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Review

Altering BDNF expression by genetics and/or environment: Impact for emotional and depression-like behaviour in laboratory mice

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ABSTRACT

According to the "neurotrophin hypothesis", brain-derived neurotrophic factor (BDNF) is an important candidate gene in depression. Moreover, environmental stress is known to represent a risk factor in the pathophysiology and treatment of this disease.

To elucidate, whether changes of BDNF availability signify cause or consequence of depressive-like alterations, it is essential to look for endophenotypes under distinct genetic conditions (e.g. altered BDNF expression). Furthermore it is crucial to examine environment-driven BDNF regulation and its effect on depressive-linked features. Consequently, gene × environment studies investigating prospective genetic mouse models of depression in different environmental contexts become increasingly important.

The present review summarizes recent findings in BDNF-mutant mice, which have been controversially discussed as models of depression and anxiety. It furthermore illustrates the potential of environment to serve as naturalistic stressor with the potential to modulate the phenotype in wildtype and mutant mice. Moreover, environment may exert protective effects by regulating BDNF levels as attributed to "environmental enrichment". The effect of this beneficial condition will also be discussed with regard to probable "curative/therapeutic" approaches.

Contents

1. Introduction

Affective disorders, such as depression and pathological anxiety which are highly concomitant, affect millions of people worldwide. Currently there are only a few effective treatments and there is no satisfying consensus concerning the pathophysiology of these devastating disorders. Former studies support the idea that the neurotrophic system plays a key role in the pathogenesis of depression (Altar, 1999; Calabrese et al., 2009; Hindmarch, 2002; Karege et al., 2002; Lang et al., 2004; Nibuya et al., 1995; Rasmusson et al., 2002; Smith et al., 1995b; Vaidya and Duman, 2001). Particularly mature brain-derived neurotrophic factor (BDNF) as a member of the neurotrophic factor family (including also nerve growth factor (NGF), Neurotrophin-3, and 4-5 (NT-3, NT-4/5) has been discussed to be involved in such processes (Bothwell, 1995). Whether changes of this system are causative or occur as a secondary phenomenon remains questionable though. On the other hand, an up-regulation of neurotrophins has been demonstrated following various antidepressant measures (Angelucci et al., 2000b;

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D'Sa and Duman, 2002; Duman and Vaidya, 1998; Russo-Neustadt et al., 1999, 2001; Siuciak et al., 1997; Zetterstrom et al., 1998), indicating that these growth factors play a key role in the treatment of affective disorders. Such antidepressant-induced increases in e.g. endogenous BDNF were furthermore accompanied by an enhanced tropomyosine-related kinase B (TrkB) receptor activity, which is required for antidepressant-induced behavioural effects (Saarelainen et al., 2003). However, the exact mechanisms through which antidepressants (which are additionally used to treat other central nervous system (CNS) disorders like chronic pain, phobia or bulimia) exert such effects remain unclear.

A major problem of research on depression to reliably prove such concepts in humans consists in the restriction of systematic approaches, because the detailed investigation of this disease requires the analysis of brain tissue at crucial time points. Consequently, valid and representative animal models are a central tool of experimental psychiatry, especially mouse models, since this species bears the advantage that particular target genes of depression, e.g. BDNF may be manipulated according to the research focus. Further arguments to use mice as model organisms are i) the equivalence to many human genes as well as ii) the similarity of numerous biological and biochemical functions. Nonetheless it is crucial to consider the mouse not only as a model organism, but also as a species by itself with a very complex behavioural repertoire and social organisation that is distinctive concerning gender and strain and therefore results are not directly transferrable to humans. Regarding such restrictions, a very promising mouse model for depression was proposed by Shannon et al. (Gourley and Taylor, 2009), in which prior corticosterone exposure produces a reliable depressive-like state. The two major benefits of this animal are that (i) the same animals may be used after corticosterone wash-out as well as (ii) the easy replication of this strategy between the laboratories, which often states a problem of animal models (Gourley and Taylor, 2009).

Nowadays it is generally accepted that the occurrence of a depressive episode results from a combination of interacting environmental and genetic factors (Mill and Petronis, 2007), which may not be sufficiently illustrated by a very specific approach like the above mentioned corticosterone exposure. Nevertheless such models may help to clarify certain aspects of specific subtypes or endophenotypes of depression, which may be characterized by various symptoms and therefore they also have to be considered in current concepts about the pathophysiology and treatment of depression. As described by many groups addressing such hypotheses by means of animal models, potentially "depressed" rodents are not able to cope/adapt to an environmental challenge (e.g. forced swimming or footshock) which may be attributed to an increased vulnerability to develop depressive-like symptoms (Chourbaji et al., 2008b; Monteggia et al., 2007; Ridder et al., 2005). Such an increased proneness is postulated to be additionally be promoted by aversive (early) experiences such as e.g. maternal separation (Lambas-Senas et al., 2009). Contrary, beneficial experiences (for instance exposure to an enriched environment) may decrease the risk in vulnerable individuals (i.e. in BDNF heterozygous mice) (Chourbaji et al., 2008a).

A malfunction evoking respective "depressive phenotypes" is frequently linked to impairments in neural resilience, with altered expression of so-called plasticity genes such as BDNF, its high-affinity receptor TrkB, or the transcription factor, cAMP response element binding protein (CREB), altering the cascade of events from intracellular signalling to gene expression (for review see (Calabrese et al., 2009)).

Here we review studies considering particularly the role of BDNF in mouse models for depression as well as the impact of various environmental factors (such as housing conditions, social stress, etc.), which may be decisive for the development or cure of depressive-like alterations primarily in rodents, and discuss their clinical implications also in terms of transferability to humans.

2. The neurotrophin hypothesis of depression

BDNF, NGF, but also NT3, and NT-4/5, are primarily synthesized as 30–35 kDa precursor proteins, which are later on cleaved by pro-convertases at a highly conserved dibasic amino acid cleavage site (Mowla et al., 2001). The resulting neurotrophins share a common basic structure with variable domains determining the binding to their specific receptors and respective biological functioning (Heumann, 1994). Noteworthy, all neurotrophins bind to unselective low-affinity p75, but exclusively interact with their individual high-affinity receptors of the *Trk* family (Lee et al., 2001). While binding to the p75 receptor has been discussed to induce not only plasticity but also apoptotic processes (Majdan et al., 1997; Rabizadeh et al., 1993; Roux et al., 1999; Underwood and Coulson, 2008), an appropriate coexpression with Trk receptors may balance such effects and enhance specificity for their primary ligands (Bibel et al., 1999; Esposito et al., 2001; Tapia-Arancibia et al., 2004).

Since it was recently shown by e.g. Lee et al. (Lee et al., 2001), that pro-neurotrophins have different receptor affinities than mature one, with high affinity for p75, but less for Trk receptors, it is important to be aware of the fact that a balanced availability of pro- and mature neurotrophins is essential to determine cell survival and cell death, which is a critical point with regard to the clarification of distinct pathologies. Besides the plasticity-relevant impact of BDNF in almost all aspects of fetal development (and also during adulthood) another classical role of the neurotrophins is known as the "neurotrophin hypothesis". This hypothesis refines one of the original theories of depression, i.e. the "monoaminergic theory" of depression (Schildkraut, 1965), by focussing on the role of mature BDNF and it postulates that reduced activity of the CREB–BDNF–TrkB pathway causes a depressive state. Contrarily, the activation of this system (i.e. BDNF–TrkB binding with subsequent receptor dimerization, phosphorylation and activation of the intracellular tyrosine kinase domain) initiates several complex intracellular signal transduction cascades thereby inducing biological responses, which are implicated in the molecular mechanisms of antidepressive therapy (Altar, 1999; Martinowich et al., 2007; Urani et al., 2003). This is a crucial fact in so far as up-regulation of monoamines occurs already within minutes after administration of antidepressants, while effects on mood often have a lag period of weeks or even months (Nestler et al., 2002). This in turn highlights the impact of other, later (potentially adaptive) appearing changes in the CREB–BDNF–TrkB pathway with regard to antidepressant efficacy (Duman et al., 1997; Nestler et al., 2002). The assumption that this pathway plays an essential role is moreover substantiated by the finding that antidepressant effects – which after chronic treatment may not be attributed to activated monoaminergic neuronal firing anymore (Szabo et al., 1999) – are mediated by activation of mediators in this system, i.e. TrkB (Saarelainen et al., 2003). It is thus conceivable that neurotrophin-evoked plastic changes may need time to develop, which might partly explain why the clinical effects arise only with a certain delay after starting the treatment.

