Neuropharmacology xxx (2013) 1–18

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Pre- and postsynaptic twists in BDNF secretion and action in synaptic plasticity

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ARTICLE INFO

Article history:
Received 4 March 2013
Received in revised form
12 May 2013
Accepted 14 May 2013

Keywords:
LTP
STDP
Spike timing
BDNF secretion
Synaptic plasticity
Neurotrophin
Mossy fiber LTP
BDNF-dependent synaptic plasticity
Long-term potentiation

ABSTRACT

Overwhelming evidence collected since the early 1990's strongly supports the notion that BDNF is among the key regulators of synaptic plasticity in many areas of the mammalian central nervous system. Still, due to the extremely low expression levels of endogenous BDNF in most brain areas, surprisingly little data i) pinpointing pre- and postsynaptic release sites, ii) unraveling the time course of release, and iii) elucidating the physiological levels of synaptic activity driving this secretion are available. Likewise, our knowledge regarding pre- and postsynaptic effects of endogenous BDNF at the single cell level in mediating long-term potentiation still is sparse. Thus, our review will discuss the data currently available regarding synaptic BDNF secretion in response to physiologically relevant levels of activity, and will discuss how endogenously secreted BDNF affects synaptic plasticity, giving a special focus on spike timing-dependent types of LTP and on mossy fiber LTP. We will attempt to open up perspectives how the remaining challenging questions regarding synaptic BDNF release and action might be addressed by future experiments.

This article is part of a Special Issue entitled 'BDNF'.

1. Introduction

There is certainly no doubt that BDNF is one of the central mediators and modulators of synaptic plasticity in the CNS. Numerous excellent previous reviews covered this topic and summarized the convincing evidence that BDNF promotes neuronal differentiation of stem cells, axonal and dendritic growth of neuronal processes, formation and maturation of glutamatergic and GABAergic synapses, and activity-dependent refinement of synaptic connections, like long-term potentiation (LTP), underlying learning and memory formation (see e.g. Bramham and Messaoudi, 2005; Gottmann et al., 2009; Park and Poo, 2013; review articles in this special issue). BDNF is such an attractive candidate for regulating synaptic transmission, since it is released locally at synapses in an activity-dependent manner, thus allowing local feedback at the level of individual synapses (Walz et al., 2006). In spite of the overwhelming evidence for BDNF in shaping synaptic plasticity, still surprisingly little is known regarding the exact location and time point of action of BDNF when synaptic plasticity is just being induced. Among the open questions are:

a) Is BDNF preferentially an ambient factor just favoring the induction and expression of synaptic plasticity (i.e. a synaptic modulator), or is it a mediator of synaptic changes representing the critical trigger for setting the changes in motion?
b) Is BDNF secreted from pre- or from postsynaptic elements to induce the specific synaptic changes, and what are the physiologically relevant patterns of synaptic activity that trigger synaptic BDNF secretion and decide whether it is pre- or postsynaptic?
c) Which parameters decide whether a certain BDNF-dependent synaptic change is mediated by pre- or postsynaptic alterations?

As will become evident from data discussed in this review, we are convinced that – depending on individual circumstances – BDNF i) can be both, a mediator or a modulator of synaptic plasticity, ii) can be released pre- and postsynaptically, and iii) can alter pre- and postsynaptic functions even simultaneously at the same individual synapse.

Importantly, intracellular as well as extracellular BDNF protein levels are extremely low, and BDNF release and action is local. Thus, to enable physiologically relevant insights into synaptic BDNF

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http://dx.doi.org/10.1016/j.neuropharm.2013.05.043

dynamics, experiments allowing space and time resolved analysis of *endogenous* BDNF are required, and will be focused on in this review, wherever respective data are available.

