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Article Addendum

Back-propagating action potential

A key contributor in activity-dependent dendritic release of BDNF

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Brain derived neurotrophic factor (BDNF) is crucial for the formation of appropriate synaptic connections during development and for learning and memory in adults. Secretion of this neurotrophin is under activity-dependent control. Understanding which patterns of physiological activity regulate BDNF secretion is therefore an important step in the comprehension of its role. We have recently shown that back propagation of action potentials (bAPs) is the principal triggering mechanism of dendritic BDNF secretion occurring during ongoing neuronal activity in neuronal cultures. In the present addendum we discuss possible implications of bAPs-induced BDNF secretion on the construction and reorganization of neuronal networks.

Brain derived neurotrophic factor (BDNF) is the most abundantly expressed neurotrophin in the mammalian nervous system. BDNF is a small-secreted homodimeric polypeptide (monomeric MW: 14 kDa) that binds to two structurally unrelated membrane receptors: the high affinity tyrosine kinase receptors (TrkB) or the low affinity pan-neurotrophin binding receptor $p75^{NTR}$.[1] Once released into the extracellular space, BDNF binds to the TrkB receptor and regulates nearly all keys steps of network development from neuronal migration and differentiation to experience-dependent refinement of local connections.[2] BDNF participates in several forms of activity-dependent synaptic plasticity in both developing and adult central nervous system.[3] The critical requirement of BDNF in brain function and development is illustrated by the observation that several neuropathological conditions in human are associated with deficits in BDNF secretion.[4-6] Given the crucial role of BDNF signaling in the functional and structural organization of both developing and adult nervous system a big effort has been initiated over the past decade to study the mode and sites of BDNF secretion.

In the CNS BDNF is synthesized by the principal, i.e., glutamatergic, neurons in which BDNF is packaged into secretory granules in both axon terminals and dendrites. Two modalities of BDNF secretion can exist in cultured neurons: a constitutive Ca^{2+}-independent secretion that occurs in the absence of any specific triggering events and a Ca^{2+}-dependent secretion that is regulated by synaptic activity.[7] Recent studies using fluorescent-labeled BDNF have directly demonstrated that BDNF can be released from both axonal[8] and dendritic processes.[9] However, although these studies have led to important information on the mechanisms and site of BDNF release, the physiologically relevant patterns of electrical activity that trigger BDNF release could not be delineated.

In our recent paper,[10] we combined electrophysiological recording, time-lapse fluorescence imaging and immuno-staining on BDNF-GFP expressing hippocampal neurons in culture to study how ongoing activity affects BDNF secretion from neuronal dendrites. Our results show that the generation of action potentials that back-propagate into the dendrites (bAPs) is the key signal for dendritic BDNF release during ongoing synaptic activity. This release is achieved through the activation of voltage-gated calcium channels and subsequent influx of Ca^{2+} into the intracellular space. As already reported, the release of BDNF is a relatively slow process (in the order of several seconds). As few as 4 bAPs are sufficient to induce dendritic BDNF secretion. Moreover the probability of b-APs to trigger BDNF secretion, but not the amount of BDNF secreted, was dependent on the number of bAPs, suggesting that bAPs acts to trigger the release, i.e., once the secretion threshold is reached additional firing activity did not further modify it. Interestingly, we also show that the spontaneous synaptic activity alone, in the absence of APs, is not sufficient to induce dendritic BDNF release (Fig. 1). This point is of particular interest because it suggests that dendritic BDNF release is a function of the neuronal output, i.e., APs, rather than its synaptic input. Therefore all mechanisms that regulate the generation of the APs, such as peri-somatic inhibition, or that affect the back propagation of the APs into the dendrites, such as the activation of the cholinergic and β-adrenergic systems,[11,12] or the shunting effect exerted by dendritic GABAergic conductance[13] would be able to control dendritic BDNF secretion independently of the synaptic drive received by the neuron. Our results also suggest