Hereby it is stated that one important second messenger system is represented by the cyclic adenosine monophosphate (cAMP) pathway (Vaidya and Duman, 2001), where the generation of cAMP results in the activation of cAMP-dependent protein kinase (PKA), which in turn triggers CREB (Duman et al., 2000). Activated CREB enhances the transcription of many target genes, e.g. BDNF, which exerts its effects principally by activation of its high-affinity receptor, the trkB, thereby influencing structural plasticity and trophic effects in neurons (Duman and Monteggia, 2006; Urani et al., 2003). Furthermore, BDNF-induced actions may be controlled by the presence of truncated TrkB receptors, which form an efficient and

Table 1
SWOT analysis of the neurotrophin hypothesis: Due to controversial debates and findings considering an association of BDNF with a depressive-like state, it is essential to regard all facts, which play a role in the interpretation of data rising from hypothesis-driven studies. Referring Literature: (Almeida et al., 2005; Barrientos et al., 2003; Berton et al., 2006; Branchi et al., 2006a; Castren and Rantamaki, 2008; Eisch et al., 2003; Hoshaw et al., 2005; Miro et al., 2002; Nibuya et al., 1995; Pizarro et al., 2004; Sartorius et al., 2009; Shirayama et al., 2002; Siuciak et al., 1997; Smith et al., 1995b; Vaidya et al., 1997; Wu and Castren, 2009).

SWOT Analysis of the Neurotrophin Hypothesis of Depression

STRENGTH

Consistent results indicate for BDNF :

Animal
- stress-induced decrease of neurotrophins
- associated hippocampal atrophy
- antiapoptotic effects
- equipotency to regular antidepressants when infused into the midbrain
- AD/ECT- induced increase of mRNA and protein

Human
- post-mortem reduction of BDNF/TrkB levels in untreated depressed suicide patients
- low serum levels in depressed individuals

Transgenic strategies may be applied using:
- heterozygotes
- conditional knockouts
- overexpressing mice

WEAKNESS

Inconsistencies due to paradoxical findings, such as :

Animal
- stress-induced increase of BDNF associated to increased depressive-like behaviour
- some SSRIs decrease hippocampal BDNF levels
- VTA infusion of BDNF increase depressive-like behaviour
- lack of TrkB in the VTA leads to antidepressive coping

knockout strategies are restricted, because:
- homozygous BDNF ko is lethal and cannot be analyzed!!
- in vivo studies in humans cannot be conducted due to ethical reasons

OPPORTUNITIES
- Research on BDNF may be directed additionally towards other emotional features accompanying depressive-like states
- New strategies to improve the antidepressive impact can be exploited
- Gender-specific regulations remains to be examined in detail to explain sex-specific pathological differences

THREATS
- Multiple factors regulate BDNF levels causing potential artefacts, if experimental conditions cannot be strictly controlled.

Abbreviations: AD = antidepressant, ECT = electroconvulsive therapy, BDNF = brain-derived neurotrophic factor, TrkB = tyrosine kinase receptor B, VTA = ventral tegmental area, ko = knockout

selective barrier to prevent diffusion and internalisation of BDNF to particular regions in the developing brain (Biffo et al., 1995; Eide et al., 1996), On the other hand, it is crucial to be aware of the role of pro-BDNF, which may exert contrary effects by exclusive high-affinity interaction with particularly p75 (Arevalo and Wu, 2006).

To clarify the postulated implication of the neurotrophic cycle in the pathogenesis of depression, several mutant mouse lines were generated to investigate the impact of a particular genetic condition (e.g. heterozygous, conditional or forebrain-specific knockouts). Such genetic strategies hereby overcome the problem that an entire knockout of BDNF is lethal and cannot be investigated behaviourally, which naturally excludes the investigation of gene-dosis effects. Consequently, such mice, in which BDNF or TrkB expression is differently regulated, may help to clarify specific questions about the functional and temporal role of BDNF-mediated actions. However, besides the possible genetic approaches for the assessment of the role of BDNF (see Table 1), there are also many alternative considerations focussing on beneficial and detrimental effects on murine behaviour induced by environmental factors. These could – possibly via regulation of BDNF levels – represent potent modulators of mood and brain morphology, and substantially support the neurotrophin hypothesis of depression. Such approaches include e.g. the investigation of stress-induced effects as well as examination of neuronal plasticity and effects of antidepressants and ECT. Despite several studies aiming at elucidating the role of BDNF in animals, there is no consensus on whether or not the "neurotrophin hypothesis", as it was originally formulated, is transferrable in terms of practical approaches, i.e. if a decrease or lack of BDNF really provokes a depression-like state. On the contrary, there are some caveats, e.g. contradictory results in models using external stress or antidepressive treatment, where BDNF is regulated opposite to what the hypothesis predicts. The SWOT (strength, weakness, opportunities, threats) analysis below (Table 1), as it is frequently used for the evaluation of economic questions, here demonstrates and simultaneously challenges the standing of this hypothesis according to current scientific concepts and sources:

2.1. Factors involved in the pathogenesis of depression

According to clinical and experimental observations, the "neurotrophin hypothesis" claims that a deficiency in BDNF contributes to the pathophysiology of depression (Altar, 1999; Duman et al., 1997). Especially a reduced expression and low serum levels of BDNF have been correlated to the depressive state of patients (Table 1) (Karege et al., 2002; Sen et al., 2008), but it has also been suggested that an imbalance of neurotrophin receptor signalling may be involved in diseases of the CNS (Dechant and Barde, 2002). Postmortem studies have furthermore revealed that untreated depressive patients have lower cortical levels of CREB and phosphorylated CREB than healthy subjects (Chen et al., 2001a; Dowlatshahi et al., 1998; Yamada et al., 2003). On the other hand it was reported

that stress, e.g. footshock stress applied to rats, induced a down-regulation of BDNF mRNA (Table 1) (Rasmusson et al., 2002). Chronic stress, and a subsequent rise in plasma corticosteroid levels, is regarded as a major cause in the pathogenesis of depressive disorders (Holsboer, 2000, 2001). Stress or corticosteroid injections cause a reduction of BDNF mRNA in the hippocampus and other brain areas postulated to be implicated in the pathogenesis of depression, most likely by activation of glucocorticoid receptors (Rasmusson et al., 2002; Smith et al., 1995b; Ueyama et al., 1997). Moreover, in a genetic rat model of depression, the Flinders Sensitive Line, several brain regions (frontal cortex, occipital cortex, and hypothalamus) have lower levels of BDNF and NGF as compared to their controls, the Flinders Resistant Line (Angelucci et al., 2000a). These results demonstrate that stress and depression correlate with a decreased activity of the CREB–BDNF–TrkB pathway, but the chronological order remains to be clarified.

