Neurotrophins and neuronal plasticity in the action of antidepressants and morphine

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Academic dissertation

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”It´s always good to know what you don´t know”

- Gil Grissom, Ph.D.

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In Lemu, May 2007

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications referred to by their corresponding Roman numerals.

I Saarelainen T, Hendolin P, Lucas G, Koponen E, **Sairanen M**, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castren E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci. 2003 Jan 1;23(1):349-57.[a]

II Lucas G, Hendolin P, Harkany T, Agerman K, Paratcha G, Holmgren C, Zilberter Y, **Sairanen M**, Minichiello L, Castren E, Ernfors P. Neurotrophin-4 mediated TrkB activation reinforces morphine-induced analgesia. Nat Neurosci. 2003 Mar;6(3):221-2.[c]

III **Sairanen M**, O'Leary O, Knuuttila J, Castren E. Chronic antidepressant treatment selectively increases expression of plasticity-related proteins in the hippocampus and medial prefrontal cortex of the rat. Neurosci. 2007 Jan 5; 144(1):368-74.[b]

IV **Sairanen M**, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J Neurosci. 2005 Feb 2;25(5):1089-94.[a]

Abbreviations

5-HT	serotonin
5-HT1A	serotonin 1A autoreceptor
BDNF	brain derived neurotrophic factor
BrdU	5-bromo-2´deoxy-uridine
cAMP	cyclic aminomonophosphate
CREB	cyclic-AMP responce element binding-protein
DG	dentate gyrus
ERK	extracellular signal regulated kinase
GABA	γ-aminobutyric acid
GAP-43	growth associated protein-43
GFAP	glial fibrillary acidic protein
HFS	high-frequency stimulation
i.p.	intraperitoneal
KO	knockout (mice)
LC	locus coeruleus
LTD	long-term depression
LTP	long-term potentiation
mRNA	messenger ribonucleic acid
NA	noradrenline
NGF	nerve growth factor
NT-3	neurotrophin-3
NT-4	neurotrophin-4
p75NTR	low-affinity receptor for neurotrophic factors
pCREB	phosphorylated form of CREB
PLCγ	phospholipase Cγ
mPFC	medial prefrontal cortex
PSA-NCAM	polysialylated form of nerve cell adhesion molecule
Shc	adaptor protein with SH2 domain
TrkB	tropomyosin-related tyrosine kinase receptor for BDNF and NT-4
TrkB.T1	mice overexpressing truncated isoform of TrkB
TUC-4	TOAD/Ulip/CRMP-4
TUNEL	TdT-mediated dUTP nick end labelling
VTA	ventral tegmental area

CONTENT

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Abstract

Neuronal plasticity is a well characterized phenomenon in the developing and adult brain. It refers to capasity of a single neuron to modify morphology, synaptic connections and activity. Neuronal connections and capacity for plastic events are compromised in several pathological disorders, such as major depression. In addition, neuronal atrophy has been reported in depressive patients. Neurotrophins are a group of secretory proteins functionally classified as neuronal survival factors. Neurotrophins, especially brain derived neurotrophic factor (BDNF), have also been associated with promoting neuronal plasticity in dysfunctional neuronal networks. Chronic antidepressant treatment increases plastic events including neurogenesis and arborization and branching of neurites in distinct brain areas, such as the hippocampus. One suggested mode of action is where the antidepressants elevate the synaptic levels of BDNF thus further activating several signaling cascades via trkB-receptor. In our studies we have tried to clarify the mechanisms of action for antidepressants and to resolve the role of BDNF in this process. We found that chronic antidepressant treatment increases amount of markers of neuronal plasticity in both hippocampus and in the medial prefrontal cortex, both of which are closely linked to the etiology of major depression. Secondary actions of antidepressants include rapid activation of the trkB receptor followed by a phosphorylation of transcription factor CREB. In addition, activation of CREB by phosphorylation appears responsible for the regulation of the expression of the BDNF gene. Using transgenic mice we found that BDNF-induced trkB-mediated signaling proved crucial for the behavioral effects of antidepressants in the forced swimming test and for the survival of newly-born neurons in the adult hippocampus. Antidepressants not only increased neurogenesis in the adult hippocampus but also elevated the turnover of hippocampal neurons. During these studies we also discovered that another trkB ligand, NT-4, is involved in morphine-mediated anti-nociception and tolerance. These results present a novel role for trkB-mediated signaling in plastic events present in the opioid system. This thesis evaluates neuronal plasticity and trkB as a target for future antidepressant treatments.

REVIEW OF THE LITERATURE

1. Introduction

The influence of neurotrophins spans from developmental neurobiology to neurodegenerative and psychiatric disorders. In addition to their classical effects on neuronal survival (Levi-Montalcini, 1987), neurotrophins can also regulate axonal and dendritic growth and guidance, synaptic structure and connections, neurotransmitter release, long-term potentiation and synaptic plasticity (Thoenen, 1995; McAllister et al., 1999; Poo, 2001; Castrén, 2005). Emerging evidence is also revealing the underlying importance of neuronal plasticity in chronic pathological disorders of the nervous system such as depression and persisting-pain states.

TrkB is one of the three trk tyrosine kinase receptors activated by the neurotrophins and two of the neurotrophins, BDNF and NT-4 are ligands for the trkB (Soppet et al., 1991; Ip et al., 1992). A fascinating quality of the neurotrophins is that they are activity dependently regulated. In addition, neurotrophins can be secreted and regulated in a synapse specific manner within neuron populations. TrkB-mediated signaling has been closely linked to the regulation of neuronal plasticity. However, recent findings from pro-neurotrophins show that many questions are still unanswered (Lu, 2005).

Major depression is a pathological disorder characterized by recurrent episodes of reduced mood and neuronal atrophy in distinct brain areas. Some genetic and epigenetic factors have been shown to increase susceptibility to development of depression. However, the effect of stress and stress hormones are the major contributors for the development of depression (Manji et al., 2001). One of the main problems of the current drug therapies, targeted at improving the quality of life of depressive patients, is the delayed onset of the antidepressive effects. While antidepressive drugs affect monoamine levels within minutes the full clinical effects take several weeks to develop. The current view is that dysfunctions in neuronal plasticity are responsible for the development of depression and that antidepressants and neurotrophins are able to partially correct these dysfunctions.

Morphine is an opiate used to treat severe pain. The major problem of morphine's clinical use is putative abuse. When it is used as an analgesic the problem is that chronic use leads to tolerance and the analgesic effects of morphine fade. With the knowledge that neurotrophins are known to mediate pain signaling (Pezet and McMahon, 2006) and that morphine tolerance is a process involving neuronal plasticity (Trujillo, 2002; Mao and Mayer, 2001) it is possible

that neurotrophins are involved in development of morphine tolerance.

2. Neurotrophins

Neurotrophins comprise secretory proteins produced by the nervous system and needed in a variety of essential functions. Neurotrophins are structurally and biologically similar, the most important factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). In addition, neurotrophin-6 (NT-6) and neurotrophin-7 (NT-7) have been characterized, but only in fish (Gotz et al., 1994; Nilsson et al., 1998). Mammalian neurotrophins are initially synthesized as pro-neurotrophins, which are cleaved to produce the mature active proteins (Seidah et al., 1996a and 1996b; Mowla et al., 2001). The mature proteins are about 12 kDa in size and normally form stable, non-covalent dimers. Neurotrophins are actively released by both pre- and postsynaptic nerve terminals.

The gene expression of neurotrophins is tightly regulated during development in the brain. The highest levels of NGF are found in the basal forebrain, hippocampus and in the pituitary gland. Significant quantities have also been reported throughout the CNS including the spinal cord (Goedert et al., 1986; Hefti et al., 1986; Maisonpierre et al., 1990). BDNF expression rises dramatically during the first postnatal weeks and it is expressed throughout life in the adult brain. BDNF is abundantly expressed with especially high levels in the hippocampus and cortex (Ernfors et al., 1990b; Hofer et al., 1990; Maisonpierre et al., 1990; Ernfors et al., 1992). NT-3 is the most abundantly expressed in the perinatal brain but levels are significantly reduced in the adult brain (Maisonpierre et al., 1990; Zhou and Rush, 1994; Ernfors et al., 1990a). NT-4 is expressed in the postnatal and adult hippocampus, neocortex and thalamic nuclei (Friedman et al., 1998). In the CNS neurotrophins are generally expressed in neurons. However NT-3 and NT-4 are also widely expressed in glial cells (Zhou and Rush, 1994; Friedman et al., 1998).

Different neurotrophins show specific binding specificity to particular receptors (Figure 1A). The synaptic actions of mature neurotrophins are mediated by a high-affinity trk (tropomyosin related kinase) family of protein tyrosine kinase receptors (Barbacid, 1994; Lewin and Barde, 1996). NGF preferably binds into trkA, BDNF and NT-4 into trkB, and NT-3 into trkC (Hempstead et al., 1991; Kaplan et al., 1991; Klein et al., 1991a; Klein et al., 1991b; Lamballe et al., 1991; Soppet et al., 1991; Ip et al., 1993; Barbacid et al., 1994). All of the mentioned ligands also bind to low-affinity neurotrophin receptor, p75NTR (Lewin and Barde; 1996; Hempstead, 2002). Pro-forms of neurotrophins also bind, with a high affinity, to p75NTR. p75NTR is a member of the tumor necrosis factor (TNF) receptor super family (Chao and Hempstead, 1995). TrkA is expressed mainly by the cholinergic neurons of the basal forebrain

(reviewed Huang and Reichardt, 2001). TrkB and TrkC are more widely expressed throughout the brain (McAllister et al., 1999; Merlio et al., 1992; Ringstedt et al., 1993). All of these receptors are encoded by a single gene that produces a number of functionally variable splice isoforms (Barbacid, 1994; Lewin and Barde, 1996). All of the trk receptors are expressed during development and also at the adulthood.

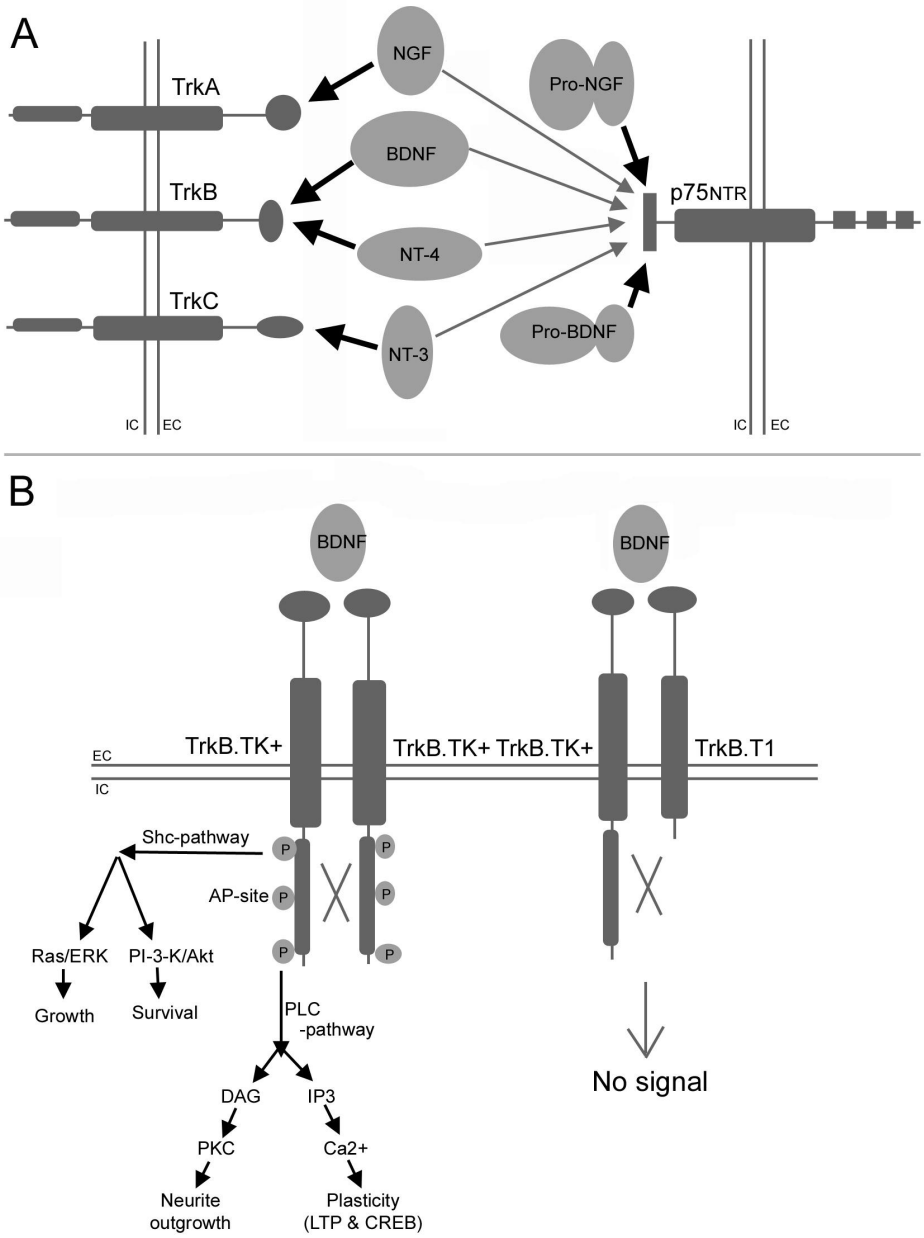

Figure 1: Schematic presentation of binding of neurotrophins into neurotrophic receptors (A) and signaling pathways activated by the phosphorylation of trkB (B). Mature forms of NTs primarily bind to trk receptors while pro-forms of NTs bind to p75NTR. Thick and thin arrows are presenting binding with high or low affinity to receptors, respectively. Signal pathways following the activation of full length trkB receptor (TrkB.TK+) are also presented. No signal cascades are activated when full length receptor makes a dimer with truncated isoform (TrkB.T1). IC=intracellular, EC=extracellular, ec=entzymatic cleavage, for other abbreviations see page 8.

2.1. BDNF

Brain-derived neurotrophic factor (BDNF) was the second member of the neurotrophin growth factor family identified (Barde et al., 1982; Leibrock et al., 1989). The genomic structure and gene regulation of rat and human bdnf gene is quite complex (Aid et al., 2006; Metsis et al., 1993; Liu et al., 2005, 2006; West et al., 2001). There are four 5' exons, each with its own promoter that are combined onto one common 3' exon with one alternative splice site consequently producing eight different transcripts in total (Aid et al., 2006). Individual promoters direct the expression of rat BDNF tissue-specificity; transcripts containing exons I, II and III are preferably expressed in brain whereas exon IV transcripts are present in heart and lung (Metsis et al., 1993; Liu et al., 2005, 2006). The transcript from exon III responds strongly to neuronal stimulation and so far two different transcription factors, cAMP response element binding (CREB) protein and calcium response factor (CaRF), have been identified to bind to BDNF promoter III for transcription regulation (Lu, 2003a; West et al., 2001). The presence of multiple promoters highlights the fact that the bdnf gene is under tight regulation.

BDNF expression levels are low during fetal development, increase after birth and then reduce to adult levels (Maisonpierre et al., 1990). In the adult brain, highest expression levels are observed in hippocampus, cortex, cerebellum, amygdala, and in various hypothalamic nuclei (Castren et al., 1995; Dugich-Djordjevic et al., 1995; Ernfors et al., 1990b; Hofer et al., 1990). Within hippocampus, pronounced expression is located in dentate granule cells and pyramidal neurons of the CA1-CA3 regions. Only a few brains areas, such as the striatum, completely lack BDNF mRNA (Castren et al., 1995). Several studies have demonstrated BDNF mRNA expression in rodent cultured glial cells (Murer et al., 2001). BDNF expression has been reported in cultured Schwann cells (Acheson et al., 1991), astroglia (Rudge et al., 1992; Condorelli et al, 1994; Rubio, 1997), and microglia (Elkabes et al., 1996).

The mature BDNF protein is a 13.5-kDa protein that is secreted as a dimer into the extracellular space (Kolbeck et al., 1994). BDNF is first generated as a precursor, pre-pro-BDNF protein. The pre-sequence is cleaved after sequestration to the endoplasmic reticulum. The remaining pro-BDNF is further processed via the Golgi apparatus into the *trans*-Golgi network and is packed into secretory vesicles. The pro-BDNF is cleaved intracellularly by furin or pro-convertase enzymes and is secreted as a mature peptide. Alternatively, protein is secreted as a pro-BDNF and cleaved by extracellular proteases such as matrix metalloproteinases (MMPs) and plasmin (Lee et al., 2001; Lessmann et al., 2003; Pang et al., 2004). Further, immunohistochemical and overexpression studies have revealed that the BDNF protein is mainly somatodendritically localized (Fawcett et al., 1997; Goodman et al.,

1996; Hartmann et al., 2001; Kojima et al., 2001; Tongiorgi et al., 1997; Wetmore et al., 1991) but axonal BDNF is also present (Kohara et al., 2001). The BDNF protein has been co-localized with synaptic markers therefore suggesting it's presence within the synapse (Fawcett et al., 1997; Goodman et al., 1996).

The first identified function for BDNF was its ability to promote survival of peripheral sensory neurons during apoptosis and these observations have been confirmed at the system level in transgenic mice (Conover et al., 1995; Ernfors et al., 1994a; Huang and Reichardt, 2001; Jones et al., 1994; Sendtner et al., 1992). In the central neurons, BDNF and NT-4 responsive neurons include cerebellar granule cells, mesensephalic dopaminergic neurons, hippocampal neurons, cortical neurons and retinal ganglion cells (Lindholm et al., 1993; Okoye et al., 2003; Segal et al., 1992; Tong and Perez-Polo, 1998). In the CNS, BDNF is primarily transported anterogradially by several neuron populations and is widely distributed in the nerve terminals, even in some areas lacking the BDNF mRNA (Fawcett et al., 1998; von Bartheld et al., 1996; Altar et al., 1997; Conner et al., 1997). In hippocampal neurons BDNF is packed in dense-core vesicles (Fawcett et al., 1997). BDNF, like classical neurotransmitters, is capable of rapidly depolarizing neurons through activation of trkB receptors (Kafitz et al., 1999). One of the rapid effects of BDNF includes a reduction in inhibitory transmission in the hippocampal CA1 field (Frerking et al., 1998).

