

Chapter 16

Metabolic Stress and Neuropsychiatric Disorders

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Abstract The complications of metabolic disorders like diabetes, obesity, and the metabolic syndrome (MetS) are well characterized in peripheral tissues, but there is a growing appreciation that the complications of metabolic disorders extend to the central nervous system (CNS). Interestingly, the structural, electrophysiological, neurochemical, and anatomical underpinnings responsible for neuroplasticity deficits associated with metabolic disorders are strikingly similar to those observed in animals subjected to chronic stress, as well as in patients with stress-related psychiatric illnesses such as major depressive disorder. This has led to the hypothesis that diabetes, obesity, and MetS may be considered chronic metabolic stressors and led to the suggestion that common mechanistic mediators are responsible for the neurological complications associated with both metabolic disorders and neuropsychiatric disorders. The goal of this chapter is to provide an overview of stress neurobiology, with a particular emphasis on the causes and consequences of the metabolic stress in the CNS. This will include a discussion of the development and progression of mood disorders in patients with metabolic disorders, as well as a discussion of a novel model of obesity/MetS developed in our laboratory that is helping to elucidate the underlying mechanistic mediators of comorbid depression and obesity.

Abbreviations

AD	Alzheimer's disease
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
EPM	Elevated plus maze
FST	Forced swim test
HFS	High frequency stimulation
HPA axis	Hypothalamic-pituitary-adrenal axis
IR	Insulin receptor
LTP	Long-term potentiation
MetS	Metabolic syndrome

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PTSD	Posttraumatic stress disorder
pSTAT3	Phosphorylated of signal transducer and activator of transcription 3

16.1 Introduction

Acute exposure to stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of epinephrine and glucocorticoids from the adrenal gland. Once released, these hormones activate a variety of responses in the periphery and central nervous system (CNS) that are proposed to be adaptive in nature. These responses are initiated by activation of the HPA axis. In the CNS, stress hormones play a critical role in the facilitation and consolidation of strong emotional memories in limbic regions such as the hippocampus and amygdala (Conrad 2005; Roozendaal et al. 2009). Unlike these adaptive responses to acute stressful stimuli, exposure to chronic stress often results in maladaptive responses that are proposed to contribute to the pathology of cardiovascular disease, hypertension, cancer metastasis, gastrointestinal disorders, and immune dysfunction, among others. In the CNS, exposure to stressful life events has been proposed to play an important role in the etiology and progression of neuropsychiatric disorders such as depressive illness, anxiety disorders, and posttraumatic stress disorder (PTSD) (Diamond et al. 2004; McEwen 2008). Beyond stressful life experiences, HPA axis dysfunction is also observed in metabolic disorders such as diabetes mellitus and obesity and the metabolic syndrome (MetS) (De Nicola et al. 1976; Leedom et al. 1987; Meehan et al. 1986; Oster et al. 1988; Plotsky et al. 1992; Scribner et al. 1991; Winocur et al. 2005). This has led to the concept that diabetes and obesity act as chronic metabolic stressors in the CNS (Dallman et al. 2006), a concept that is supported by studies indicating that the neurological consequences of metabolic disorders is strikingly similar to the effects of chronic stress (Reagan 2012). Indeed, clinical studies indicate that there is an association between metabolic disorders and mood disorders (Andersen 2010; Anderson 2001 and Anderson 2010; Fabricatore and Wadden 2006; Luppino et al. 2010; McElroy et al. 2004; Simon et al. 2006; Stunkard et al. 2003) and ongoing preclinical studies are investigating the underlying mechanisms that link neuropsychiatric disorders, obesity, and diabetes. This chapter will review these relationships between metabolic and mood disorders, but we will begin with a discussion of more general issues related to experimental models of stress.

