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STRESS EFFECTS ON BDNF EXPRESSION: EFFECTS OF AGE, SEX, AND FORM OF STRESS

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Abstract—Stress has long been associated with the development of neuropsychiatric and neurological disorders. The effects of stress vary depending upon the age during which the stress is incurred, the duration and severity of the stressor, and can further be influenced by levels of circulating gonadal hormones. To date, the majority of research investigating the link between stress and pathology development has focused on stress hormone secretion, receptor activity, and their impact on neuronal development and functioning in developing and adult male and female rodents. In recent years, work has begun to focus on additional neuromodulatory systems that may be significantly impacted by stress that may explain changes in developmental and sex-based susceptibility to stress. New research targets include molecules that play a role in neuronal development and plasticity. Specifically, stress-induced alterations in growth factors such as neurotrophins, in particular brain-derived neurotrophic factor (BDNF), have been identified as a strong candidate modulating stress-associated pathology. Furthermore, changing expression of BDNF and its receptors over development and in response to circulating gonadal hormones extend the attractiveness of this candidate signaling pathway for understanding differences in susceptibility to stress. This review focuses on what is known with regard to the effects of stress on neurotrophin expression in rodents, and the varied effects of stress on BDNF levels as a function of developmental status and sex.

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Key words: depression, anxiety, neurotrophins, plasticity, development, translational models.

INTRODUCTION

Stress has long been associated with the development of a variety of neuropsychiatric conditions and significantly influences the development and course of neurological disorders (Sapolsky et al., 1984; Sapolsky, 1999, 2000; Karatsoreos and McEwen, 2011). The effects of stress vary depending upon the age during which the stress is incurred and levels of circulating gonadal hormones (Luine, 2002; Luine et al., 2007). The primary targets for many researchers investigating stress-associated pathology have been the stress hormone corticosterone, factors mediating its release (corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH)), and the activation of its receptors (mineralocorticoid and glucocorticoid receptors). However, in recent years work has begun to focus on additional neuromodulatory systems that may be significantly impacted by stress. New research targets include molecules and that play a role in neuronal development, plasticity, and have been implicated in stress-associated pathology development. Specifically, stress-induced alterations in growth factors such as neurotrophins, in particular brain-derived neurotrophic factor (BDNF), have been identified a strong candidate pathway underlying stress-associated pathology. BDNF represents a particularly attractive target, as it expression is significantly influenced by stress, and altered neurotrophin expression has been associated with the development of affective pathology. Furthermore, BDNF levels change dramatically over development and in response to changes in circulating gonadal hormones, providing a potential additional mechanism through which the effects of stress vary as a function of age and sex. Here, we review recent work assessing the consequences of stress on neurotrophin expression throughout the brains of rodents. We highlight the complex relationship between stress and its impact on gene expression as a function of sex and age.

BDNF AND AFFECTIVE PATHOLOGY

In the clinic and in animal models, BDNF has been reliably linked with the development of affective disorders, including major depressive disorder (MDD), anxiety disorders, and post-traumatic stress disorder (PTSD) (Karege et al., 2002; Duman and Monteggia, 2006; Castren and Rantamaki, 2010; Dwivedi, 2010). Plasma BDNF levels are significantly lower in MDD patients compared with matched controls, and antidepressant treatment normalizes peripheral BDNF levels (Aydemir et al., 2005; Castren and Rantamaki, 2010; Molendijk

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Abbreviations: AMG, amygdala; BDNF, brain-derived neurotrophic factor; HC, Hippocampus; HYP, hypothalamus; MDD, major depressive disorder; PFC, prefrontal cortex; PirCTX, piriform cortex; VTA, ventral tegmental area.