2.1.1. Activity-dependent regulation of BDNF

Neuronal activity regulates the expression levels and release of BDNF. There are several observations of an upregulation of the BDNF mRNA in response to epileptiform activity induced by lesions, kindling or pharmacological agents such as kainate (Ballarin et al., 1991; Dugich-Djordjevic et al., 1992; Ernfors et al., 1991; Isackson et al., 1991; Zafra et al., 1990). The response to these seizures is specifically pronounced in the hippocampus and occurs rapidly. Interestingly, if BDNF signalling is repressed as in mice overexpressing a truncated form of trkB (trkB.T1), the kainate induced increase in BDNF transcript is less pronounced (Saarelainen et al., 2001). Furthermore, neuronal depolarization by either glutamate receptor agonist MK-801 or high potassium levels (Zafra et al., 1991; Zafra et al., 1990), osmotic stimulus (Castren et al., 1995), or brain insults such as ischemia (Kokaia et al., 1996; Lindvall et al., 1992), all strongly elevate BDNF mRNA expression in brain. The neurotransmitter GABA (γ-aminobutyric acid) also regulates expression of BDNF. Stimulation of the GABAergic system by GABA agonists reduces hippocampal BDNF mRNA whereas inhibiting the GABAergic system has the opposite effect (Lindholm et al., 1994; Zafra et al., 1991; Zafra et al., 1990). In addition to these rather dramatic stimulations, physiological stimuli also evoke BDNF transcription. Light or visual deprivation rapidly regulates levels of BDNF mRNA and

protein (Capsoni et al., 1999; Castren et al., 1992). Even such delicate stimuli as whisker stimulation can induce BDNF mRNA expression in rodents (Rocamora et al., 1996). Furthermore, voluntary exercise increases hippocampal BDNF mRNA (Gomez-Pinilla et al., 2001; Neeper et al., 1996; Russo-Neustadt et al., 1999; Vaynman et al., 2003), whereas a diet rich in fat and sugar has the opposite effect (Molteni et al., 2002; Molteni et al., 2004). Induction of hippocampal long-term potentiation (LTP) has been reported to upregulate BDNF mRNA both *in vivo* and *in vitro* conditions (Bramham et al., 1996; Castren et al., 1993; Patterson et al., 1992). Equally, induction of the hippocampal BDNF expression is observed after hippocampus-dependent forms of learning (Gomez-Pinilla et al., 2001; Hall et al., 2000; Kesslak et al., 1998) whereas amygdala-dependent fear conditioning increases amygdaloid BDNF mRNA (Rattiner et al., 2004). Conversely, stress that is induced by repeated footshock delivery downregulates the levels of the BDNF transcripts (Rasmusson et al., 2002). Finally, the neurotrophin levels are regulated by NTs themselves (Lindholm et al., 1994; Patz and Wahle, 2004). Subcellularly, the nuclear transcript may be selectively transported to active dendrites and translated locally. Depolarization of hippocampal neurons leads to more dendritic distribution of BDNF and trkB transcripts and is suggested to induce local protein synthesis in dendrites (Righi et al., 2000; Tongiorgi et al., 1997).

Both mature and pro-NTs can be secreted and they have distinct biological actions upon release (Lee et al., 2001; Lu, 2003b). The secretion from the cell can be either constitutive or regulated dependent on the cellular context and the efficiency of furin cleavage (Lu, 2003a; Farhadi et al., 2000; Mowla et al., 1999). Genetic mutations that alter the balance between secretory pathways can cause physiological consequences. For example, the amino acid substitution of Val66 to Met in the human pro- BDNF reduces the regulated secretion and results in deficits in episodic memory (Egan et al., 2003).

One activity-dependent feature of BDNF is its spatially and temporally controlled release. The regulated BDNF secretion from hippocampal neurons is induced by a variety of stimuli such as high levels of potassium, glutamate or neurotrophins themselves (Blochl and Thoenen, 1995; Canossa et al., 1997). Both depolarization and neurotrophin-induced BDNF release depend on increase in the intracellular Ca2+ concentration (Canossa et al., 1997; Goodman et al., 1996). Moreover, electrical stimulation robustly induces BDNF secretion (reviewed by Poo, 2001). The pattern of electrical stimulation is regulates the BDNF release response in the central neurons (Gartner and Staiger, 2002; Goodman et al., 1996). These studies have additionally demonstrated that BDNF can be released from both postsynaptic and presynaptic compartments (Balkowiec and Katz, 2002; Hartmann et al., 2001; Kohara et al., 2001). BDNF is more potent in modulating active synapses (Boulanger and Poo, 1999) and as expected,

secretion occurs in active synapses (Hartmann et al., 2001; Kojima et al., 2001). As the effects of BDNF are restricted within a 60 µm distance from the release site (Zhang and Poo, 2002), the local synaptic release provides an additional way to enhance BDNF signalling specificity. Altogether, these results indicate that BDNF expression and release are highly regulated by neuronal activity.

2.2. NT-4

Neurotrophin-4 was first isolated from Xenopus and viper (Hallbook et al., 1991), and shortly after the mammalian form was presented in two separate reports (NT-4, Ip et al., 1992; NT-5, Berkemeier et al., 1991). The abbreviation NT-4/5 is therefore also used in the literary. These first reports also identified trkB as the main signaling receptor. NT-4 promotes the survival of several types of neurons (Schober et al., 1998; Hynes et al., 1994; Meyer et al., 2001; Alexi and Hefti, 1996; Lingor et al., 2000; Spalding et al., 2002). NT-4 is required for the survival of adult sensory neurons (Stucky et al., 2002). NT-4 application in hippocampal slice culture induces an up-regulation of the GAP-43 and alterations in dentritic branching (Schwyzer et al., 2002).

Although NT-4 and BDNF mediate their signals using the same trkB receptor and share many similarities in their actions, differences have been reported. Both factors protect cerebellar granule cells against apoptosis (Kubo et al., 1995) and support the survival of hippocampal neurons (Lindholm et al., 1996). However NT-4 knockout (KO) mice appear normal and fertile without neurological defects unlike mice lacking BDNF (Conover et al., 1995; Ernfors et al., 1994a; Jones et al., 1994). When compared to trkB KOs, the NT-4 KO mice have normal motoneuron populations and mainly unaltered sensory neurons (Conover et al., 1995; Klein et al., 1993). As BDNF heterozygotes, the NT-4 KO mice show deficits in both long-term memory and late-phase LTP (Xie et al., 2000). Targeted mutation of the Shc-binding site of trkB-receptor revealed the vital importance of this pathway for neurons depending on NT-4 mediated survival, whereas BDNF dependent neurons are unaffected by this mutation (Minichiello et al.,1998). Both NT-4 and BDNF signal via the same trkB receptor, however the two ligands are able to elicit distinct downstream responses.

2.3. TrkB

Reports by Squinto and Soppett characterising a novel receptor (trkB) for BDNF and NT3 were published at the same time (Squinto et al., 1991; Soppet et al., 1991). The gene coding the trkB receptor produces several transcripts ranging in size from 0.7 to 9.0 kb. These transcripts produce at least two types of receptors: the full-length and truncated trkB (Middlemas et al., 1991; Barbacid, 1994). The extracellular parts of these receptors are identical but truncated receptors lack the entire intracellular tyrosine kinase region. There are two such truncated receptors identified, TrkB.T1 and TrkB.T2. The full-length TrkB receptor is predominantly of neuronal origin, whereas truncated forms are often expressed by non-neuronal cells such as glia. However, trkB.T1 is widely expressed in the rodent brain. While T1 is coded by the human trkB gene, T2 form apparently is not (Stoilov et al., 2002). Instead, the human gene produces another truncated isoform, trkB.shc, with a longer intracellular tail when compared to T1 (Stoilov et al., 2002).

The trkB mRNA encodes a 145-kDa glycoprotein forming a 821 amino acids long plasma membrane receptor (Figure 2) (Klein et al., 1989). At the N-terminus, three leucine-rich repeats are flanked by two cysteine clusters. A recent data obtained from the crystallized extracellular domain of trkA receptor indicates that these five domains, that are present in all trk receptors, are essentially integrated as one structural domain (Wehrman et al., 2007). Adjacent to these, there are two C2-type immunoglobulin-like domains that are followed by a single transmembrane domain and the cytoplasmic tyrosine kinase region (Schneider and Schweiger, 1991). The major ligand-binding structure has been localized to the second IgG domain (O'Connell et al., 2000; Urfer et al., 1998; Urfer et al., 1995), other extracellular structures contribute to ligand binding as well (Ninkina et al., 1997; Windisch et al., 1995). In the absence of available ligands the IgG domains regulate the spontaneous dimerization (Arevalo et al., 2001).

The intracellular domain is the most conserved region between trk family members (Klein et al., 1989; Middlemas et al., 1991). The intracellular region of the trkB contains ten conserved tyrosine residues that phosphorylates in response to ligand binding and serve as docking sites for downstream adaptor molecules. Tyrosines 670, 674 and 675 (according to human trkA nomenclature) and (in trkB) form the autophosphorylation loop that upon activation potentiates the phosphorylation of other tyrosines. The activity of Y670/674/675 loop is necessary for BDNF inducible phosphorylation as well as for mediation of cell proliferation (McCarty and Feinstein, 1998). Additionally, these tyrosines may also directly bind downstream adaptor molecules (Huang and Reichardt, 2003). Tyrosine 490 in trkA (Y515 in human trkB) provides

a docking site for Shc and Frs-2, and tyrosine 785 (Y816 in human trkB) binds phospholipase Cγ (Huang and Reichardt, 2003; Patapoutian and Reichardt, 2001).

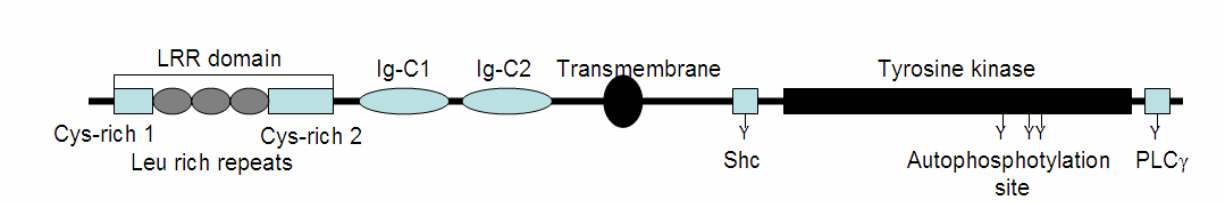

Figure 2: Structure of trkB protein.

2.3.1. TrkB-activation

Two of the neurotrophic factors, BDNF and NT-4, selectively bind to the trkB receptor. They both have distinct binding domains but BDNF demonstrates a higher affinity to trkB than NT-4 (Klein et al., 1992). NT-3 can also bind to trkB and activate the receptor, albeit with a lower affinity than with the primary ligands (Ip et al., 1993). However, NT-3 induced autophosphorylation of trkB produces a different temporal pattern *in vitro* from BDNF (Soppet et al., 1991) suggesting different allosteric modulation of trkB by the two factors. In some neuronal polulations BDNF co-localizes with the full-length trkB indicating that BDNF exerts autocrine trophic support for these neurons (Kokaia et al., 1993).

The primary activating step for the full-length trkB receptor is the ligand binding to the extracellular domain. This results in homodimerization and phosphorylation of tyrosines in the kinase activation loop (Ibanez et al., 1993; Jing et al., 1992). The subsequently activated tyrosine residues provide the docking sites for cytoplasmic downstream effectors. The adaptor proteins Shc and phospholipaseC-γ were the first recognized trkB substrates that bind to trkB tyrosine residues at positions 515 and 816, respectively (Figure 1B) (Middlemas et al., 1991; Stephens et al., 1994; Vetter et al., 1991). However, the formation of heterodimers with .T1 or homodimers of .T1 abolish this ligand-induced signalling (Figure 1B) (Haapasalo et al., 2001). NT signaling via trkB generally mediates actions such as survival and plasticity whereas the p75NTR-mediated actions often stimulate pro-apoptotic pathways (Huang and Reichardt, 2003; Kaplan and Miller, 2000; Patapoutian and Reichardt, 2001). Finally, p75NTR can modify ligand specificity to trk receptors (Benedetti et al., 1993; Bibel et al., 1999; Hempstead et al., 1991), binding kinetics (Mahadeo et al., 1994), and receptor activation (Vesa et al., 2000) by forming heterodimer receptors with trk-receptors. Pro-BDNF can bind with high affinity to p75NTR and can activate pro-apoptotic actions (Lee et al., 2001; Teng et al., 2005).

In the absence of ligands, trk receptors can also be activated in response to G-protein coupled receptor (GPCR) activation. This transactivation of trk receptors has been reported to occur via the GPCR-ligands adenosine, neuropeptide PACAP and endocannabinoids (Chao, 2003; Lee and Chao, 2001; Lee FS et al., 2002a; Lee FS et al., 2002b; Berghuis et al., 2005). Two main differences separate NT-induced trk activation from GPCR transactivation. Firstly, trk phosphorylation via transactivation occurs at a much slower rate than NT-induced activation (Lee and Chao, 2001). Secondly, GPCR-mediated trk activation selectively promotes signaling via the PI3K/AKT pathway, thus promoting survival (Lee and Chao, 2001; Lee et al., 2002b). Recently, the trk transactivation was reported to take place at the intracellular membranes instead of the cell surface (Rajagopal et al., 2004). Altogether, transactivation through GPCRs provides an alternative route for trk signaling in the absence of a neurotrophin ligand.

2.3.2. Shc-signaling pathway

After the initial trkB phosphorylation at residue Y515, at least two possible adaptor molecules compete for direct binding to this phosphorylated tyrosine residue, adaptor protein with SH2 domain (Shc) and fibroblast receptor substrate-2 (Frs-2) (Huang and Reichardt, 2001; Huang and Reichardt, 2003; Meakin et al., 1999; Stephens et al., 1994).

Signaling through the Shc pathway mediates a transient activation of the ERK pathway (Grewal et al., 1999). In mature neurons binding of the ShcC isoform is preferred over the two other isoforms (Conti et al., 2001). Upon ligand binding, the Y515-site provides a recruitment site for the Shc PTB (phosphotyrosine binding) domain. Binding of Shc is followed by the phosphorylation and recruitment of a protein complex containing the adaptor Grb2 and the Ras exchange factor SOS. In the following step, SOS activates Ras and the activated Ras stimulates several downstream pathways including PI3K, c-Raf/ERK and p38MAPK/MAPK-activating protein kinase 2 (Segal, 2003). The Ras activation has proven to be a critical event for NT-induced differentiation in neuronal PC12 cells (Segal et al., 1996).

Prolonged extracellular signal regulated kinase (ERK) activation is dependent on a separate signaling pathway initiated with the recruitment of Frs-2. Activated Frs-2 provides several binding sites to downstream elements including adaptors Grb-2 and Crk, the protein phosphatase Shp2, and Src-kinase (Huang and Reichardt, 2001; Huang and Reichardt, 2003; Meakin et al., 1999). Crk binds and activates the exchange factor C3G that in turn activates a small G protein Rap-1 that stimulates B-raf, which initiates the ERK cascade (Meakin et al., 1999; Segal, 2003). Therefore, the Frs-2 provides an alternative, Shc-independent

mechanism to activate the Grb2/SOS/Ras pathway. Overexpression of the members of the Frs-2 pathway in PC12 cells promotes differentiation (Hempstead et al., 1994; Meakin et al., 1999). The standard Ras/MAPK-pathway model consists of a G-protein (such as Ras) initiated cascade where the three kinases activate one another in a cascade-like manner eventually leading to activation of a MAP (mitogen activated protein) kinase such as ERK1/2 (Segal and Greenberg, 1996). Of the various MAP kinases activated through Ras/Raf/MEK pathways, four are known to respond to NT/trk signaling: ERK 1, 2, 4 and 5 (Segal, 2003). The major role for neuronal ERKs is the regulation of gene expression. ERK 1, 2 and 5 can for example activate the members of the RSK protein kinases that further activate transcription factor CREB.

ERKs may also act directly on the CREB-binding protein (CBP), however for this to hapen; ERKs have to be translocated to the nucleus. In the nucleus, ERKs regulate transcription factors such as Elk-1 or Egr-1 (Grewal et al., 1999). In addition to the nuclear actions, MAP kinase activity can also regulate axonal elongation (Atwal et al., 2000). Together, the multiple Ras- MAPK signaling pathways of trkB provide a wide variability of signals, both divergent and convergent, in response to ligand stimulation.

2.3.3. PLCγ-signaling pathway

Activation of the trkB residue Y816 through ligand engagement, recruits the cytoplasmic enzyme protein phospholipaseC (PLC) that is directly bound to trkB through its internal SH2-domain and is in turn itself activated by phosphorylation by the trk kinase (Figure 1) (Patapoutian and Reichardt, 2001; Segal and Greenberg, 1996). Only the PLCγ-1 isoform has been shown to be bound and activated downstream of trkB (Middlemas et al., 1994; Obermeier et al., 1994; Obermeier et al., 1993; Vetter et al., 1991). Activated PLCγ-1 then binds to phosphatidylinositides (PIP2) and enzymatic activity hydrolyzes it to diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 induces an increase in the intracellular Ca2+ levels by releasing Ca2+ from intracellular stores. As a consequence, enzymatic pathways controlled by intracellular Ca2+ concentrations, such as synaptic Ca2+-calmodulin (CaM) kinases, are activated (Ouyang et al., 1997). On the other hand, DAG stimulates protein kinase C isoforms, such as PKCδ (Bibel and Barde, 2000; Huang and Reichardt, 2003). Finally, an increase in the intracellular Ca2+ level enhances neurotransmitter release (Lessmann, 1998). Targeted mutant mice where the PLCγ binding site has been disrupted by changing the tyrosine residue to phenylalanine (Y816F), demonstrate the importance of proper PLCγ signaling in hippocampal plasticity (Minichiello et al., 2002). Similar to trkB and BDNF null mice, the PLCγ targeted mutants show impaired hippocampal LTP. In agreement,

in vitro studies have shown that PLC inhibitors block BDNF dependent synaptic potentiation (Kleiman et al., 2000; Yang et al., 2001). The PLCγ pathway is thus critical for the neurotrophin-mediated effects on synaptic plasticity.

2.3.4. PI3 kinase signaling-pathway

Phosphatidylinositol-3-kinases (PI3Ks) are critical in mediating NT-induced survival and in regulating vesicular trafficking (Brunet et al., 2001; Datta et al., 1999). The heterodimeric PI3 kinase enzyme that is activated by neurotrophins consists of regulatory (p85) and catalytic (p110) subunits of which both have several splicing variants (Bartlett et al., 1999; Bartlett et al., 1997; Fruman et al., 1998). The catalytic and regulatory subunits are constitutively associated. Activated trks can stimulate PI3 kinase through at least two distinct pathways and the choice between pathways depends on the cell type (Vaillant et al., 1999). Firstly, PI3 kinase is stimulated when catalytic subunit p110 directly binds to active Ras (Kaplan and Miller, 2000; Rodriguez- Viciana et al., 1994). This Ras-dependent pathway is utilized by many survival-promoting signals in neurons (Huang and Reichardt, 2001; Vaillant et al., 1999). Alternatively, PI3K may be activated through a Shc/Grb-2/Gab-1 pathway in a Ras-independent manner (Holgado-Madruga et al., 1997; Kaplan and Miller, 2000). Lipid products generated by the activated PI3K, the phosphatidylinositides, bind and directly activate their target proteins that include serine/threonine protein kinase (Akt, also known as protein kinase B, PKB) (Huang and Reichardt, 2001; Kaplan and Miller, 2000; Segal, 2003).