16.2 Experimental Models of Stress: Controversies Versus Consensus

A review of the literature will quickly determine that there is controversy related to the causes and consequences of chronic stress. However, closer examination of these studies provides several explanations for these disparate findings. An obvious

source of these sometimes equivocal findings is the variety of stress paradigms employed by investigators, which have particular advantages as well as disadvantages as it relates to their translational potential. For example, many investigators examine the effects of early life stress, including the effects of prenatal stress, postnatal handling or maternal separation. Such paradigms may be particularly useful for the examination of the potential role of epigenetic mechanisms in the development of stress-related mood disorders. Stress paradigms performed in adult animals may include restraint stress, exposure to variable or unpredictable stress, psychosocial stress such as resident intruder stress, and social hierarchy stress such as the visible burrow system. An advantage of these various stress paradigms is their ability to elicit neuroplasticity deficits that are similar to those observed in patients with neuropsychiatric disorders, such as neuroanatomical alterations and deficits in cognitive performance. A major limitation of these studies is reproducibility from laboratory to laboratory. However, the inability of stress paradigms to result in universally consistent findings should not be unexpected given the fundamental differences in how the paradigms are performed, the duration of the various paradigms, the choice of animal in the studies, and the endpoint measures that are used to evaluate the effects of stress. For example, the duration of a “chronic” stress paradigm can vary from several days to several weeks to several months depending on the laboratory performing the studies. There are also variable findings from endpoint measures ranging from molecular assays to behavioral analyses, which may be related to the experimental approaches utilized by a given laboratory. For example, the effects of repeated stress on neurochemical parameters such as measurement of extracellular levels of the excitatory amino acid neurotransmitter glutamate may be assessed through superfusion assays of synaptosomal preparations or via *in vivo* microdialysis. Since extracellular glutamate may originate from the vesicular pool or the metabolic pool (Timmerman and Westerink 1997), an advantage of the superfusion approach is that it can directly examine the readily releasable pool of glutamate in response to stress and antidepressant treatment, as shown by Popoli and colleagues (Barbiero et al. 2007; Bonanno et al. 2005; Musazzi et al. 2010). Conversely, microdialysis allows for the analysis of the effects of stress *in vivo* through the real-time assessment of glutamate efflux in relatively discrete brain regions (Bagley and Moghaddam 1997; Lowy et al. 1993). In this regard, our prior *in vivo* microdialysis studies indicate that the effects of acute versus chronic stress differentially impact extracellular glutamate efflux and that some but not all antidepressants may inhibit the effects of stress (Piroli et al. 2013; Reagan et al. 2012; Reznikov et al. 2007). Although these studies employed slightly different stress paradigms of dissimilar durations, used different experimental approaches (superfusion of synaptosomes vs. *in vivo* microdialysis), and also examined the effects of different antidepressants, the important take-home message is the same: stress adversely affects glutamate neurochemistry in stress responsive regions like the hippocampus, amygdala, and prefrontal cortex, findings that may be directly relevant to the clinical setting (McEwen et al. 2010; Popoli et al. 2012). As such, these results are representative of the sometimes equivocal findings from experimental models of stress. More importantly, these findings are consistent with the heterogeneity in the clinical features

and differential responses to antidepressant treatments observed in patients with mood disorders. Beyond the effects of stressful life events, it is also clear that metabolic stress associated with diabetes and obesity is associated with increased risk of developing mood disorders, thereby providing another level of complexity in determining the mechanistic mediators of neuropsychiatric disorders.

