BDNF Met Prodomain Changes BDNF Signaling

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ABSTRACT Everything we remember is encoded as plastic changes at small protrusions called spines, located on the dendritic branches of nerve cells. A molecule implicated in governing these changes, brain-derived neurotrophic factor (BDNF), binds to TrkB, a post-synaptic receptor for BDNF, and is internalized, mediating spine head diameter and synaptic plasticity. BDNF is synthesized in an immature form containing a prodomain, which is subsequently cleaved, yielding functional BDNF and an independent prodomain, which was thought to have no biological function. Giza et al. (Neuron, 2018) found that the independent prodomain is a biologically active molecule that shrinks spines and eliminates synapses in neurons. Additionally, Giza et al. found that a single polymorphism, changing Valine (Val) at position 66 to Methionine (Met), present in 30% of the population, predisposes carriers to neuropsychiatric disorders with underlying effects on synaptic plasticity, including Alzheimer's and PTSD. Here, using super-resolution microscopy 3D SIM, we show that mature BDNF and Met prodomain exist as separate molecules and in complexes at the level of the dendritic spine. Further, the presence of the Met prodomain abolishes the effect of BDNF on spines. We hypothesize that the BDNF-Met complex interferes with BDNF-TrkB signaling by abolishing BDNF-TrkB internalization and signaling at the spine, and possibly recruiting other pro-shrinkage proteins into a complex with BDNF and TrkB.

Fig.1 Brain-Derived Neurotrophic Factor (BDNF) is a Growth Factor Regulating Synaptic Plasticity in the Brain

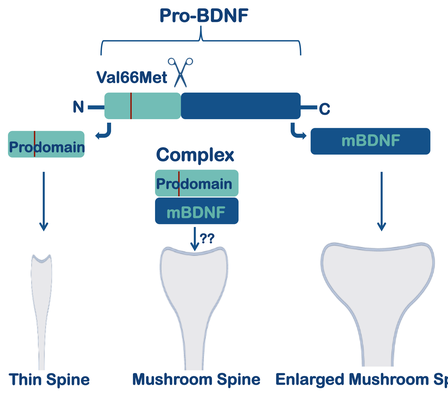

Fig. 1. A common single nucleotide polymorphism (SNP) in *Bdnf* region encoding prodomain changes valine to methionine (~30% prevalence). BDNF and Met prodomain have opposite effects on synaptic plasticity through their action on dendritic spines.

Fig.2 Prodomain and BDNF Can Be Found Separately or In Complex With Each Other

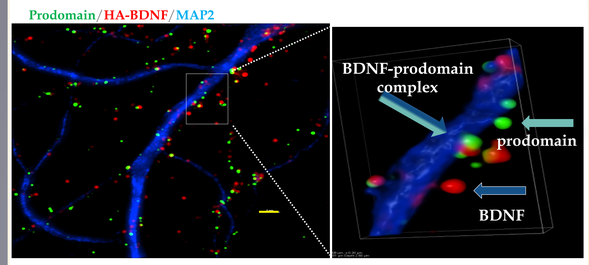

Fig. 2. Left: dendritic segment (DIV21) (scale bar 5um) ; right: zoomed-in segment shows dendrite (MAP2) with mature BDNF (red) and prodomain (green) stained and visualized with Nikon 3D SIM super-resolution microscope. Mature BDNF and prodomain can exist separately and in complexes.

Fig.3 Experimental Design Set-up

Fig. 3. In order to understand the consequence of the BDNF-Met prodomain complex on BDNF function and spine dynamics, mouse neuronal cells were grown on coverslips to examine their morphology and BDNF-TrkB signaling. After 15 min of treatment with exogenous BDNF and BDNF-Met prodomain complexes, the cells were stained and visualized with a Nikon 3D SIM super-resolution microscope.

Fig.4 Met Prodomain Counteracts the Effects of BDNF on Spine Morphology

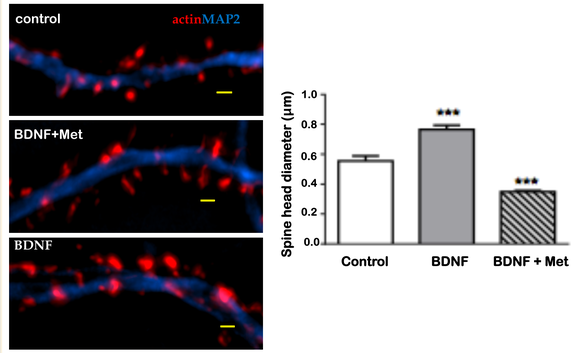

Fig. 4. After 1 hour of treatment with BDNF or with pre-incubated BDNF-Met complex, spine head diameter was measured. The BDNF in complex with prodomain prevented BDNF-mediated spine head expansion, and further decreased spine head diameter.