Again, an alternative pathway to Akt activation exists. Phosphatidylinositides can also activate PDK-1 kinase, which in turn activates Akt (Alessi et al., 1997). Akt substrates include several important survival regulating proteins: BAD, Forkhead family (FKH) transcription factors, IκB and glycogen synthase kinase 3β (GSK-3β). The Bcl-2 family member BAD, promotes apoptosis via Bcl-XL/Baxdependent mechanisms when dephosphorylated. However, Akt-dependent phosphorylation inactivates BAD and subsequently suppresses BAD-induced cell death (Bonni et al., 1999; Datta et al., 1999). Neurons from the BAD knockout mice show no alterations in apoptosis therefore suggesting a non-essential role for BAD in cell survival (Shindler et al., 1998). Another target, cytoplasmic IκB functions as a trapper for the transcription factor NF-κB (Datta et al., 1999). Upon Akt-induced phosphorylation, IκB is degraded and the NF-κB is translocated to nucleus where it promotes survival. Furthermore, Akt kinase phosphorylates members of the Forkhead family of transcription factors (FKHR; (Biggs et al., 1999; Brunet et al., 1999) and promotes cell survival through regulation of cell death genes. In the presence of Akt, the phosphorylated Forkhead remains in the cytoplasm whereas in the absence of Akt activation Forkhead is translocated to the nucleus where it

promotes the transcription of cell death genes including the Fas ligand (Biggs et al., 1999; Brunet et al., 1999). Finally, Akt kinase phosphorylates and inactivates the proapoptotic GSK-3β thus enhancing cell survival (Pap and Cooper, 1998). In summary, the PI3K/Akt pathway is the major regulator of cell survival in neurons (Aloyz et al., 1998; Datta et al., 1999; Mazzoni et al., 1999). The Akt protein is at the center of several distinct regulatory pathways, probably mediating survival at a number of levels depending on the cellular surroundings. In addition to survival, the PI3K-Akt pathway may also regulate vesicular transport and mRNA translation (see references in reviews by Huang and Reichardt, 2001; Segal, 2003).

2.3.5. Regulation of trkB signalling

The expression of trkB is regulated by diverse neuronal activation. Fiber transections (Beck et al., 1993), forebrain ischemia (Arai et al., 1996), and seizure inducing activity (Aloyz et al., 1999; Binder et al., 1999; Dugich-Djordjevic et al., 1995; Merlio et al., 1993) all increase trkB transcription and receptor activation. Potassium-induced neuronal depolarization increases the transcription (Kingsbury et al., 2003) and dendritic localization (Tongiorgi et al., 1997) of the full-length trkB. Long-term locomotor activity (Gomez-Pinilla et al., 2002; Skup et al., 2002) and circadian rhythm (Dolci et al., 2003) are also shown to modulate trkB in brain. Processes activated in learning and memory formation also induce trkB transcription and receptor activation (Broad et al., 2002; Gomez-Pinilla et al., 2001; Mizuno et al., 2003).

Control of the number of trkB receptors present on the cell surface can modulate the responsiveness to BDNF. Neuronal activity, induced by either depolarization or tetanic stimulation, and elevation in the second messengers such as cAMP, both increase the number of trkB receptors on the cell surface (Du et al., 2000; Meyer-Franke et al., 1998). The increase in the surface trkB presence is observed along dendrites, axons and cell soma. BDNF rapidly increases the number of trkB receptors on cell surface (Ji et al., 2005; Haapasalo et al., 2003) Prolonged BDNF treatment has been shown to result in receptor desensitization (Carter et al., 1995; Frank et al., 1996; Haapasalo et al., 2002). Further, electrical stimulation, such as LTP-inducing theta burst stimulation, enhances the trkB internalization in a Ca2+ dependent manner, therefore depleting trkB from the cell surface (Du et al., 2003). Accordingly, tyrosine kinase activation was suggested to directly regulate receptor internalization (Du et al., 2003). The activity-dependent regulation of trkB receptors on the cell surface provides one mechanism as to how BDNF signalling could be restricted to active neurons.

The regulation of trk signaling is carefully controlled on several levels. Firstly, the bound ligand specifies the elicited downstream responses. Site-directed mutagenesis in trkB mice demonstrated the importance of the stimulating ligand (Minichiello et al., 1998). In mice in which the Shc docking site was disabled the (Y490F mutation) the NT-4 dependent survival was dramatically reduced, whereas the BDNF dependent cell populations were only modestly affected (Minichiello et al., 1998). These results suggest that trkB ligands use separate downstream pathways when mediating survival. The distinct activities of trkB ligands were further confirmed by another mouse model where the NT-4 gene was inserted at the BDNF gene locus (Fan et al., 2000). This study showed differences in the survival promoting potential of trkB ligands and further corroborated that the trkB-Shc signaling pathway is more crucial for NT-4 actions (Fan et al., 2000).

Secondly, the timing of the ligand binding regulates downstream responses. A rapid 2-minute pulse of NGF activates efficiently the PLC-γ signaling (Choi et al., 2001). Additionally, a brief pulse of BDNF triggers a postsynaptic action potential (Kafitz et al., 1999) and exerts the BDNF-derived effects on LTP in slices (Schuman, 1999).

Finally, the location of the ligand-receptor interaction determines the activated downstream pathways. Local signaling at the axon terminals regulates the axonal outgrowth. Axonal neurotrophin stimulation leads to phosphorylation of axonal trks and activation of the Ras/MAPK pathway (Atwal et al., 2000; Riccio et al., 1997; Senger and Campenot, 1997; Watson et al., 2001). Conflicting evidence has suggested that the trk signaling pathways via Shc or PLCγ is responsible for the growth cone guidance (Atwal et al., 2000 vs. Ming et al., 1999). Additionally, local neurotrophin signaling within axons contributes to axonal elongation and promotes endocytosis (Beattie et al., 2000; Kuruvilla et al., 2000). In contrast, the long-term trk signaling in the cell body is essential for the survival and differentiation effects. If neurotrophins are applied to distal axons, trk activation rapidly occurs along the axons and within the cell body in complex with the stimulating neurotrophin (Bhattacharyya et al., 1997; Riccio et al., 1997; Tsui-Pierchala and Ginty, 1999; Watson et al., 1999). These complexes are found within vesicles designated as signaling endosomes together with the downstream signaling factors PI3 kinase, PLCγ and Shc (Beattie et al., 1996; Grimes et al., 1997; Grimes et al., 1996; Howe et al., 2001). The signaling endosome is formed when the ligand induced receptor activation leads to the internalization of the ligand –receptor complex through clathrin-mediated endocytosis. The transport of the signaling endosome is most probably carried out by the motor protein dynein along the microtubules (Heerssen and Segal, 2002). The receptors within the endosome remain catalytically active and continue signaling as they travel towards the cell body however it is unclear how trk activity is maintained in the vesicles.

Presumably, the basal trk activity is enough to maintain the active state and the vesicular localization of the complex would protect the phosphorylated trk against the actions of phosphatases (Miller and Kaplan, 2001).

In the dorsal root ganglion cell cultures, a neurotrophin stimulus applied to the cell body, activates two separate MAP kinase pathways within the cell body: Erk1/2 and Erk5 (Watson et al., 2001). However, if the stimulation is applied on distal axons, only the Erk5 activation occurs in the cell body. Similarly, within the retinal system BDNF has opposing effects on the dendritic growth depending on the location of stimulation (Lom et al., 2002). These results suggest that the location of the neurotrophin stimulus is an important regulatory step for the responses elicited.

3. Neurotrophins and neuronal plasticity

Neuronal plasticity refers to the capability of neurons to respond to signals from their surrounding and elicit activity-dependent changes in their morphology, connections and function. Neuronal plasticity occurs in different levels, from minor changes in activity to a generation of totally new neuronal cells. Neurogenesis refers to a proliferation of totally new cells that later differentiate into neurons. Sprouting includes elongation, migration and branching of neurites towards the target area of each neuron. Formation of new synaptic connections between neurons is designated as synaptogenesis. Finally the subtlest form of neuronal plasticity is strengthening or fading of existing synaptic connections. Even though primary actions of NTs are related to neuronal survival emerging evidence indicate the key roles of NTs in mediating the plasticity of neuronal networks in the adult CNS (Thoenen, 1995; McAllister et al., 1999; Poo, 2001; Castrén, 2005).

3.1. BDNF in LTP and synaptogenesis

Synaptic plasticity refers to an experiment-dependent change in synaptic strength, a fundamental property of the CNS. Application of a high-frequency stimulation (HFS) of the presynaptic excitatory pathway rapidly induces a long-lasting enhancement of synaptic strength that is measured as increased amplitude of excitatory postsynaptic potentials (EPSPs). In the postsynaptic neuron; this phenomenon is referred as long-term potentiation (LTP) (Malenka and Bear, 2004). LTP is restricted to the activated synapse and can be sustained for weeks or even up to several months. LTP occurs in many brain regions, however the classic experimental design in hippocampal slices monitors the Schaffer collateral → CA1 (CA3-CA1) synapse responses to stimulation. During measurement, test stimuli are first delivered repeatedly at a low frequency to induce stable EPSPs for baseline determination, and eventually LTP is induced by high-frequency stimulation. If LTP is evoked, the subsequent test stimuli will produce enhanced EPSPs. LTP is divided into two different modes; early-phase-LTP (E-LTP) requires covalent modification of existing proteins, whereas formation of late-phase-LTP (L-LTP) requires new gene transcription and protein synthesis (Voronin et al., 1995). Stress and depression are known to affect synaptic plasticity in several ways (Popoli et al., 2002) identifying LTP as a putative target for antidepressant drugs.

LTP and long-term depression (LTD) are typically presented as cellular mechanisms for memory storage. Recently this view has been expanded to cover other long-term adaptive responses, such as mood, addiction and pain control (Malenka and Bear, 2004). The

mechanisms behind the maintenance of LTP are complex and partly unknown. The entry of calcium through glutamate NMDA receptors is considered a key event for the triggering of LTP. However, not all forms of LTP are NMDA-dependent, even within the hippocampus. LTP present in the hippocampal mossy fibers is the most marked form of NMDA-independent LTP (Zalutsky and Nicoll, 1990; Bortolotto et la., 1999). It has been shown that application of a permeable analog of cAMP, which mimics the late phase of LTP at CA3-CA1 hippocampal synapses, induces the recruitment of pre-existing presynaptically silent synapses (Ma et al., 1999). LTP is also associated with the induction of several immediate early genes (eg, arc, tPA, zif268) (Link et al., 1995).

The contribution of the BDNF-trkB signalling system to LTP is crucial (Ernfors and Bramham, 2003). Induction of hippocampal LTP rapidly increases BDNF mRNA expression (Castrén et al., 1993; Dragunow et al., 1993; Patterson et al., 1992). Furthermore, induction of LTP at the CA3-CA1 synapse has been impaired in independent lines of transgenic mice with BDNF defiency (Korte et al., 1995; Patterson et al., 1996; Pozzo- Miller et al., 1999) of which only one line, of which, shows defects in the basal synaptic transmission (Patterson et al., 1996; Pozzo-Miller et al., 1999). LTP can be rescued by re-expression of BDNF through by virus-mediated gene transfer or exogenous application (Korte et al., 1996; Patterson et al., 1996) thus suggesting that this impairment is not due to developmental deficits. Likewise, cortical LTP impairment is observed in heterozygous BDNF null mice in a third independently generated mutant (Bartoletti et al., 2002). Additional evidence to support the role of BDNF was provided by studies where LTP was attenuated by the application of function-blocking BDNF antibodies or BDNF scavenging trkB-IgG proteins to *in vitro* slices (Chen G et al., 1999; Figurov et al., 1996; Kang et al., 1997).

Besides the immediate actions in hippocampal potentiation, BDNF is essential during the long-term LTP (L-LTP) that requires *de novo* protein synthesis (Bradshaw et al., 2003; Kang et al., 1997; Korte et al., 1998). Interestingly, microinfusion of BDNF directly into dentate gyrus induces a long-lasting enhancement of transmission at the perforant path → granule cell (PP-GR) synapse (Messaoudi et al., 1998; Messaoudi et al., 2002; Ying et al., 2002). LTP-inducing tetanic stimulation enhances regulated BDNF release and leads to increased CREB activation through a trkB-ERK pathway (Gooney and Lynch, 2001; Patterson et al., 2001). Interestingly, during L-LTP, trkB signalling seems to regulate the redistribution of activated MAPK towards the nuclear compartment (Patterson et al., 2001). Genetically modified mice have also clarified the role of trkB signalling in synaptic potentiation. Conditional trkB mutant mice, in which the full-length receptor is eliminated specifically from the forebrain (trkB-CRE), exhibit markedly reduced CA3-CA1 potentiation in response to stimulation (Minichiello et al., 1999).

This deficit is comparable to that observed in BDNF null mice (Korte et al., 1995; Patterson et al., 1996). In accordance with the BDNF null mice, control experiments indicated that basal synaptic transmission was normal for the trkB conditional mutants (Korte et al., 1995; Minichiello et al., 1999). Another conditional mouse model lacking all trkB isoforms in the forebrain region (*trkB* CA1-KO) confirms the results (Xu et al., 2000a). In these mice, the absence of trkB in hippocampal CA1 region led to a reduction in CA3-CA1 synapse potentiation and provides evidence for presynaptic BDNF action in the modulation of LTP. Mice with targeted mutations in the trkB binding sites for Shc and PLCγ have demonstrated some functional differences among pathways downstream to trkB (Korte et al., 2000; Minichiello et al., 2002). These studies reported that successful induction of theta burst stimulation-induced E-LTP and L-LTP in the CA3-CA1 synapse requires PLCγ-mediated signalling (Minichiello et al., 2002). More precisely, the concurrent blockade of both pre- and postsynaptic PLCγ-mediated signalling is required to reduce LTP (Gärtner et al., 2006). Interestingly, trkB-Shc mutants display intact E-LTP and L-LTP (Korte et al., 2000) therefore suggesting that signalling via Shc pathways is not required for hippocampal LTP. These results are surprising since previous data connected the Ras/MAPK pathway to synaptic potentiation (English and Sweatt, 1996; English and Sweatt, 1997; Patterson et al., 2001; Ying et al., 2002). However it is possible that the cross-talk between signalling pathways downstream of trkB might rescue the Shc-deficit in terms of LTP induction. It seems that BDNF by itself is sufficient for LTP (Pang and Lu, 2004) even though there have been some contradictory results (Messaoudi et al., 2002). However, reports that the over-expression of trkB abolishes LTP (Koponen et al., 2004) suggest that a lot is yet to be resolved.

One possible group of proposed modulators of synaptic plasticity are the pro-neurotrophins (Lu, 2003b). When pro-neurotrophins are secreted at the synapse, they could regulate synaptic transmission and plasticity through several mechanisms (Lu et al., 2005). For example, uncleaved pro-neurotrophins, when secreted (Mowla et al., 2001; Teng et al., 2005), could act on p75NTR and elicit effects distinct to those mediated by trk receptors. Secondly, activity dependent control of proteolytic cleavage represents one mechanism for local and synapse specific regulation by BDNF (Chao and Bothwell, 2002; Pang and Lu, 2004). To balance BDNF actions, pro-BDNF is able to promote NMDA receptor-dependent hippocampal LTD (Woo et al., 2005). Hippocampal LTD is impaired in p75NTR deficient mouse strains, while LTP was found to be unaffected (Rösch et al., 2005). Stress affects both LTP and LTD, and these effects originate from the corticosterone-induced sustained activation of ERK1/2-coupled signalling cascades (Yang et al., 2004). It is likely that complexity of factors modulating both presynaptic and postsynaptic actions will contribute to the generation and maintenance of LTP; however, the evidence pointing to a significant role of BDNF and trkB

signaling in LTP is undeniable.

It is widely accepted that neuronal activity plays a pivotal role in synaptic formation. The number and strength of synapses can be changed by neuronal activity (Bliss and Collinridge, 1993; Linden, 1994; Malenka and Nicoll, 1999; McEwen, 1999). Remodelling of synaptic structures also contributes to the formation of new synapses. Excitatory synapses on dendritic spines exhibit a high degree of structural plasticity (Luscher et al., 2000). Such spines are characterized by dynamic movements triggered by actin-based mechanisms (Fischer et al., 1998; Star et al., 2002) that may change their shape (Korkotian and Segal, 1999, 2001; Segal et al., 2000), exhibit remodeling of their postsynaptic density (PSD) (Geinisman, 1993; Buchs and Muller, 1996; Marrs et al., 2001; Toni et al., 2001), or may be formed *de novo* (Engert and Bonhoeffer, 1999; Goldin et al., 2001; Jourdain et al., 2002) under the influence of neuronal activity and calcium. Studies have shown that the induction of LTP triggers the formation of dendritic filopodia (Maletic-Savatic et al., 1999), these are considered as precursors of spines (Dailey and Smith, 1996; Ziv and Smith, 1996; Fiala et al., 1998). LTP may also lead to direct formation of new spines or new types of synapses (Engert and Bonhoeffer, 1999; Toni et al., 1999). Remodeling of postsynaptic structures has thus been proposed to play a major role in activity-dependent synaptogenesis. Other studies also provide evidence for presynaptic morphological changes. The stimulation of developing neuronal cultures results in actin-dependent formation and growth of axonal filopodia (Hatada et al., 2000; Chang and De Camilli, 2001; Colicos et al., 2001; Tashiro et al., 2003) and the formation of functional presynaptic boutons (Ma et al., 1999; De Paola et al., 2003).

Depending on the external signal (e.g. neuronal activity, neurotransmitters, and hormones) a neuron can either sprout axons/dendrites or retract them (atrophy). Inappropriate stimuli such as excessive stimuli or a total lack of activity can ultimately lead to pathological sprouting or to programmed cell death (apoptosis), respectively. Synaptic connections are continuously eliminated, generated or modulated (LTD, LTP) depending on their external cues. Regulation of the relative amounts of pro- and matureBDNF in synapses may be one mechanism behind these events (Lu et al., 2005). Increased and reduced BDNF levels correlate with increased or reduced number of synapses, respectively (Causing et al., 1997; Huang ZJ et al., 1999).

Besides the traditional role as a survival factor during development, extensive evidence points to a perhaps even more important role for BDNF in the regulation of synaptic transmission (Lu, 2003a; Poo, 2001; Thoenen, 1995; Vicario-Abejon et al., 2002). BDNF potentiates excitatory synaptic transmission by promoting presynaptic transmitter release. Acute BDNF application to developing *Xenopus* neuromuscular synapses rapidly potentiates basal synaptic

transmission by increasing neurotransmitter release (Lohof et al., 1993). In the central excitatory synapses, a similar enhancement is observed upon BDNF application into hippocampal and cortical cultures (Lessmann, 1998; Levine et al., 1995), slice preparations (Kang et al., 1996; Kang and Schuman, 1995; Kang et al., 1997) and intrahippocampal infusions (Messaoudi et al., 1998; Ying et al., 2002). Furthermore, addition of BDNF causes hyperexcitability in slices (Scharfman, 1997) that is similar to that observed in BDNF transgenic mice (Croll et al., 1999). As expected, the BDNF-induced potentiation of synaptic transmission is enhanced by simultaneous presynaptic neuronal activity (Boulanger and Poo, 1999). The site of BDNF action is, however, still a matter of controversy. Some studies have demonstrated that BDNF acts postsynaptically (Henneberger et al., 2002; Kovalchuk et al., 2002; Levine et al., 1995; Suen et al., 1997) whereas strong data also supports action via presynaptic transmitter release as well (Frerking et al., 1998; Gottschalk et al., 1998; Lohof et al., 1993; Olofsdotter et al., 2000; Vicario-Abejon et al., 1998). In line with the presynaptic actions of BDNF, a reduced number of docked vesicles are observed at excitatory synapses on CA1 dendritic spines of BDNF knockout mice (Pozzo-Miller et al., 1999). A reduced level of the vesicular proteins synaptobrevin and synaptophysin is observed in these BDNF mutants. Furthermore, presynaptic, but not postsynaptic, expression of dominant negative trkB.T1 receptor inhibits synaptic potentiation in cultured neurons (Li et al., 1998). TrkB.T1 overexpressing mice have impaired long-term spatial learning but normal LTP (Saarelainen et al., 2000b). BDNF-mediated activation of trkB stabilizes synapses while activation of p75 actively removes this (Zagrebelsky et al., 2005).