16.3 Neuroplasticity Deficits in Metabolic Disorders

The hypothesis that activation of insulin receptor (IR) signaling improves cognitive performance has been supported by both clinical and preclinical studies. For example, it has been established that insulin enhances cognitive performance in healthy subjects (Benedict et al. 2004, 2007), in aged subjects (Manning et al. 1998), and in Alzheimer's Disease (AD) patients (Craft et al. 1999, 2012; Reger et al. 2008). Animal studies also support the hypothesis that insulin enhances behavioral performance (Park et al. 2000). For example, icv injection of insulin enhances spatial memory in male rats in a dose-dependent fashion (Haj-ali et al. 2009), whereas intra-CA1 insulin microinjections have been shown to improve behavioral performance in the water maze (Moosavi et al. 2007). Studies that have examined the behavioral consequences of decreasing CNS IRs also support the hypothesis that insulin promotes cognitive function (Nistico et al. 2012). Interestingly, decreases in insulin activity observed in diabetes, obesity, and the MetS elicit neuroplasticity deficits that are similar to those observed in experimental models of stress. These observations provide possible causes for the increased risk of comorbid depressive illness in patients with metabolic disorders (see Reagan 2012). For example, changes in the metabolic and endocrine milieu, including impairments in HPA axis activity, hyperglycemia, insulin and leptin resistance, and increased productions of pro-inflammatory cytokines represent potential causes for the neurological consequences of metabolic disorders, including neurochemical, electrophysiological, and neuroanatomical deficits that ultimately lead to cognitive impairments. Indeed, there is a large body of work supporting the consensus that metabolic disorders adversely affect neuroplasticity. For instance, defective insulin signaling is a characteristic feature of the AD brain (Talbot et al. 2012) and as noted above intranasal insulin administration promotes cognitive function in adults with early-stage AD (Craft et al. 2012). Undoubtedly, defective insulin signaling contributes to AD pathogenesis, as Hoyer proposed nearly 25 years ago (Hoyer and Nitsch 1989). In experimental models of diabetes, the morphological deficits in the hippocampus include neuronal atrophy (Magariños and McEwen 2000; Martinez-Tellez et al. 2005), decreases in neuronal density (Beauquis et al. 2006), synaptic reorganization (Grillo et al. 2005), as well as decreases in neurogenesis/cell proliferation (Beauquis et al. 2008; Kim et al. 2003; Stranahan et al. 2008). Additional neuroplasticity deficits include decreases in synaptic transmission (Alzoubi et al. 2005; Artola et al. 2005; Biessels et al. 1996; Gerges et al. 2003; Izumi et al. 2003; Kamal et al. 1999; Oomura et al. 2006; Stranahan et al. 2008; Valastro et al. 2002), which may result

from changes in glutamate receptor expression and trafficking (Chabot et al. 1997; Di Luca et al. 1999; Gagne et al. 1997; Gardoni et al. 2002), as well as increases in oxidative stress mediators (Grillo et al. 2003; Reagan et al. 2008; Tuzcu and Baydas 2006). Ultimately, the long-term consequence of diabetes-induced neuroplasticity deficits is cognitive impairments (see Biessels et al. 2008; Reagan 2012).

Beyond deficits in spatial learning, changes in anxiety-like behaviors are among the earliest behavioral changes observed in experimental models of metabolic disorders. For example, decreases in social interactions and fear-related behaviors are observed in type 1 diabetic rats, including increases in passive avoidance, defensive postures, and submissive-like behaviors (Leedom et al. 1987; Meehan et al. 1986). Anxiety-like behaviors, such as decreases in open arm time or open arm entries in the elevated plus maze (EPM) or reduced behaviors in the open field test, are also observed in diabetic rodents (Asakawa et al. 2003; Miyata et al. 2007; Ramanathan et al. 1998; Sharma et al. 2010; Thorre et al. 1997). Deficits in the forced swim test (FST) have also been reported in leptin-deficient *ob/ob* mice (Collin et al. 2000; Yamada et al. 2011), leptin receptor deficient *db/db* mice (Sharma et al. 2010), and in rodents fed a high fat diet (Yamada et al. 2011). In summary, the clinical and preclinical literature indicate that metabolic disorders impair neuroplasticity, which includes deficits in behavioral performance and the development of depressive-like and anxiety-like behaviors. While there may be consensus regarding the neurological consequences of metabolic disorders, the underlying mechanisms responsible for these deficits remain a subject of debate.

16.4 Disentangling the Causes and Consequences of Metabolic Stress

The wide variety of endocrine and metabolic changes associated with obesity and diabetes is an obvious obstacle in accurately identifying the mechanistic links between metabolic stress and neuropsychiatric disorders. Due to the absence of good pharmacological tools such as an IR antagonist, we have developed an alternative molecular strategy to more selectively examine the role of IRs in neuroplasticity deficits observed in diabetes and obesity phenotypes. In this regard, we have developed and characterized a lentivirus vector that produces an antisense RNA selective for the insulin receptor (IRAS) and performed site-specific injections of this virus to differentiate between the functional activities of different IR populations in the rat brain. Our initial studies focused on the hypothalamus due to the well-described role of hypothalamic IRs in the regulation of body weight, body composition, food intake, and metabolism (see Schwartz et al. 2000). When injected into the hypothalamus to target IRs expressed in the arcuate nucleus (Hypo-IRAS), the LV-IRAS construct decreases the expression and activity of hypothalamic IRs, while not affecting IR expression or activity in the hippocampus. In agreement with previous studies using different molecular approaches (Bruning et al. 2000; Obici