2.2. Mechanisms affected in the therapeutic process

The stress-induced decrease of BDNF is reversed by antidepressants or ECT (Nibuya et al., 1995). This effect is enhanced by combination with physical activity which is regarded as a form of behavioural therapy in rodents (Russo-Neustadt et al., 2001) by increasing cell proliferation and mRNA expression in this region (Neeper et al., 1996; Oliff et al., 1998). Even without stress, hippocampal BDNF (and TrkB) mRNA expression and adult neurogenesis is induced by chronic antidepressant treatments (Malberg et al., 2000; Nibuya et al., 1995; Saarelainen et al., 2003; Smith et al., 1997) or ECT (Nibuya et al., 1995; Zetterstrom et al., 1998). Irrespective of the consistency of such findings with the effectiveness of antidepressants, the mechanisms of how such drugs activate e.g. TrkB receptor signalling remain unclear. It is assumed that antidepressants modify the BDNF content and release as well as further activation of TrkB receptors by improving monoaminergic neurotransmission (Tapia-Arancibia et al., 2004). Moreover, chronic administration of several distinct classes of antidepressant treatments up-regulates CREB mRNA expression (Blom et al., 2002; Nibuya et al., 1996) and CREB phosphorylation (Saarelainen et al., 2003; Thome et al., 2000) within the hippocampus and other brain areas. Hereby, one should note that regions exhibiting an up-regulation of BDNF in response to antidepressant administration overlap closely with the regions that show an up-regulation of CREB. This correlation suggests that CREB may contribute to the antidepressant-induced increase in hippocampal BDNF expression and may be furthermore supported by a finding of Conti et al. Interestingly, when investigating CREB-deficient mice, they neither found any antidepressant-induced alterations at the behavioural level (unchanged despair behaviour in the forced swim test (FST) and tail suspension test (TST)), nor were they able to detect an up-regulation of BDNF after treatment with desipramine, indicating that CREB is critical to target gene regulation after chronic drug administration, which may contribute to long-term adaptations of the system to antidepressant drug treatment (Conti et al., 2002). At the clinical level, higher concentrations of CREB (Dowlatshahi et al., 1998), BDNF (Chen et al., 2001b) and TrkB (Bayer et al., 2000) are found in different brain regions of patients under antidepressive medication as compared to untreated patients. These data propose that the effects of antidepressants are mediated by an activation of the CREB–BDNF–TrkB pathway.

3. Balanced BDNF levels: impact of environmental and genetic factors

According to current theories, different types of environmental stressors (e.g. restraint stress, high density-/or isolated housing) lead to a reduction of neural plasticity (Kim and Yoon, 1998) and decreased BDNF levels in mice (Barrientos et al., 2003), while treatment such as medication with several classes of antidepressants, ECT as well as psychotherapeutic methods, all equally stating external factors, evoke a normalization of BDNF (Castren and Rantamaki, 2008). Thus, the "neurotrophin hypothesis", which illustrates alterations occurring during depression without any interpretation of the origin of such modulating factors, is substantiated by the fact that not only environmental factors such as stress and antidepressive treatment, but also genetic conditions may regulate BDNF expression in a positive or negative way, thereby modulating the "allostatic" load of an individual, i.e. the risk (or resistance) to develop a pathological state (McEwen, 2000) (see Box 1). Hereby it is postulated that environmental factors (depending on their impact for the allostatic load, see Box 1) are capable to bidirectionally alter genetic programming, i.e. induction or repression of gene expression (Johansson, 2007). During a depressive episode which is associated with decreased BDNF levels mainly detected in the hippocampus, however, it remains questionable, whether e.g. external (environmental) stress represents the major cause for a down-regulation of BDNF on mRNA and protein level, or if an

Box 1: The role of BDNF in depression: state of the art.
In the literature there is considerable evidence supporting the idea that the neurotrophic system and in particular the brain-derived neurotrophic factor BDNF plays a key role in the pathogenesis of depression (Altar, 1999; Hindmarch, 2002; Karege et al., 2002; Lang et al., 2004; Nibuya et al., 1995; Rasmusson et al., 2002; Smith et al., 1995a,b; Vaidya and Duman, 2001). A major study in relatives of depressive patients revealed, that the BDNF gene represents a potential risk locus for bipolar disorders after genotyping and haplotyping assessments (Petryshen et al., 2009). Such concepts are supported by findings that BDNF levels are reduced in post mortem brain tissue samples and blood probes of depressed patients (Castren and Rantamaki, 2008) while treatment with antidepressants increased BDNF immunoreactivity (Chen et al., 2001a,b). A recent study moreover Documented, that antidepressant drugs not only increased endogenous BDNF, but also TrkB receptor activity, which is important in terms of mediating antidepressant-induced behavioural effects (Saarelainen et al., 2003). The fact that electroconvulsive shock therapy induces long-lasting enhancement of BDNF mRNA in the hippocampal dentate gyrus furthermore strengthens the impact of BDNF in current theories about the pathophysiology and tnerapy of depression (Zetterstrom et al., 1998). Another notable finding is, that BDNF, when administered exogenously enhances neuronal plasticity (Altar, 1999) and produces antidepressive effects in an animal model, i.e. the Learned Helplessness paradigm (Shirayama et al., 2002; Siuciak et al., 1997). A quite recent milestone in neurotrophin-related research is the finding of a specific polymorphism in the BDNF gene (VAl66Met), which has been associated with environment-induced anxiety, namely when animals with a mutation for that gene, i.e. BDNFMet/Met, were placed in stressful settings. The observed emotional changes could not be reverted by the antidepressant Fluoxetine indicating that a variant of BDNF may play a key role in the genetic predisposition for affective disorders as well as human memory-, and hippocampal function (Chen et al., 2006). In summary, these facts suggest a BDNF-driven enhancement of neuronal functioning, which may be disturbed in depressed individuals.
Referring Literature: (Altar, 1999; Castren and Rantamaki, 2008; Chen et al., 2001b; Chen et al., 2006; Hindmarch, 2002; Karege et al., 2002; Lang et al., 2004; Nibuya et al., 1995; Petryshen et al., 2009; Rasmusson et al., 2002; Saarelainen et al., 2003; Shirayama et al., 2002; Siuciak et al., 1997; Smith et al., 1995a; Vaidya and Duman, 2001; Zetterstrom et al., 1998).