Since BDNF is known to contribute to synaptic transmission, it is also likely to modulate the morphology of synapses and spines. Indeed, BDNF promotes the formation and stabilization of both excitatory and inhibitory synapses (Alsina et al., 2001; Huang ZJ et al., 1999; Martinez et al., 1998; Seil and Drake-Baumann, 2000; Vicario-Abejon et al., 1998; Vicario-Abejon et al., 2002). Treatment of hippocampal slices with BDNF enhances spine formation in apical dendrites, even in the absence of action potentials (Tyler and Pozzo-Miller, 2003; Tyler and Pozzo-Miller, 2001). Additionally, activity-dependent synapse control in the adult cortex appears to require BDNF, since the whisker stimulation does not induce increased spine density in heterozygous BDNF mutant mice as observed in controls (Genoud et al., 2004). BDNF has been shown to regulate synapse maturation and to promote dentritic spine growth in hippocampal CA1 neurons (Tyler and Pozzo-Miller, 2003). Specifically, the number of synaptic vesicles at the active zones is reduced in mice lacking BDNF or trkB (Martinez et al., 1998; Tyler and Pozzo-Miller, 2001).

BDNF is also a modulator of the GABAergic transmission although the mechanisms through which this is mediated are not clear. Evidence suggests that BDNF application reduces GABAergic inhibitory transmission and mIPSCs in hippocampal CA1 region (Brunig et al., 2001; Frerking et al., 1998; Tanaka et al., 1997) and depresses the excitatory synaptic transmission to GABAergic cortical neurons (Jiang et al., 2004) in a trkB-dependent manner. In contrast, in hippocampal slice preparations from mice lacking BDNF, synaptic inhibition was enhanced while granule cell excitability was reduced (Henneberger et al., 2002; Olofsdotter et al., 2000). In support of this, BDNF regulates the development and maturation of GABAergic inhibitory interneurons (Huang EJ et al., 1999; Marty et al., 1996; Marty et al., 1997), and modulates the expression of GABAA receptors by recruiting trkB (Brunig et al., 2001; Elmariah et al., 2004; Jovanovic et al., 2004; Thompson et al., 1998). Chloride transport, which is maintained by a K+-Cl- transporter (KCC2), plays a critical role in the development and maintenance of inhibitory GABAergic transmission (Ben-Ari, 2002; Kaila, 1994; Rivera et al., 1999). The expression and activity of KCC2 is regulated among others by BDNF signaling via trkB (Rivera et al., 2002; Rivera et al., 2004; Wardle and Poo, 2003). Taken together, BDNF modulates inhibitory synaptic transmission through regulation of postsynaptic expression levels of GABAA receptors and chloride transporter KCC2.

3.2. BDNF and Neuronal sprouting

Since the neurotrophin NGF, was originally identified as a stimulator of neurite outgrowth in peripheral neurons it may be conceivable to propose a similar role for BDNF in central neurons. BDNF regulates the dendritic growth of cortical neurons (Horch and Katz, 2002; Horch et al., 1999; McAllister et al., 1996; McAllister et al., 1995) and dentate granule cells (Danzer et al., 2002). Exogenous BDNF application or transfection, results in increased dendritic length and complexity in a layer-specific manner. Furthermore, the effect could be blocked by either inhibiting neuronal activity or by applying tyrosine kinase inhibitor K252a (Danzer et al., 2002; McAllister et al., 1996). Accordingly, scavenging the endogenous BDNF causes dramatic dendritic retraction in one study (McAllister et al., 1997). This study also demonstrate a spatial distinction in the BDNF response of cortical neurons: basal dendrites were more affected by a BDNF shortage. Besides BDNF, trkB receptor isoforms differentially regulate dendritic morphology. BDNF produces a significant increase in axonal branching and in the complexity and length of dendrites in CNS neurons (Cohen-Cory and Fraser, 1995; McAllister et al., 1995; Gallo and Letourneau, 1998). As transfection of full-length trkB promoted the proximal dendritic branching and inhibited elongation, the transfected trkB.T1 had counteracting actions instead and the ratio of T1 to full-length trkB was suggested to serve as a switch between the distinct modes of dendritic growth (Yacoubian and Lo, 2000). If

so, it may provide an important mechanism in the regulation of dendritic structure, i.e. during development when trkB isoform ratios are changing.

Analogous to the above *in vitro* data, transgenic mice overexpressing BDNF display increased dendritic complexity in the dentate gyrus (Tolwani et al., 2002) whereas both BDNF and trkB knockout mice exhibit reduced dendritic structure (Gorski et al., 2003; Xu et al., 2000b). In the latter case, BDNF or trkB is ablated from cortex and hippocampus, and as a result, substantial loss of dendrites and cell soma shrinkage is observed. Further information on the spatial restrictions of BDNF responses is provided by studies on *Xenopus* retinal ganglion cells. Increase in the tectal target-derived BDNF supports the formation of dendrites in retinal ganglion cells whereas locally increased BDNF levels within the retina lead to decreased dendritic branching (Lom et al., 2002; Lom and Cohen-Cory, 1999). Finally, neuronal activity is a key signal for dendrite formation in general (Lohmann et al., 2002; Miller and Kaplan, 2003). Two main signaling pathways, the calcium/calmodulin kinases (CaMKs) and the MEK/MAPK pathway have been suggested to regulate the activity-dependent dendrite formation, often in cohort (Miller and Kaplan, 2003; Redmond et al., 2002; Vaillant et al., 2002; Wu et al., 2001). Neurotrophins activate both CaMKII and CaMKIV via a mechanism suggested to engage trk-mediated activation of PLCγ, generation of IP3 and subsequent release of Ca2+ (He et al., 2000; Kaplan and Miller, 2000; Minichiello et al., 2002). Therefore, neural activity and neurotrophins might act in parallel to promote dendrite formation.

In addition to dendrites, exogenous BDNF can potently enhance the axonal arborization of retinal ganglion cells (Cohen-Cory, 1999; Cohen-Cory and Fraser, 1995; Inoue and Sanes, 1997) and dentate granule cells (Danzer et al., 2002). These effects are abolished by antibodies to BDNF or by activity blockade. In cultured *Xenopus* spinal neurons, BDNF may act in a chemoattractive manner and trigger growth cone turning via a mechanism requiring cAMP/ protein kinase A signaling (Markus et al., 2002; Song et al., 1997). Knockout mice lacking trkB have a reduced number of axonal collaterals and varicosities in the hippocampus (Martinez et al., 1998). Likewise, axonal fragmentation is present in the amygdala of trkB/trkC double heterozygous mutants (von Bohlen und Halbach et al., 2003). Plasticity marker, GAP-43, has been suggested as a mediator of BDNF-derived modifications of axonal plasticity (Elmer et al., 1996; Klocker et al., 2001; Kobayashi et al., 1996). In conclusion, BDNF signaling via trkB regulates the formation and maintenance of dendrites and axons, and therefore promotes the establishment of functional neuronal circuitry.

3.3. BDNF and Neurogenesis

The general understanding has been that new neurons are not created by the adult brain. Evidence of newly born neurons was first seen in the 1960's by Altman (1965) and later by Kaplan (1981) and others. For some time these findings were believed an artifact with no functional relevance. Neurogenesis re-emerged during the 1990's when research methods developed such that dividing cells could be identified as neurons. At present neurogenesis in adult brain is under extensive study and has been well accepted as a phenomenon. Neurogenesis is found in numerous mammalian species, including rodents (Cameron and McKay, 2001), primates (Gould et al., 1997; Gould et al., 1999; Kornack and Rakic, 1999) and human (Eriksson et al., 1998). New neurons are born in two brain areas; the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus (DG) of hippocampal formation. Neurogenesis has also been reported in several other brain regions, including the neocortex (Gould et al., 1999), striatum (Dayer et al., 2005) and hypothalamus (Kokoeva et al., 2005). However it is unclear whether new neurons in these areas are born in situ or migrated from elsewhere. Neurogenesis is regulated by age (Kuhn et al., 1996; Seki and Arai, 1995), stress (Gould et al., 1997), exercise (van Praag et al., 1999), learning (Gould et al., 1999) and seizures (Parent et al., 1997). Furthermore, the production rate of new neurons in aged rats is reportedly restored by the reduction of corticosterone (Cameron and McKay, 1999) and enriched environment (Kempermann et al., 1998).

The majority of neurons born in the adult SVZ migrate along the rostral migratory stream (RMS) to the olfactory bulb. In the olfactory bulb neurons differentiate into the granule and periglomerular inhibitory neurons (Doetsch and Hen, 2005). Neurons born in the SGZ migrate into granular cell layer and mature into granule cells. Hippocampal cells in the SGZ are classified as neuronal progenitors not as stem cells which are differentiated by their self renewal rates (Bull and Bartlett, 2005). Only little is known about the factors that affect differentiation of these newly-born cells. If progenitor cells are grown in the presence of mitogens alone, only glial cells are generated (Bull and Bartlett, 2005; Seaberg and van der Kooy, 2002). Growth with even a low concentration of BDNF induces neurogenesis indicating the high sensitivity of the hippocampal progenitors to this neurotrophin (Bull and Bartlett, 2005). In addition, GABAergic excitation was recently shown to promote neuronal differentiation in adult hippocampal progenitor cells (Tozuka et al., 2005). After differentiation the new neurons extend their neurites and integrate into the existing neuronal network (Figure 3) (van Praag et al., 2002; Markakis and Gage, 1999). A recent study showed that SVZ-derived progenitor cells from the trkB.T1 over-expressing mice possess increased replicative capacity *in vitro* (Tervonen et al., 2006).

This robust form of neuronal plasticity has developed into a theme of great interest among neuroscientists. For example, the infusion of BDNF into the lateral ventricle of the adult rat brain leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus (Pencea et al., 2001). Similarly, BDNF infusion to the adult hippocampus (hilus) increases the formation of new granule cells (Scharfman et al., 2005). Recent evidence also suggests that BDNF promotes the survival of these newly generated neurons (Barnabe-Heider and Miller, 2003). Baseline neurogenesis is lower in one BDNF +/- mice indicating that BDNF is needed for maintaining basal hippocampal neurogenesis (Lee J et al., 2002). Age-related decline in neurogenesis is associated with reductions in BDNF and pCREB immunoreactivity (Kuhn et al., 1996; Hattingady et al., 2005).

New-born neurons located near the SGZ produce LTP more readily than mature neurons (Wang et al., 2000). One reason for this difference is the lack of GABAergic inhibition in the young neurons. It has been established that the granule neuron excitation is strongly modulated by GABAergic synapses both *in vitro* (Wigstrom and Gustafsson, 1983) and *in vivo* (Buckmaster and Schwartzkroin, 1995). Induction of LTP in DG in hippocampal slices is often difficult (Hanse and Gustafsson, 1992; Nguyen and Kandel, 1996) presumably due to the strong GABAergic inhibition. Results obtained *in vivo* show a more consistent LTP in DG perforant pathway synapses (Bramham et al., 1997; Nosten-Bertran et al., 1996). It is also generally accepted that the LTP induction in the medial perforant pathway (MPP) is NMDA-receptor dependent *in vivo* (Morris et al., 1986) and *in vitro* (Trommer et al., 1995). Two pharmacologically and physiologically distinct types of LTP in MPP have been found in hippocampal slices, consistent with the presence of young and mature populations of neurons (Snyder et al., 2001). One possible explanation might be that during maturation, new neurons downregulate NKCC1 and upregulate KCC2 expression producing a significant change in GABAergic inhibition (Ge et al., 2006).

Although the activity-dependent organizations of major neuronal networks are set up during early brain development these networks are most likely plastic in nature throughout life and consequently are modulated by variety of factors. BDNF and its receptor trkB, together with their counter actors pro-BDNF and p75NTR, are important mediators of all the aforementioned changes in neuronal plasticity in both the developing and adult CNS and are thus crucial factors for the proper organization and maintenance of neuronal networks.

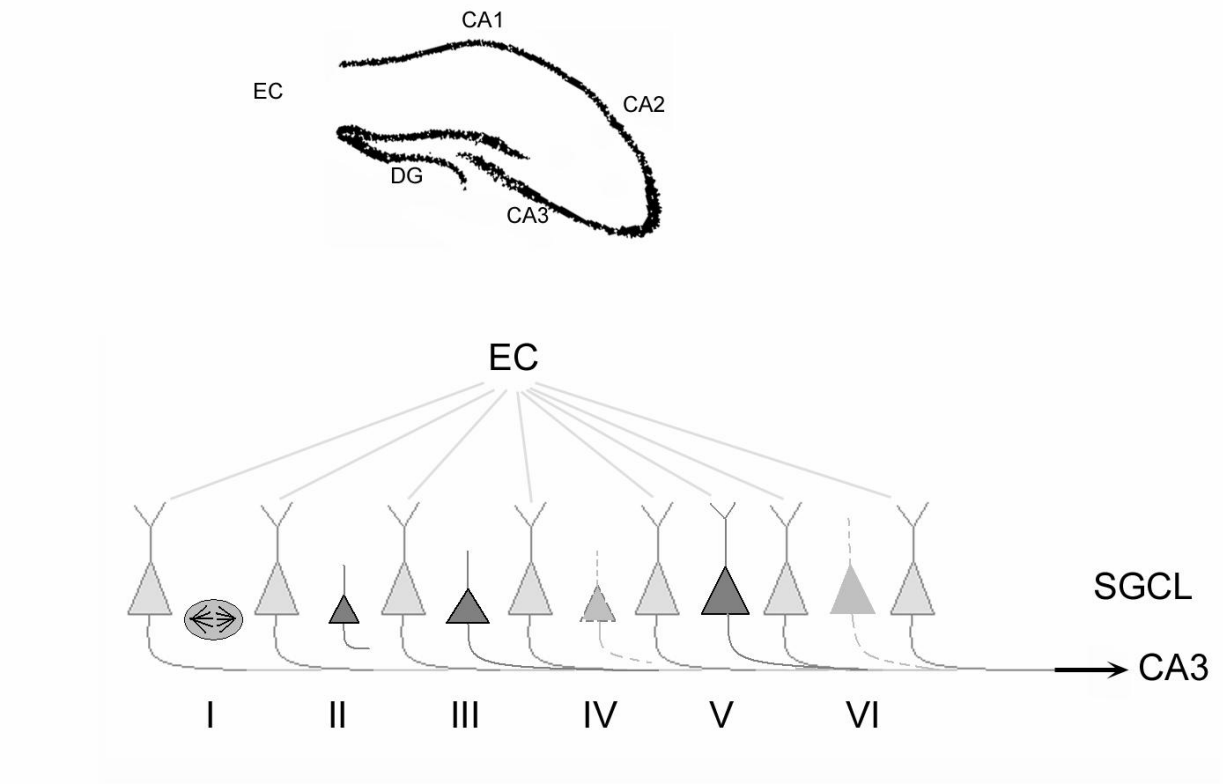

Figure 3: Neurotrophic model for the turn-over of hippocampal neurons. I: Neuronal precursors proliferate in the subgranula cell layer (SGCL) of dentate gyrus (DG). This process is inhibited by stress and stimulated by antidepressants. II: Newborn cells differentiate into neurons and extend their axons towards their target region in the CA3 area. III: After synapse formation with the dendrites of CA3 pyramidal neuron, they become dependent on neurotrophic factors. IV: Neurons that fail to form an active synapse are eliminated by apoptosis. V: Neurons that are able to mediate activity from the entorhinal cortex (EC) to an active synapse in the CA3 area survive and integrate into the neuronal network within the hippocampus. VI: In addition, existing granular neurons that lose in the competition for active synaptic transmission to the newborn neurons are eliminated. BDNF from the CA3 seems to be essential for integration and survival of the granule neurons. On the other hand, lack of BDNF leads to decreased integration and increased apoptosis.

4. Neurotrophins and neuronal plasticity in the actions of antidepressants and morphine

4.1. Depression

Despite the fact that affective (mood) disorders have been characterised for a long time, little is known about the cellular mechanisms that lead to these disorders. Today mood disorders are classified into two major categories: major depression (MD) and bipolar disorder (BD). Mood disorders are one of the most common and disabling chronic diseases worldwide and often precipitate or coexist with other psychiatric or somatic diseases (e.g. anxiety or coronary heart disease, respectively) (Wong and Licinio, 2001; Dubovsky et al., 2003). The estimate of prevalence of MD varies a lot and in Finland, the estimate for 12-month prevalence of a depressive episode hes been estimated to be 6.5% in adult population (Pirkola et al., 2005). MD is about 2-3 times more common in females than males (Wong and Licinio et al., 2001). However, suicide rates are higher among male patients. The onset age of MD has decreased rapidly during the last decades from 45-50 to 25-30 years, on average. MD is characterized by recurring episodes of depressed mood and negative thinking. Although stress often precedes the first episode of depression, later episodes are more likely to occur without the influence of psychosocial stress. Even though mood disorders are frequently familial, the exact genes that are behind affective disorders are still unknown (Dubovsky et al., 2003). However, certain polymorphisms in BDNF (Val66Met) and serotonin transporter genes have been associates to an increased susceptibility for affective disorders, although there is variation between the results from different populations and study samples (Neves-Pereira et al., 2002; Schuele et al., 2006; Furlong et al., 1998; Caspi et al., 2003; Kendler et al., 2005). The latest report indicates a significant association between combined polymorphisms in 5-HT1A and BDNF genes and the risk of treatment-resistant depression (Anttila et al., 2007).

Aetiology of depression is widely unknown. Classical monoamine hypothesis is based to the observation that depressive patients have lowered levels on monoamines in the brain and majority of the current antidepressive drugs such as, monoamine oxidase (MAO) inhibitors, serotonin and noradrenaline reuptake inhibitors (SSRI, SNRI), are targeted to affect monoaminergic neurotransmitter systems. Stress is also a major contributor to the development of depression and increased levels of stress hormones and abnormalities in function of HPA-axis are frequently found in depressed individuals. In fact, glucocorticoid hypothesis has been developed on the strong and clear role of stress in affective disorders

(reviewed by Arborelius et al., 1999). In addition, dysfunctions in neuronal circuits and neuronal loss in distinct brain areas have led to the neurotrophic hypothesis of depression (Duman and Monteggia, 2006). Due to the obvious multi-origination of the disease, there is not any single, reliable and valid animal model. Several animal models have been developed to model the different aspects of depression (Table 1). Despite the limitations, these animal models of depression have been frequently used (Porsolt, 2000).

