Neuronal plasticity: A link between stress and mood disorders

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Summary
Although stress represents the major environmental element of susceptibility for mood disorders, the relationship between stress and disease remains to be fully established. In the present article we review the evidence in support for a role of neuronal plasticity, and in particular of neurotrophic factors. Even though decreased levels of norepinephrine and serotonin may underlie depressive symptoms, compelling evidence now suggests that mood disorders are characterized by reduced neuronal plasticity, which can be brought about by exposure to stress at different stages of life. Indeed the expression of neurotrophic molecules, such as the neurotrophin BDNF, is reduced in depressed subjects as well as in experimental animals exposed to adverse experience at early stages of life or at adulthood. These changes show an anatomical specificity and might be sustained by epigenetic mechanisms.

Pharmacological intervention may normalize such defects and improve neuronal function through the modulation of the same factors that are defective in depression. Several studies have demonstrated that chronic, but not acute, antidepressant treatment increases the expression of BDNF and may enhance its localization at synaptic level. Antidepressant treatment can normalize deficits in neurotrophin expression produced by chronic stress paradigms, but may also alter the modulation of BDNF under acute stressful conditions. In summary, there is good agreement in considering neuronal plasticity, and the expression of key proteins such as the neurotrophin BDNF, as a central player for the effects of stress on brain function and its implication for psycho-pathology. Accordingly, effective treatments should not limit their effects to the control of neurotransmitter and hormonal dysfunctions, but should be able to normalize defective mechanisms that sustain the impairment of neuronal plasticity.

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1. Neuronal plasticity and psychiatric illness

Neuronal plasticity refers to the ability of the nervous system to respond and adapt to environmental challenges and encompasses a series of functional and structural mechanisms that may lead to neuronal remodelling, formation of novel synapses and birth of new neurons. However, in a broader sense, neuronal plasticity is intimately linked to cellular responsiveness and may therefore be considered an index of the neuronal capability to adapt its function to a different demand. Failure of such mechanisms might enhance the susceptibility to environmental challenges, such as stress, and ultimately lead to psychopathology. That is to say that the brain, or more specifically, some brain structures or circuits, may become more vulnerable by losing progressively (or suddenly) the ability to adapt and maintain their homeostasis. The manifestation of such vulnerability can be quite different according to the pathologic condition and may lead to overt degeneration (as occurring in neurodegenerative disorders) or to more subtle changes, leading to functional impairment, which represents a feature of psychiatric illness.

During the last few years it has indeed become apparent that several psychiatric conditions, such as mood disorders, are associated with deficits or impairment of neuronal plasticity (Castren, 2005; Krishnan and Nestler, 2008; Pittenger and Duman, 2008). Although for many years depression has been linked to abnormalities in monoaminergic neurotransmission, it is now well accepted that this condition is characterized by profound alterations of brain function and responsiveness. Hence depressed subjects display an inability to cope or adapt to the environment and may be more vulnerable to challenging experiences. These abnormalities may be intimately linked with neuronal plasticity and the ability to modulate a cascade of events from intracellular signaling mechanisms to gene expression.

Although the individual susceptibility threshold to environmental events may be genetically determined, it is believed that life events occurring during brain development may be critical for later psychopathology. Traumatic experiences occurring early in life may herein disrupt the correct program of maturation and eventually impact on brain function leading to a deterioration of neuronal plasticity. Indeed the brains of depressed subjects show structural abnormalities and reduced expression of several markers for neuronal function and viability, among which neurotrophic factors seem to be playing a pivotal role (aan het Rot et al., 2009; Sheline et al., 2003).

These new concepts imply a reconsideration of the mechanisms that may be relevant for clinical achievements. In agreement with the well-known delay for therapeutic responses, psychotropic drugs, should be able to restore these defective systems around a physiological set point in order to alleviate symptoms and reduce the susceptibility to environmental challenges. In a word, these treatments might contribute to maintain stability.