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et al., 2010). The degree of BDNF normalization is significantly correlated with symptom abatement (Gervasoni et al., 2005; Yoshimura et al., 2007; Tadic et al., 2010). In mouse models, genetically reducing BDNF levels, leads to increased anxiety and depressive-like behaviors (Chen et al., 2006; Duman and Monteggia, 2006). The direct administration or overexpression of BDNF has anxiolytic and antidepressant effects (Gourley et al., 2008; Deltheil et al., 2009). Exercise as well as antidepressant regimens augment BDNF in the hippocampus and are associated with decreased anxiety and positive outcomes (Nibuya et al., 1996; Russo-Neustadt et al., 2001; Garza et al., 2004; Koponen et al., 2004; Chen and Russo-Neustadt, 2007; Schmidt and Duman, 2010). Blocking the treatment induced augmentation of BDNF blocks the behavioral effects of antidepressants (Saarelainen et al., 2003; Chen et al., 2006; Ibarguen-Vargas et al., 2009). The culmination of these results have led to the development of a neurotrophic hypothesis of depression (Duman et al., 1997; Duman and Monteggia, 2006). The model suggests that diminished BDNF (through stress, genetic mutations, or pharmacological insult) leads to decreased trophic support, neuronal atrophy and death, and diminished neurogenesis which may underlie pathology development.

THE CHANGING ROLE OF BDNF OVER DEVELOPMENT

The expression of BDNF and its two primary receptors (TrkB and $p75^{NTR}$) are strictly controlled across development to guide the survival, differentiation, and plasticity of cells of the central nervous system (Labelle and Leclerc, 2000; Kuma et al., 2004). In rodents, throughout prenatal and early postnatal development, BDNF is expressed at very low levels. BDNF then undergoes a rapid increase in expression and peaks around 4 weeks of age followed by a decline over the lifespan (Kolbeck et al., 1999; Teng et al., 2005; Yang et al., 2009). BDNF exists in two forms, the preprocessed form (proBDNF) and the mature form which lacks the prodomain. These two isoforms of BDNF have differing affinities for the neurotrophin receptors TrkB and $p75^{NTR}$. Prototypically, mature BDNF binds to TrkB to promote neuronal survival, cellular differentiation, long-term potentiation (LTP), and dendritic outgrowth (Chao, 2003). proBDNF preferentially binds $p75^{NTR}$ to mediate cell cycle arrest (Lopez-Sanchez and Frade, 2002; Cragnolini et al., 2009), synaptic long-term depression (LTD) (Woo et al., 2005), or apoptosis (Teng et al., 2005). In the embryonic and early postnatal brain, $p75^{NTR}$ is highly expressed and then rapidly suppressed prior to elevations in BDNF expression, while levels of the full length form of TrkB remain relatively stable throughout the life of the animal (Yang et al., 2009). Interestingly, the expression or release of BDNF is significantly increased in response to estrogen (Sohrabji and Lewis, 2006; Begliuomini et al., 2007; Sato et al., 2007) with progesterone serving to counteract the effects of estrogen on BDNF expression (Bimonte-Nelson et al., 2004). The modulation of BDNF by estrogen and progesterone may contribute to alterations in the expression of emotional pathology across sexual maturation and the estrous cycle and during the transitional period of peri-menopause (Forty et al., 2006; Cubeddu et al., 2010; Spencer et al., 2010). Environmental perturbations, such as stress or genetic mutation, which disrupt the fine balance in neurotrophin expression during sensitive periods in development can have lasting and deleterious effects on neural development and functioning, and may either contribute to the emergence of pathology (Bath et al., 2012) or diminish the effects of stress. An understanding of how these internal factors and environmental manipulations interact to potentially buffer or increase the likelihood of pathology, and the possible critical role played by BDNF, may provide important insights into the mechanisms underlying these debilitating and highly prevalent disorders.

IMPACT OF EARLY LIFE STRESS ON NEUROTROPHIN EXPRESSION

Prenatal stress exposure

Exposure to stress hormones *in utero* are known to have significant and detrimental effects on brain development. A number of lines of evidence have linked prenatal stress with increased risk for later development of anxiety and depressive disorders in rodent models (Weinstock, 2001, 2007; Abe et al., 2007). Recent work has begun to assess the impact of *in utero* stress exposure on neurotrophin expression. Interestingly, many of the studies only report the effects of prenatal stress on basal and stress-induced changes in neurotrophin gene expression when animals reach adulthood.