Table 1: The most frequently used animal models of depression.

Targeted	Animal model
Behavioral despair assays	Forced swim test
	Tail suspension test
	Learned helplessness test
Stress assays	Maternal separation test
	Chronic mild stress test
Sensory deprivation assays	Olfactory bulbectomy test

4.2. Neuronal atrophy in depression

Recent neuropathological and brain imaging studies suggest that neuronal connections are compromised in patients suffering from mood disorders (reviewed by Drevets, 2000; Manji et al., 2001; Castrén, 2004a; Castrén, 2005; Ebmeier et al., 2006). A consistent observation is that the size of the hippocampus is reduced in patients suffering from major depression and other stress-related psychiatric disorders (e.g. Bremner et al., 1995; Sheline et al., 1996; Sheline et al., 1999; Bremner et al., 2000; Steffens et al., 2000; Vythilingam et al., 2002; MacQueen et al., 2003; Kitayama et al., 2005). The duration of the illness, repeated episodes, treatment resistance and previous abuse are associated with more pronounced hippocampal damage (Ebmeier et al., 2006). However, abnormal changes in hippocampal volume are sometimes observed very early in the disease process (Frodl et al., 2002).

Reductions in mean grey matter volume have been observed in the prefrontal cortex of both MD and BP patients (Drevets et al., 1997; Rajkovska et al., 1999; Botteron et al., 2002; Bremner et al., 2002). These structural impairments are also associated with functional deficits in cerebral blood flow and glucose metabolism (Drevets, 2000). Such reductions in hippocampal volume do not appear to be due to the loss of cells or reduced neurogenesis (Lucassen et al., 2001; Reif et al., 2006) suggesting that mood disorders are associated with neuronal atrophy and a reduced number of synapses (Figure 4). Indeed, mood disorders are

often associated with abnormal changes in many cognitive functions (for review Ebmeier et al., 2006). In addition, post-mortem studies indicate that glial cell numbers are reduced in the cortex of mood disorder patients (Ongur et al., 1998; Rajkowska et al., 1999). Since glial cells are crucial for the maintenance of synaptic connections, the reduced number of these cells is an indirect indicator of reduced neuronal connections. Although all the factors mediating these atrophic changes are not known, it is noteworthy that uncontrollable stress often has a pronounced (and similar to that seen in mood disorders) impact on cellular survival and morphology, particularly in the hippocampus (reviewed in McEwen, 1999). For example, several forms of stress inhibit hippocampal neurogenesis (Gould et al., 1997; Tanapat et al., 1998; Vollmayr et al., 2003; Pham et al., 2003) and produce atrophy in the hippocampal pyramidal neurons (Watanabe et al., 1992; Fuchs et al., 1995; Magarinos et al., 1996; Magarinos et al., 1998). Brain imaging studies demonstrate a reduction in hippocampal volume in depressed subjects and this reduction is reversible with antidepressant treatments (Sheline et al., 1996, 2003; Vermetten et al., 2003). Importantly, an effective antidepressant treatment seems to protect against hippocampal volume loss in humans (Sheline et al., 2003) and prevents stress-induced atrophic changes in the hippocampus (Czeh et al., 2001) (Figure 4). Hippocampal neurons express high levels of receptors for glucocorticoids, the major stress reactive adrenal steroid (Sapolsky, 1996; McEwen, 1999) suggesting that glucocorticoid actions may be direct. The hippocampus has connections with the amygdala and prefrontal cortex, regions that are more directly involved in emotion and cognition and thereby contributing to the major symptoms of depression.

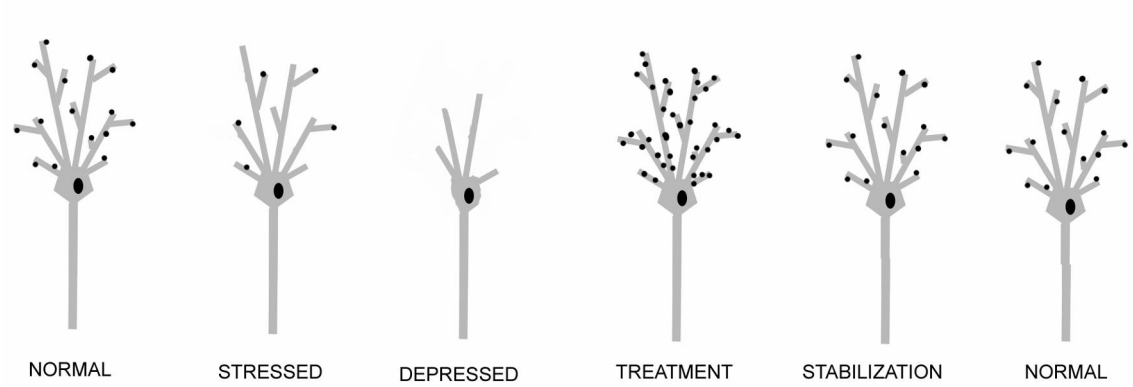

Figure 4: Neuronal connections in different phases of depression. Stress decreases functional connections in existing neurons and beginning atrophy. In clinical depression severe atrophy and loss of synaptic connections occur. Antidepressant treatment produces excess amount of new projections and synapses (smaller black dots). After stabilization of new and functional neuronal network recovery is complete. Schematic drawing of a neuron were the large black dot is nucleus, smaller black dots are synapses, the axon is facing down, and the dentrites are pointing upwards.

4.3. Neurotrophins and action mechanism of antidepressants

The primary action of antidepressants is to elevate monoamine levels in the brain by blocking their breakdown or re-uptake from the synaptic cleft (for review Duman et al., 1997; Manji et al., 2001, Nestler et al., 2002). First-generation antidepressants included monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Both increase available concentrations of extracellular monoamine neurotransmitters and in particular noradrenalin and serotonin thorough inhibition of catabolism (MAOIs) or of the reuptake transporter (TCAs). Most of the newer antidepressants, with similar clinical efficacy but an improved side-effect profile, inhibit the seroronin transporter and are therefore classified as selective serotonin reuptake inhibitors (SSRIs) (Nemeroff and Owens, 2006).
Alterations in monoamine levels induced by antidepressants occur within minutes while the full clinical effects takes several weeks to develop (Frazer and Benmansour, 2002; Nestler et al., 2002). This long delay of antidepressive effects is a major problem in the clinical treatment of mood disorders. Electro convulsive shock (ECS) therapy is the most effective treatment form of major depression but the effect needs still repeated administration (Duman and Vaidya, 1998). These data suggest that changes in synaptic connections may underlie the effect of antidepressants. Neurotrophins and especially BDNF have been shown to function as the key regulator of neurite outgrowth, synaptic plasticity and selection of functional connections in the CNS (Katz and Shatz, 1996; McAllister et al., 1999; Mamounas et al., 2000; Huang and Reichardt, 2001; Poo, 2001). These facts make neurotrophins and above all BDNF a potent mediator of plastic changes induced by antidepressants (Castren et al., 2004b; Duman and Monteggia, 2006; Duman, 1997; Altar, 1999; Manji et al., 2001, Nestler et al., 2002). Finally, it is good to bear in mind that pro-neurotrophin cleavage by tPA/plasmin has proved to be an essential step in the formation of the mature BDNF and that this process has also been hinted at in the pathophysiology of depression (Pang et al., 2004; Tsai, 2006).

ECS and chronic antidepressant treatment have been shown to elevate mRNA levels for BDNF and trkB in the hippocampus and cortex (Nibuya et al., 1995; Russo-Neustadt et al., 2000). Infusion of exogenous BDNF protein into the adult rodent brain has demonstrated behavioral effects similar to those produced by antidepressants (Siuciak et al., 1997; Shirayama et al., 2002). Administration of exogenous BDNF also increases the 5-HT innervation in brain (Mamounas et al., 2000) and levels of both 5-HT itself and its metabolites in the forebrain (Siuciak et al., 1994, 1996).

In animal studies chronic stress-related impairment of cognitive functions are associated with increased plasma corticosteroid levels and decreased BDNF mRNA in the hippocampus

(Song et al., 2006). It has been shown that stress diminishes hippocampal BDNF mRNA levels in a glucocorticoid-dependent manner (Smith et al., 1995; Ueyama et al., 1997; Rasmusson et al., 2002). This effect is reversible with antidepressant treatment (Smith et al., 1995). On the other hand, repeated stress has been associated with an increase of trkB mRNA in the hippocampus (Nibuya et al., 1999). These observations are reminiscent of the dynamic regulation seen in several brain functions whilst trying to achieve homeostatic balance.

Increased BDNF immunoreactivity has been observed in humans after antidepressant medication (Chen B et al., 2001). Post-mortem studies show that the expression of BDNF in hippocampus is decreased in depressed suicide patients and increased in patients receiving antidepressant treatment (Chen B et al., 2001; Dwivedi et al., 2003; Karege et al., 2005). Depressed non-medicated patients show lowered serum BDNF levels than antidepressant treated patients (Hashimoto et al., 2004), and serum levels of BDNF positively correlate with the response to medication (Gervasoni et al., 2005; Gonul et al., 2005).

The findings that show that antidepressants increase BDNF gene expression and trkB signalling suggest that antidepressants produce long-term structural neurotrophic changes in brain. Duman and co-workers were the first to demonstrate that long-term treatment with antidepressants produces an increase in cellular proliferation in the hippocampus (Malberg et al., 2000). In tissue sections, these newborn cells are co-labelled with neuronal, but not glial, markers (Malberg et al., 2000) further supporting that antidepressants specifically increase the proliferation of new neurons. Many subsequent studies have confirmed these observations (Manev et al., 2001; Khawaja et al., 2004). In addition, lithium and ECS, when administered several times, were also shown to increase hippocampal neurogenesis (Chen et al., 2000; Madsen et al., 2000). Lithium and antidepressants both seem to induce the division of hippocampal progenitor cells *in vitro* (Manev et al., 2001; Kim et al., 2004). The antidepressant tianeptine also blocks the stress-induced decrease of hippocampal neurogenesis (Czeh et al., 2001) and reduces hippocampal apoptosis (Lucassen et al., 2004). Chronic ECS promotes a long-lasting sprouting of mossy fiber axons in the rodent hippocampus (Gombos et al., 1999; Vaidya et al., 1999). Similarly to BDNF, antidepressants produce trophic actions on brain monoaminergic neurons (Kitayama et al., 1997). Taken together, current literature strongly implicates that stress and antidepressants have opposing effects on adult hippocampal neurogenesis (Warner-Schmidt and Duman, 2006).

The molecular mechanism and role of neurogenesis in mediating the therapeutic actions of antidepressants is not known. However, the behavioural effects of antidepressants are

abolished in rodents whose hippocampal neurogenesis has been inhibited (Santarelli et al., 2003). In addition, in 5-HT1A knock-out mice, fluoxetine failed to induce neurogenesis (Santarelli et al., 2003). 5-HT1A antagonists have shown to decrease cell proliferation in DG of hippocampus (Radley and Jacobs, 2002). Yet, 5-HT1A knock-out mice responded to imipramine and desipramine suggesting that different antidepressants may induce neurogenesis through separate molecular routes. Furthermore, a recent study implicates that behavioral effects of chronic fluoxetine do not require hippocampal neurogenesis or 5-HT1A receptor in some mouse strains (Holick et al., 2007).

Fluoxetine produces a robust increase in the synaptic spine density in the CA1 within 5 days and in the CA3 after 2 weeks of treatment (Hajszan et al 2005). In addition, chronic but not acute fluoxetine treatment results in region-specific changes in the activity of translation factors (Dagestad et al., 2006).

Evidence suggests that cAMP signalling is involved in the action of antidepressants (D'Sa and Duman, 2002). In contrast, normal CREB function is required for the antidepressant-induced elevation of BDNF mRNA, but not for the behavioural effects (Conti et al., 2002). Increasing evidence suggests that antidepressant-induced changes in pCREB and trkB signalling mediate antidepressant-induced neurogenesis and survival. Increased and decreased expression of pCREB in the hippocampus promotes and reduces, respectively, hippocampal neurogenesis (Nakagawa et al., 2002a; Nakagawa et al., 2002b). CREB is one of the key intracellular targets of trkB activation and thus one of the candidates regulating BDNF-induced behaviours. Indeed, over-expression of CREB in the hippocampus produces an antidepressant effect (Chen AC et al., 2001). The behavioural effects of BDNF in the forced swimming test are dependent on ERK signalling (upstream of CREB) since a selective ERK inhibitor blocked the effects of BDNF (Shirayama et al., 2002) indicating the key role of Ras-ERK-CREB cascade in regulating these effects. However, the behavioural response to antidepressants is not abolished in CREB deficient mice (Conti et al., 2002). In addition, agents which stimulate the intracellular cAMP cascade increase hippocampal neurogenesis (Nakagawa et al., 2002b). Importantly, prolonged antidepressant and lithium treatment reverses or protects against stress induced atrophic changes in hippocampus (Malberg et al., 2000; Czeh et al., 2001; van der Hart et al., 2002; Vermetten et al., 2003; Wood et al., 2004).

Epigenetic modifications have emerged to be one possible mechanism behind the development of depression and antidepressive effects. Maternal behavior was found to affect DNA methylation in the promoter region of the glucocorticoid receptor gene (Weaver et al., 2004). These studies suggested a causal relationship between epigenomic state,

glucocorticoid receptor expression and the maternal effect on stress responses in the offspring. One suggested mechanism behind the functional modulation of NTs suggests the involvement of post-translational modifications of pre-existing synaptic components by cytoplasmic effectors of the NT-induced signalling cascade.

Recently, the post-translational modifications of histones, a major form of chromatin remodelling, were found to be altered at several gene promoters in rat hippocampus after acute or repeated ECS. Nestler and co-workers (Tsankova et al., 2004) found that, chronic upregulation of BDNF transcription may be sustained via control of H3 acetylation, selectively at the BDNF P3 and P4 promoters. This data provided the first *in vivo* demonstration of the involvement of chromatin remodeling in ECS-induced regulation of gene expression in the brain. Another recent report announced that Mecp2, as well as MBD1, were significantly induced in normal adult rat brain after repeated injections of fluoxetine or cocaine for 10 days (Cassel et al., 2006). The effect was characterized in three serotonin projection areas, the caudate-putamen, the frontal cortex, and the dentate gyrus. This data highlighted GABAergic neurons as major target cells expressing Mecp2 in response to the serotonin-elevating agents, and suggest that serotonin signaling enhances gene silencing in postmitotic neurons. Stress has been shown to induce lasting downregulation of BDNF transcripts III and IV and robustly increased repressive histone methylation at their corresponding promoters (Tsankova et al., 2006). Chronic imipramine reversed this downregulation and increased histone acetylation at these promoters. These studies underscore an important role for histone remodeling in the pathophysiology and treatment of depression and highlight the therapeutic potential for histone methylation and deacetylation inhibitors in depression.

Administration of other psychotropic drugs, such as opiates, antipsychotics, and psychostimulants, does not increase BDNF expression in the hippocampus, demonstrating the pharmacological specificity of antidepressants. Furthermore, other treatments known to have antidepressant efficacy, such as NMDA receptor antagonists and transcranial magnetic stimulation (TMS), also increase the expression of BDNF in the hippocampus (Marvanova et al., 2001; Muller et al., 2000).

4.4. Opioid-mediated analgesia and neuronal plasticity

Opioid analgesics, such as morphine, are effective for treating many pain conditions. Opioids modulate pain directly in the spinal cord and through regulation of the descending pain inhibitory pathways ending in the spinal cord. Significant opioid actions occur in other supraspinal locations, including higher sensory areas and limbic structures. A high concentration of endogenous opioids and the presence of opiate receptors suggest that these areas may be responsible for the emotional component of pain. In a PET study, when the scores on the affective component of pain were evaluated, increased μ-opioid activity was found in the bilateral anterior cingulate cortex, thalamus and nucleus accumbens (Zubieta et al., 2001).

Opioid analgesic tolerance is a pharmacological phenomenon that affects the clinical use of opioid analgesics. Activation of NMDA receptors and PKC as well as glutamate transporters has been implicated in the mechanism of opioid tolerance, suggesting a possible link between neuronal plasticity and opioid tolerance (Trujillo, 2002; Mao and Mayer, 2001). Recent studies have shown that neuronal plasticity associated with the development of opioid tolerance may activate a pronociceptive mechanism within the CNS that could counteract the analgesic effects of opioids. It has been proposed that opioid tolerance is a model of neuronal plasticity similar to learning and memory. Like cognitive functions, μ-opioid receptor desensitisation by morphine is dependent on protein kinase C (PKC) (Bailey et al., 2006).

PKC is not only responsible for the induction of morphine tolerance, but is also important in the long-term maintenance of it (Smith et al., 1999 and 2002). Indeed, PKC inhibitors are able to reverse tolerance even when they are first administered after 3 days of morphine infusion and reinstate morphine-induced behaviours in morphine tolerant mice (Smith et al., 1999 and 2006). In addition, there are lines of evidence indicating that NMDA receptors are involved in the neural plasticity underlying the development of opiate tolerance. Molecular adaptations to chronic morphine alter cre-mediated transcription during opiate withdrawal in physiologically salient regions involved in arousal, reward, mood and affective responses. In the locus coruleus (LC), the phosphorylation of CREB is homeostatically regulated by activity at the μ-opioid receptor, which inhibits the cAMP pathway via the inhibitory G-protein G_i.

Chronic administration of opioids such as morphine, produce long-lasting plastic changes in synaptic function and signal transduction in dopaminergic and noradrenergic neurons, involving cAMP signaling and tyrosine hydroxylase activity (Williams et al., 2001). Interestingly, chronic morphine administration has been shown to produce morphological

changes in the mesolimbic dopamine neurons, hinting towards the involvement of an increase in plastic changes in neuronal network by opioids. It remains to be resolved whether these changes in the structure and function of synaptic connections are able to explain the behavioral changes produced by repeated administration of opioids.

LTP was originally demonstrated in the hippocampus but also occurs in the nucleus accumbens and ventral tegmental area (VTA), where it has been hypothesized to contribute to addictive processes (Bonci and Malenka, 1999; Nestler, 2001; Wolf, 2002, 2003). Since elevation of intracellular Ca^{2+} via glutamate receptors in the VTA has been implicated in increasing sensitivity to the reward and locomotor activating properties of morphine (Carlezon et al., 1997), it is conceivable that upregulation of PLCγ and IP3 could contribute to morphine induced neuronal plasticity by increasing levels of Ca^{2+} in VTA neurons.

Two systems closely associated with depression, serotonergic and glucocorticoid signaling are also affected in opioid functions. The spinal serotonergic system strongly affects the development of morphine tolerance (Li et al., 2001, 1999). More specifically, 5-HT1A modulation has been shown to play a major role in opioid analgesia and tolerance (Bardin and Colpaert, 2004). Spinal glucocorticoid signalling also has an important role in the development of morphine tolerance (Lim et al., 2005a; Mao, 2005); glucocorticoid receptors regulate the expression of spinal NMDA receptors and PKCγ through the CREB-dependent pathway (Lim et al., 2005b).

