



ONE MORE VIEW OF NEUROTROPHIN-NEUROTRANSMITTER SIGNALING IN NEURONS: BDNF-AMPA CROSSTALK

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*And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!*

John Godfrey Saxe (1816-1887)

INTRODUCTION

Although knowing much about the neuronal life and death, we remain unsure of their exact molecular nature. As often occurs, the framework of an initial concept of the physiological role of a newly discovered molecules extends in the light of emerging findings. This is also the case with the neurotrophin brain-derived neurotrophic factor (BDNF) and the neurotransmitter glutamate. Recent data suggests that the protein family of the neurotrophins, consisting of nerve growth factor (NGF), BDNF and neurotrophin-3, -4/5, and -6, might act as 'neurotransmitters' exerting modulating effects on synaptic structure and function, while glutamate might have 'trophic' effects in neurons. Though neurotransmitters and neurotrophins have overlapping functions *in vivo*, they operate in concert to finely

tune the neuronal physiology as reviewed in the state-of-the-science article by Georgiev and colleagues (1).

BDNF

Neurotrophins, particularly, NGF and BDNF are now well recognized to mediate a dizzying number of effects, ranging from the Rita Levi-Montalcini's neurotrophic (2) through immunotrophic (3) to metabotropic (4) and synaptotrophic (5) effects. There is a compelling evidence indicating that in addition to their actions on neuronal differentiation and survival, BDNF and its receptor tropomyosin-related receptor kinase B (TrkB) are uniquely important for the process of activity-dependent synaptic plasticity including long-term potentia-

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tion, long-term depression, and dendritic spine density and cytoskeletal dynamics, underlying various cognitive functions such as learning and memory encoding and storage (6-9). Localization of BDNF and TrkB receptor to glutamate synapses makes this system intriguing as a dynamic, activity-dependent regulator of excitatory transmission that is implicated in the mechanisms of memory storage and mood control (10-12) as well as neuropsychiatric diseases (13-15).

BDNF-NMDAR CROSSTALK

The influx of Ca^{2+} through ionotropic glutamate receptor channels is thought to contribute to synaptic function, and when this influx is in excess, it results in the loss of neurons associated with a number of brain disorders. Georgiev and colleagues (1) focused their review on the multiple crosstalk possibilities between BDNF and N-methyl-D-aspartate receptor (NMDAR) prosurvival signaling pathways, both of which utilize Ca^{2+} , calmodulin/CaMK, Ras, PI3/Akt and ERK-1/2 as messengers. A caveat however is necessary - the intraneuronal space is far from being disorganized chemical solution of electrolytes, neurotransmitters and enzymes, so that each cascade *in vivo* is highly organized and localized to nanosized subplasmalemmal domains (typically) under lipid raft, structurally stabilized by various (and in most cases unknown yet) scaffold proteins. This is the case of synaptic *versus* extrasynaptic NMDAR signaling, the former exerting prosurvival effect upon neurons, while the latter triggers prosurvival-“shut off” pathways. The mystery seems to be intractable by the older hypothesis according to which extrasynaptic receptors are composed of different subunits (16) since in immature neurons both synaptic and extrasynaptic NMDARs are composed of NR1/NR2B assemblies (17). The puzzle was recently solved by proving experimentally the existence of nanodomains: NMDAR-mediated ERK-1/2 activation requires a specific coupling of NMDAR, Src and ERK, via caveolin-1, which helps the assembly of the signaling cascade within the neuronal lipid rafts (18). The crosstalk between synaptic and extrasynaptic NMDARs is thus precluded by the nanodomain organization of the intraneuronal space and neuronal plasmalemma, while synaptic NMDAR/TrkB crosstalk is made possible due to formation of macromolecular protein-protein assembly composed of TrkB, Fyn kinase and NR2B NMDAR (19).

AMPA-TYPE GLUTAMATE RECEPTORS (AMPA)

Until 20 years ago, the NMDAR was the only glutamate recep-

tor known to be Ca^{2+} -permeable. It is now well established that the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) of glutamate (and structurally related kainate receptors) are densely distributed in the mammalian brain and are primarily involved in mediating fast excitatory synaptic transmission (20-22). The AMPAR can be phosphorylated on their subunits (GluR1, GluR2, and GluR4), several key protein kinases, such as protein kinase A, protein kinase C, Ca^{2+} /calmodulin-dependent protein kinase II, and also TrkB receptor being involved in this phosphorylation. Further, a family of transmembrane AMPAR regulatory proteins (TARPs) profoundly affects the trafficking and gating of AMPARs (23).

AMPARs are tetrameric assemblies of GluR1-4 subunits, which form predominantly Na^{+} -permeable ion channels. A notable exception is the GluR2 subunit containing AMPARs, which might be permeable for Ca^{2+} , depending on the Q/R site editing. In adult neurons GluR2 gene encoded glutamine (Q) codon in the channel-forming intramembrane segment is changed to an arginine (R) codon, which results in Ca^{2+} -impermeable AMPARs (24).

BDNF-AMPA CROSSTALK

Notably, neuronal depolarization induced via small doses of AMPAR agonists known as ampakines has been shown to markedly raise the BDNF expression levels and lead to cognitive enhancement (25-31). At present, there is no much data on the biochemical cascades following AMPAR activation, which are to explain the increased BDNF expression, though main players after the AMPAR-mediated depolarization are L-type voltage-gated calcium channels (VGCCs) and AMPAR-associated Lyn kinase, which is activated by phosphorylation at Tyr⁵⁰⁷ and NMDARs. Not surprisingly, the signal further utilizes the PI3K/Akt and ERK-1/2 highways to promote BDNF gene expression (32). It has been also shown that AMPAR-mediated activation of L-type VGCCs leads to subsequent BDNF release that has trophic effect upon GABAergic synapses in the newborn rat hippocampus (33). Conversely, though BDNF seems to have no fast effect on modulating synaptic AMPAR currents (34), BDNF/TrkB signaling enhances mRNA^{GluR1-4} expression (35,36), triggers local translation of mRNA^{GluR1} under dendritic spines (12) and regulates the AMPAR trafficking to postsynaptic densities (37). Noteworthy, BDNF enhances tyrosine phosphorylation of the AMPAR subunit GluR1 via NMDA receptor-dependent mechanisms (38).

BLIND MAN-ELEPHANT CROSSTALK

In a 19th century poem by John Godfrey Saxe (39) based on Indian parable, six blind men touch an elephant to learn what it is like. Each one touches a different, but only one part, obtaining varying views depending upon one's perspective. Like the elephant to blind men, the glutamatergic signaling machinery has different components to be analyzed. To conceive its entirety, further multidisciplinary research is required - it may hopefully provide us with a better understanding of the emerging roles BDNF-NMDAR and BDNF-AMPA signaling pathways play in neuronal health and disease. Moreover, they may represent potential therapeutic targets that will allow us to holistically see the picture rather than just individual parts. For example, several evidences show impaired synaptic plasticity of glutamatergic synapses in diseases where compromised BDNF function has been observed, such as Huntington's disease, Alzheimer's disease, depression and Rett syndrome (13-15,28,30), suggesting that BDNF-AMPA and BDNF-NMDAR crosstalks may be therapeutically relevant. Noteworthy, transactivation of Trk receptors by G protein-coupled receptor ligands has recently emerged as a novel biology of neurotrophin actions (40-42, for BDNF-serotonin tandem, see 43). Whether these molecules may be involved in BDNF-NMDAR and/or BDNF-AMPA crosstalk remains to be elucidated.

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