1.1. BDNF secretion from neurons

Secretion of BDNF requires the previous expression of BDNF mRNA, the subsequent translation of proBDNF protein, and the targeting of proBDNF and processed mature BDNF into exocytotic vesicles (for review compare: Lessmann et al., 2003; Lessmann and Brigadski, 2009). Alternatively, previously secreted BDNF can be endocytosed at primary sites of release and be recycled for additional rounds of secretion even at far distant sites in the same neuron (Santi et al., 2006; von Bartheld et al., 2001). Thus, any knowledge about the brain areas and subcellular neuronal compartments containing BDNF mRNA and protein give first important hints at loci of BDNF secretion.

1.1.1. Distribution of BDNF in different brain areas

The existence of mRNA is a prerequisite for the synthesis of proteins. Consequently, the presence of BDNF mRNA in rodents correlates very well with the site of synthesis of BDNF protein in specific tissues and cells (Conner et al., 1997). The **mRNA for BDNF** is widely distributed throughout the central nervous system (CNS) of rat and mice, including brain regions like the hippocampal formation (Conner et al., 1997; Connor and Dragunow, 1998; Ernfors et al., 1990; Hofer et al., 1990; Phillips et al., 1990; Schmidt-Kastner et al., 1996; Son and Winzer-Serhan, 2009; Wetmore et al., 1990, 1991), cerebral cortex (Conner et al., 1997; Hofer et al., 1990; Huntley et al., 1992; Phillips et al., 1990; Schmidt-Kastner et al., 1996; Timmusk et al., 1993; Wetmore et al., 1990, 1991), thalamus (Conner et al., 1997; Hofer et al., 1990; Schmidt-Kastner et al., 1996; Timmusk et al., 1993), hypothalamus (Conner et al., 1997; Hofer et al., 1990; Liao et al., 2012), olfactory bulb (Conner et al., 1997; Hofer et al., 1990; Phillips et al., 1990), amygdala (Conner et al., 1997; Phillips et al., 1990; Schmidt-Kastner et al., 1996; Wetmore et al., 1991), cerebellar granule cell layer (Hofer et al., 1990; Vazquez-Sanroman et al., 2013; Wetmore et al., 1990) and spinal cord (Conner et al., 1997; Hofer et al., 1990; Luo et al., 2001). In the hippocampus a similar distribution of BDNF mRNA was described for rodents and primates (Phillips et al., 1990). Similar to this pattern of BDNF mRNA expression, **BDNF protein** can be detected throughout the CNS, with highest expression levels in the hippocampal formation and cerebral cortex (Conner et al., 1997; Yan et al., 1997; Dugich-Djordjevic et al., 1995; Kokaia et al., 1996; Schmidt-Kastner et al., 1996; Wetmore et al., 1991). However, conflicting results regarding the expression of BDNF protein were observed in the hippocampal formation. While there is consensus in the literature that CA1 pyramidal cells of the hippocampus contain BDNF mRNA (An et al., 2008; Conner et al., 1997; Hofer et al., 1990; Kokaia et al., 1996; Schmidt-Kastner et al., 1996; Son and Winzer-Serhan, 2009; Timmusk et al., 1993; Tongiorgi et al., 2004; Wetmore et al., 1990, 1991; reviewed in Tongiorgi, 2008), the expression of BDNF protein in this cell type is discussed controversially. Numerous previous studies from different labs using distinct antibodies provided clear evidence that endogenous BDNF protein can be detected in somata and dendrites of CA1 pyramidal cells (see e.g. Conner et al., 1997; Dugich-Djordjevic et al., 1995; Schmidt-Kastner et al., 1996; Wetmore et al., 1991; reviewed in Lessmann et al., 2003). However, other studies (also using distinct antibodies) failed to observe such BDNF immunoreactivity in CA1 pyramidal cells, or observed only a weak immunoreactivity in some individual neurons in the temporal hippocampus (Dieni et al., 2012; Yan et al., 1997). There are several possible explanations for these discordant results: for example different BDNF antibodies are known to show cross-reactivity with non-BDNF protein species, which might give rise to false positive results for BDNF immunohistochemical detection (Matsuda et al., 2009; Matsumoto et al., 2008; compare Dieni et al., 2012). On the other hand, highly specific antibodies which avoid false positive BDNF detection might work at the expense of sensitivity for the low levels of BDNF expressed in CA1 of the hippocampus, which might explain the absence of BDNF protein detection in CA1 in some studies. Furthermore, critical parameters of immunohistochemical staining procedures, like fixation (Yan et al., 1997) or permeabilisation can decrease BDNF immunreactivity or give rise to differential access of antibodies to the interior of the distinct subsets of BDNF vesicles. In addition, BDNF expression is highly regulated not only by electrical activity but also by enriched environment, dietary restriction, light, stress, and circadian rhythm (reviewed in Chourbaji et al., 2011). Different housing conditions of the animals, like enriched environment or lower amount of stress, increase the expression of BDNF in CA1 dendrites (Chourbaji et al., 2011; Falkenberg et al., 1992; Ickes et al., 2000; Smith et al., 1995). Since the hippocampal formation is a brain region of utmost interest, further efforts are clearly required to solve these conflicting results about BDNF protein level in CA1 pyramidal cells. Due to the unambiguous consensus about BDNF mRNA level in this cell type, the question remains, whether BDNF expression might be regulated more tightly in CA1 pyramidal cells than in other brain areas.