We will discuss neuronal plasticity in the context of stress-related situations and mood disorders by focusing on neurotrophic factors, and in particular the neurotrophin brain-derived neurotrophic factor (BDNF), although several other mechanisms should also be taken into account, since most of these systems are interrelated and may represent different facets of the same condition.

2. Stress and susceptibility to mood disorders

Stress represents the major precipitating factor in mood disorders. It may be inferred that affected subjects have a different threshold for stress susceptibility, which means that mechanisms that are required to cope with stress can be altered or less functional. The effects of stress on brain function depend on the timing and duration of the adverse experience. As already mentioned, adverse events early in life can be particularly relevant for later psychopathology since they will impact on structures that are not fully matured. According to the period when the adverse experience is taking place, different structures can be affected. Another critical factor is the duration of the stressful experience according to the concept of allostatic and allostatic load (McEwen, 2000). Indeed the same mediators or system involved in the adaptation to acute challenges, can also participate in pathological effects determined by prolonged repetitive exposure to stressful conditions. For example within the hippocampus, a mild stress can enhance learning and memory (Luine et al., 1996), whereas chronic or severe stressors, as well as high doses of glucocorticoid, have detrimental effects on hippocampus dependent memory (Sapolsky, 2003) and impair LTP (Kim and Diamond, 2002). Sustained stress or glucocorticoid levels can lead to neuronal atrophy, in hippocampus and prefrontal cortex, whereas other regions, such as the amygdala, can become hypertrophic (Sapolsky, 2003). These changes resemble functional and structural alterations found in depressed subjects (aan het Rot et al., 2009; Sheline et al., 2003), suggesting that they may indeed represent a long-lasting consequence of stress on a vulnerable individual.

Several mechanisms can be responsible for these alterations. First of all there is a well-established dysfunction of the hypothalamus–pituitary–adrenal (HPA) axis, according to which altered expression and function of glucocorticoid receptors in the hypothalamus and the hippocampus may lead to reduced feed-back that is responsible for elevated levels of circulating glucocorticoids and protracted responses.
to stressors. However the effects of stress on brain structure and function, and its possible relationship to depression susceptibility, may also be mediated by an impairment of neuronal plasticity. According to this possibility stress can modulate a series of mechanisms that are important for neuronal resilience. If under acute conditions some of these mechanisms can be ‘protective’ or may activate ‘defensive’ pathways, more protracted adverse experiences can produce an impairment of such mechanisms that will ultimately lead to reduced neuronal plasticity. Within this context, neurotrophic factors may play a central role. Some of these factors, such as the neurotrophin BDNF, are valuable markers of neuronal plasticity and may therefore represent an important element in order to understand the relationship between stress and mood disorders. We will recapitulate evidence for the involvement of trophic molecules, in particular BDNF, in stress and major depression.

3. Neurotrophic factors as markers of plasticity

Network construction and reorganization, which are the main processes involved in neuroplasticity, are regulated by the level and pattern of synaptic activity generated in the nervous system. The discovery that excitatory neurotransmitters can stimulate new gene transcription by triggering an influx of calcium into postsynaptic suggested a mechanism by which stimulus-evoked neuronal activity might lead long-lasting changes in the structure and function of the nervous system. Specifically, activity-dependent gene expression occurs when the calcium influx induced by synaptic activation initiates calcium-dependent signaling cascades that drive gene expression through the activation of specific transcription factors (West et al., 2002). Among the activity-regulated genes responsive to neuronal activity, neurotrophic factors (NTFs), and in particular the neurotrophin family, play an important role. In fact, besides their classical role in supporting neuronal survival, NTFs finely modulate all the crucial steps of network construction, from neuronal migration to experience-dependent refinement of local connections (Poo, 2001). These functions were first reported based on the observation that during the development of the nervous system neuron survival depends on the limited amount of specific NTFs secreted by target cells (Huang and Reichardt, 2001). However, it is now well established that NTFs are important mediators of neuronal plasticity also in adulthood where they modulate axonal and dendritic growth and remodelling, membrane receptor trafficking, neurotransmitter release, synapse formation and function (Lu et al., 2005). The neurotrophin BDNF has emerged as crucial mediator of neuronal plasticity, not only because it is abundant in brain regions that are particularly relevant for plasticity, but because it shows a remarkable activity-dependent regulation of its expression and secretion (Bramham and Messaoudi, 2005), suggesting that it might indeed bridge experience with enduring change in neuronal function.