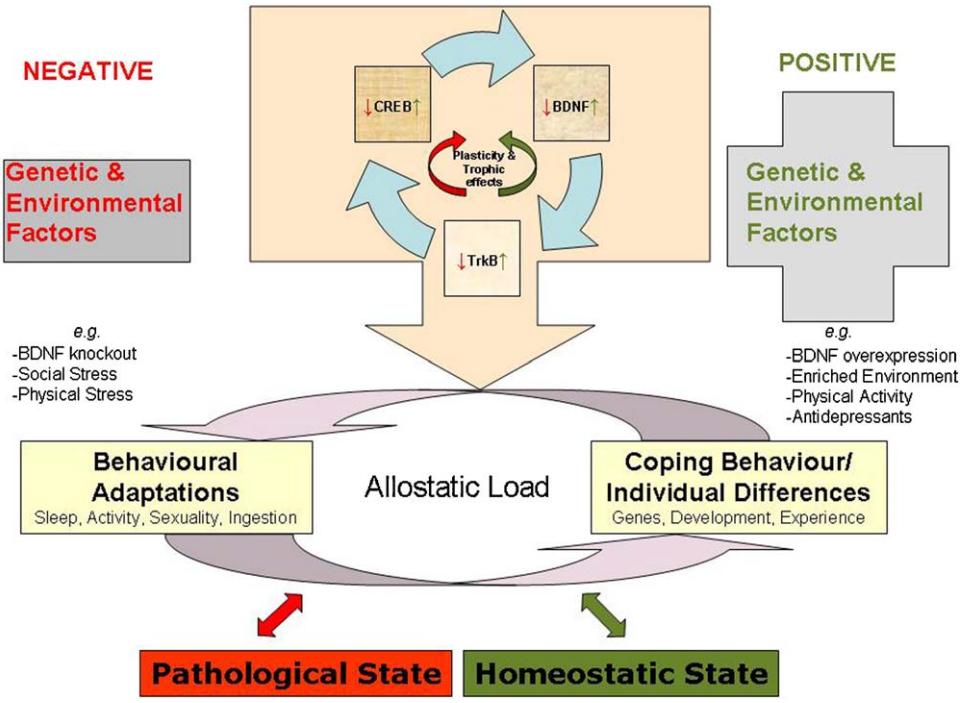


Fig. 1. Contribution of BDNF to homeostasis: The capability of BDNF to be bidirectionally regulated makes it an interesting target for the investigation of positive and negative effects of several genetic and environmental factors. Positive and negative modulators may interfere with an intact functioning of the neurotrophic cycle at any level, hereby damaging the homeostatic state of a subject by increasing the allostatic load decisively, which can then result in a pathological state of increased vulnerability to a stress-related disease such as depression. Since there are individual susceptibilities (capability to cope/adapt to a challenging, or profit from a beneficial condition), originating for instance from different development and experiences, which consequently alters the ability of the subject to adapt to and cope with a distinct situation, it is essential to always approach depression considering the multifactorial background.

already existing genetic reduction of this neurotrophin predisposes a subject to become depressive.

However, sometimes such particular genetic conditions – as e.g. given in mice carrying a heterozygous mutation for BDNF – do not directly affect the occurrence of pathological alterations. In a study of Ibarguen-Vargas for instance, BDNF heterozygous did not demonstrate an increased vulnerability in the chronic mild stress (CMS) paradigm, but exhibited dampened response to antidepressive treatment (Ibarguen-Vargas et al., 2009). Another interesting approach in this respect is the inducible knockout system, in which also the impact of an early lack of BDNF during critical periods in earlier stages of development can be analysed. Hereby in becomes obvious that particular periods during development are differently decisive with regard to the behavioural outcome (Monteggia et al., 2004).

BDNF, due to its association to stress-, and depression-related alterations, represents a target gene for the development of novel, more accurately acting drugs and additional or alternative environment-supported therapeutic strategies aiming to restore homeostasis and normalize allostasis. Hereby it is crucial to have a reliable description of the *individual* background of depressive-like state (which emphasizes the grading of the characteristic symptoms), since it is essential for successful therapy.

Accordingly, an alternative and promising approach to optimize the functioning of the neurotrophic cycle is the combination of appropriate drug treatment with environment-supported methods (enrichment in animals, psychotherapy in humans), which bears the chance of reducing the lag period until depressive symptoms are ameliorated, increases the number of responders and decreases side effects due to parallel-therapeutic approaches. BDNF, due to its large molecular size, cannot cross the blood–brain barrier and therefore mechanisms have to be found by which the synthesis and release of BDNF is regulated within the neurotrophic cycle. Hereby the goal is to optimize the neuronal activity involving BDNF, which drives critical processes such as synaptic reorganization-shaping neural networks that optimally code for environmentally relevant information (Castren and Rantamaki, 2008), which ultimately serves to stabilize an organism's homeostasis (Fig. 1).

While working with an entire organism (e.g. a mutant mouse), one has to keep in mind that BDNF may not only be controlled by antidepressive treatment, but is also influenced by other external factors, such as housing conditions, communal nesting and the access to physical exercise (Berchtold et al., 2002; Branchi et al., 2006a,b; Chourbaji et al., 2008a; Fuss et al., 2009; Neeper et al., 1996; Russo-Neustadt et al., 2001; Turner and Lewis, 2003). Recent work has thus shown that enriching the environment induces various molecular and cellular changes in particular brain regions of wildtype animals, including changes in gene expression, enhanced neurogenesis and synaptic plasticity (Branchi et al., 2006a,b; Mohammed et al., 2002; Nguyen and Woo, 2003; Spires and Hannan, 2005; Turner and Lewis, 2003; van Praag et al., 2000; Zhu et al., 2006), which might interfere with any kind of drug treatment (e.g. by pronunciation or amelioration of the expected effects). Hereby it is interesting to note that enriched environments also affect animals with a lack of BDNF (BDNF heterozygous animals), but less pronounced (Zhu et al., 2009) Therefore it seems a promising approach to investigate the role of BDNF in the pathophysiology and treatment of depression, from a genetic and also an environmental point of view.

4. BDNF-mutant mice: models for depression?

Genetically modified mice that either over-, or underexpress the neuronal growth factor BDNF theoretically represent valuable tools in the study of the role of BDNF in development, physiology and behaviour (Conover et al., 1995; Croll et al., 1999; Ernfors et al., 1994; Kernie et al., 2000). To assess decisive clinical parameters with regard to depression and emotionality, several

Table 2
Evaluation of mouse models for depression and anxiety: The diagnostic and statistical Manual IV diagnosis comprises characteristic symptoms with regard to depression and anxiety. For a great number of symptoms it is possible to transfer them, however, some particular symptoms like feelings of guilt, suicide and loss of controllability may not be mimicked in animals.

How to model in mice...	
Depressive-like alterations	Applicable methods
Anhedonia	Intracranial self-stimulation Sucrose consumption Social withdrawal
Helplessness/hopelessness	Learned helplessness (LH)
Despair behaviour	Forced swim test (FST), tail suspension test (TST)
Changes in appetite/weight	Weight monitoring
Changes of sleep structure	Electroencephalography
Psychomotor dysregulation	Openfield (OF) Homecage monitoring
Loss of energy	Wheel running/homecage monitoring Observation of sexual activity Observation of nestbuilding Awake EEG
Decreased ability to think/concentrate	T-Maze testing Watermaze 8-arrn-radial maze
Inability to perform minor tasks (e.g. selfcare)	Fur scoring
Thoughts of suicide	None
Feelings of guilt/worthlessness	None
Emotional changes	Applicable methods
Agoraphobia	Dark–light box (DLB) Openfield (OF)
Social phobia	Social interaction
Specific phobia	Conditioned taste avoidance
Post traumatic stress dsorder	Fear conditioning (cue and/or context) (FC)
Obsessive compulsive behaviour	Marble burial
Changes of sleep structure	Electroencephalography
Autonomic hyperarousal	Stress-induced hyperthermia
Flashback of trauma	Fear conditioning (cue and/or context) (FC)
Increased startle response	Startle response test
Separation anxiety	Maternal separation, ultrasonic vocalization
Loss of control during panic	None

meanwhile well-established behavioural paradigms have been created (Table 2). In recent years many lines of mice carrying different mutations of BDNF have been designed to explore the role of this neurotrophin with regard to depression (Table 3).