et al. 2002), downregulation of hypothalamic IRs produced significant increases in body weight gain and body adiposity, as well as increases in plasma leptin levels and plasma triglyceride levels (Grillo et al. 2007, 2011a). Subsequent studies determined that downregulation of hypothalamic IRs elicited leptin resistance (Grillo et al. 2011b) and hepatic insulin resistance (Paranjape et al. 2011) while not affecting HPA axis function or plasma adiponectin, estrogen or testosterone levels (Grillo et al. 2007, 2011b). Collectively, these endocrine and metabolic changes are consistent with features of the MetS and as such the Hypo-IRAS rat provides a unique model system to examine the deleterious consequences of obesity on the CNS.

Since diabetes/obesity phenotypes are associated with decreases in hippocampal synaptic plasticity, we compared several endpoint measures of neuroplasticity in the hippocampus of Hypo-IRAS rats to rats that received the LV-Control construct in the hypothalamus (Hypo-Con). In this regard, while high frequency stimulation (HFS) of the Schaffer collaterals elicited long-term potentiation (LTP) in CA1 pyramidal neurons in the hippocampus of Hypo-Con rats, HFS failed to produce LTP in CA1 pyramidal neurons of Hypo-IRAS rats (Grillo et al. 2011a). Paired pulse facilitation was similar in both Hypo-IRAS and Hypo-Con rats, suggesting that the deficits in synaptic transmission were specific for the postsynaptic side. Subsequent immunoblot analysis determined that the phosphorylation of Ser845 on the GluA1 receptor subunit was significantly reduced in the hippocampus of Hypo-IRAS rats compared to Hypo-Con rats (Grillo et al. 2011a), thereby providing a potential mechanistic basis for these electrophysiological deficits. We also measured dendritic morphology via confocal immunofluorescence using the presynaptic protein synaptophysin and the postsynaptic protein PSD-95 in the hippocampus of Hypo-IRAS. Similar to our previous observations in type 1 diabetes rats (Grillo et al. 2005), Hypo-IRAS rats exhibited significant redistribution and clustering of synaptophysin and PSD-95 immunoreactivity, suggesting the obesity/MetS phenotype elicits changes in hippocampal synaptic organization and dendritic morphology. Lastly, we examined contextual fear conditioned responses in Hypo-IRAS rats and Hypo-Con rats as a measure of hippocampal-dependent performance. While unconditioned freezing and freezing during the acquisition period were the same in both groups, Hypo-IRAS rats exhibited a significant reduction in retention freezing behaviors compared to Hypo-Con rats (Grillo et al. 2011b). These behavioral deficits were associated with decreases in behaviorally induced fos-like immunoreactivity in the CA1 region of Hypo-IRAS rats, thereby providing another indicator of decreased functional activity in the CA1 region of Hypo-IRAS rats. Importantly, these changes in retention freezing behaviors occurred in the absence of changes in locomotor activity, illustrating that the obesity/MetS phenotype does not elicit generalized behavioral deficits. Collectively, these data demonstrate that the obesity/MetS phenotype elicited by the downregulation of hypothalamic IRs impairs hippocampal synaptic plasticity in a similar manner as has been observed in experimental models of diabetes and obesity. However, it is important to note that unlike our previous studies in type 1 diabetes rats (McEwen and Reagan 2004; Piroli et al. 2004; 2007) or obese Zucker rats (Winocur et al. 2005), hippocampal IR expression and/or activity is unaffected in Hypo-IRAS rats, suggesting that the neuroplasticity

