Development of small molecule agonists of TrkB receptors

Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) are a family of secreted growth factors that bind to their cell surface receptors as homodimers and lead to receptor dimerisation and intracellular signal transduction (Figure 1). Neurotrophins promote the survival, differentiation and maintenance of specific neuronal populations and regulate synaptic plasticity, neurite outgrowth, and protection and repair of neurons during tissue injury. All neurotrophins bind to $p75^{NGFR}$ receptor but selectively interact with their individual high-affinity protein tyrosine kinase receptors of the Trk family (TrkA, TrkB and TrkC). BDNF mediates majority of its biological effects via TrkB receptor.

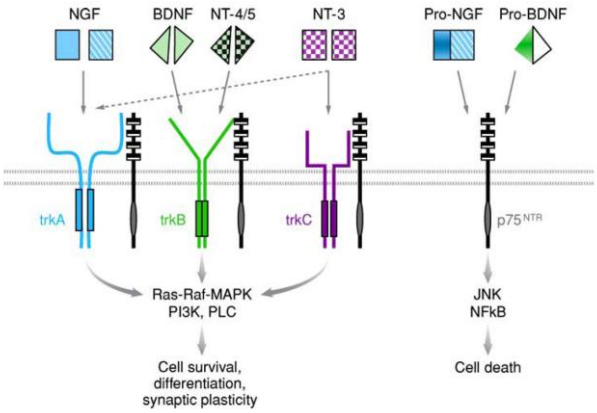

Figure 1. Neurotrophins and their receptors.

Among neurotrophins, BDNF have received particular interest for their role in the nervous system function. Both in rodents and human decreases of BDNF levels and/or its receptor TrkB activity are accompanied by and are believed to lead to several pathologies, like obesity, aggression, impairement of learning and memory, neuropsychiatric disorders like anxiety, depression (Figure 2), bipolar disorder and neurodegenerative disorders like Huntington's, Parkinson's and Alzheimer's diseases.

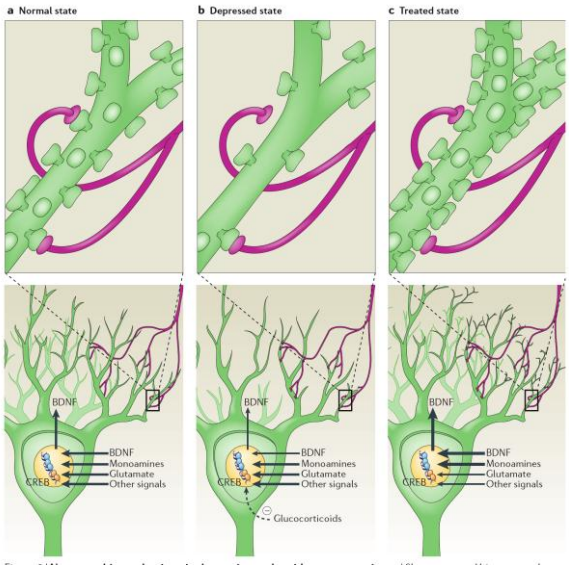

Figure 2. BDNF and depression.

Therefore developing small molecule agonists of TrkB receptor is a novel therapeutic strategy for the treatment of several nervous system diseases. BTD, Ltd. has aimed to develop efficient low molecular weight agonistic compounds for TrkB receptors.

We have already successfully identified several compounds, including CB1, CB2 and CB3, that can act as agonists of TrkB leading to TrkB phosphorylation in cultured rat primary cortical neurons. Induction of TrkB phosphorylation by these compounds is apparent although it is approximately 9 times lower than the induction seen in by BDNF (Figure 3).

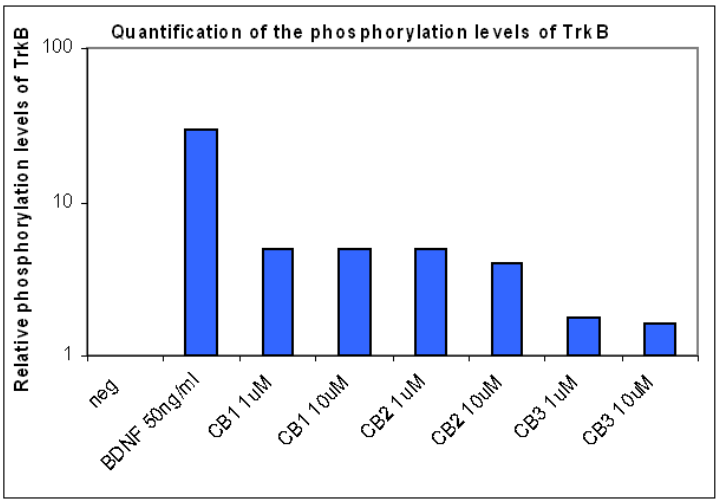

Figure 3. Effect of TrkB agonists on TrkB phosphorylation in rat primary neurons. Induction of TrkB phosphorylation by CB1, CB2 and CB3 as compared to BDNF in cultured embryonic rat cortical neurons. After treatment with indicated compounds, the cells were lysed and immunoprecipitated with anti-phosphotyrosine antibody. Precipitated proteins were later analysed using Western blotting and anti-TrkB antibody. The graph shows results from quantification of a representative Western blot image.

Conclusion: CB1, CB2 and CB3 are good candidates as lead compounds for the development of TrkB agonists.

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