4. BDNF: a neurotrophin with multiple sites of regulation

BDNF is a member of the neurotrophin family that has an important role in development as well as in adult neuronal plasticity. A number of studies carried out in the last few years have demonstrated that BDNF has a sophisticated organization in terms of transcriptional, translational and posttranslational regulatory mechanisms.

With regard to BDNF transcription, its gene consists of nine 5’ untranslated exons (some of which are enriched in the CNS), each linked to individual promoter regions, and a 3’ coding exon (IX), which codes for the BDNF pre-protein amino acid sequence (Aid et al., 2007). The transcription of each exon is driven by separate promoters in turn controlled by an array of signaling mechanisms, including calcium, CREB, MEK, PECP2, CaMKII and hormones (Lu, 2003; Molteni et al., 2009a; Zhou et al., 2006). Furthermore it has been demonstrated that the transcription of specific BDNF splice variants is controlled by a variety of epigenetic mechanisms, including DNA methylation and posttranslational modifications of histones (Lubin et al., 2008; Roth et al., 2009). The regulation of specific promoters causes the temporal and spatial expression of specific BDNF transcripts (Lauterborn et al., 1996), some of which can undergo trafficking and targeting to dendrites (Chiaruttini et al., 2008), a process that may also be influenced by the 3’ untranslated region (UTR) of the neurotrophin (An et al., 2008; Ghosh et al., 1994).

BDNF is initially synthesized as proform that can either be cleaved into the mature neurotrophin or transported to the plasma membrane and released in an unprocessed manner. Several matrix metalloproteases (MMP) as well as plasmin are responsible for extracellular cleavage of the neurotrophin, whereas furin and specific proconvertases control its intracellular processing (Schweigreiter, 2006). Differently from other neurotrophins, BDNF can be secreted through a constitutive as well as a regulated pathway.

Interestingly, the prodomain of the neurotrophin contains a single nucleotide polymorphism leading to a Val/Met substitution, which results in a less efficient sorting of BDNF protein into the regulated secretory pathway (Chen et al., 2006). Although, this polymorphism has been associated with the risk of psychiatric disorders, not all studies support these findings, and the overall evidence for an association of BDNF Val/Met polymorphism with disease risk is still weak (Peterson et al., 2009).

The prodomain interacts with sortilin that promote an appropriate configuration of proBDNF. This, in turn, allows the sorting motif in the mature domain of BDNF to interact with carboxypeptidase E (CPE), and, therefore, to sort BDNF into the regulated secretory pathway. Thus, BDNF protein can be packaged into secretory vesicles (Lessmann et al., 2003) that are present in both axon terminals (presynaptic site) and dendrites (postsynaptic site) of glutamatergic neurons (Fawcett et al., 1997), from which the neurotrophin can be released in a Ca ++-dependent manner. Upon release, proBDNF and mBDNF have divergent activities, since the former binds with high affinity to p75NTR leading to apoptosis, whereas mBDNF binds to TrkB receptors promoting cell survival (Lu et al., 2005). Activated receptors in general are capable of triggering a number of signal transduction cascades including the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and the phospholipase C-γ (PLC-γ) pathway (Huang and Reichardt, 2001; Huang and Reichardt, 2003), which can also be used to monitor neurotrophin release and receptor activation.
Interestingly, as we will see in the next sections, most of these events, including transcription, translation and synaptic storage of the neurotrophin, can be modulated by pharmacological treatments or environmental manipulations, suggesting that the BDNF system offers multiple sites for modulation, which lead to changes of neuronal plasticity that will ultimately affect the function and structure of selected brain regions.

5. Neurotrophic factors in depression

Several papers have demonstrated, with different approaches, the relationship between neurotrophic factors and depression.