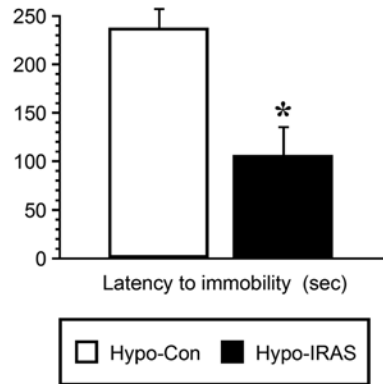
deficits in Hypo-IRAS rats result from changes in the endocrine and metabolic milieu and not from deficits in hippocampal IR activity. Moreover, several endocrine measures, including HPA axis activity, are unaffected in Hypo-IRAS rats compared to Hypo-Con rats (Grillo et al. 2007, 2011c), demonstrating that Hypo-IRAS rats exhibit more selective metabolic and endocrine changes compared to experimental models of diabetes or obesity. As a result, the Hypo-IRAS model allows for a more discrete examination of the potential metabolic and endocrine causes of hippocampal neuroplasticity deficits in metabolic disorders.

16.5 Mechanistic Links Between Metabolic Disorders and Neuropsychiatric Disorders

In view of the increased risk of neuropsychiatric disorders in patients with obesity and diabetes (Andersen et al. 2010; Anderson et al. 2001, 2010; Fabricatore and Wadden 2006; Luppino et al. 2010; McElroy et al. 2004; Simon et al. 2006; Stunkard et al. 2003), we examined whether Hypo-IRAS rats exhibit depressive-like and anxiety-like behaviors. Specifically, we examined behavioral performance of Hypo-IRAS rats and Hypo-Con rats in the FST, the sucrose preference test and the EPM. In the FST (Porsolt et al. 1977, 1978), behaviors are considered to be either “active” (i.e., swimming or climbing) or “immobility” (little or no movement). In the pretest of the FST, both Hypo-IRAS and Hypo-Con rats exhibited similar levels of immobility and active behaviors. However, in the test phase of the FST performed 24 h later, Hypo-IRAS rats exhibited a significant increase in immobility behaviors with a corresponding decrease in active behaviors when compared to Hypo-Con rats. This included a significant decrease in the latency to exhibit immobility behavior in Hypo-IRAS rats (Fig. 16.1). Collectively, these behavioral changes indicate that rats with the obesity/MetS phenotype are exhibiting “behavioral despair” (Grillo et al. 2011c). As another measure of “depressive-like behaviors,” we examined sucrose preference in Hypo-IRAS and Hypo-Con rats. While total fluid intake did not change, Hypo-IRAS rats exhibited a significant decrease in sucrose consumption, indicating that these rats are exhibiting anhedonia. Lastly, Hypo-IRAS rats exhibited significant decreases in open arm time in the EPM in the absence of differences in locomotor activity or total distance traveled in the maze. Such results suggest that Hypo-IRAS rats are exhibiting “anxiety-like behaviors” (Grillo et al. 2011c).

While these studies indicate that Hypo-IRAS rats develop a depressive-like and anxiety-like phenotype, the question that remains to be answered is what are the potential mechanistic links between obesity and mood disorders? Our ongoing studies are beginning to address these questions. An obvious candidate is the adipocyte derived hormone leptin. While leptin is known to facilitate hippocampal synaptic plasticity under physiological settings (for review, see Harvey 2007), leptin resistance (i.e., decreases in leptin signalin and/or leptin transport across the blood–brain barrier) is a hallmark feature of metabolic disorders (Banks et al. 1999; Banks 2004;

Fig. 16.1 Hypo-*IRAS* rats exhibit behavioral despair in the FST. In addition to increases in immobility behaviors (Grillo et al. 2011c), Hypo-*IRAS* rats also exhibit significant decreases in latency to exhibit immobility behaviors when compared to Hypo-Con rats. See text for details. * $p < 0.05$ compared to Hypo-Con rats; data based upon at least 10 rats/group.