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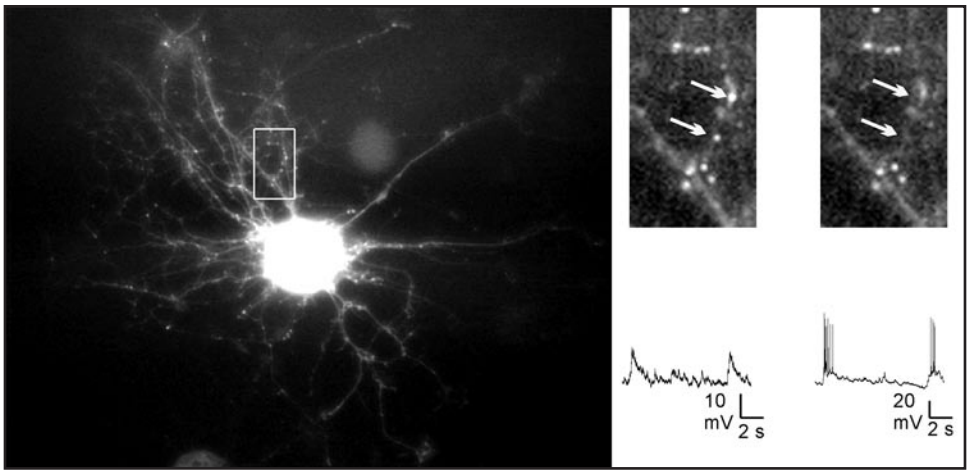

Figure 1. b-APs trigger dendritic BDNF secretion. Neuron transfected with BDNF-GPF show a dendritic distribution of BDNF into secretory granules. BDNF-GFP release (decreased of granular fluorescence) is triggered by firing activity (right) but not by synaptic activity (left).

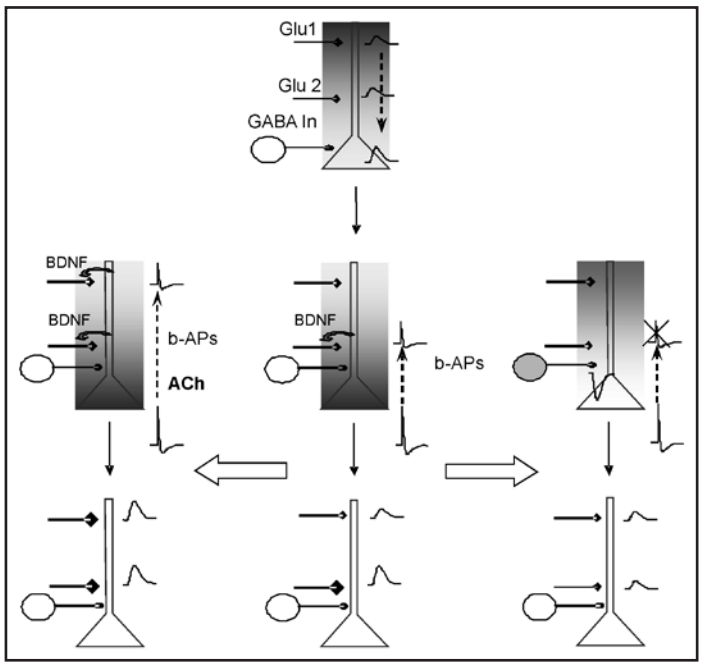

Figure 2. BDNF secretion depends on the neuronal output rather than synaptic inputs. Supra-threshold excitatory postsynaptic potentials (EPSPs) trigger action potentials that back-propagate (b-APs) from the soma to the dendrites. Center: the b-APs induced BDNF secretion and synaptic strengthening. Left: this process can be reinforced by conditions that facilitate the back propagation of APs such as the neuromodulatory action of ACh. Right: when the same supra-threshold glutamatergic activity is generated in a context that prevents APs backpropagation, such as a concomitant activation of dendritic inhibition (GABA), BDNF secretion and synaptic strengthening will not occur.

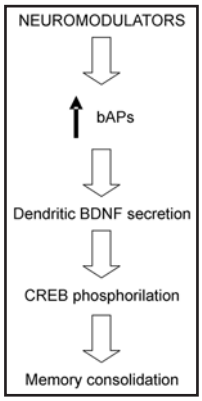

Figure 3. Modulation of back propagating action potentials can affect memory consolidation through dendritic BDNF release and CREB phosphorylation.

that in response to identical synaptic inputs, a neuron could undergo BDNF-dependent morphological and physiological reorganization depending on whether or not the environmental conditions allow APs to back propagate into the dendrites (Fig. 2). In that respect, it is interesting to note that suppressing AP generation in a single neuron within a network of active cultured neurons, by overexpressing an inward-rectifier potassium channel, affects the strength of the glutamatergic synapses impinging on that specific neuron.[14] In light of our results and the known action of BDNF on synaptic plasticity it is plausible that such effect could be, at least in part, mediated by a reduction of dendritic BDNF secretion.