First of all, postmortem studies suggest that the expression of selected neurotrophic molecules is altered in the brain of depressed patients. Accordingly Evans and co-workers have shown a decreased expression of several genes associated with the fibroblast growth factor family (Evans et al., 2004). In particular the expression of FGF-1, FGF-2, and their receptors FGFR2 and FGFR3, is decreased throughout the limbic system, whereas the levels of FGF-9 and FGF-12 appear to be up-regulated (Evans et al., 2004). Reduced BDNF expression (mRNA as well as protein) has been detected in the hippocampus and prefrontal cortex of postmortem brains from suicide victims (Dwivedi et al., 2003). These changes were associated with a significant down-regulation of TrkB, the high affinity receptor of the neurotrophin (Dwivedi et al., 2003). Moreover, consistent data suggest that serum BDNF levels are reduced in depressed subjects, an effect that can be normalized by antidepressant treatment or electroconvulsive therapy (ECT) (Boccio-Chiavetto et al., 2006; Sen et al., 2008).

Large support for a role of neurotrophic factors, and related deficits of neuronal plasticity, in mood disorders comes from animal studies, either through the knockout of genes encoding for neurotrophic factors or through exogenous administration of recombinant proteins.

Microinjection of FGF-2 into the lateral ventricle of adult rats at the end of day 1 of the forced swim test induces less depression-like behaviour on the 2nd day of the test (Turner et al., 2006). Other neurotrophic molecules, such as VEGF (vascular endothelial growth factor) or VGF (nonacronymic), mimic the action of antidepressants in behavioural tests like the forced swim test or learned helplessness (Hunsberger et al., 2007; Thakker-Varia et al., 2007; Warner-Schmidt and Duman, 2008). Similar finding have been observed with BDNF, whose infusion into the brain results in antidepressant-like behaviour (Shirayama et al., 2002).

BDNF’s role in depression has also been extensively studied in mutant mice. Lack of BDNF is not sufficient to produce a depressive phenotype (Chourbaji et al., 2004), but the neurotrophin is required for the behavioural response to antidepressant since the selective deletion of the BDNF gene in the hippocampal dentate gyrus, as well as the impaired function of its high affinity receptor TrkB, prevents behavioural responses to antidepressant drugs (Adachi et al., 2008; Monteggia et al., 2004; Saarelainen et al., 2003). However, BDNF appears to have an opposite role in the ventral tegmental area (VTA): its over-expression at this level determines a depression-like phenotype, whereas animals with a selective knockout of BDNF in the VTA are protected from the depressive effects produced by the social defeat stress (Berton et al., 2006). These data suggest that the role of BDNF in mood disorders and stress responsiveness is complex and strictly anatomical-dependent.

Further, as we will discuss in more detail later in this article, antidepressant drugs can up-regulate the expression of neurotrophic factors, an effect that might normalize defective systems or increase neuronal plasticity through alternative strategies. In fact ECT and antidepressant treatments increased, in addition to BDNF (see later in the review), the expression for different neurotrophic molecules, including FGF-2, VEGF and VGF (Maragnoli et al., 2004; Newton et al., 2003).

6. Modulation of BDNF expression by stress

A modulation of BDNF by stress was originally shown several years ago (Smith et al., 1995). Since than, evidence has been produced demonstrating the complex outcome of stress on the BDNF system. Because epidemiological studies have shown that stressful episodes in early life can increase the risk to develop depression (Heim et al., 2004), several authors have investigated the expression of BDNF in animal models that reproduce exposure to adverse life events.

These paradigms are based on the exposure of pregnant dams to repetitive stress (prenatal stress) or rely on the disruption of mother–pup interaction early in life (maternal separation). As previously mentioned, the susceptibility to such events may depend upon the type and timing of the manipulation. Indeed we have shown that strong stressors, such as a 24 h maternal separation on postnatal day 9 can reduce BDNF expression in the rat hippocampus (Roceri et al., 2002), although more protracted manipulations during gestation or the early phase of postnatal life do not produce significant changes on hippocampal BDNF levels (Fumagalli et al., 2004; Koo et al., 2003; Roceri et al., 2004).