4.5. Neurotrophins and opioid-mediated analgesia

There is strong evidence that in a variety of circumstances two neurotrophins, NGF and BDNF, act as important mediators and modulators of pain (Pezet and McMahon, 2006). NGF is upregulated in many chronically painful conditions, particularly in inflamed tissues, and acts as a peripheral pain mediator while BDNF appears to act as a modulator, altering the effectiveness of the central nociceptive signals. Two other neurotrophins, NT-3 and NT-4, appear to have a more modest role in pain processing.

In the spinal cord, a form of synaptic plasticity termed central sensitization underlies many forms of hyperalgesia, and neurotrophins play an important role in this process (Lewin and Mendell, 1993; Heppenstall and Lewin, 2000). Neurotrophins affect central transmission postsynaptically by enhancing NMDA receptor responsiveness.

Nestler and co-workers have in several studies revealed a role for the neurotrophic factors in the action mechanism of addictive drugs, such as opioids (Nestler and Aghajanian, 1997; Nestler, 2001; 2002). Chronic morphine treatment induced a modest increase in the BDNF and NT-3 mRNA levels in neurons in LC but not VTA (Numan et al., 1998). However, in the same study withdrawal from chronic opioid treatment rapidly increased BDNF and trkB mRNA levels in the LC. TrkB mRNA was also increased in the VTA by morphine withdrawal. The injection of BDNF into the VTA prevents many of the adaptational and morphological changes observed in DA neurons following chronic morphine administration (Sklair-Tavron et al., 1996; Berhow et al., 1995). Chronic morphine administration to conditional BDNF knockout mice revealed an essential role for BDNF in neuronal adaptations after opiate treatment in the LC (Akbarian et al., 2002). Furthermore, these mice failed to upregulate TH levels in the LC region in response to chronic morphine administration. Chronic administration of morphine also differentially regulates the activity of downstream pathways of trkB receptor: the PLCγ and ERK pathways are potentiated, while PI-3-K pathway is attenuated (Berhow et al., 1996; Ortiz et al., 1995; Wolf et al., 1999).

4.6. NT-4 in modulation of nociception

While the other trkB-ligand, BDNF, has proven to modulate multiple functions in chronic pain states (Obata and Noquchi, 2006), there are few studies linking NT-4 to pain-signaling systems. NT-4 has shown to facilitate, in an NGF-like manner, capsaicin evoked inward currents in dorsal root ganglion neurons *in vitro* (Shu and Mendell, 1999). NT-4 appears to have some sensitizing activity in the response to noxious heat (Shu et al., 1999). All published studies that have investigated the role of spinal NT-4 in the development of pain have proven negative (e.g. Yajima et al., 2002; Heppenstall and Lewin, 2001). A Chinese study found that NT-4 promotes spinal cord plasticity induced by acupuncture treatment (Long et al., 2005).

Instead of participating in nociception, NT-4 has been linked more closely to the modulation of plasticity leading to morphine tolerance (Smith 2003). In addition, it was recently shown that the chronic concomitant treatment of anti-NT-4 with morphine inhibits the development of morphine tolerance (Hatami et al., 2006). In the same study dextromethorphan produced an additive effect on the inhibitory effect with anti-NT-4 in the reversal of morphine tolerance. These findings provide additional support for the hypothesis that the NMDA receptor and NT-4 may be involved in neural plasticity underlying opiate tolerance. Taken together these observations indicate that NT-4 is required for the synaptic plasticity that mediates opioid tolerance.

EXPERIMENTAL SECTION

AIMS

The purpose of this work was to investigate, using transgenic mice, the participation of neurotrophic signaling, via the trkB receptor, in drug-induced changes in neuronal plasticity. Depression and chronic pain are two pathological states associated with dysfunctions in neuronal plasticity. Our initial aim was to study:

1. the role of trkB-mediated signalling in the action mechanism of antidepressants and

2. the role of trkB-mediated signaling in the action mechanism of morphine.

3. After the findings in the initial studies, we decided to concentrate on the mechanism of action of antidepressants and BDNF with an aim to identify the distinct brain areas exhibiting neuronal plasticity induced by the antidepressant treatment.

4. The final goal was to clarify the role of the BDNF-trkB signaling pathway in antidepressant-induced hippocampal neurogenesis.

5. MATERIALS AND METHODS

5.1. Animals

In publications **I-II, IV** transgenic mice with compromised neuronal trkB-signaling were used as a model. Production of the trkB.T1 transgenic mice is described in (Saarelainen et al., 2000a). In summary, viable heterozygote mice overexpress trkB.T1, the dominant negative splice variant of trkB under the neuronal Thy1 promoter. In publication **I** adult male mice were used in all experiments. In publications **I and IV** heterozygote BDNF null mice ($BDNF^{+/-}$) and their corresponding wild-type littermates were used. In publication **I** $NT\text{-}3^{+/-}$ transgenic mice were used. Production of the $BDNF^{+/-}$ and $NT\text{-}3^{+/-}$ mice has been described previously (Ernfors et al., 1994a; Ernfors et al., 1994b), the genetic background of both strains and their wild type littermates was 129Sv x BALB/c. In publication **II** $NT\text{-}4^{-/-}$ mice (Liu et al., 1995) and $TrkB^{shc/shc}$ mice (Minichiello et al., 1998) were also used. In publication **III** adult male Wistar rats were used in all experiments. For the fluoxetine study in publication **IV**, wild type NMRI mice were also used.

All animals were housed in groups in a temperature- and humidity-controlled environment and maintained on a 12h light/dark cycle with free access to food and water. In all of the publications (**I-IV**) the animal experiments performed in our lab were conducted according to the guidelines of The Society for Neuroscience and were approved, by the Experimental Animal Ethics Committee of the National Laboratory center, University of Kuopio, Finland. For all animal experiments performed there were no corresponding *in vitro* methods available, and the number of animals used was kept as low as possible.

Transgenic animals were identified using polymerase chain reaction (PCR) method. Small pieces of tissue cut from the end of the tail were digested in lysis buffer (200mM NaCl, 20mM EDTA, 40mM Tris-HCl, pH 8.0, 0.5% SDS, 0.5% β-mercaptoethanol, 0.8 mg/ml proteinase K) overnight at 60ºC. Debris was pelleted by centrifugation and genomic DNA was precipitated from the lysate using isopropanol and washed with ice-cold 70% ethanol. The precipitate was briefly air-dried and then dissolved into TE-buffer (pH 8.0). Transgenic animals were identified by PCR using Flag-trkBT1-primers, while the plasmid construct thy1-flag served as positive control.

5.2. Treatments

In **I**, physiological saline (0.9% NaCl), imipramine HCl (30 mg/kg, Sigma, St. Louis, MO, USA) or fluoxetine (20 mg/kg, Orion Pharma, Turku, Finland) were injected intraperitoneally (i.p.) to assess antidepressant responses in transgenic and wild type mice. In **II**, morphine (3.0 mg/kg, s.c.) and naloxone (1.0 mg/kg, i.p.) were used to evaluate trkB involvement in opioid-mediated analgesia. In **III**, imipramine HCl (Sigma) was administered i.p. either acutely (30 mg/kg) or chronically (15 mg/kg, 21 days). The acute imipramine group received saline injections for 20 days followed by a single imipramine injection on day 21. Therefore, the same control group could be used for the acutely and chronically-treated animals. Control animals received 0.9% NaCl solution (i.p.) daily for 21 days. In **IV**, imipramine hydrochloride (20 mg/kg for $BDNF^{+/-}$ and 30 mg/kg for trkB.T1, Sigma) and fluoxetine (10 mg/kg, Sigma) was administrated i.p., once daily for 20 or 21 d. For the proliferation assay bromo-deoxyuridine (BrdU, 50 mg/kg) was administered i.p. 4 times at intervals of two hours (total of 200 mg/kg) during the day following the last antidepressant injection. During chronic administrations the i.p. injection site was alternated between the left and right sides. There was no irritation at the injection sites observed in any of the studies.

5.3. Tissue processing

In **I** and **II** animals were rapidly dissected at the times indicated after saline or drug injections. For western blot analysis, tissue samples were lysed in buffer containing 137 mM NaCl, 20 mM Tris (pH 8.0), 1% NP-40, 10% glycerol, 50 mM sodium fluoride, 2x Complete Mini (Roche Diagnostics) and 2 mM sodium vanadate. After homogenization, homogenate was incubated at +4ºC for 20 min and centrifuged at 13,000 rpm for 15 min. For immunohistochemistry in **I, III** and **IV,** animals were deeply anesthetized with pentobarbital (Mebunat, Orion Pharma, Espoo, Finland) and transcardially perfused with cold PBS followed by 4% paraformaldehyde (PFA/PBS). Brains were removed and postfixed in 4% PFA/PBS, cryoprotected in 20% sucrose/4% PFA/PBS over night at +4ºC and stored at -70ºC. Floating coronal sections were sliced with a microtome (Leica SM2000R), and stored at +4ºC in tissue collection solution (TCS).

5.4. Western blotting

In publications **I** and **II** western blotting was used to detect antidepressant and morphine modulated activation of trkB receptor via phosphorylation. Western blot was performed according to previously described methods (Aloyz et al., 1999) with slight modifications. TrkB

was precipitated using either 50 µl wheat germ agglutinin (WGA, Pharmacia) or 10 µl of anti-trk antibody (sc-11, St. Cruz Biotechnology) and collected using protein-A sepharose (Pharmacia). Electrophoresis was performed with 7.5% SDS-polyacrylamide gels. Samples were transferred to PVDF filters (Amersham). Anti-phosphotyrosine (4G10, UBI, dilution 1:10000), anti-phospho-trk pY490 (New England Biolabs), pY674/675 (New England Biolabs) and anti-trkB_{out} (provided by Dr. David Kaplan, dilution 1:5000) antibodies were used to detect phosphorylated and total trkB, respectively. Western blots were scanned and image intesity was quantitated with image analysis software. Data are presented as mean percentages of the ratio of phosphorylated trk (4G10, pY674/675, pY490) to the full-length trkB (anti-trkB_{out}) signal intensity found in saline treated animals.

5.5. Behavioral tests

Behavioral tests were performed mainly by Tommi Saarelainen (**I**) and Guilherme Lucas (**II**). For the analysis of behavioral effects of antidepressant drugs in publication **I**, the forced swim test (FST) was used. FST has a rather high predictive value for antidepressant activity and is applicable to mice (Porsolt et al., 1977; Cryan et al., 2002). Adult male transgenic mice and wild-type littermates were allowed to adapt to the test room for several days and were then randomly submitted to a forced swim test without a pre-swim. Saline, imipramine or fluoxetine were injected i.p., and after 30 min, the mice were placed in a clear glass cylinder of diameter of 16 cm, half-filled with clear water at 24°C (water depth of 14 cm did not allow the mice to reach the bottom of the cylinder, water was changed after each mouse) for a total of 6 min. Immobility was recorded during the last 4 min by an investigator blind to the genotype and treatment.

The hot-plate test and tail-flick assay were used to asses pain behaviour in **II.** In the hot-plate test the animal was placed on a heated metal surface and the latency to the first heat related reaction was recorded. Similarly, the tail flick test measures the latency until the animal moves its tail when heated. For the hot-plate test, mice were individually placed on the hot-plate at 55ºC and the latency until mice showed first signs of discomfort (hindpaw-lifting, -licking/biting, -shaking or jumping) were recorded. To avoid tissue damage, an artificial maximum time for exposure was imposed (cut-off time), which was 30 sec. The tail-flick test consists of lightly restraining the mice and immersing two thirds of the tail in water heated to 50ºC (cut-off time 15 sec). The latency to the first movement of the tail was recorded. The basal threshold for each test was obtained by running the assay twice a day (2 hours apart), for 3 consecutive days. The last 3 measurements were averaged and considered as the 'basal' latency for each animal. Morphine dose-response experiment was performed on the fourth day. Paw

withdrawal latencies were measured 30 min after the first dose of morphine (3.0 mg/kg, s.c.). At this time point animals were repeatedly injected every 30 min with morphine to yield a final cumulative dose of 12 mg/kg in the hot-plate test and 24 mg/kg for the tail-flick assay. Immediately after the last withdrawal latency measurement, mice were injected with naloxone (1.0 mg/kg; i.p.) and the antinociception was assessed again after 15 min. In some experiments, the heat stimulus source was a highintensity beam (H 45 W) from a projector lamp bulb aimed at the 3 cm far from the end of the tail (cut-off time 15 sec). Latency to respond to the heat stimulus with vigorous flexing of the tail was measured to the nearest 0.1s. Three separated withdrawal latency determinations (30 min apart) were averaged as the 'basal' latency for each mouse.

5.6. Immunohistochemistry

Several markers of neuronal plasticity were chosen for immunohistochemistry. These markers are expressed in different phases of neuronal plasticity (Figure 5).

CREB is a transcription factor regulating the expression of several proteins related to neuronal plasticity (Shaywitz and Greenberg, 1999). We used an activated, phosphorylated, form of CREB (pCREB) to assess plastic events in the adult brain. For example, virtually all immature neurons, identified by BrdU and PSA-NCAM immunostainings, are also positive for pCREB (Nakagawa et al., 2002b). Furthermore, antidepressants have been shown to upregulate CREB-mediated gene expression (Thome et al., 2000). In addition, CREB phosphorylation is accompanies long-term LTP in hippocampus (Impey et al., 1996). Over-expression of CREB in the dentate gyrus, but not in the CA1 or PFC, produces an antidepressant effect in the learned helplessness test (Chen AC et al., 2001). Although behavioural and endocrine responses may occur through CREB-independent mechanisms, CREB has proven to be critical to target gene regulation after chronic antidepressant administration, which may contribute to long-term adaptations of the system (Conti et al., 2002). Based on these observations, pCREB is an excellent marker to quantify activation of plastic events.

The polysialylated-nerve cell adhesion molecule (PSA-NCAM) is a developmental form of NCAM. In hippocampus NCAM is essential both for correct axonal growth and synaptogenesis and for long-term changes in synaptic strength (Cremer et al., 1998)

The growth associated protein 43, GAP-43, is a neural cell specific phosphoprotein associated with the development and regeneration of axons and the functional modulation of synaptic relationships (Jacobson et al., 1986; Skene, 1989). It is especially prominent in the neuronal

growth cone (Skene et al., 1986). Levels of GAP-43 are highly elevated during development (Gorgels et al., 1987; Perrone-Bizzozero et al., 1993) and after injury (Curtis et al., 1993; Sommervaille et al., 1992). Levels of GAP-43 are reduced in the hippocampus and cingulate cortex in an age-dependent manner and so decrease the ability to sustain synaptic turnover (Casoli et al., 1996). GAP-43 has also been shown to be altered in stressed and antidepressant treated animals (Iwata et al., 2006).

TOAD/Ulip/CRMP-4 (TUC-4) is expressed early in neuronal differentiation and its expression is largely suppressed in the adult brain (Minturn et al., 1995). TUC-4 has a major role in axonal outgrowth and pathfinding (Qiunn et al., 1999 and 2003).

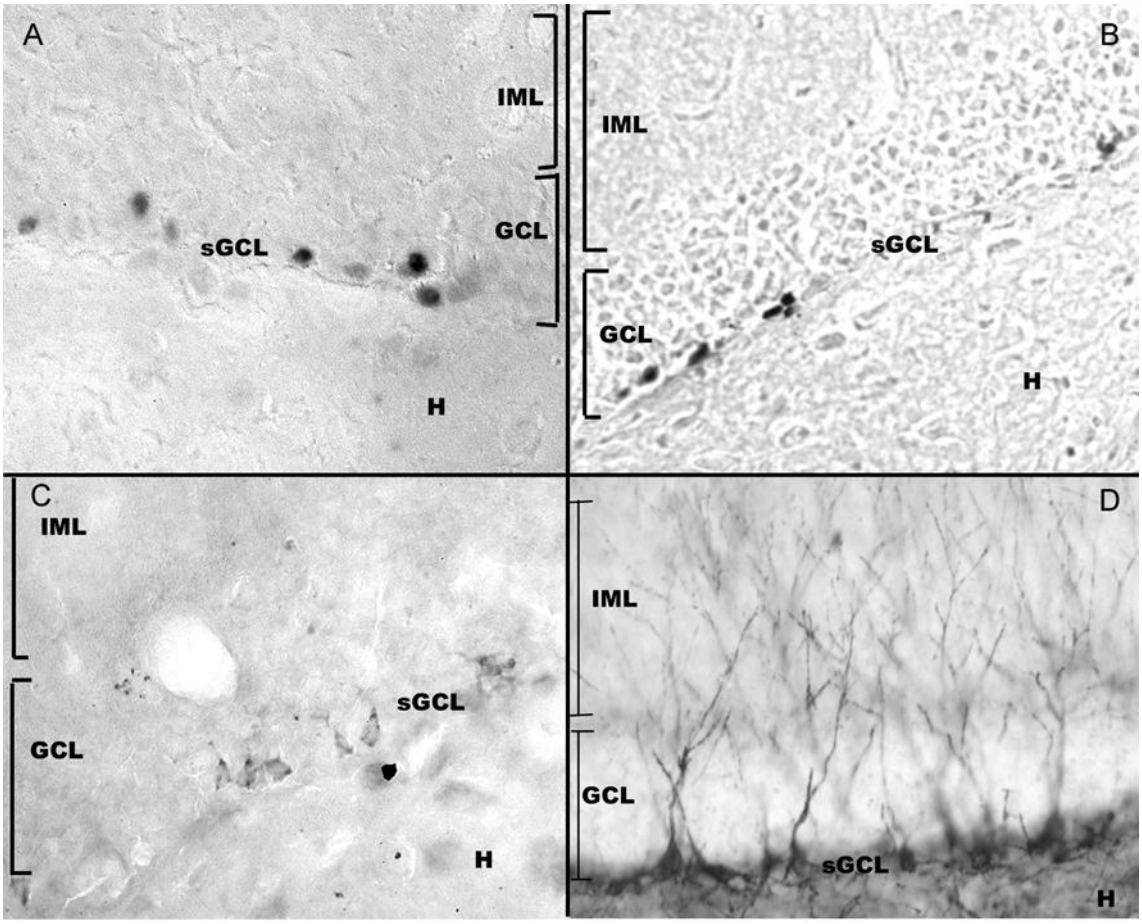

Figure 5: Hippocampal plasticity in temporal perspective. Activity dependent phosphorylation of CREB (anti-pCREB stained) in subgranular cell layer (sGCL) of dentate gyrus (**A**) occurs just minutes after original stimulus (for exemple antidepressant treatment). Approximately a week later activated cells are increasingly proliferated in sGCL (**B**) (BrdU tagged). Faith of the newly-born cells is to die or they can differentiate into glial cells or neurons (**C**) (anti-TUC-4 stained) New neurons elongate their axons and dendrites (anti-PSA-NCAM stained) (**D**) to integrate into existing neuronal network. This whole process takes up to several weeks and could explain the delayed effect of antidepressants in clinical use.

In publication **I** we used pCREB (New England Biolabs, Ipswich, MA, USA), a marker known to be activated by trkB and antidepressants, to confirm earlier observations. We counted stained cells in the anterior cingulate and prefrontal cortex using an unbiased stereological method (StereoInvestigator, MicroBrightField Inc., Williston, VT, USA).