However, BDNF-mutant mice bear a number of problems: The detailed investigation of BDNF in living animals (e.g. assessing a gene-dosage effect in homozygous and heterozygous mice) is restricted due to the lack of possibility to examine animals carrying a null mutation of this neurotrophin, since such mice are not viable (Conover et al., 1995; Ernfors et al., 1994). Hereby and in any other transgenic strategies, one has to keep in mind that a heterozygous mutation resembles the situation in humans more closely, since a complete knockout causing a depressive state is very unlikely to occur naturally in humans. Mutant mice, in which only 50% of BDNF is deleted (BDNF+/−) are viable, though, but controversially discussed to represent valid animal models for depression. This results from a number of studies, which could not identify any depressive-like alterations in mice with a heterozygous mutation of the BDNF gene (Chourbaji et al., 2004; MacQueen et al., 2001). When examined for hedonic features, which were assessed in a sucrose consumption analysis, mutant mice failed to demonstrate depression-characteristic changes (Chourbaji et al., 2004; MacQueen et al., 2001). One of the most problematic points with regard to the characterization of a depressive phenotype is the altered pain sensitivity of BDNF heterozygous animals, which does not allow a valid behavioural characterization by means of the "learned helplessness" paradigm (MacQueen et al., 2001). This, however, represents an other interesting aspect, since it was recently described that depressed patients have an increased pain threshold for externally administered pain (Schwier et al., 2010). On the other hand, there are other common and representative depression tests to assess pathological alterations, e.g. FST or the TST (Porsolt et al., 1977; Steru et al., 1985). When analyzed in these paradigms, BDNF+/− mice fail to present a depressive-like phenotype (Chourbaji et al., 2004; MacQueen et al., 2001). It has therefore been argued that compensatory mechanisms possibly accommodate the chronic low levels of BDNF which results in an essentially normal behavioural profile.

However, mice with a conditional depletion of BDNF, showed a depressive-like phenotype in the TST, but not FST (Chan et al., 2006). Measures of anxiety were not changed in these mice when examined on the elevated plus maze (EPM) (Chan et al., 2006). Contrary, in a former study the same group had demonstrated an increased anxiety-like behaviour in the light-dark exploration test (Rios et al., 2001). Earlier studies, which analyzed different mouse strains in terms of anxiety-like behaviour, stated that behavioural discrepancies may be caused by different test situations (van Gaalen and Steckler, 2000), e.g. by the fact that the EPM is considered more stressful than a free exploration paradigm and that impulsivity-related approach behaviour impacts the performance in avoidance tests (Cryan and Holmes, 2005). Interestingly, not only the test conditions but also the selection of the gender seems to be a critical point. The group of Monteggia published a study in which depression-related behaviours of both genders of forebrain-conditional knockout mice were compared (Autry et al., 2009). Here is was shown that only in females this mutation affected the classical depressive-like behavioural performance (e.g. decreased sucrose preference, bad fur score) without any effects on locomotion, while males demonstrated hyperactivity and no change in depressive-like behaviour (Autry et al., 2009).

While such inconsistent findings evoke reasonable doubts, one may not fully declare or reject BDNF heterozygous mice as animal models for depression, and it remains debatable, whether they could represent models for a *predisposition* for depression (Groves, 2007). It could be argued that the reduction of 50% may not be sufficient to cause an obvious depressive phenotype, but possibly these mice are rendered more vulnerable to develop an emotional phenotype when exposed to a stressful context (see also "BDNF-mutant mice: models for emotionality"). Indeed stressful environmental conditions produced an emotional phenotype while enrichment evoked a rescue on the behavioural level. Therefore it should be noted that BDNF+/− mice may not directly elucidate pathogenetic effects, but in combination with particular environmental conditions, they should be considered in terms of "proneness for depression" in future experiments. On the level of corticosterone regulation and sleep this proneness may also be observed in humans as it was shown in the "Munich vulnerability study" (Friess et al., 2008). In this study it was demonstrated that healthy relatives of depressed patients show characteristic endophenotypes. This underscores the potential of animal models, in which distinct genetic predispositions may be investigated to increase the knowledge about possible underlying mechanisms in the development of depression.

To fully comprehend how and if the mutation of BDNF affects the behavioural phenotype of the respective mutant lines, is essential to recognize, that the overexpression of BDNF causes antidepres-

Table 3
BDNF-mutant mice and their validity to be used as mouse models for depression: Since the complete knockout of BDNF is lethal and BDNF homozygous mice are therefore not available for detailed behavioural analyses, several alternative strategies have been developed to investigate the consequences of increased/decreased levels of this neurotrophin. While heterozygous animals fail to represent an obvious depressive phenotype, the conditional forebrain-specific knockout produces controversial findings depending on test conditions or gender, respectively. *Abbreviations*: FST = Forced Swim test, NA = noradrenaline, DA = dopamine, cort = corticosterone, ACTH = adrenocorticotrophic hormone, TST = Tail suspension test. Referring Literature: (Adachi et al., 2008; Autry et al., 2009; Chan et al., 2006; Chourbaji et al., 2004; Govindarajan et al., 2006; Ibarguen-Vargas et al., 2009; MacQueen et al., 2001; Monteggia et al., 2007).

Mutation	Study	Decisive parameters assessed	Depression model	Comments/restrictions
BDNF heterozygous ko	MacQueen et al. (2001)	FST, Learned Helplessness, anhedonia	No	Altered pain sensitivity, LH questionable
BDNF heterozygous ko	Chourbaji et al. (2004)	Serotonergic system, NA, DA, FST, cort.ACTH	No	
Conditional BDNF ko (fetal and postnatal)	Chan et al. (2006)	TST, FST	Yes/no	TST: depressed, FST: not depressed
Conditional BDNF ko (hippocarnpus/forebrain)	Monteggia et al. (2007)	Anhedonia, FST	Yes/no	Gender-specific: females yes, males no
Hippocampus specific BDNFko (DG, CA1)	Adachi et al. (2008)	Anhedonia, FST	No	DG: attenuation of antidepressants
Forebrain-specific inducible BDNF ko	Autry et al. (2009)	Anhedonia, TST, FST, cort, fur scoring	Yes/no	Gender-specific: females yes, males no
BDNF heterozygous ko	Ibarguen-Vargas et al. (2009)	Fur scoring, TST, cort	No	
Mutation	Study	Indicative parameters	Resistance to depression	Comments/restrictions
BDNF overexpression	Govindarajan et al. (2006)	Hippocampal atrophy, FST	Yes	

sive effects in the FST (Govindarajan et al., 2006) (as one would expect it). This effect may be modulated by the serotonergic or noradrenergic systems, which are affected in BDNF-mutant mice, and which are both discussed to be crucial factors in the pathophysiology of mood disorders (Daws et al., 2007; Duman et al., 1999; Ressler and Nemeroff, 1999; Vaidya et al., 1997). Hence, what becomes obvious when working with mice carrying mutations of BDNF, is the fact, that here theoretic assumptions concerning particular features of depression are not easy to realize in practical courses, which may be caused by the abstractness of these animal models or the miscellaneous function of BDNF, which is hard to capture.

5. BDNF-mutant mice: models for emotionality?

Since transitions are smooth between defined depressive-like characteristics and emotional alterations, it is important to address this point separately. While a major part of the studies performed with BDNF-mutant mice failed to detect obvious depressive phenotypes, there are other studies, which describe BDNF dependent alterations on the emotional level (Table 4).

Such examinations include the observation of aggressive characteristics (e.g. coping in the resident-intruder paradigm) in viral-mediated, mesolimbic dopamine pathway-specific knockdown BDNF animals (Berton et al., 2006), heterozygous mice (Lyons et al., 1999) and a conditional knockout model (Chan et al., 2006). Further experiments assess anxiety-related behaviour in mice with a genetic variant BDNF (Val66Met) polymorphism (Chen et al., 2006) and with a conditional deletion of BDNF (Rios et al., 2001). However, there are also studies, which show that if the mutation of BDNF is restricted to the forebrain, it does not induce alterations of anxiety (Gorski et al., 2003). In addition there are findings, which demonstrate hyperactivity in BDNF heterozygotes (Duan et al., 2003) and conditional knockouts in a time-dependent pattern,

Table 4
BDNF-mutant mice and their validity to be used as mouse models for emotionality: Many mutant strains have been analyzed in terms of alterations in locomotion, exploration, anxiety and particular types of learning. The presented potential mouse models for emotionality were not conform to suggest a change of BDNF to be directly involved in emotional behaviour, but it seems obvious that external conditions like housing or gender have a great impact on the outcome of the experiments. *Abbreviations*: OF = Openfield, EPM = Elevated Plus Maze, BW = Black White, NO = Novel Object, FC = Fear Conditioning, DLB = Dark–Light Box. Referring Literature: (Adachi et al., 2008; Autry et al., 2009; Chan et al., 2006; Chen et al., 2006; Chourbaji et al., 2008a; Duan et al., 2003; Gorski et al., 2003; Lyons et al., 1999; MacQueen et al., 2001; Monteggia et al., 2007; Rios et al., 2001).