Fig.5 Met Prodomain Binding to BDNF Interferes with BDNF Signaling

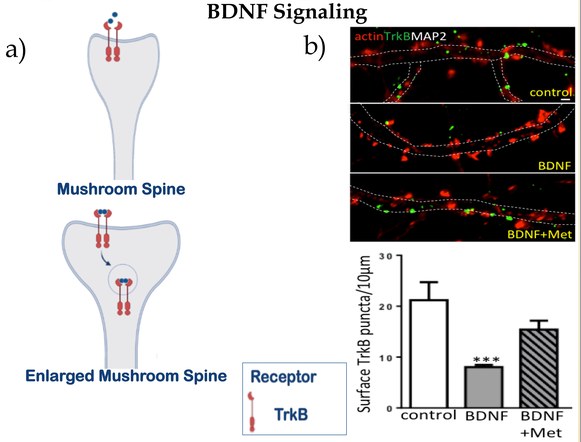

Fig. 5a. BDNF binding to TrkB causes internalization required for BDNF signaling, leading to spine head expansion.
Fig. 5b. In the presence of Met prodomain TrkB is not internalized.

Fig.6 Met Prodomain recruits another Receptor, $p75^{NTR}$ to TrkB within 15 min

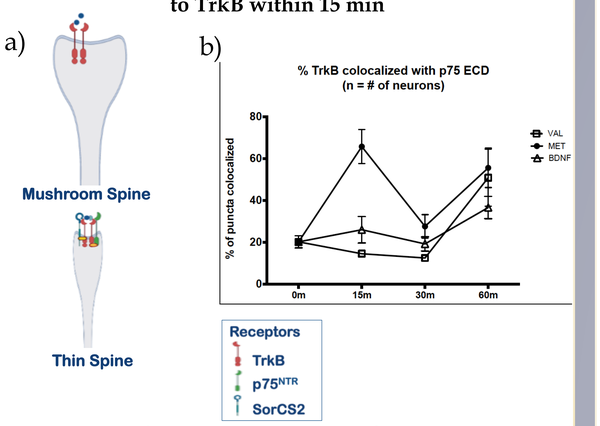

Fig. 6a. Met prodomain requires two sets of receptors, SorCS2 and $p75^{NTR}$ to shrink spines.
Fig. 6b. The presence of Met prodomain increases colocalization of TrkB with $p75^{NTR}$.

Fig.7 Hypothesis Model of BDNF Signaling in Presence of Met Prodomain

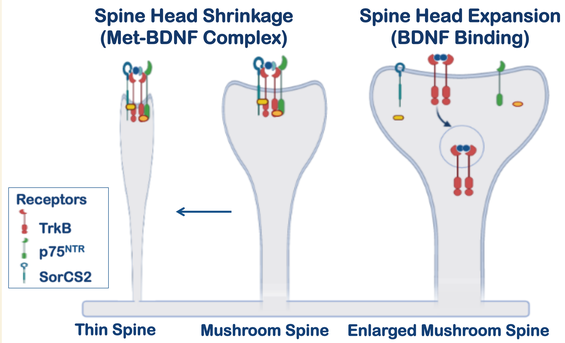

Fig. 7. Our data suggests that Met prodomain binding to BDNF recruits p75NTR receptor to TrkB, preventing its internalization and spine head expansion, while directing signaling towards spine shrinkage. Met prodomain may also recruit other pro-shrinkage proteins such as SorCS2.

SUMMARY:

Dysfunctional growth and pruning of synaptic connections is implicated in several neuropsychiatric disorders, including PTSD, schizophrenia, and Alzheimer's. Understanding the mechanisms behind synaptic plasticity, particularly among those underlying the Met prodomain polymorphism, may lead to novel points for prevention and treatment of these disorders.
Preliminary data analyzed in this project suggests that the Met prodomain changes BDNF signaling in dendritic spines by blocking BDNF-TrkB internalization and by recruiting pro-shrinkage receptor(s).

References:

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