In rats, stress incurred during the last 7–10 days of gestation leads to alterations in BDNF expression that are strain and brain region dependent. The use of a variable stress (paradigm) in pregnant dams led to increased BDNF mRNA and decreased BDNF protein levels (proBDNF and mature BDNF) in the hippocampus of male Sprague Dawley and Lewis rats when pups reached adulthood, but had no effect on Fischer 344 rats (Neeley et al., 2011). Interestingly, prenatal stress impacted the way that BDNF changes in response to stress exposure in adulthood. In those same rats, Lewis and Sprague Dawley strains exposed to acute restraint showed a suppression in BDNF expression if the animal was previously stressed, whereas Fischer 344 rats that were previously stressed showed no change in BDNF expression following an acute stressor in adulthood (Neeley et al., 2011). Work by other groups have found that restraint stress of the pregnant dam leads to a significant decrease in BDNF protein levels in the prefrontal cortex and striatum of males when they reach adulthood (Fumagalli et al., 2004). However, these studies are contradictory to work by Zuena et al. (2008) who found that restraint of the pregnant rat led instead

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to an increase in BDNF expression in male rat, and no change in BDNF expression in the female.

These studies are important, and indicate that early life stress can have long lasting effects on the expression of genes associated with neural development and ongoing plasticity. In addition, such findings suggest that early life stress can program later life stress-responsiveness of key genes involved in emotional regulation and cognitive functioning. These results also indicate that significant sex and strain differences in stress sensitivity with regard to neurotrophin expression, which would allow for the unique ability to compare and contrast the effects of these forms of stress on behavioral outcomes and relate them the effects on neurotrophin expression. However, more work is needed to assess the direct impact of prenatal stress on developmental expression of BDNF, and the impact of such changes on neurodevelopmental processes such as cell proliferation, migration, synaptogenesis, and apoptosis during early time points. In addition, more studies will be valuable in clarifying discrepancies in the literature at adult time points.

Stress as a consequence of diminished maternal care

Manipulations of maternal care are commonly used to induce stress in young rodents. In rats and mice, these manipulations often occur during the first 14 days of postnatal life, which approximate the third trimester of fetal development and early postnatal development in humans. The most commonly employed methods include the use of maternal separation (removing the mother daily for short bouts of time across several days), maternal deprivation (removing the mother for an extended time on a single occasion), and finally investigating the effects of natural variations in maternal care (high vs low care). Many of these paradigms have been associated with disruptions in later cognitive and emotional functioning of the animal (Romeo et al., 2003; Millstein and Holmes, 2007) and have potent and long lasting effects on neurotrophin expression.

In rats, maternal separation stress leads to decreased BDNF protein and mRNA levels in hippocampus (HC) of stressed relative to control rats as they reached adulthood (Lippmann et al., 2007; Maniam and Morris, 2011; Lee et al., 2012). These effects were largely restricted to the mature form of BDNF, with no changes being reported for proBDNF levels (Lippmann et al., 2007). The effects of maternal separation appear to be region specific, as this same manipulation led to increased BDNF expression in the ventral tegmental area (VTA) (Lippmann et al., 2007). In addition, levels of BDNF vary over development, as do the effects of stress on BDNF expression relative to control animals. For example, in the cerebral cortex, maternal separation stress led to a transient increase in BDNF mRNA expression from P15–P30, followed by reduced BDNF levels compared with control rats at P60 (Lee et al., 2012). The impact of this form of stress on neurotrophin receptor expression has also been studied. Maternal separation led to a transient increase in TrkB expression in the cortex during the preadolescent and adolescence period (P16–P30) and a significant reduction in TrkB expression in early adulthood (P60) (Lee et al., 2012). Using similar paradigms, others have found that maternal separation leads to elevations in the expression of the pan-neurotrophin receptor, $p75^{NTR}$, in the medial septum (mS) that appears to persist into adulthood (Aisa et al., 2009).