Mutation	Study	Indicative parameters	Model for emotional behaviour	Comments/restrictions
BDNF heterozygous ko	Lyons et al. (1999)	Aggression, OF	Yes	
Conditional BDNF ko in brain (postnatal)	Rios et al. (2001)	Novel cage exploration, dark–light exploration	Yes	
BDNF heterozygous ko	MacQueen et al. (2001)	OF, NO, EPM, staircase test	No	
Forebrain-specific BDNF ko	Gorski et al. (2003)	FC, OF, BW and mirror chamber	No	
BDNF heterozygous ko	Duan et al. (2003)	Locomotion	Yes	
Val66Met	Chen et al. (2006)	Context conditioning, aggression, OF, EPM	Yes	
Conditional BDNF ko (fetal and postnatal)	Chan et al. (2006)	Locomotion, aggression, EPM	Yes	
Conditional BDNF ko (hippocarnpus/forebrain)	Monteggia et al. (2007)	OF, EPM	No	Gender-specific: females less anxious, males hyperactive
Hippocampus specific BDNF ko (DG, CA1)	Adachi et al. (2008)	Locomotion, EPM, FC	No	
BDNF heterozygous ko	Chourbaji et al. (2008a,b)	OF, NO, DLB.T-maze	Yes	Dependent on housing conditions
Forebrain-specific inducible BDNF ko	Autry et al. (2009)	Locomotion, OF, novelty-suppressed feeding	Yes	Gender-specific

i.e. when the conditional knockout in broad forebrain regions is induced early in development (Chan et al., 2006; Monteggia et al., 2004). Remarkably, when the knockout becomes activated in adulthood, these mice demonstrate normal locomotor behaviour (Monteggia et al., 2004). Contrarily hypoactivity has been detected in mice with a forebrain-restricted mutation of BDNF (Gorski et al., 2003). Furthermore, effects on locomotion seem to be gender specific, since animals with an inducible forebrain-specific BDNF knockout (during infancy) presented different phenotypes in locomotion, whereby males in contrast to females presented hyperlocomotion (Autry et al., 2009). Interestingly, when these animals undergo a chronic unpredictable stress (CUS) procedure, females demonstrate significantly decreased locomotion, while males are not affected (Autry et al., 2009). This gender-specific pattern may, however, not be generally transferred, Though, BDNF heterozygous mice develop an emotional phenotype when housed under particular stressful conditions, while the same mutant line reared in "enriched" environments does not present any emotional alterations (Chourbaji et al., 2008a). This may suggest that such inconsistent findings could result from an interaction of internal (genetic) and external (environmental) factors, which, if employed adequately, can contribute to investigate epigenetic mechanisms regulating a potentially increased vulnerability regarding emotional and depressive-like symptoms.

Another important analysis with regard to emotion is the "fear conditioning" paradigm, a standard procedure to assess hippocampus-, and amygdala dependent alterations of emotional learning. When exposed to this test situation there are also controversial findings in BDNF-mutant mice. Liu et al. and Monteggia were able to demonstrate a critical role of a heterozygous mutation (Liu et al., 2004), and inducible forebrain-specific knockout (at an early stage of development) in terms of emotional learning, i.e. fear conditioning performance (Monteggia et al., 2004). Other studies, however, did not find any effect in contextual and cued fear conditioning in BDNF+/− mice (Chourbaji et al., 2004) or mice with an either dentate gyrus,- (DG) or CA1-specific knockout of BDNF (Adachi et al., 2008).

6. Beneficial and detrimental environmental conditions in mice

The quality of environment plays an essential role in the pathophysiology of stress-related diseases such as depression. This has been recognized for human patients, but also for experimental animals. Enriched environment in mutant mice for instance is not only essential to preserve animal welfare and improve the quality of experimental results in animals, which are then able to behave more naturalistic and exploit their behavioural repertoire, but it is equally important to consider in terms of environmentally induced diseases (Chourbaji et al., 2008a; Fox et al., 2006) (see Picture 1).

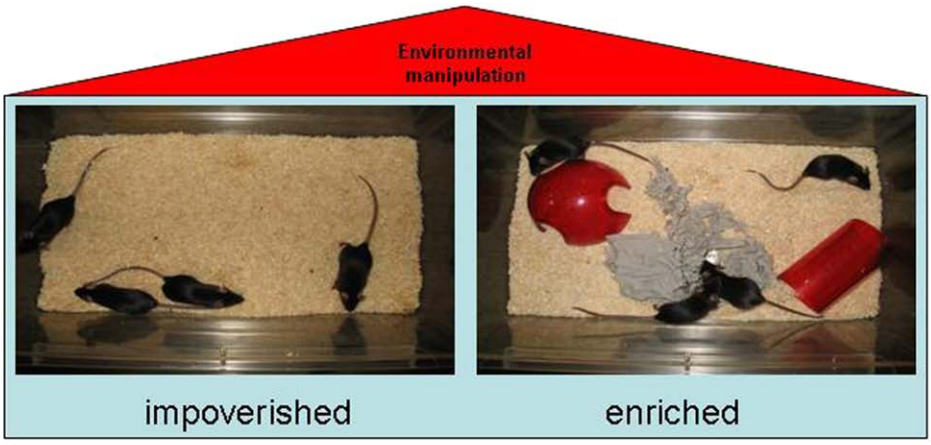
According to recent findings, especially early environmental experiences exert profound effects on e.g. the behavioural phenotype of MeCP2 null mice (Lonetti et al., 2010) or wildtype mice housed under a particular type of enrichment such as communal nesting (Branchi et al., 2006a) or housing with multi-access to running wheels, nesting material, different objects, etc. (Viola et al., 2010). Furthermore it is known that specific early experiences such as maternal separation (i.e. a poor environmental condition) decrease adult BDNF levels (Cirulli et al., 2003), while e.g. the above mentioned communal nest (i.e. a beneficial form of environment) leads to an increase of NGF as well as BDNF in many brain regions (Branchi et al., 2006a). Interestingly, different periods of exposition to an enriched environment may exert various effects on e.g. BDNF and (full-length or truncated) TrkB levels in the rat visual system, which may be up-, or down-regulated dependent on the duration of exposition (Franklin et al., 2006). This indicates that not only the quality of a respective surrounding, but also the timing of the exposition to a "beneficial" or "detrimental" condition plays a key role in modulating behavioural as well as physiological effects. Hereby enriched environment is proposed to exert sustained epigenetic modification increasing hippocampal BDNF mRNA (Kuzumaki et al., 2010).

