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Invited Review

Neurotrophin receptors in the pathogenesis, diagnosis and therapy of neurodegenerative diseases

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ABSTRACT

In the last few years, exciting properties have emerged regarding the activation, signaling, mechanisms of action, and therapeutic targeting of the two types of neurotrophin receptors: the $p75^{NTR}$ with its intracellular and extracellular peptides, the Trks, their precursors and their complexes. This review summarizes these new developments, with particular focus on neurodegenerative diseases. Based on the evolving knowledge, innovative concepts have been formulated regarding the pathogenesis of these diseases, especially the Alzheimer's and two other, the Parkinson's and Huntington's diseases. The medical progresses include original procedures of diagnosis, started from studies in mice and now investigated for human application, based on innovative classes of receptor agonists and blockers. In parallel, comprehensive studies have been and are being carried out for the development of drugs. The relevance of these studies is based on the limitations of the therapies employed until recently, especially for the treatment of Alzheimer's patients. Starting from well known drugs, previously employed for non-neurodegenerative diseases, the ongoing progress has lead to the development of small molecules that cross rapidly the blood-brain barrier. Among these molecules the most promising are specific blockers of the $p75^{NTR}$ receptor. Additional drugs, that activate Trk receptors, were shown effective against synaptic loss and memory deficits. In the near future such approaches, coordinated with treatments with monoclonal antibodies and with developments in the microRNA field, are expected to improve the therapy of neurodegenerative diseases, and may be relevant also for other human disease conditions.

Contents

Abbreviations: Aβs, Aβ 1-40 and Aβ 1-42, amyloid β peptides; AD, Alzheimer's disease; APP, trans-membrane amyloid protein precursor; BDNF, brain-derived neural factor, the neurotrophin agonist of $p75^{NTR}$ and TrkB receptors; Calpains, Ca^{2+-} dependent intracellular cysteine proteases that cleave Trks; Caspases, intracellular proteases; CNS, central nervous system; CSF, cerebro-spinal fluid; C57BL/6, a Parkinson's disease murine model; HD, Huntington's disease; HdhQ111/111, N171-82Q and R6/1, mouse models of Huntington's disease; K252a, a blocker of TrkB; LINGO-1, leucine-rich repeat and Ig domain-containing 1, associated to $p75^{NTR}$ and NgR, inhibits axonal outgrowth; LM11A, family of small molecule drugs targeted to individual receptors, such as TrkA, TrkB, TrkC, $p75^{NTR}$ or sortilin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a molecule that triggers Parkinson's disease in mice and men; NGF, nerve growth factor, agonist of $p75^{NTR}$ and TrkA receptors; NgR, also known as Nogo-66, a receptor that associates with $p75^{NTR}$ and LINGO-1, inhibits axonal outgrowth; NTs, neurotrophins; NTRK1 and NTRK2, the genes coding for TrkA and TrkB; nu/nu athymic xenograft, a mouse model employed for cancer studies; PC12, a cell line from a rat pheohromocytoma; PD90780, drug blocker of $p75^{NTR}$; PNS, peripheral nervous system; $p75^{NTR}$, a non-enzymatic, pan-neurotrophin receptor of the tumor necrosis receptor family; p75-ECD and p75-ICD, the extracellular and intracellular domains, peptides cleaved from $p75^{NTR}$; PD, Parkinson's disease; proNT, proNGF, proBDNF, precursors of NTs; SALL2, transcription factor transferred to the nucleus upon Trk activation; SH2-B-1β, adaptor protein controlling vesicle traffic and neurite outgrowth; Sortilin, a neurotensin-like, non-G protein-coupled stimulatory receptor, complexed to various NT receptors to induce peculiar effects; Tg2576, APPL/S, CaM/Tet-$DT_{A,}$ and APP-PS1, murine models of AD; TrkA, TrkB and TrkC, tropomysin-related kinases A, B and C, the three tyrosine kinase receptors of NTs; TRPV1, TRansient potential vanilloid 1 receptor, controlled by TrkA, governs pain expression.

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Box 1: Historical perspective of NT receptors.
The study of NT receptors, initiated shortly after their discovery, led to a large accumulation of knowledge [8,70]. Binding of NTs was initially shown to occur by two processes, one slow and the other fast, with dissociation constant (K_d) of 10^{-9} and 10^{-11}, respectively. The first, lower affinity value, due to $p75^{NTR}$, occurs with all NTs, which however bind at non-identical sites of the receptor. Binding of $p75^{NTR}$ to proNTs occurs in all cases at higher affinity. Among the problems solved within the first two decades in the $p75^{NTR}$ field were the identification of the receptor signaling pathways and the multiplicity of effects induced by receptor activation on neurons and other cell types. Signaling of the three Trk receptors is known since the early 90s. Also established has been the intracellular traffic of activated $p75^{NTR}$ and Trk receptors initiated by their internalization into distinct endocytic vesicles.
Many of the critical roles of NT receptors in the regulation of important functions of neurons and other cell types, were also established during the first two decades of investigation. Concomitantly, the relevance of NT receptors in various, neural and non-neural diseases and cancers, was also demonstrated. Recent developments of NT receptor studies, highly relevant in cell physiology and diseases (diagnosis and therapy), are illustrated in the present review.