1.1.2. Subcellular distribution of BDNF mRNA and protein

At subcellular level, BDNF mRNA is distributed not only in somatic structures but also in dendritic compartments, both, in cultured neurons and *in vivo* (An et al., 2008; Capsoni et al., 1999; Lau et al., 2010; Liao et al., 2012; Righi et al., 2000; Tongiorgi et al., 1997, 2004, 2006; Tongiorgi, 2008; Waterhouse et al., 2012), but it is absent in axons (Tongiorgi et al., 1997; but see Ma et al., 2012). Dendritic BDNF mRNA was observed in hippocampal CA1, CA2 and CA3 pyramidal cells, granule cells, cortical neurons and hypothalamic neurons, and increased levels were detected in response to electrical activity (Wetmore et al., 1994; reviewed in Tongiorgi, 2008). In addition, dendritic localization of BDNF mRNA is dependent on polyadenylation of mRNA transcripts. In conditional transgenic animals which lacked the long 3′untranslated region (UTR) mRNA, dendritic targeting of BDNF mRNA was impaired in cortical and hippocampal neurons (An et al., 2008). While somatic localization of BDNF mRNA was observed for short and long 3′UTR BDNF mRNA, only long 3′UTR transcripts were targeted to dendrites of cortical and hippocampal CA1 neurons. Since the appearance of BDNF mRNA in dendrites indicates local protein synthesis followed by dendritic release of endogenous BDNF in these cells, this difference in dendritic BDNF mRNA localization has impact on physiological functions (An et al., 2008; Lau et al., 2010; Waterhouse et al., 2012). In accordance with this subcellular pattern of BDNF mRNA expression, endogenous BDNF protein was detected in somatic compartments and dendrites of cultured neurons as well as in dendrites of hippocampal neurons, cortical neurons and hypothalamic neurons *in vivo* (Adachi et al., 2012; Aoki et al., 2000; Jakawich et al., 2010; Ma et al., 2012; Matsuda et al., 2009; Swanwick et al., 2004; Tongiorgi et al., 2004; Wetmore et al., 1991; Yang et al., 2009b). However, Dieni and colleagues could not detect any endogenous BDNF in dendrites of hippocampal neurons. According to the conflicting results of BDNF protein expression in CA1 pyramidal cells, several explanations for this outcome are possible (see above). Besides dendritic localization, endogenous BDNF was also found in axons of cultured neurons and *in vivo* (Aoki et al., 2000; Buldyrev et al., 2006; Dieni et al., 2012; Fawcett et al., 1997; Matsuda et al., 2009; Michael et al., 1997; Swanwick et al., 2004). The subcellular distribution of

Please cite this article in press as: Edelmann, E., et al., Pre- and postsynaptic twists in BDNF secretion and action in synaptic plasticity, Neuropharmacology (2013), http://dx.doi.org/10.1016/j.neuropharm.2013.05.043