In publication **III** for preliminary semi quantitative screening of antidepressant-induced changes in protein expression, pCREB was used as a plasticity marker based on the available literature (Nibuya et al., 1996). Areas with a clear increase in the expression of pCREB after imipramine treatment were searched for throughout the brain. Once affected brain regions had been identified, subsequent quantitative analyses were performed using 10-12 sections per

animal. The following primary antibodies were used: rabbit anti-pCREB, 1:1000, Cell signaling; mouse anti-PSA-NCAM, 1:3000, courtesy of Prof. Seki (Department of Anatomy, Juntendo University School of Medicine, Tokyo, Japan); mouse anti-GAP-43 antibody, 1:2000, Sigma, St. Louis, MO, USA.

In publication **IV** for BrdU detection, animals were injected with BrdU prior to sacrifice. Proliferation was detected using the anti-BrdU antibody (Sigma, 1:400). Newborn neurons were identified with the anti-TUC-4 antibody (Chemicon, 1: 4000). Cells undergoing apoptosis were detected with DeadEnd^{TM} colorimetric TUNEL system (Promega).
Quantitation of BrdU, TUNEL and TUC-4 positive cells was performed with Olympus BX50 microscope and Stereo Investigator software. Three coronal sections were randomly selected from throughout the hippocampus for each mouse and immunopositive cells in the granule cell layer of the dentate gyrus were counted.

5.7. Data and statistical analyses

All the data in **I-IV** are presented as means ± SEM. In publication **I** Student's t-test and one-way analysis of variance (ANOVA) together with Bonferroni as a *post-hoc* test were used for statistical analysis. **II** The behavioral results are presented as percent MPE (maximum possible effect) in which MPE = (test - control)/(cut-off - control) X 100. Statistical comparisons were made with repeated measures ANOVA. The effects of treatments in **III** and **IV** were analyzed by one-factor ANOVA. Comparison of individual treatment groups with their respective control group was conducted using Dunnett's t-test. The pairwise effect on pCREB immunoreactivity in **III** was analyzed using Student's *t*-test. SPSS software was used for all analyses. For all comparisons, $P < 0.05$ was used as the criterion for statistical significance.

6. RESULTS

Publication **I** used two transgenic mice lines with compromised trkB signalling to demonstrate that normal trkB activation is necessary for the behavioural effects produced by the antidepressants. There were no differences observed between saline treated trkB.T1 and wild-type mice in the immobisation time in FST. Both imipramine and fluoxetine significantly reduced immobility in the wild-type mice. Neither of the antidepressants had any significant effect on the immobilisation time in trkB.T1 mice. Examination of cortical 5-HT levels with HPLC revealed no basal differences between transgenic and wild-type mice. However, the 5-HT metabolite, 5-HIAA, levels were reduced in the prefrontal cortex, but not in the anterior cingulate cortex, of trkB.T1 mice. Treatment with SSRI, fluoxetine, as expected increased the levels of 5-HT in both genotypes. To investigate ligand specificity of the behavioural effects seen in trkB.T1 mice we used $BDNF^{+/-}$ and $NT\text{-}3^{+/-}$ heterozygote mice. After imipramine treatment the immobilisation times of wildtype and $NT\text{-}3^{+/-}$ mice were reduced this was not observed for $BDNF^{+/-}$. These results suggest that BDNF-mediated trkB activation is required for a normal behaviour response to antidepressants in the FST.

Western blot studies with cortical extracts revealed that both imipramine and fluoxetine significantly increased trkB phosphorylation at 30 min after the injection. However, the total trkB levels were not altered by antidepressants. In trkB.T1 mice trkB activation was inhibited by the dominant-negative isoform. Further experiments revealed that phosphorylation of the autophosphorylation site, but not the shc-signaling pathway, was involved in antidepressant induced trkB signaling. The time course analysis of trkB activation revealed that an increase in trkB activation, at 30 min after injection, was followed by a reduction in phosphorylation levels at 6h, most probably reflecting desensitisation after stimulation. At 24 h, autophosphorylation was again at the baseline level. In chronically (21 days) treated mice similar increase was observed at 30 min after the last injection. This increase was again attenuated at the 6 h and 24 h time points. No desensitization was seen at 6 h after the chronic treatments, as was observed after the acute injection.

To investigate brain area-dependent differences in the response of trkB phosphorylation to antidepressants, various areas were dissected from brains of mice treated either acutely (30 min) or chronically (21 d) with imipramine. Acute imipramine treatment was followed with a small but consistent increase in trkB phosphorylation in all cortical areas examined, with the exception of the anterior cingulate cortex which showed a robust response to antidepressants. After chronic treatment significant increase was also observed in the hippocampus.

We investigated whether trkB activation in response to antidepressants is followed by activation of CREB. A robust increase in CREB activation was seen at 30 min after imipramine injection in the anterior cingulate and prefrontal cortex. A similar, albeit less pronounced response was also seen in the prefrontal cortex after a single fluoxetine injection. In trkB.T1 mice induction of CREB phosphorylation was weaker.

Finally, to correlate the lack of behavioural responsiveness to antidepressants in trkB.T1 mice with the trkB autophosphorylation status, we investigated the trkB phosphorylation status in a group of mice subjected to the FST. FST alone did not alter the trkB phosphorylation, indicating that observed changes can be attributed to the antidepressant treatment. In trkB.T1 mice, the basal trkB phosphorylation status was significantly lower than in wild-type mice. Fluoxetine injection did not increase trkB phosphorylation in these transgenic mice, which is consistent with the behavioural effects of fluoxetine in same mice. In short, these data indicate that antidepressants rapidly phosphorylate the trkB-receptor and that BDNF-mediated signaling is needed for the behavioral effects of antidepressants in the FST.

In publication **II** acute morphine injection significantly increased trkB autophosphorylation in the brain stem, spinal trigeminal nucleus and locus coeruleus within 30 min. However, saline and morphine injected mice did not differ in phosphorylation at the shc-binding site. In contrast, morphine did not increase autophosphorylation or shc-site phosphorylation in NT-4$^{-/-}$ mice. To assess the physiological role of trkB activation in morphine-induced analgesia, we measured subraspinally and spinally mediated nociceptive responses after acute morphine in NT-4$^{-/-}$ mice. The basal thermal nociception of NT-4$^{-/-}$ mice was normal. Wild-type and NT-4 KO mice showed dose-dependent and naloxone-reversible morphine anti-nociception, but responsiveness to morphine was significantly reduced in NT-4$^{-/-}$ mice. In spinal morphine analgesia, both genotypes again responded to morphine in a dose-dependent manner, as evaluated using tail-flick test although NT-4$^{-/-}$ mice required a higher dose of morphine to produce an equivalent analgesic effect to the control mice. The time course of the responses was similar between genotypes, although the maximum response at the dose of mg/kg was markedly attenuated in NT-4$^{-/-}$ mice. TrkB.T1 mice, with compromised trkB signalling, also showed normal basal nociception and dose-dependent and naloxone-reversible morphine analgesia. As with the NT-4$^{-/-}$ mice, trkB.T1 mice needed a higher dose of morphine to produce similar analgesia to control littermates. The participation of BDNF in activation of trkB after morphine was assessed using transgenic mice with a point mutation at the shc-site. TrkB$^{shc/shc}$ mice showed similar analgesia to control littermates, further indicating that the Shc site was not involved.

These results indicated that morphine induces NT-4 release. Superfusion of brainstem slices with morphine consistently increased NT-4 release, which was abolished by naloxone. In addition, different administration paradigms excluded an independent analgesic effect induced by NT-4. Taken together, NT-4 participates in opiate –mediated analgesia and is required for the development of morphine tolerance.

In publication **III** an activated form of transcription factor CREB (pCREB) was used as a marker for plasticity. All of the brain areas were analysed in a semi quantitative manner to select for areas of interest for a more detailed analysis using multiple markers to detect any plastic effects. Antidepressant treatment markedly changed the expression of pCREB in the medial prefrontal cortex, hippocampus and piriform cortex. In a subsequent analysis, chronic imipramine increased expression of PSA-NCAM in the mPFC, especially in layer II. Expression of PSA-NCAM was strongly elevated in DG after chronic imipramine treatment. Finally, PSA-NCAM was also increased in the piriform cortex. Expression of pCREB was significantly increased in mPFC after both acute and chronic imipramine treatment. In the hippocampus an acute injection significantly elevated pCREB expression but chronic administration produced an increase of borderline significance (P=0.054). However, the effect of chronic treatment in piriform cortex on pCREB levels was clear. Neither acute nor chronic imipramine altered GAP-43 immunoreactivity in mPFC. In the hippocampus chronic, but not acute, imipramine treatment increased GAP-43 immunoreactivity in the IML of DG and LML of CA1. These results demonstrate that antidepressants selectively induce neuronal plasticity in certain brain areas.

The studies presented in **IV** show that in wild-type mice, chronic antidepressant treatment increases the number of BrdU-positive cells in the DG. A corresponding and parallel increase in the number of apoptotic, TUNEL-positive, cells was seen following chronic imipramine treatment. Similar results were also obtained with another antidepressant, fluoxetine. The increase in proliferation and apoptosis were temporally matched. The number of both BrdU- and TUNEL-positive cell were not different after 5 days of treatment compared to control levels, but a significant increase in both was observed after 10 and 20 days fluoxetine treatment.

Imipramine was administered for 21 days to $BDNF^{+/-}$ and trkB.T1 transgenic mice to assess the role of BDNF-mediated trkB signalling in hippocampal neurogenesis. In wild-type mice imipramine significantly increased cell proliferation. Unexpectedly, both transgenic mouse lines presented an elevated basal proliferation rate in DG, when compared to saline treated wild-type mice. Nevertheless, imipramine produced an additional and significant increase in

cell proliferation in transgenic mice. The effect was of the same magnitude to that seen in wild-type mice. The role of BDNF/trkB-signalling in the long-term survival of newborn neurons, as identified by BrdU and TUC-4 staining, was evaluated. Three weeks after the cessation of chronic imipramine treatment and BrdU administration, about half of the new cells were still alive when compared to the number of labelled cells at 24 h after antidepressant treatment. In the imipramine-treated wild-type animals, the increased proliferation rate was still seen in the form of increased number of surviving neurons. In transgenic $BDNF^{+/-}$ and trkB.T1 mouse lines the number of BrdU-positive cells was significantly decreased when compared to wild-type mice, suggesting the importance of BDNF-TrkB-signalling for the long-term survival of newly-born neurons in the adult hippocampus. Furthermore, no significant drug effect was seen in $BDNF^{+/-}$ mice at three weeks after cell labelling. In summary, antidepressants increase neuronal turnover in the normal adult hippocampus. BDNF-mediated signaling via trkB is not required for the proliferation of new cells but is essential for the long-term survival of new-born neurons.

7. DISCUSSION

Major depression and chronic pain, among other neuronal disorders, have been associated with dysfunctional neuronal circuitry. There is a huge effort trying to resolve factors and pathways behind these dysfunctions and to develop drugs able to repair these dysfunctional neuronal networks. Increasing evidence indicates that neurotrophins are important modulators of neuronal plasticity. Based on these notions, we aimed to partly clarify the role of trkB and its ligands, BDNF and NT-4, in drug-induced changes in neuronal plasticity. In publications **I** and **II**, we investigated the role of trkB-mediated signalling in the mechanism of action of two types of drugs, antidepressants and opioids. In these studies BDNF involvement proved to be closely linked to the effects of antidepressants and NT-4 to opiate-mediated analgesia. Following these observations we decided to continue to explore closely the involvement of trkB in the mechanisms of antidepressant action. In **III** we screened for brain areas showing observable changes in the markers of neuronal plasticity following antidepressant treatment. Finally, in **IV** we studied the role of trkB-mediated signalling in antidepressant induced neurogenesis.

7.1. Methodological considerations

Transgenic (TG) animals are very often used in research when addressing the physiological function of single factor. When TG animals are used, it should be remembered that with the knocking down or over-expressing genes that the target could also have different functions during development and adulthood. This has led to the use of conditional knock-out mice. In addition, the promoter used critically affects the function of the target and is crucial for the relevancy of the used TG animals. With these considerations in mind, all data produced using TG animals should be interpreted carefully.

BDNF heterozygous mice have approximately half of the normal amount of BDNF throughout their body and may still exhibit developmental abnormalities that further complicate the utility of these mice in studies of the role of BDNF in the adult brain. It is possible that half of the normal amount of BDNF is sufficient to sustain some but not all the physiological actions that are critical to responses in the models of depression. Conditional KO mice, in which BDNF or trkB has been deleted in the broad forebrain regions of adult animals, did not show a depressive phenotype when compared to normal littermates but displayed an attenuated response to antidepressants in the FST (Monteggia et al., 2004; Zorner et al., 2003).

The biggest challenge in histological staining methods was the optimization of tissue permeabilisation and DNA denaturation steps so that brain sections remained in one piece during the staining procedures. Immunohistological markers were chosen based on the literature. CREB is a transcription factor that is well validated marker for plastic events. Activation of CREB by phosphorylation is followed by transcription of several plasticity related genes, such as bdnf and Blc2. pCREB is excellent marker for studying rapid activation of plastic events. Quantification of nuclear markers, such as pCREB and BrdU, was simple when compared to markers located in neurites (PSA-NCAM and GAP-43).

The behavioral assays used (FST, hot-plate and tail-flick) have good prediction value, but are still highly dependent on the performer. Although several drugs give false positive results in the FST, the test is excellent for screening for novel drug with potential antidepressant effects. Observed behavioral effects should be repeated and extended in behavioral paradigms such as learned helplessness or chronic mild stress. The pain assays used are validated for thermal pain processes. Similar experiments using chronic pain models and additional test measuring also inflammatory and mechanical pain would be interesting in clarifying the precise function of NT-4 in opioid function.

In **IV**, the selected time points (5, 10, and 20 days) in fluoxetine study were chosen based on a previous report that hippocampal cell proliferation increases slowly and reaches a significant level at between 5 and 14 days (Malberg et al., 2000). Long-term (around 3 weeks) antidepressant treatment is followed by a significant increase in cell proliferation (Malberg et al., 2000; Manev et al., 2001). We wanted to add some time points to resolve the delay in cell proliferation after initiation of the antidepressant treatment. The same time points were also chosen to resolve whether apoptosis precedes or follows changes in hippocampal cell proliferation.

7.2. TrkB-mediated signaling in action mechanism of antidepressants

As their primary pharmacological function antidepressant drugs, such as MAO inhibitors, tricyclics, and SSRI´s, increase the intrasynaptic availability of monoamine neurotransmitters (Duman et al., 1997; Manji et al., 2001; Skolnick, 1999). Although changes in the monoamine levels appear rapidly, the therapeutic effects emerge after a delay of several weeks. Clinically effective long-term antidepressant treatment and ECS therapy have been shown to increase BDNF mRNA expression in the brain (Duman et al., 1997; Nibuya et al., 1995). The role of neurotrophins, as mediators of antidepressive effects was under examination in these studies. We measured the action of the BDNF-elicited signalling by assaying the phosphorylation of trkB in mouse cortical samples. The data obtained indicates that two commonly used

antidepressants elicit a rapid and significant induction of trkB phosphorylation in the mouse cortex. Consequently, our laboratory has provided evidence which suggests that rapid increase in trkB phosphorylation may be a common mechanism for all antidepressant drugs (Rantamäki et al., 2006)

We also analyzed the time course within which the trkB phosphorylation is increased after antidepressant injection. Our results suggest that trkB activation by antidepressants is dynamically regulated, acute phosphorylation was gone within six hours but even after long-term treatment no desensitization was observed and trkB was activated as after first injection. Furthermore, previous studies have demonstrated that trkB activation and chronic antidepressant treatment induce the phosphorylation of transcription factor CREB. We also showed that the phosphorylation of CREB was significantly increased in the cingulate cortex after acute imipramine and this response was attenuated in trkB.T1 mice.

The most obvious explanation for the increased trkB activation would be that antidepressants promote an increased release of BDNF, which then binds to trkB. However, no differences were detected in the BDNF protein levels between antidepressant and saline treated mouse cortex samples. It seems that using BDNF protein levels as indicators of release may not be the best approach. Even if the BDNF levels between individual synapses would vary, the total amount of BDNF in the brain area could remain unaltered. Indeed, the rapidi nature of the antidepressant induced p-trkB response suggests that it is independent of BDNF synthesis. Even though acute antidepressant treatments produce significant changes in BDNF mRNA levels (e.g. Zetterström et al., 1999) this does not directly indicate that BDNF is released (Mowla et al., 1999). It seems that the rapid trkB activation is dependent on activity induced release of BDNF but not transcription from the BDNF gene.

We also tested whether the behavioural effects of antidepressant in forced swim test (FST) are dependent on trkB signalling. The data gathered showed that antidepressants produced the expected reduction in immobility time in wild-type mice. TrkB.T1 mice, however, did not respond to the administered antidepressants, as shown by an unchanged immobility time. We also tested $BDNF^{+/-}$ and $NT\text{-}3^{+/-}$ mice which revealed that this effect was ligand specific. Using another set of wild-type and transgenic mice we further examined trkB phosphorylation after FST and fluoxetine treatment and found that reduced trkB signalling is associated with unresponsiveness to antidepressants. These observations have subsequently been confirmed using forebrain-selective conditional BDNF KO mice (Monteggia et al., 2004). This data is further supported by a study which showed that repeated intracerebral injections of BDNF into rats results in an antidepressant-like behaviour in the FST (Siuciak et al., 1997). Interestingly,

reduced BDNF mediated trkB signalling did not augment depressive-like behaviours in this test (**I**; MacQueen et al., 2001). On the other hand, a recent study suggests that the effect of BDNF defiency on depressive behaviour may be sex-dependent (Monteggia et al., 2006). Another reason may be that antidepressants may exert their therapeutic actions in a disturbed (stressed) system but not in a normal brain (Tsankova et al., 2006). Subsequent studies in our laboratory have shown that whereas the behavioural effects of the selective serotonergic antidepressant citalopram were abolished in the FST, the behavioural effects of a selective noradrenergic antidepressant were not (Rantamäki, 2006). This result together with earlier findings supports a role for trkB signalling in mediating the plasticity and functionality of serotonergic networks (Altar, 1999). Finally, enhanced trkB signalling produced by the overexpression of trkB in brain is sufficient to promote antidepressant-like behaviour in the FST (Koponen et al., 2005). The pronounced phenotype of TrkB.TK+ mice was not further augmented with acute fluoxetine treatment.