Conversely, the length of the manipulation appears to be more important than the timing for changes that might occur at cortical level. Prenatal stress as well as repeated maternal separation determine a significant reduction of BDNF levels in prefrontal cortex of adult animals (Fumagalli et al., 2004; Koo et al., 2003; Roceri et al., 2004), whereas a single maternal deprivation did not elicit any change on cortical neurotrophin expression (Roceri et al., 2002). Hence developmental events can have enduring effects on BDNF expression that, based on its role in information processing as well as on cognition, may contribute to the persistent changes on brain function and their relative contribution to psychopathology.

The long-lasting nature of neurotrophin changes appears to be due epigenetic mechanisms. A recent study has demonstrated that early maltreatment (exposure of infant rats to a stressed “abusive” mother 30 min daily during the first postnatal week) elicited a reduction of BDNF mRNA levels in prefrontal cortex of adult offspring, which was associated with an increased methylation of the Bdnf gene on specific promoters (Roth et al., 2009). These results are of extreme interest since they could provide a molecular basis for enduring changes in neuronal plasticity that are associated with a reduced ability to turn on the transcription of activity-regulated genes, such as the neurotrophin BDNF.

As we have mentioned, the expression of BDNF is also significantly affected by stress at adulthood, although the
final outcome depends on several variables, particularly the duration of stress and the time elapsed between the end of the stressful experience and the sacrifice.

Acute stressors can produce a rapid facilitation of the BDNF system. In fact, a significant and transient increase of BDNF mRNA levels has been observed in the rat (Marmigere et al., 2003) as well as in the prefrontal and cingulate cortex of rats (Molteni et al., 2001) and in the frontal lobe of mice (Molteni et al., 2009a) exposed to an acute restraint stress.

We have recently shown that an acute stress (restraint or swim) can also regulate the subcellular localization of the neurotrophin, with a significant increase of the mature form of the neurotrophin in the synaptic compartment (Molteni et al., 2009a). The synaptic increase of mBDNF in response to the acute stress may be part of a cellular ‘defensive strategy’ aimed at increasing the pool of the mature neurotrophin that, upon release, might interact with its high affinity receptor TrkB and promote synaptic function and cell survival (Bramham and Messaoudi, 2005; Chao et al., 2006). Interestingly the increased synaptic levels of BDNF after stress are not observed in animal with a compromised function of glucocorticoid receptors (Molteni et al., 2009b), which represent a good model for susceptibility to depression (Ridder et al., 2005), suggesting that indeed rapid changes in BDNF under challenging conditions may reflect an active response strategy to preserve neuronal homeostasis (McEwen, 2008). Moreover, it has been recently demonstrated that glucocorticoids can also activate trkB receptor tyrosine kinases in vivo and in vitro, leading to neuroprotective effects (Jeanneteau et al., 2008), suggesting a further mechanism of integration between glucocorticoid hormones and neurotrophins.

If the rapid increase of BDNF expression following a single stress may represent a short-term protective mechanism, a prolonged stressful experience may have a detrimental effect on neuroplasticity, an observation supported by the overall negative impact of chronic stress on BDNF expression at hippocampal and cortical level. The initial observation of Smith et al. (1995) reporting reduced BDNF expression in the rat hippocampus after chronic immobilization stress has been confirmed by several subsequent studies (Nair et al., 2007; Roceri et al., 2002; Vollmayr et al., 2001). Additionally, stress-induced down-regulation of hippocampal BDNF expression was observed not only after physical—but also following psychological stress (Rasmusson et al., 2002). We found reduced BDNF mRNA levels after different paradigms of chronic stress in rat prefrontal cortex (Fumagalli et al., 2004; Roceri et al., 2004) and in mouse frontal cortex (Fumagalli et al., 2003). Although the exact mechanism by which prolonged stressful experiences regulate BDNF is still unknown, the involvement of hormonal and neurotransmitter systems, has to be taken into consideration (Joca et al., 2007; Molteni et al., 2009a).