Box 2: NT Receptors and Neural Disorders.
Pain, due to heat, inflammation, or neuropathic hyperalgesia, can depend on the transient receptor potential vanilloid 1 (**TRPV1**), a non-NT receptor expressed by afferent neurons, ganglia and spinal cord [16,17,22]. TRPV1, however, is sensitized by NGF activation of TrkA via direct phosphorylation and membrane trafficking [16,17]. Thus TrkA plays a key role in pain.
NT receptors are also critical in epilepsy and ischemic injury. For example, kainite, the agonist of a glutamate receptor-channel, induces in mouse hippocampal neurons an increase in the levels of microRNA 1-32, which in turn induces alteration of NT receptors: increase of proBDNF and $p75^{NTR}$ levels and suppressed TrkB signaling, together with enhanced activity of voltage-gated Ca^{2+} channels, with ensuing appearance of epileptiform discharges [94]. Likewise, in an *in vivo* mouse model of brain local ischemia, the microRNA 592 induces increases of both pro-NGF and $p75^{NTR}$ [33]. However, a concomitant over-expression of the enzyme heme oxygenase activates TrkB signaling, with attenuation of the local neuronal injury [68]. It appears therefore that, in epileptic and ischemic injuries, Trk and $p75^{NTR}$ receptors play protective and deleterious roles, respectively, analogous to those observed in certain neurodegenerative diseases.
Involvement of NGF, BDNF, and Trks has also been recently reported for psychiatric diseases For example, BDNF and TrkB appear to participate in the induction of social defeat stress and anxiety by acting in human neurons of the nucleus accumbens, hippocampus, and other brain areas [27]. In contrast, results of depression disorders in mouse models suggest such diseases to be sustained by loss of functional BDNF and TrkB [85]. Analogous defects of TrkA and TrkB in patients affected by schizophrenia may depend on altered plasticity of synapses [100].

1. Introduction (For classical data sia Box 1)

Neurotrophins (**NT**s), a group of specific factors, operate through the activation of two distinct types of receptor (Fig. 1) inducing different signals and effects in neurons and other cell types, such as astrocytes, oligodendrocytes, macrophages, pancreatic β cells, smooth/striated muscle fibers [8,70]. The 75 kDa receptor (**$p75^{NTR}$**), a receptor activated by all NTs, is a non-enzymatic, transmembrane protein of the tumor necrosis receptor (**TNFR**) family. The other types of receptor, the tyrosine kinase receptors (**Trks) A, B,** and **C**, are activated, specifically, and with high affinity, by nerve growth factor (**NGF**) (TrkA), brain derived growth factor and neurotrophin 4 (**BDNF** and **NT4)** (TrkB), and neuroptrophin 3 **(NT3)** (TrkC). Our Graphical Abstract summarizes properties of all NT receptors.

Based on the extensive studies in the last few years, our knowledge on NT receptors has been expanded. Given the complexity of their signaling pathways, they are now known to play numerous roles relevant in cell physiology. Moreover, the results obtained are critical for the understanding of various diseases. In the central and peripheral nervous system (**CNS and PNS**), NT receptor-regulated processes include neuronal differentiation, survival and death, axonal outgrowth, synapse generation and plasticity. These processes have been particularly investigated during various neurodegenerative diseases [8,70]. Concomitantly, the relevance of NT receptors has also been demonstrated in the pathogenesis of other diseases known to affect large populations of patients [8,11,70], including various neural disorders (Box 2), a few non-neural diseases, such as cardiovascular diseases and diabetes (Box 3), and a number of cancers such as breast, lung and colon-rectum cancers, myelomas, lymphoid tumors and gliomas (Box 4).

Here, we summarize the current state of knowledge on the properties of $p75^{NTR}$ and Trk receptors. The review is focused especially on new information about the pathogenesis of neurodegenerative diseases, revealed by recent *in vitro* and *in vivo* studies in rodents and humans. Our major interest is on the discussion of diagnosis and therapy. In particular, the latter is highly promising and therefore at the moment is attracting great interest. In addition, NTs and their receptors are envisaged as novel candidate targets to treat not only neurodegenerative but also a variety of other diseases, specified in the Boxes 2–4 of this review.