Investigators using the more acute maternal deprivation stress paradigm, have found similar effects on BDNF levels to those reported following maternal separation. Exposing rat pups to maternal deprivation from P9 to P10 led to decreased expression of BDNF mRNA and protein in the adult HC compared with typically reared animals. However, other groups, using virtually identical procedures, have failed to replicate that effect (Choy et al., 2008), but found that maternal deprivation led to a more robust decrease in BDNF when rats were later exposed to corticosterone. The effects of maternal deprivation stress also depended upon the time at which BDNF levels are assayed and the sex of the animal being tested. Viveros et al. (2010) found that maternal deprivation led to a blunting of circadian changes in BDNF expression in the hypothalamus (HYP) of male but not female rat pups. Interestingly, in that same study, following the return of rats to the dam, females showed a significant augmentation in BDNF expression compared with levels observed at the same time in control rats.

The use of more naturalistic manipulations, in which investigators track the quality of maternal behavior, or expose animals to poor maternal care during the first week of life, have also provided interesting results. Rat pups that received low levels of maternal care showed significant reductions in BDNF expression throughout the HC as adults (Liu et al., 2000). These results appear to mirror what is seen at younger ages, where other groups have found that at weaning, rat litters receiving low care have reduced BDNF levels in the HC compared with litters receiving high care (Macri et al., 2010). Studies by Roth et al., using a paradigm in which rat pups are exposed to abusive dams, found a similar decrease in BDNF expression in the prefrontal cortex (PFC, but no change in the HC), and identified epigenetic changes as a potential mechanism mediating this effect (Roth et al., 2009).

These results provide interesting parallels to findings in human population. Work by Grassi-Oliveira and colleagues found that women who were exposed to maternal neglect tend to have higher rates of MDD in adulthood, and that exposure to physical neglect leads to decreased levels of salivary BDNF, even below that of patients with MDD who did not experience early life physical neglect (Grassi-Oliveira et al., 2008). Ongoing work in this area has the potential to more clearly identify the consequences of decreased BDNF levels following early life stress on neural development and functioning to better understand the neural basis of stress-associated pathology.

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IMPACT OF LATER LIFE STRESSORS ON NEUROTROPHIN EXPRESSION

Social stress and neurotrophin expression

Manipulating social interactions in rodents have become a powerful methodology for the induction of pathological behavior, including the development of anxiety and depressive-like behaviors (Berton et al., 2006; Vialou et al., 2010). In these model systems, the time of stress induction can vary from prepubescent animals to aged models. Paradigms in which stress is induced through modulation of social interaction include the use of repeated social defeat, social isolation, or the implementation of a high degree of social variability (which often involves increased levels of social agonism as a function of repeated development of social hierarchies when new cage mates are introduced).

The majority of studies investigating effects on neurotrophin expression have used the social defeat paradigm. For this form of stress, effects have been reported across species, with repeated social defeat leading to an acute increase in BDNF expression in the PFC, nucleus accumbens (nAcc), amygdala (AMG), and VTA of rats (Nikulina et al., 2012), while defeat stress leads to a decreased BDNF levels in HC and piriform cortex (PirCTX) of golden hamster (Arendt et al., 2012), and decreased BDNF mRNA in the HC, PirCTX, and AMG of male mice (Pizarro et al., 2004).

Studies in which high degrees of social variability have been used as a means to induce stress have found significant decreases in BDNF levels in the HC of these animals as they reach old age (12 months), suggesting a potential impact of this form of stress on age related changes in markers of plasticity (Sterlemann et al., 2010). The use of social isolation as a means of inducing stress, leads to a similar decrease in BDNF expression in nearly all brain regions studied, with similar effects being observed in mice and rats. Specifically, social isolation of mice leads to decreased BDNF protein levels in the midbrain, HYP, PFC, and HC (Berry et al., 2012), and social isolation in rats leading to decreased BDNF levels in the HC and parietal cortex (ParCTX) (Barrientos et al., 2003).