Burguera et al. 2000; Levin et al. 2004; Levin and Dunn-Meynell 2002). These observations have led to the suggestion that reduced CNS leptin activity may be a mechanistic link between obesity and major depressive illness (Lu 2007); our studies provide support for this hypothesis. For example, Hypo-*IRAS* rats exhibit decreases in leptin-stimulated phosphorylation of STAT3 (pSTAT3), which may result from a combination of decreased leptin transport and/or leptin signaling (Grillo et al. 2011b). It is also interesting to note that studies by Banks and coworkers have shown that increases in plasma triglycerides, a characteristic feature of obesity, directly inhibits BBB leptin transport (Banks et al. 2004; Farr et al. 2008). As such, impairments in hippocampal plasticity and development of behavioral deficits in obesity phenotypes may result from a combination of increases in plasma leptin and triglyceride levels. One way to begin to address this question would be to return plasma leptin and plasma triglyceride levels to those observed in Hypo-Con rats. To achieve this objective, we subjected Hypo-*IRAS* rats to two different food restriction paradigms to more selectively examine whether normalization of plasma leptin and triglycerides levels would restore hippocampal synaptic plasticity. In one group of rats, a mild food restriction paradigm was initiated prior to the development of the obesity/MetS phenotype (Prevention group); in the second group of Hypo-*IRAS* rats, we allowed the obesity/MetS phenotype develop before initiation of food restriction (Reversal group). As expected, these food restriction paradigms effectively inhibited (Prevention) or reversed (Reversal) the Hypo-*IRAS*-induced increases in plasma leptin and triglyceride levels. These food restriction paradigms also restored synaptic transmission and phosphorylation state of GluA1 receptors in the hippocampus of Hypo-*IRAS* rats (Grillo et al. 2011a). Collectively, these data suggest that central leptin resistance, perhaps facilitated by increases in plasma triglyceride levels, is a key mechanistic mediator of comorbid obesity and depressive illness. In addition, data from the literature suggest that triglycerides may directly impair hippocampal plasticity (Farr et al. 2008) and thereby also serve as a link between obesity and mood disorders.

Beyond leptin and triglycerides, there is also a potential role for pro-inflammatory cytokines. For example, clinical studies indicate that plasma levels of IL-6 and

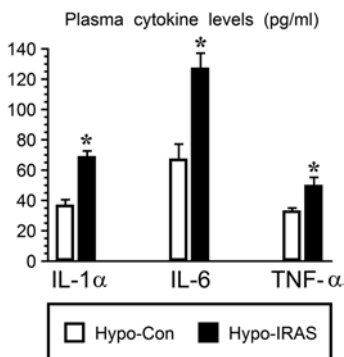


Fig. 16.2 Hypo-IRAS rats exhibit significant increases in plasma interleukin (*IL*)-1 α , *IL*-6, and tumor necrosis factor (*TNF*)- α levels. Plasma levels of the pro-inflammatory cytokines *IL*-1 α , *IL*-6, and *TNF*- α are increased in Hypo-IRAS rats that develop the MetS/obesity phenotype compared to Hypo-Con rats, thereby providing a potential cause of the neurological consequences of metabolic disorders, including the increased risk for the development and progression of neuropsychiatric disorders. See text for details. * $p < 0.05$ compared to Hypo-Con rats; data based upon at least 10 rats/group.

tumor necrosis factor (*TNF*)- α are elevated in patients with depression and pro-inflammatory cytokines are linked to treatment-resistant depression (Raison et al. 2006). Moreover, preclinical studies demonstrate that pro-inflammatory cytokines elicit depressive-like symptoms in animals (Capuron and Miller 2011). In obesity phenotypes, macrophage accumulation in adipose tissue leads to increased secretion of pro-inflammatory cytokines and as a result chronic mild inflammation is a characteristic feature of obesity (Lumeng and Saltiel 2011). Interestingly, we have found that plasma levels of *IL*-1 α , *IL*-6, and *TNF*- α are increased in Hypo-IRAS rats (Fig. 16.2), suggesting that adipocyte derived pro-inflammatory cytokines may also be mechanistic links between obesity and mood disorders. Mechanistically, pro-inflammatory cytokines are proposed to impair the activity of neural networks implicated in the pathology of depressive illness, in part by decreasing brain-derived neurotrophic factor (BDNF) levels (Capuron and Miller 2011). In support of this hypothesis, BDNF protein expression is reduced in the plasma, hippocampus and amygdala of Hypo-IRAS rats (Grillo et al. 2011c).