Environmental enrichment evokes profound neurochemical, neuroanatomical and behavioural alterations, including e.g. experience-dependent plasticity (for review see (Nithianantharajah and Hannan, 2006)), and sex-specific changes in serotonin, noradrenaline and dopamine (Beck and Luine, 2002; Naka et al., 2002; Ren-Patterson et al., 2006) which have been proven in many studies (for reviews see (Mohammed et al., 2002; van Praag et al., 2000)). Hereby the hippocampus has been shown to be one of the most susceptible brain areas regarding enriched husbandry, with different distribution of neurotrophins in the dorsal and ventral part (Zhu et al., 2006) as well as BDNF driven enhancement of hippocampal neurogenesis (Rossi et al., 2006). Moreover it was shown that environmental enrichment regulates gene expression in the striatum of mice, especially coding for proteins involved in cell structure-, proliferation-, and differentiation, signal transduction, transcription, translation as well as metabolism (Thiriet et al., 2008).

Particularly emotional features such as anxiety in the EPM and in the openfield were described to be affected by certain conditions, e.g. stimulating environment (plastic igloos, houses, and running wheels) or handling the animals (Chapillon et al., 1999; Fernandez-Teruel et al., 2002; Wolfer et al., 2004; Zhu et al., 2006). In our hands, as mentioned above, BDNF heterozygous mice reared in a stimulating environment were indeed protected from developing an emotional phenotype while BDNF-mutant mice reared under impoverished conditions presented an emotional phenotype (Chourbaji et al., 2008a). In contrast, in a recent study of Ibarguen-Vargas, poor environmental quality – produced by chronic unpredictable stress – did not increase the stress vulnerability of BDNF heterozygous mice. (Ibarguen-Vargas et al., 2009). Besides the predominantly beneficial effects on behaviour exerted by enrichment, it has been shown that environmental conditions like physical exercise, dietary restriction or specific motivating housing conditions may evoke variations in BDNF levels in particular brain regions. Especially in the hippocampus an elevation of BDNF mRNA and protein could be demonstrated (Falkenberg et al., 1992; Gobbo and O'Mara, 2004; Ickes et al., 2000; Pham et al., 2002). We substantiated such findings, showing that environmental enrichment increases BDNF levels on protein-, and mRNA level in both wildtypes and BDNF heterozygous male mice (Chourbaji et al., submitted). Furthermore, it was shown that even the exposure to behavioural testing itself may induce complex changes of neurotrophin levels, i.e. hippocampal BDNF and NGF (Zhu et al., 2006), a fact which suggests that any kind of incentive activates the neurotrophic system. Remarkably, there are gender-specific differences regarding BDNF regulation to respond to stressful situations such as e.g. a chronic mild stress paradigm, which may be explained by different stress sensitivity in both genders (Autry et al., 2009; Zhu et al., 2006). Environment-regulated gender differences are furthermore described in mice with a forebrain-specific knockout, in which a particular stress paradigm evokes a female-specific increased proneness to show depressive-like symptoms (Autry et al., 2009).

At this point, one should keep in mind that different housing procedures such as single or group housing provide different social environments (more or less enriching the animals' lives) that may oppositely induce mild stress in males and females (Palanza et al., 2001) or different mouse strains (Marashi et al., 2004). With regard to the potentially higher stress score in group-housed males, it is also important to consider a possible interaction between

(A)



An example for different environmental conditions, as we use them in our lab: Mice are housed with four littermates of the same gender in type III cages for 6-8 weeks under a reversed dark-light cycle. Impoverished cages contain only sawdust, while enriched cages are additionally equipped with plastic tunnels and igloos as well as tissue material. The animals are monitored daily, the cages are cleaned weekly. Water and regular food pellets are available ad libitum. Housing the animals under respective conditions was approved by german animal welfare authorities.

(B)

Stressful environmental conditions	Effects on BDNF mutant animals/ Effects on BDNF levels in wildtype animals
-Impoverished environment (see above, Chourbaji, 2008)	-emotional phenotype in both genders of BDNF heterozygous mice
-Unpredictable chronic mild stress (UCMS): altered bedding, cage-tilting or shaking, induced defensive posture, changed light conditions on a „random" schedule. (Ibarguen-Vargas, 2009).	-no effect on the stress vulnerability of BDNF heterozygous mice, but shapes antidepressive response
-Chronic unpredictable stress (CUS): food/water deprivation, changed light conditions, cage tilting, isolated housing, wet bedding, rat feces exposition (Autry, 2009)	-female-specific increase of vulnerability to develop emotional and depressive-like symptoms

Beneficial environmental conditions	Effects on BDNF mutant animals/ Effects on BDNF levels in wildtype animals
-Communal nesting (CN): Three mothers kept in one cage with their pups (Branchi, 2006, 2006)	-increased BDNF levels in the hippocampus, striatum and hypothalamus of wildtype animals deriving from the CN, increased anxiety and depression-like behaviour in the FST
-Dietrary restriction (DR): restriction by fasting animals for 24 h on alternate days (Koizumi, 2006)	-ameliorated emotionality and increased serotonin levels in BDNF heterozygous animals
-Enriched environment (see above, Chourbaji, 2008)	-rescue of a phenotype in both genders of BDNF heterozygous mice
-Enriched environment : 13/14 mice in large cages equipped with ladders, shelters, tunnels, toys changed twice a week(Zhu, 2009)	-impact on exploratory behaviour and increase of dendritic spines in male wildtype and to a lesser extent also in BDNF heterozygote mice
- Voluntary exercise: wheel Running (Fuss, 2010)	-increase of BDNF and anxiety behavior, increased corticosterone metabolites in feces

Picture 1. Modulating housing conditions for C57Bl/6 mice: Mice housed under stressful or beneficial conditions exhibit different vulnerabilities to develop depressive-like features. The studies depicted here exemplify how environmental conditions may interfere with the regulation of BDNF, either in mice with a mutated genetic background or wildtype mice, in which the effects of an external stimulation on the expression of BDNF was examined. Referring Literature: (Autry et al., 2009; Branchi, 2008; Branchi et al., 2006a; Chourbaji et al., 2008a; Fuss et al., 2009; Ibarguen-Vargas et al., 2009; Koizumi et al., 2006; Zhu et al., 2009).

social and structural environments. In a study of Haemisch et al. it was reported for DBA/2J male mice that keeping those animals in enriched cages can also result in increased aggression (Haemisch et al., 1994). On the other hand it was shown that if enrichment was offered to the AGB inbred strain, it exerted only positive effects in male mice like increased general activity and playing, without adverse effects on behaviour, physiology, and standardization (Marashi et al., 2004). In a study in which three laboratories independently investigated the effects of enrichment in four commonly used behavioural tests, it was also confirmed that the enrichment did not increase individual variability or the risk of obtaining conflicting behavioural data in replicate studies (Wolfer et al., 2004). Hereby there is no consensus about which types of environmental enrichment (steady access, varying objects, cage size, group constellation, etc.) are ideal with respect to beneficial effects on brain plasticity and behaviour, which is caused by the great number of mouse strains, handling procedures, experimental designs.

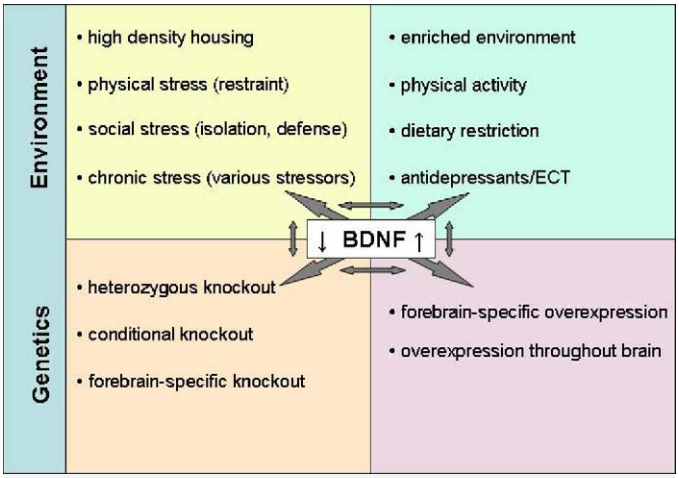
According to such results, it seems mandatory to regard the modulating effects of different environmental conditions. Thus, being aware of the aversive or beneficial effect, it represents an interesting goal to examine the role of BDNF in depression by combining "internal" factors (genetic background, targeted mutation, gender) with "external" factors (housing, social environment). Procedural methods that consider such potential interactions bear the advantage of a higher construct validity, which often poses a challenge, especially when working with multifactorial diseases such as that may be evoked by a genetic vulnerability and/or stressful experiences.