The results of studies using social defeat in many models are difficult to interpret as the level and duration of agonistic behavior is often difficult to accurately quantify or control. In addition, agonism can lead to significant physical pain as a consequence of bites, and the contribution of chronic pain are similarly difficult to disentangle. However, the presence of reliable effects, despite a lack of clear control, suggest the potency of this form of stress to induce significant and lasting changes in gene expression. Furthermore, many of these studies are restricted to male rodents, as eliciting agonism in female rodents over the course of multiple days can be significantly affected by changes in circulating gonadal hormones and changes in sexual receptivity, limiting our ability to generalize these effects across sexes.

Restraint/immobilization (chronic and acute)

Restraint stress is one of the most commonly used means to induce stress in rodent models. Unlike social stressors, it is highly controllable, and can be employed to assess acute stress or repeated stress events. In addition, restraint stress can be combined with other stressors, such as predator odor to enhance the effectiveness of this form of stress. A variety of studies have employed this methodology to assess its effect on neuronal plasticity, including neurogenesis and dendritic remodeling, as well as its impact on long-term behavioral outcomes (including enhanced anxiety and depressive-like behaviors).

Many studies have focused on the use of the acute form of this stress which include the restraint of the animal in wire mesh restrainer, plastic cone, or strapping an animal to a board in the supine position on a single occasion for between 30 min and 6 h. Using these forms of stress, multiple groups have shown dynamic changes in BDNF expression as a function of the duration and type of stressor and time at which BDNF levels were assayed.

In rats, acute restraint led to rapid increase in HC BDNF mRNA (as soon as 60 min following the beginning of stress. By 180 min, mRNA levels in stressed rats had decreased rapidly to levels significantly below that of controls. This is effect was also evident at the level of BDNF protein level, which were elevated in HC compared with controls at 180 min, and then fell to levels that were indistinguishable from controls by 300 min (Marmigere et al., 2003). Other groups using slightly different stress paradigms, often with shorter duration, found that acute stress led to decrease in HC BDNF protein expression (Franklin and Perrot-Sinal, 2006; Roth and Sweatt, 2011), while mRNA levels were found by some to decrease (Ueyama et al., 1997; Lee et al., 2008; Roth and Sweatt, 2011) and other to increase (Nair et al., 2007; Alboni et al., 2011) relative to unstressed controls. The effects of this form of stress were not uniform across all brain regions, with some groups demonstrating a transient upregulation of BDNF in the HYP (Rage et al., 2002), and other demonstrating no effect of this form of stress on BDNF levels in the basolateral amygdala (BLA) or PFC (Roth and Sweatt, 2011).

Several groups have employed the use of more prolonged restraint stress paradigms to assess its impact on neurotrophin expression, with varied results. Repeated restraint led to a significant decrease in BDNF levels in the HC (Naert et al., 2011; Lakshminarasimhan and Chattarji, 2012), an effect that also occurs in females (Takuma et al., 2007) and is exacerbated by ovariectromy (Takuma et al., 2007). However, some groups have failed to find any changes in BDNF levels following repeated restraint stress (Kuroda and McEwen, 1998; Rosenbrock et al., 2005; Magarinos et al., 2011), and others have suggested that the effects on BDNF levels in the HC are present but transient (Lakshminarasimhan and Chattarji, 2012). The same groups that find transient effects of chronic restraint stress in HC have found that this same stressor leads to

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Table 1. Summary of the effects of various forms of stress on BDNF levels in the hippocampus, amygdala, and cortex of rodents. These results highlight the varied effects of stress on BDNF as a function of age, brain region, and timing between cessation of stress and assay of BDNF levels. Given the very small number of studies assessing BDNF in females, outcomes were not further broken down by sex, and thus results are largely indicative of effects in male rodents