While these results identify leptin resistance, increases in triglycerides and pro-inflammatory cytokines as potential mechanistic links between metabolic disorders and neuropsychiatric disorders, obviously there are other endocrine and/or metabolic changes that may contribute these comorbidities. As noted above, impairments in HPA axis activity are often observed in metabolic disorders and HPA axis activity may be correlated with the degree of glycemic control in diabetes patients (Oltmanns et al. 2006). In this context, our findings that HPA axis dysfunction is not observed in Hypo-IRAS rats that develop a depressive-like phenotype is somewhat puzzling. However, a recent clinical study identified associations between inflammation, dyslipidemia, and obesity in patients with depressive illness, but did not identify an association with HPA axis activity (Reedt Dortland et al. 2013).

Therefore, while HPA axis impairments are implicated in the pathophysiology of mood disorders and diabetes/obesity phenotypes, our data in Hypo-IRAS rats suggest that obesity-induced anhedonia may be detected in the absence of HPA axis deficits.

Based on these observations, we have developed a working model of the mechanistic links that connect metabolic disorders and neuropsychiatric disorders (Fig. 16.3). In hypo-IRAS rats, lentivirus-mediated downregulation of hypothalamic IRs increases body adiposity, thereby leading to increases in plasma leptin levels. An additional endocrine change is the increase in plasma triglyceride levels, presumably from the gastrointestinal tract. Previous studies indicate that triglycerides impair blood-brain barrier transport of leptin (Banks et al. 2004), which when combined with decreases in leptin signaling, leads to the development of a CNS-deficient leptin state. Triglycerides have also been shown to directly impact hippocampal synaptic transmission and the performance of hippocampal-dependent behaviors (Farr et al. 2008). Increases in adiposity will also facilitate macrophage recruitment, which will lead to increased synthesis and secretion of adipocyte-derived pro-inflammatory cytokines implicated in the pathogenesis of depressive illness, like IL-1 α , IL-6, and TNF- α . Collectively, the changes in endocrine, metabolic, and inflammatory milieu are at least in part responsible for neuroplasticity deficits in the neural circuits implicated in the pathophysiology of neuropsychiatric disorders. For example, decreases in CNS leptin activity (Harvey et al. 2006), as well as increases in triglyceride levels (Farr et al. 2008), may directly impair glutamatergic function and hippocampal synaptic transmission. Deficient CNS leptin activity is also associated with hippocampal morphological changes, including decreases in spine density (Stranahan et al. 2009) and synaptic reorganization (Grillo et al. 2011b). While the exact mechanisms remain to be determined, pro-inflammatory cytokines are proposed to downregulate neurotrophic factor levels and also negatively affect neurotransmitter synthesis and activity (Raison et al. 2006), a hypothesis that has been extended to comorbid depression and obesity (Capuron et al. 2008). Beyond these identified causes in Hypo-IRAS rats, the neurological consequences of metabolic disorders may also result from changes in HPA axis activity (Reagan et al. 2008), as well as from cerebrovascular complications (Biessels et al. 2008).

16.6 Conclusions and Future Directions

The clinical and epidemiological data clearly indicate that the development and progression of neuropsychiatric disorders is a long-term complication of metabolic disorders like diabetes, obesity, and MetS. Indeed, these patients populations are two- to threefold more likely to develop comorbid depression when compared to nondiabetic individuals, have a more severe course of illness, and exhibit a tenfold increased risk of suicide (Ali et al. 2006; Anderson et al. 2001). The positive view from the evaluation of these studies is that there appear to be common mechanistic mediators in the development of comorbid depression and obesity/diabetes phenotypes. However, the pessimistic perspective is that given the wide variety of