As previously mentioned for developmental manipulations, also chronic stress in adult life can alter the expression of BDNF, and in particular of some of its transcripts, through epigenetic mechanisms. Indeed, Tsankova and collaborators have shown that chronic defeat stress down-regulated total hippocampal BDNF mRNA levels, primarly through a decrease of BDNF exon IV and VI. Such effect was paralleled by an increased dimethylation of histone H3 at their relative promoters (Tsankova et al., 2006).

Furthermore a prior history of stress can alter the pattern of changes produced by adult-onset stress on BDNF expression. For example, chronic immobilization stress reduced BDNF levels in the prefrontal cortex of ‘normal’ rats, while increasing its gene expression in prenatally stressed rats (Fumagalli et al., 2004). Similarly acute stress is not able to alter BDNF in rats previously exposed to MD (Nair et al., 2007; Roceri et al., 2002).

7. Modulation of BDNF by antidepressant treatment

Since depression is characterized by a reduction of neuronal plasticity, which can be produced as a consequence of exposure to stress at different stages of life, it may be inferred that effective pharmacological treatments should be able to correct or normalize such deficits in order to achieve functional recovery. Indeed, speaking of depression, a key question has always been why therapeutic responses with antidepressants could only be achieved after at least 2—3 weeks of treatment, whereas their synaptic effects occur without any significant delay. Hence, during the last decade it has become well accepted the idea that this delay is required in order to produce neuroadaptive mechanisms that may enhance neuronal plasticity and resilience (Castren, 2005; Kozisek et al., 2008; Pittenger and Duman, 2008).

Along this line of reasoning, several studies have shown that BDNF may mediate the therapeutic action of antidepressants (Berton and Nestler, 2006; Groves, 2007; Martino-wich et al., 2007). The expression of BDNF increases in the hippocampus in response to repeat but not acute treatment with major classes of antidepressants (Calabrese et al., 2007; Castren et al., 2007; Russo-Neustadt and Chen, 2005). Despite the well accepted effects of antidepressant drugs on BDNF expression, during the last 5 years, it has become apparent that this modulation can occur at several levels. Transcriptional changes can be due to the selective modulation of BDNF transcripts (Calabrese et al., 2007; Russo-Neustadt et al., 2004), an effect that may be related to the modulation of specific transcription factors. Since some BDNF mRNA species can undergo dendritic targeting (Chiaruttini et al., 2008), these changes may also affect the subcellular distribution of the neurotrophin. Indeed we have shown that chronic treatment with the novel antidepressant duloxetine increases the levels of mBDNF in the synaptic compartment (Calabrese et al., 2007) a mechanism that can be relevant for the control of the local release of the neurotrophin. Furthermore antidepressant treatment can also change the levels and the activation of TrkB, the high affinity receptor of BDNF, and its signaling (Duman et al., 2007; Fumagalli et al., 2005; Saarelainen et al., 2003; Wyneken et al., 2006).

8. Antidepressant treatment modulate stress-induced changes of BDNF

Since stress is a major causative factor in depression, it is expected that antidepressant drugs could modulate stress responsiveness and susceptibility, which is altered in affected individuals.
First of all antidepressants can regulate the HPA axis, whose function is altered in stress and mood disorders. Indeed, it has been found that different stressors decrease glucocorticoid receptor (GR) levels in the hippocampus (Chen et al., 2008; Meyer et al., 2001), while antidepressant treatment can up-regulate their expression (Przegalinski and Budziszewska, 1993). Moreover, antidepressant treatment is able to alter the stress responsiveness in terms of translocation of glucocorticoids receptors from the cytoplasm to the nucleus. We demonstrated that chronic antidepressant treatment increase the nuclear GR levels after an acute stress (Molteni et al., 2009a), in accordance with a previous study showing that antidepressant increase dexamethasone-induced GR traslocation (Pariante et al., 1997). In a recent study it has been shown that chronic treatment with different antidepressants normalizes hippocampal alterations of GR levels due to prenatal manipulation (Szymanska et al., 2009). Moreover, the levels of FKBP51, a GR co-chaperon that retains GR in the cytoplasm, are restored in the prefrontal cortex of the same animals. These results suggest that GR and FKBP51 may represent key molecules in the alteration of HPA axis seen in depressed patients. Alterations of GR expression and function have also been reported in human cells and some of these changes may be normalized by antidepressant treatment (Carvalho and Pariante, 2008).