Stressor	Stress period	Assay period	Species	Region Assayed		
				Hippocampus	Amygdala	Cortex
Maternal stress						
Maternal deprivation	P9–P10	Adult	Rat	Mixed		
Maternal separation	P2–P14	Adolescent	Rat	Increase		Increase
Maternal separation	P2–P14	Adult	Rat	Decrease		Decrease
Social stress						
Social defeat	Early adult	Adult	Rat		Increase	Increase
Social defeat	Early adult	Adult	Mouse	Decrease	Decrease	Decrease
Social isolation	Adult	Adult	Rat/mouse	Decrease		Decreased
Social variability	Adult	Aged	Mouse	Decrease		
Other stressors						
Acute restraint	Adult	Immediate	Rat	Increase		
Acute restraint	Adult	Delayed	Rat	Decrease		
chronic Restraint	Adult	Adult	Rat	Decrease and N/C	Increase	
Unpredictable stressor	Adult	Adult	Rat/mouse	Decrease		

a significant and lasting increase in BDNF levels in the AMG, which is associated with hypertrophy of this region and increased anxiety-like behavior (Lakshminarasimhan and Chattarji, 2012).

These results taken together suggest a complex relationship between the dose and duration of stress on neurotrophin levels, that appears to depend significantly on the region being studied as well as the duration between the cessation of stress and the time at which you measure BDNF levels. Such effects could explain transient changes in affect and cognition following either acute or chronic stress, however, more studies will be needed to bear out the direction relationship between changing BDNF levels and these measures.

Footshock/unpredictable stress

The use of repeated variable footshock has been used to induce a form of learned helplessness in animals, and milder forms of this paradigm can contribute to the development of anxiety and depressive-like phenotypes in rodents. A number of groups have indicated that males and females respond quite differently to this form of stress (Shors et al., 2007; Dalla et al., 2008). Several studies have begun to assess the effects of this form of stress on neurotrophin levels in the brain of rats and mice, with interesting results across sexes being observed. In adult male rats, repeated footshock leads to decrease in the expression of BDNF in the dentate gyrus of these animals (Rasmusson et al., 2002). Using a similar paradigm in rats, the acute application of footshock led to an increase in BDNF expression in the hippocampus of female but not male rats (Lin et al., 2009). When this paradigm was extended to multiple sessions of footshock over several days, again females were solely affected and were found to have a significant decrease in BDNF levels in both the hippocampus and PFC compared with control animals (Lin et al., 2009). These results are similar to those obtained in mice using a variable stress paradigm that included the use of footshock. However, in mice chronic stress led to decreased BDNF expression in the hippocampus of both males and females (Autry et al., 2009). Based upon these findings, BDNF levels in female appear to be particularly susceptible to this form of physical stress.

CONCLUSIONS

Throughout this review we have highlighted the effects of various forms of stress on BDNF expression in males and females rodents across development (summarized in Table 1). In reviewing this literature, it has become clear that stress can have potent effects on the on expression of neurotrophins, in particular BDNF, and that these effects are highly sensitive to the form, duration, and timing of stress as well as the sex of the subject receiving the stress and the brain region being studied. Based upon the previously established linkage between neurotrophin expression and affective pathology development and the emerging linkage between stress and neurotrophin expression, more work will be required in this area to understand the potential direct contributions of stress associated changes in BDNF expression with pathology development. The emergence of new genetic and molecular tools which will allow for timed elimination or expression of neurotrophins or direct modulation of their receptors in the context of stress have the potential to more clearly delineate the relationship between gene expression and stress-associated outcomes. Should this relationship bear out, targeting of neurotrophins and their receptors may provide a novel target for the treatment of stress associated illness, including affective pathology.

CONFLICTS OF INTEREST

Francis Lee is a consultant for Ono Pharmaceuticals.

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