; Ikonomidou et al., 1999; Miller et al., 1997; Papadia et al., 2005). The resulting view from these studies is that basal electrical activity acts to suppress the intrinsic apoptotic machinery, thereby ensuring the survival of those neurons that are well integrated into synaptic networks. This appears to be especially important during the development of neuronal circuits. While basal activity is sufficient to keep neurons alive under physiological conditions, it still leaves them highly vulnerable to cellular stress. In contrast, enhanced neuronal activity leads to the build-up of a protective shield against harmful conditions. For example, placing rats into an enriched environment, and thus increasing neuronal activity *in vivo*, leads to protection against brain damage caused by kainate-induced seizures (Young et al., 1999). Similarly, increasing synaptic activity in cultured neurons by inducing action potential (AP) bursting renders neurons resistant to various harmful conditions including glutamate excitotoxicity, trophic deprivation, and treatment with chemical inducers of apoptosis including staurosporine, okadaic acid, C-2 ceramide, and retinoic acid (Hardingham et al., 2002; Lee et al., 2005; Papadia et al., 2005; Soriano et al., 2006). This effect, which has been termed 'acquired neuroprotection', depends on gene transcription, takes several hours to be implemented and lasts for up to several days after its initiation. Thus, acquired neuroprotection is distinct from survival afforded by basal synaptic activity; it is defined as an increased and long-lasting robustness against diverse cellular stresses induced by episodes of enhanced synaptic activity.

3. Molecular mechanisms of acquired neuroprotection

3.1. *Enhanced synaptic activity turns on a genomic pro-survival program*

The build-up of acquired neuroprotection is a transcription-dependent process. Thus, to achieve its full neuroprotective effect, enhanced synaptic activity needs to be translated into changes in gene expression. How is this achieved? The signaling mechanisms that link synaptic activity to the regulation of gene transcription in neurons have been studied extensively and have been covered comprehensively in several recent reviews (Bengtson and Bading, 2012; Greer and Greenberg, 2008; Hagenston and Bading, 2011; Mellstrom et al., 2008). Due to space limitations we will focus on two major mechanisms that work together to alter neuronal gene expression in response to synaptic activity.

3.1.1. *Nuclear calcium-dependent gene transcription*

It is now well established that calcium signaling plays a central role in activity-dependent gene transcription. A major route of synapse-to-nucleus communication is initiated by influx of calcium through synaptic NMDA receptors (NMDARs); this can lead to intracellular calcium transients that invade the nucleus to activate calcium-dependent transcription factors such as CREB and MEF2. Genome-wide expression studies revealed that signaling via synaptic NMDARs and nuclear calcium drives the expression of a comprehensive genomic pro-survival program (Zhang et al., 2007). Zhang et al. (2009) found that AP bursting in cultured hippocampal neurons regulates the expression of 431 genes and of those 185 depend on nuclear calcium signaling. From the list of nuclear calcium dependent genes, a core set of pro-survival factors, termed *Activity-regulated Inhibitors of Death* (AID) genes, was identified. These genes comprise Atf3, Btg2, GADD45b, GADD45c, Inhibin b-A, Interferon activated gene 202B, Npas4, Nr4a1, and Serpinb2. The central role of these genes was established by demonstrating that overexpression of individual AID genes is neuroprotective both *in vitro* and *in vivo*. Several AID genes are transcription factors that further contribute to activity-induced changes in gene expression by regulating down-stream targets.

3.1.2. *Activity-dependent nucleo-cytoplasmic shuttling*

Besides calcium-dependent activation of transcription factors, additional mechanisms participate in shaping the genomic response to survival-promoting synaptic activity. One of these mechanisms is activity-dependent nucleo-cytoplasmic shuttling of transcriptional regulators. FoxO3a, a member of the forkhead transcription factor family, usually acts to con-