7. Depression: genes or environment?

Since depression may be "endogenous", i.e. occurring without any obvious reason, or "reactive", i.e. evoked by detrimental external factors (e.g. unemployment, death of a beloved person), it is hard to tell, if depression is a more environmentally or genetically induced disease and certainly both aspects affecting the target gene BDNF have to be considered as important in the pathophysiology and treatment of this illness (see Table 5). Furthermore there is a great individual variation concerning the ability to recover both in mice and men, a phenomenon which is yet poorly understood.

Apart from the mutant mouse strains that were generated to clarify the development of depressive-like phenotypes, defined environmental stressors such as isolation, defence, etc. have to be regarded critically in the respective strains in terms of inducing depression (see Picture 1). Moreover, external stressors may be not be related only to depression, but also to "vulnerability" and "resilience" in terms of recovery (Schmidt et al., 2009). Furthermore, it is known, for instance that wildtype animals kept under stressful conditions such as "impoverished" group housing are more prone to display a depressive-like phenotype (Chourbaji et al.,

Table 5
Regulation of BDNF expression: BDNF is influenced by several internal and external factors, such as environmental conditions ("Environment") and genetic aspects ("Genetics"). Environment-related facets with a negative impact on BDNF levels are poor environmental stimulation as well as different types of stressors. Contrary, environmentally driven factors may exert beneficial effects induced e.g. by enriched surroundings, physical activity, balanced nutrition as well as antidepressive treatment (including electroconvulsive therapy (ECT)). Regarding the regulation of BDNF by genetics, it is known, that different variants of mutating the BDNF gene results in quantitative changes of this neurotrophin in different regions, hereby inducing increased or decreased expression, respectively. Besides these effects, there is a stong interplay between the genetic-, and environment-regulated BDNF expression, e.g. distinct environmental conditions may shape the experimental outcome due to a genetic predisposition. On the other hand, a certain genetic background may facilitate the impact of external manipulations, such as stress-sensitivity or response to antidepressive treatment. Referring Literature: (Adachi et al., 2008; Barrientos et al., 2003; Bjornebekk et al., 2008; Branchi et al., 2006a; Chourbaji et al., 2008a; Chourbaji et al., 2004; Croll et al., 1999; Duan et al., 2003; Duman and Monteggia, 2006; Falkenberg et al., 1992; Gobbo and O'Mara, 2004; Gorski et al., 2003; Ickes et al., 2000; Koizumi et al., 2006; Nibuya et al., 1995; Palanza et al., 2001; Pham et al., 2002; Pizarro et al., 2004; Rios et al., 2001; Rossi et al., 2006; Russo-Neustadt et al., 2001; Smith et al., 1995b; Torasdotter et al., 1998; Zhu et al., 2006).



2005; Karolewicz and Paul, 2001). Additionally, particular adverse social constellations, such as the exposure to potential rivals, may induce increased depression-related behaviour as demonstrated by increased immobility in the FST and TST, which is in agreement with the consideration of social interaction as an important factor regarding stress vulnerability in demanding situations in humans and animals (Calvo-Torrent et al., 1999; Cobb, 1976; Karolewicz and Paul, 2001; Monleon et al., 1995). This suggests that environmental factors may serve as a source of stress sufficient to evoke pathological alterations in "normal" subjects.

Supporting the importance of external stress are studies, which describe depressive-like or emotional phenotypes only in a distinct environmental constellation. In such studies it could be demonstrated that a hypothesized genetic predisposition induced by a heterozygous knockout of the glucocorticoid receptor (GR) alone did not induce depressive-like alterations, while the exposition of the subjects to stress, evoked a clear phenotype (Chourbaji et al., 2008a; Ridder et al., 2005). Since environmental conditions may induce compensational effects or, contrarily, increase the pathogenetic risk, it is essential not to focus on genetic aspects alone, but to consider the combination of the factors, which could be decisively linked to the modulation of a disease state. Though gaining further insights into such mechanisms supports not only the clarification of the pathophysiology of this disease, but may also help to develop new "therapeutical" approaches. Thereby it could be of great importance to improve the responsiveness of antidepressive therapies by combining promising medication with concrete beneficial environmental conditions, which enormously support the success of modern psychiatry in an adequate way.

8. Conclusion and preview

Mouse models for depression state a valuable tool for the investigation of human diseases such as depression. Despite the fact that not all aspects of the human disease can be mimicked by animals (i.e. feelings of guilt, suicide), such models provide important insights into relevant mechanisms involved in pathophysiology and treatment of this disease, and thus facilitate the detailed investigation of endophenotypes or drug-regulated therapeutic mechanisms.

According to current findings and studies, BDNF represents an important aspect in psychiatric research (especially with regard to depression and anxiety disorders) that is modulated by many internal and external factors. The lack of consistent results confirming the neurotrophin hypothesis of depression, however, raises the question, whether BDNF by itself may be the only explanatory factor within this theory. BDNF might be differently involved in particular processes in depression and may be more important for antidepressive therapy than for pathophysiological courses. On the other hand, it still remains unclear why there are so many non-responding patients, where antidepressive treatment does not exert sufficient positive effects which would be predicted by current hypotheses.

What may be concluded, however, is an involvement of the neurotrophic cycle in depression-related contexts. Hereby it seems obvious that the regulation of BDNF, given by a specific genetic predisposition or induced by stress or epigenetic mechanisms, plays a crucial role at least with regard to the vulnerability. With respect to current concepts, it remains to be investigated which systems may be affected by BDNF directly or indirectly, and in which chronological order they possibly exert effects on depressive-like alterations on the behavioural, stress-physiological and/or morphological level. Further exploration about potential systems that could be linked to BDNF-directed alterations would also be expected to be helpful in combined depression treatments, where physiological and environmental factors might act in a synergistic way and therefore improve health and stabilize homeostasis.

An alternative approach would not only be directed at neurotrophins in their mature form, but also consider pro-neurotrophins that regulate e.g. synaptic plasticity bidirectionally. In a recent article by Lu et al. this topic was addressed and described as the "Yin and Yang" of neurotrophins (Lu et al., 2005). The fact that those pro-neurotrophins can have opposite biological effects than mature ones by interacting with different receptor systems has been a great progress in neurotrophin research and would be an interesting aspect to imply in the investigation of environmental-induced pathophysiological changes in mice and men.

For clinical research the most important aim obviously is an improvement of ameliorating acting treatments of depression. Thus new strategies target at overcoming the long latency of antidepressive efficiency and the questionable potency of the common medication. Since the current hypotheses cannot fully explain the pathophysiology and therapy of depression and it is not possible to generally transfer such theoretical concept to animal models or the human situation, there is an immense need to revise, e.g. the neurotrophin hypothesis of depression and to imply the details and restriction from previous studies. This more focussed perspective of this hypothesis would bear the advantage of being able to optimize potential targets for novel drugs or psychotherapeutic approaches possibly by combining particular (epi-)genetic and environmental factors, which act complementary.

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