While the studies mentioned above suggest that prolonged treatment with antidepressant drugs have a positive impact on neuronal plasticity, an important point is to understand if and how antidepressants could correct stress-induced modifications or, eventually if they may alter stress responsiveness. With regard to the first issue, it has been demonstrated that antidepressant treatment can normalize the reduced expression of BDNF following chronic stress. For example chronically venlafaxine administration is able to restore BDNF levels and neurogenesis that are reduced by after an immobilization stress (Xu et al., 2004). Similarly, prolonged treatment with imipramine normalizes behavioural alterations in the chronic social defeat stress protocol while restoring reduced levels of the neurotrophin (Tsankova et al., 2006). Both stress and antidepressant treatment may alter BDNF expression through epigenetic mechanisms. However while prolonged stress may repress BDNF transcription through a hypermethylation of histone proteins that lead to a more ‘closed’ chromatin state, chronic imipramine increases H3 histone acetylation in the promoter regions of exon IV and exon VI, which may overcome the repressing changes leading to an open chromatin conformation (Tsankova et al., 2006). These studies provide a good example of the possibility that disease-related factors (stress) and drug treatments may exert their effects on the same protein although not through overlapping mechanisms.

Since the concept of neuronal plasticity implies that adaptive changes are set in motion in response to ‘external’ stimuli, it is expected that antidepressants should not only improve compromised neuronal plasticity by affecting the expression of key proteins, but they may also modulate the responsiveness of these systems under challenging conditions. Accordingly, we have recently shown that antidepressant drugs do not only modulate BDNF expression under basal conditions, but can also alter its responsiveness under challenging circumstances. In fact we found that total BDNF expression was slightly increased by chronic duloxetine treatment and further enhanced when antidepressant-treated rats were exposed to a short swim stress (Molteni et al., 2009a). The antidepressant treatment was able to affect the stress modulation of BDNF exon VI, whereas exon IV was regulated by stress independently from the pharmacological treatment. Moreover, we found that the subcellular trafficking of the neurotrophin after stress was significantly affected by duloxetine treatment. In fact only animals that were chronically injected with the antidepressant showed a significant increase of synapticosomal mBDNF levels when exposed to the acute challenging condition (Molteni et al., 2009a). These data suggest that chronic antidepressant treatment can affect cellular resilience not only by increasing the expression of ‘protective’ proteins, but also by altering the coping ability under potential ‘threatening’ situations.

Figure 1  Mechanisms underlying the impact of stress or depression on the BDNF system and the potential effects of antidepressant drugs. Stress can reduce the expression of the neurotrophin through epigenetic (1), transcriptional (2 and 3) and translational mechanisms (4). On the other hand antidepressant drugs can restore normal levels of the neurotrophin by different mechanisms including: increase histone acetylation or reduced DNA methylation (5) at specific BDNF promoters; increase transcription of different exons (6 and 7); elevated synthesis and trafficking of BDNF protein (8); stimulation of protein release and increase receptor interaction (9).
9. Concluding remarks

In summary, the data herein reviewed suggest a close link between stress, neuronal plasticity and major depression. We believe that a putative mechanism through which stress can alter the susceptibility to mood disorders is the modulation of neuroplastic molecules, such as neurotrophins. Accordingly, antidepressant drugs are able to normalize defective mechanisms that sustain the impairment of neuronal plasticity and can increase neuronal resilience (Fig. 1). The understanding of these adaptive mechanisms may lead to the identification of molecular targets for the development of novel and more effective drugs.

Conflict of interest

None.

References


None.


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