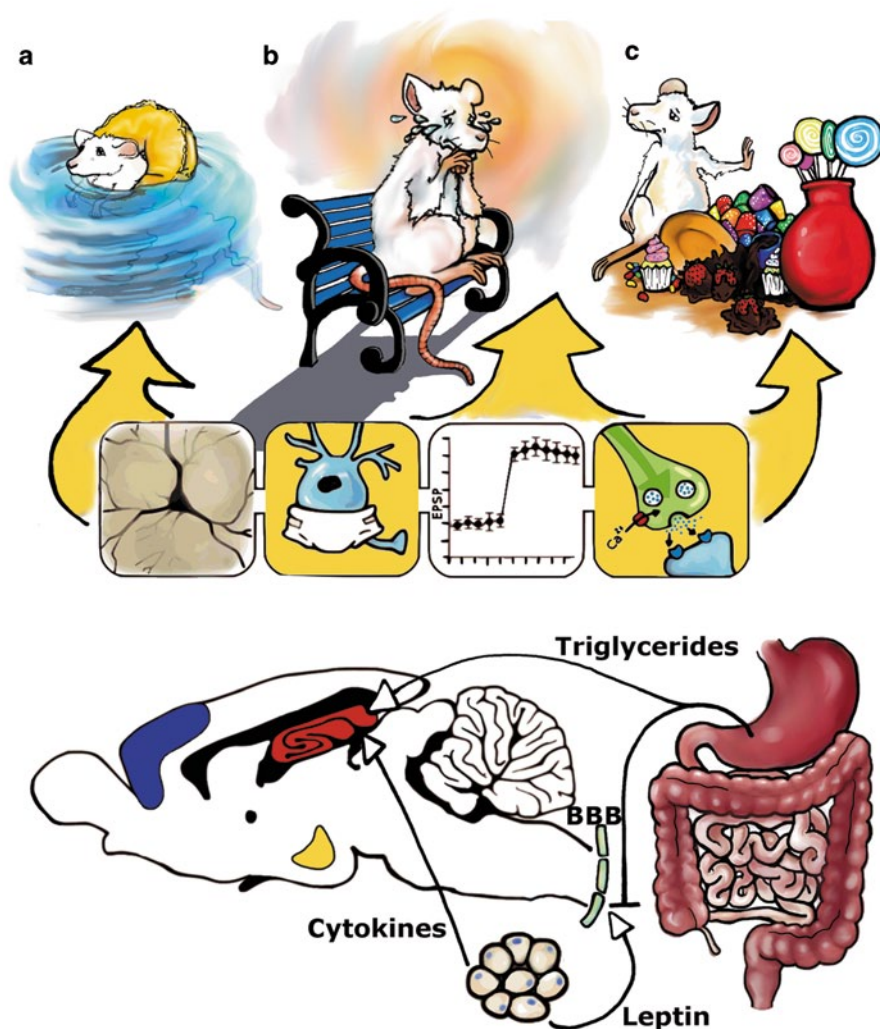


Fig. 16.3 Changes in the metabolic, endocrine, and inflammatory milieu are mechanistic links in comorbid neuropsychiatric disorders and metabolic disorders. Leptin resistance, involving decreases in leptin signaling and triglyceride-mediated decreases in blood–brain barrier (BBB) leptin transport, is a hallmark feature of metabolic disorders and impairs hippocampal synaptic plasticity. Beyond effects at the BBB, triglycerides may act directly in the hippocampus to adversely affect synaptic transmission and behavior. Increases in adiposity associated with metabolic disorders will lead to macrophage recruitment, which will lead to the increased synthesis and secretion of pro-inflammatory cytokines. When combined with additional alterations, such as deficits in HPA axis function (not shown), these changes will reduce morphological, electrophysiological, and neurochemical plasticity in the brain regions such as the hippocampus (shown in red), prefrontal cortex (blue), and the amygdala (yellow), and thereby increase the risk of comorbid mood disorders in patients with diabetes, obesity, and MetS. See text for details. (Figure adapted from Fadel et al. 2013 and Grillo et al. 2011b)

potential mechanistic links, development of a specific strategy to successfully manage mood disorders in patients with diabetes, obesity or MetS will be extremely challenging. Accordingly, evaluation of a combination of lifestyle interventions (diet and exercise) and pharmacological strategies represents an important future direction for clinical and preclinical studies in subjects with comorbid neuropsychiatric and metabolic disorders.

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