Is the amount of endogenous BDNF released from a single neuron following b-APs sufficient to have a physiological effect? To answer this question, we have shown that AP firing triggered in one single neuron induced a BDNF-dependent phosphorylation of the cyclic AMP response element-binding protein (CREB) in the neighboring neurons.[15] CREB phosphorylation represents one of the early steps in synaptic plasticity consolidation subtending memory formation.[16] In light of the fact that the activity of the modulatory systems such as the cholinergic system is involved in synaptic plasticity as well as in mnemonic processes,[17] our results suggest a possible means by which neuromodulator action could affect memory formation through facilitation of bAPs that, in turn, trigger dendritic release of BDNF and CREB activation (Fig. 3). The question how localized the secretion of BDNF induced by b-APs can be, and identifying the associated biological effects underlying synapse specific release of BDNF, will be challenging tasks for future investigations. Previous studies have reported a contribution of NMDA receptors in dendritic BDNF release induced by tetanic stimulation.[9] Release confined to

individual synapses could influence synapse development and plasticity locally. In contrast, because APs and Ca^{2+} rise travel backward from the soma and have the capacity to invade the dendritic tree, BDNF secretion under these circumstances could influence synapse development and strength globally. Alternatively presynaptic activity concomitant with BDNF secretion can still constitute the discriminating factor for plastic modifications as recently shown by Tanaka and collaborators.[18]

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References

1. Lessmann V, Gottmann K, Malcangio M. Neurotrophin secretion: current facts and future prospects. Prog Neurobiol 2003; 69:341-74.
2. Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci 2005; 6:603-14.
3. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci 2001; 2:24-32.
4. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003; 112:257-69.
5. Gauthier LR, Charrin BC, Borrell-Pagès M, et al. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 2004; 118:127-38.
6. Chang Q, Khare G, Dani V, et al. The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression. Neuron 2006; 49:341-8.
7. Brigadski T, Hartmann M, Lessmann V. Differential vesicular targeting and time course of synaptic secretion of the mammalian neurotrophins. J Neurosci 2005; 25:7601-14.
8. Kohara K, Kitamura A, Morishima M, et al. Activity-dependent transfer of brain-derived neurotrophic factor to postsynaptic neurons. Science 2001; 291:2419-23.
9. Hartmann M, Heumann R, Lessmann V. Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. EMBO J 2001; 20:5887-97.
10. Kuczewski N, Porcher C, Ferrand N, et al. Backpropagating action potentials trigger dendritic release of BDNF during spontaneous network activity. J Neurosci 2008; 28:7013-23.
11. Tsubokawa H, Ross WN. IPSPs modulate spike backpropagation and associated $[Ca^{2+}]_i$ changes in the dendrites of hippocampal CA1 pyramidal neurons. J Neurophysiol 1996; 76:2896-906.
12. Hoffman DA, Johnston D. Neuromodulation of dendritic action potentials. J Neurophysiol 1999; 81:408-11.
13. Lowe G. Inhibition of backpropagating action potentials in mitral cell secondary dendrites. J Neurophysiol 2002; 88:64-85.
14. Burrone J, O'Byrne M, Murthy VN. Multiple forms of synaptic plasticity triggered by selective suppression of activity in individual neurons. Nature 2002; 420:414-8.
15. Finkbeiner S, Tavazoie SF, Maloratsky A, et al. CREB: A major mediator of neuronal neurotrophin responses. Neuron 1997; 19:1031-47.
16. Milner B, Squire LR, Kandel ER. Cognitive neuroscience and the study of memory. Neuron 1998; 20:445-68.
17. Hasselmo ME, Schnell E, Barkai E. Dynamics of learning and recall at excitatory recurrent synapses and cholinergic modulation in rat hippocampal region CA3. J Neurosci 1995; 15:5249-62.
18. Tanaka J, Horiike Y, Matsuzaki M, et al. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science 2008; 319:1683-7.