7.3. TrkB-mediated signaling in action mechanism of morphine

We investigated the participation of NTs in the action mechanisms of opiates. Chronic opiate treatment is known to induce a variety of changes in neuronal plasticity. In publication **II**, we found evidence that NT-4, but not BDNF, is closely linked with the action mechanism of morphine. In NT-4 null mice, a larger dose of morphine was needed to produce an analgesic response of the same magnitude as that observed in wild-type mice. This altered effect in analgesic response may be due to an altered opiate tolerance in these mice. One interpretation of the results was that the activation of opioid receptors directly or indirectly increases the release of NT-4, followed by trkB activation. This is supported by the finding that BDNF infusion in the midbrain region produces naloxone-reversible analgesia (Siuciak et al., 1994). Our results offered a new perspective where NT-4 and trkB activation participate on opioid-mediated anti-nociception. At the same time with publication **II** there was a report (Smith et al., 2003) that linked NT-4 into morphine tolerance. In the same study the authors showed that NT-4 KO mice had impaired tolerance to morphine. Opiod tolerance is suggested to be a model of neuronal plasticity similar to learning and memory (Xie et al., 2000). There is some evidence indicating the involvement of NMDA receptors in the neuronal plasticity underlying the development of opiate tolerance (Trujillo and Akil, 1991). Furthermore, a recent article by Hatami and co-workers (2006) demonstrated that NT-4 modulation of opioid tolerance indeed depends on NMDA receptor activation.

Even though, tricyclic antidepressants are known to alleviate certain types of pain (Duric and McCarson, 2006; Tsai, 2005), different mechanisms lie behind the action mechanisms of

antidepressants in pain and depression. In one study antidepressants have been shown to elevate the levels of BDNF mRNA, but morphine had no measurable effect (Nibuya et al., 1995). Same study also suggested that NT-4, rather than BDNF, is involved in the action mechanism of opioids. According to our findings chronic morphine administration leads to the chronic release of NT-4, and trkB-signalling is required for tolerance. Since in NT-4 KO mice have impaired development of opiate tolerance (Smith et al., 2003) and anti-NT-4 attenuates the development of morphine tolerance (Hatami et al., 2006), these studies are therefore in line with each other, and indirectly indicate that NT-4 is required for opiate tolerance and pain relief. In future, attenuation of morphine tolerance will be one key target to improve the clinical use of morphine. Indeed, the novel antinociceptive drug, gabapentin, attenuates morphine tolerance, probably via suppression of morphine-evoked excitatory amino acid release in the spinal cord (Lin et al., 2005). In addition, kappa-agonist, nalbuphine, and D3/2 agonist, 7-OH-DPAT, have shown to attenuate the development of a morphine tolerance (Jang et al., 2006; Cook et al., 2000).

7.4. Antidepressant induced changes in neuronal plasticity

Depression is closely associated with structural impairments in the prefrontal cortex and hippocampal formation. We investigated whether antidepressants could correct these morphological atrophies by enhancing neuronal plasticity at these sites. Chronic antidepressant treatments are shown to affect function of transcription factors in the hippocampus and prefrontal cortex (Frechilla et al., 1998) thus indicating molecular changes in these brain areas. There is evidence that antidepressants affect the expression of markers implicated in neuronal plasticity (Laifenfeld et al., 2005). We presented new evidence that chronic antidepressant treatment elevated expression of the plasticity marker PSA-NCAM in the mPFC, thus indicating enhanced sprouting. Our findings were simultaneously confirmed by Varea and co-workers (Varea et al., 2006). They also found an increase in PSA-NCAM expression in rat mPFC after a chronic (14d) fluoxetine treatment. In addition, they had evidence that at least the 5-HT3 receptor is involved in this form of neuronal plasticity. Earlylife stress also affects to the PSA-NCAM/NCAM expression ratio in adult rats with depressive behavior, suggesting a potential relevance of PSA-NCAM alterations for mood disorders (Tsoory et al., 2007). Fluoxetine has been associated in changed fibroblast growth factor 2 (FGF2) levels in the prefrontal cortex (Maragnoli et al., 2004), suggesting multiple antidepressant-induced plasticity related changes in this brain area.

Antidepressants and ECS induce cell proliferation in the PFC, a region where proliferation of new cells is not found under normal conditions (Kodama et al., 2004; Madsen et al., 2005).

However, these cells fail to differentiate into neurons but, differentiate into non-neuronal cells, such as glia (Madsen et al., 2005). In addition, it was recently shown that a cluster of previously unrecognized nestin immunoreactive neurons were found in the basal forebrain (Wang et al., 2006). The basal forebrain neurons mainly receive cholinergic and GABAergic projections from hippocampus (Rye et al., 1984; Freund, 1989). However, these newly identified neurons did not express markers for these populations, indicating a new functional population of septo-hippocampal neurons.

It is well established that both the hippocampus and the PFC are affected by depression and antidepressant drugs. The signaling and function between these two brain areas may be crucial for the development and treatment of depression. In fact, there is a direct monosynaptic pathway between the hippocampus and the prefrontal cortex (Ferino et al., 1987; Jay and Witter, 1991). This pathway presents synaptic plasticity in the forms of LTP and LTD (Jay et al., 1996; Takita et al., 1999). In addition to memory processing (Wang and Cai, 2006; Degenetais et al., 2003) this pathway is linked to psychiatric disorders. Stress affects LTP in this pathway and this alteration can be corrected with antidepressant treatment (Rocher et al, 2004) thus highlighting the importance of this pathway for future research.

Although hippocampal neurogenesis was shown to be essential for the behavioral effects of antidepressants (Santarelli et al., 2003) and contextual fear conditioning (Saxe et al., 2006), adult neurogenesis is apparently not needed for the behavioral effects of environmental enrichment (EE), spatial learning or anxiety (Meshi et al., 2006). EE, however, is known to enhance hippocampal neurogenesis (Kempermann and Gage, 1999), and this event requires BDNF (Rossi et al., 2006). These studies suggested that the hippocampus participates in the formation of some but not all behavioral responses and that neurogenesis is an epiphenomenon correlating with other unrelated events. With these assumptions, it seems that antidepressant induced hippocampal neurogenesis is a balancing event in the process of producing a sufficient number of synaptic connections to maintain a functional neuronal network. Furthermore, a depression resistant phenotype was recently observed in Kcnk2$^{-/-}$ KO mice (a background potassium channel) (Heurteaux et al., 2006). Although antidepressants produced a robust increase in hippocampal cell proliferation in these mice no other behavioral changes were observed. A recent report, however, indicates that as new granule cells mature, they are increasingly likely to be incorporated into the neuronal network when compared to the existing granule neurons in memory formation (Kee et al., 2007). This suggests, on the other hand, a significant role for adult hippocampal neurogenesis in behavioral modulation. In non-pathological conditions, enhanced neurogenesis is accompanied by apoptosis because there is no loss of connections, or need for additional ones (**IV**). In contrast, stress and disrupted

neuronal network benefit from the AD-induced neurogenesis when repairing formed damage. Apoptosis is not present because these new cells are integrated into the neuronal network (Czeh et al., 2001). Based on these and other studies a new model for stress-related mood disorders has been developed (Sandi and Bisaz, 2007). This hypothesis implicates alterations in the levels of neuronal cell adhesion molecules among the mechanisms contributing to mood disorders and, potentially, in antidepressant action.

7.5. Role of TrkB in antidepressant mediated effect on neurogenesis

Participation of BDNF in hippocampal neurogenesis in the adult brain has been well accepted for some time. However, the precise role of BDNF in hippocampal neurogenesis is still unresolved. Classically NTs have been associated as survival-factors. Our goal was to clarify the role of BDNF-mediated signaling in adult neurogenesis. We discovered that trkB-mediated signalling is not needed for the antidepressant induced increase in cell proliferation. However, BDNF and trkB proved to be essential for the long-term survival of new born neurons. Similar results are seen *in vitro* (Tervonen et al., 2006) although these studies were performed using progenitors of subventricular origin. The increased proliferation rate seen in trkB.T1 mice may be due to a compensatory effect to the decreased survival of new neurons. This increased proliferation was also seen in $BDNF^{+/-}$ mice and reported in *in vitro* neurospheres derived from trkB.T1 mice (Tervonen et al., 2006). Increased apoptosis has also been reported in BDNF deficient mice (Linnarsson et al., 2000). However, the role of BDNF as a survival factor for new neurons was questioned with the observation that the chronic mild stress test did not affect cell proliferation but rather impaired survival of new neurons even if BDNF mRNA levels were unaltered in granule cell layer (Lee et al., 2006). This finding contrasts with earlier studies that have reported decreased BDNF expression following stress (Smith et al., 1995). This discrepancy underlines the importance of the BDNF protein levels and trkB receptor number or that crucial trophic support of new neurons is produced from their target areas.

7.6. Neuronal plasticity as a target for novel antidepressant treatments

Neuronal plasticity has emerged as an exciting target for novel antidepressant drug development. This is due to the fact that plastic events take time and are thought to be behind the delay of action of antidepressant treatments observed in depressive patients. The BDNF protein itself is not a functional drug candidate because it does not penetrate the blood brain barrier. Some of the current approaches being pursued by the pharmaceutical companies, looking beyond monoamines are summarized below.

Direct BDNF mimetics present a very appealing way to affect disrupted neuronal networks seen in depressive patients. A recent review by Fletcher and Hughes (2006) updated new progress in the design of BDNF mimetics to treat neurodegenerative diseases. The biggest problems so far have been the size of the current mimetics. Another attempt to utilize BDNF-mediated actions can be seen with the drugs called ampakines (Rex et al., 2006). Primary function of ampakines is to elongate the “open-time” of AMPA-channels. Indirectly these novel drugs increase BDNF levels and so restore the age-related deficit in hippocampal LTP. Directly affecting the cAMP-CREB system has identified phosphodiesterase-4 (PDE4) inhibitors as a therapeutic target for depression. These inhibitors, such as rolipram, block the breakdown of cAMP, thus increasing the phosphorylation of CREB. Unwanted side-effects have however prevented the launch of these drugs. Specificity has emerged as the main problem since there are several members of the PDE4 family and variability of compartmentalisation and since cAMP is the key second messenger in all cells (Houslay et al., 2005). It seems that there is still a lot to be done in this field. The fact that noradrenergic afferents make direct contact with the hippocampal neurons (Loy et al., 1980) has driven interest to study other approaches to modulate plasticity via the noradrenergic system in the hippocampus. Recently, an alpha-2-adrenoceptor antagonist was shown to enhance hippocampal neurogenesis by increasing BDNF-mediated survival of new born neurons (Rizk et al., 2005). In a near future, a receptor subtype specific alpha-2-adrenergic antagonist could be a potential drug candidate for affective disorders.

A reduced tone in the fibroblast growth factor (FGF) system might alter brain development, or remodelling, and result in a predisposition or vulnerability to mood disorders, including major depression (reviewed in Turner et al., 2006). Antidepressants increase the expression of FGF2 in the hippocampus (Mallei et al., 2002). Altered expression of FGF2 and FGF receptors has been reported in depressive patients (Evans et al., 2004): medicated patients had FGF transcript levels more similar to control subjects than unmedicated patients. One approach was based on the fact that NCAM signals via a direct homophilic interaction with the fibroblast growth factor receptor (FGFR) (Reviewed in Kiselyov et al., 2005). FGFR1 is one possible drug target because it promotes the proliferation of both hippocampal progenitors and stem cells during development (Ohkubo et al., 2004). There is already a synthetic NCAM-derived peptide (FGL by ENKAM pharmaceuticals A/S, Denmark), that is under development to treat Alzheimer’s disease. This peptide drug is a FGFR agonist and has proven to activate FGFR1. The drug positively affects the sensorimotor development and enhances social memory (Secher et al., 2006). In addition, this drug induces neurite outgrowth and neuronal survival (Neiiendam et al., 2004) and protects hippocampal neurons against ischemic insult both in vitro and in vivo (Skibo et al., 2005). The drug has thus proven to be safe and well

tolerated in clinical testing. If the development of this drug continues it will be interesting to find out the efficacy and effect on mood after long-term treatments.

Also under development is an activator of GAP-43 transcription, HUO622 (Uwabe et al., 2006). The strategy behind this approach is somewhat different. While the molecule mimics the effects of NGF by activating the ERK-signaling pathway, this is achieved without actual trkA activation. Under intensive research is the role of the glial cell in neuronal plasticity. The negledged glial cells may be a novel direction for future drug development. It has been shown that CNS synapse number can be profoundly regulated by nonneuronal signals (Ullian et al., 2001), and thus raise the possibility that glia may actively participate in synaptic plasticity. A recent study (Stellwagen and Malenka, 2006) demonstrated that synaptic scaling can be induced by activity-dependent changes in release of the cytokine tumor necrosis factor-alpha (TNF-alpha) and, surprisingly, that the source of TNF-alpha is glial rather than neuronal. In addition to providing insight into the mechanisms of homeostatic plasticity, these data argue for the first time, that equal partnership between glial cells and neurons is needed in the generation of an important form of synaptic plasticity.

Several other interesting drug candidates, including CRF1 antagonists, CRF2 agonists and various serotonin receptor subtype selective drugs, are also under active development and the number is increasing. Several of these drug candidates target hippocampal plasticity and are primarily designed to treat memory deficiencies, due to the observation that changes occur in “the memory center”, hippocampus. The heterogeneity seen among depressive patients and a strong placebo-effect might also be factors affecting strategy in the clinical testing of novel antidepressants.

Although rapid events, such as the strengthening of available synapses and synaptogenesis in existing neurons could be induced by novel antidepressant drugs it may be that in major depression the cell loss is too massive and the brain has not enough processes to repair the damage quickly enough. This hypothesis (Figure 6) leads to the conclusion that in major depression the treatment delay is inevitable due to requirement for a sufficient amount of new neurons and glial cells to repair the damaged networks. However, there is a need for novel drug therapies to temporarily alleviate symptoms while antidepressant-induced repair of the neuronal network takes place. If these new connections do not receive adequate support from the molecular factors and not actively used they will perish quickly. This may be the mechanism behind the recurrent episodes seen in humans. It should be kept in mind that new synaptic connections in the brain, induced by drugs or physiological stimuli, rely on neuronal activation and will again perish without usage.

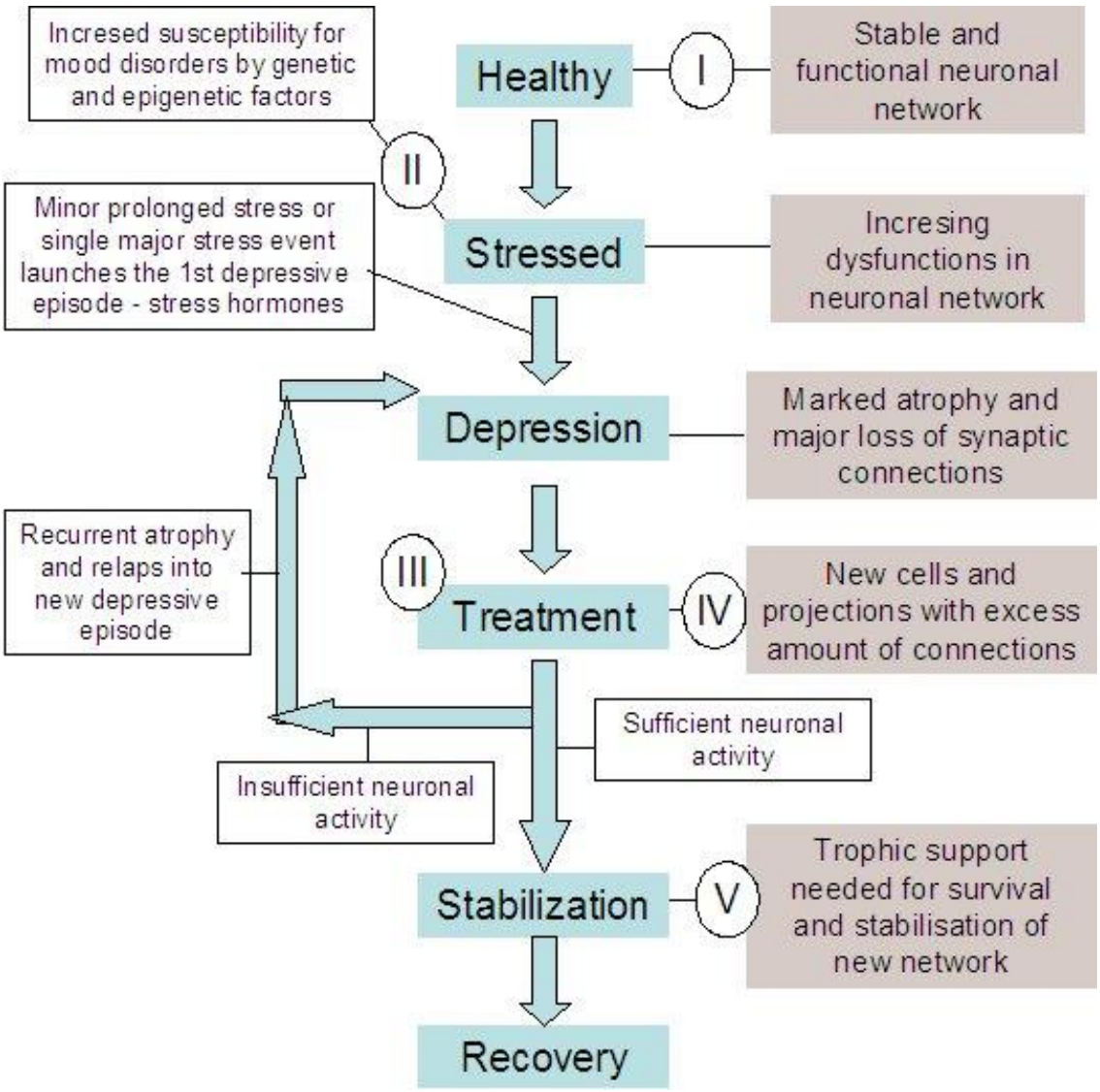

Figure 6: Role of neuronal plasticity and trkB-mediated signalling in different phases of depression. I: BDNF supports existing neuronal network. II: Polymorphism and histone modifications in the BDNF gene have been associated into increased susceptibility for mood disorders. III: Rapid activation of trkB IV: Pivotal role in L-LTP V: BDNF stabilizes the new functional neurons. The positive effects of BDNF/trkB-signaling can be counteracted by stress hormones and pro-BDNF/p75NTR-signaling.

Based on the current literature and results from the present thesis patophysiology of depression includes neuronal atrophy and dysfunctional neuronal networks. Neuronal network restoring and neuroprotective disease modifying drugs might be achievable when targeted to affect plastic events such as modification of synaptic connections. On the other hand, there is still a need for more fast-acting symptomatic drug therapies, targeted to affect directly monoaminergic or other neurotransmitter systems.

8. CONCLUSIONS

Taken together, the present results have revealed the essential role of trkB-receptor mediated signalling in action mechanism of antidepressants and morphine. Furthermore, we have partly clarified the role of neuronal plasticity at least as a one potential mechanism of action of antidepressants.

Essential findings:

1. Antidepressant drugs rapidly increase the phosphorylation of trkB receptor

2. BDNF-mediated activation of trkB is crucial for the behavioural effects of antidepressants.

3. Morphine increases NT-4 release in brain, and NT-4-mediated activation of trkB is involved in the modulation of morphine induced analgesia and development of tolerance.

4. Antidepressants induce plastic changes in distinct brain sites, hippocampus, medial prefrontal cortex and piriform cortex.

5. Antidepressants increase neuronal turn-over in adult rodent hippocampus.

6. BDNF-mediated activation of trkB is essential for the long-term survival of newborn neurons in hippocampus.

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