Prefrontal cortical regulation of hypothalamic–pituitary–adrenal function in the rat and implications for psychopathology: side matters

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Abstract

In recent years, dysfunction of hypothalamic–pituitary–adrenal (HPA) axis function has been implicated in a wide variety of psychiatric conditions. The importance of this system in responding to and coping with stress is well documented, and the integrity of such systems is of obvious significance to good mental health. The prefrontal cortex (PFC) is also heavily implicated in numerous psychopathological conditions. There is thus a growing interest in the potential role the PFC might play in regulating HPA function, and whether abnormalities of these systems are linked. The present paper reviews a number of recent animal studies which have attempted to elucidate the role of the PFC in regulation of HPA axis function, and how these systems may interact. It is concluded that the PFC is involved both in activating HPA responses to stress and in the negative feedback regulation of this system. Cerebral laterality is an important feature of this regulation, with the right PFC being most directly linked to stress–regulatory systems. On this basis, a number of parallels are drawn to the human literature, where asymmetrical disturbances in PFC activity may help explain associated patterns of HPA dysfunction. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

It is widely appreciated that the hypothalamic–pituitary–adrenal (HPA) axis is of central importance to the individual in dealing with the stresses of life, be they physical, psychological or social. Efficient activation and feedback inhibition of the HPA axis are essential components for optimal coping ability and long-term well-being.

In the past twenty-five years, great strides have been made in understanding the cellular and molecular regulators of HPA function (De Kloet and McEwen, 1976a,b; Rivier et al., 1982; Reul and De Kloet, 1985; McEwen et al., 1986). While the hypothalamic paraventricular nucleus (PVN) is considered the neural control center for HPA activation, and ultimately adrenal corticosteroid release into the circulation, many extrahypothalamic structures are involved in either facilitating this activation or providing homeostatic feedback control (McEwen et al., 1986; Sapolsky et al., 1984; Feldman et al., 1995; Herman and Cullinan, 1997). Such control is achieved through the actions of central corticosteroid receptors. Both type I (mineralocorticoid) and type II (glucocorticoid) receptors are involved in the regulation of HPA function (Ratka et al., 1989; Bradbury et al., 1994). The high affinity type I receptors (MRs) mediate the effects of corticosterone, the predominant corticosteroid in the rat, on maintenance of basal HPA activity and essentially set the threshold of the central stress response system. Type II receptors (GRs) are occupied during times of higher circulating corticosterone levels and suppress subsequent HPA activation in times of stress (McEwen et al., 1986; De Kloet et al., 1998).

Anatomically, the hippocampus has deservedly received much attention in the study of HPA regulation, given its high concentration of both MR and GR in the rat. Indeed, despite the widespread distribution of central corticosteroid receptors, the hippocampus has long been regarded as the principal target site in the brain for adrenocortical steroids (Sapolsky et al., 1984). Comparatively few studies, however, have directly examined the role of higher cortical areas in HPA regulation and, in general, much less is known of cortical regulation of neuroendocrine function than of its role in autonomic function (e.g., Cechetto and Saper, 1990; Damasio, 1994).

The need to better understand the role of higher cortical areas in the modulation of HPA function is underscored by two converging lines of evidence. Namely, a wide variety of psychiatric conditions are associated with both dysfunction in HPA axis regulation and prefrontal cortical functional abnormalities. The present paper therefore reviews a number of recent animal studies which have attempted to delineate the role of the PFC in HPA regulation. These studies reveal, somewhat surprisingly, the importance of cerebral lateralization in this modulation. This latter aspect of stress-regulatory systems is suggested to be a potentially crucial factor in understanding the patterns of HPA dysregulation seen in a number of psychopathological states, which demonstrate lateralized abnormalities in prefrontal cortical activity.
2. Role of the prefrontal cortex in regulation of HPA axis function

It has been known for some time that high levels of corticosteroid receptor binding are found in the frontal cortex of the rat. Homogenates of the anterior third of neocortex were found to contain total GR binding levels which were 75–80% that of hippocampus (Meaney and Aitken, 1985). Autoradiographic studies revealed a high retention of labeled corticosterone, particularly in the medial regions of frontal cortex (McEwen et al., 1986). Additional techniques have confirmed a high density of GR immunoreactivity in the medial aspects of PFC, including anterior cingulate, prelimbic and more ventral infralimbic cortices (Cintra et al., 1994).

As with the hippocampus, frontal cortical GRs are responsive to changes in circulating corticosterone levels, as GR binding is down-regulated by a one-week treatment with corticosterone, and up-regulated by long-term adrenalectomy (Meaney and Aitken, 1985). The prefrontal and hippocampal GR systems are also unique among brain regions in being up-regulated by early environmental stimulation or postnatal handling (Meaney et al., 1985) — a treatment associated with increased efficiency of HPA feedback regulation, and whose effects are mediated by maternal behavior (Liu et al. 1997, 2000). Conversely, early maternal deprivation has been shown to decrease levels of GR–mRNA in frontal cortex, as well as hippocampus and PVN (Avishai-Eliner et al., 1999).

The important role of the medial PFC as part of the stress circuitry in the rat has been well documented. Exposure to a wide variety of stressors causes marked increases in neuronal and genomic activation of medial PFC neurons, as reflected in the expression of the immediate early gene c-fos (e.g. Handa et al., 1993; Beck and Fibiger, 1995; Morrow et al., 2000). Stress also results in the pronounced release of the excitatory neurotransmitter glutamate in this area (Moghaddam, 1993), an effect which is significantly, although not totally, suppressed by adrenalectomy, and restored with corticosterone replacement (Moghaddam et al., 1994). Numerous ascending afferent pathways modulate medial PFC activity in times of stress, most notably and selectively, the mesocortical dopamine (DA) system, as well as noradrenergic and serotonergic inputs (e.g., Thierry et al., 1976; Deutch and Roth, 1990; Sullivan and Gratton, 1998; Finlay et al., 1995; Jedema et al., 1999; Yoshioka et al., 1995).

That the medial PFC is indeed a target site for circulating glucocorticoids in the negative feedback regulation of HPA activity, has been confirmed by Diorio et al. (1993). In response to a 20 min restraint stress, rats with corticosterone stereotaxically implanted in anterior cingulate/prelimbic cortex showed a significant blunting of the peak stress response for both plasma adrenocorticotrophic hormone (ACTH) and corticosterone, without affecting basal HPA activity. As stated earlier, this effect is believed to be mediated by GR activation. This may be particularly true of PFC, where GR levels are four- to five-fold higher than MR levels; whereas in the hippocampus, they are roughly equivalent (Diorio et al., 1993). It is also interesting to note that in rhesus monkey brain, GR immunoreactivity in general is much greater in the PFC than in the hippocampus (Sanchez et al., 2000). This strongly suggests that in primates, the PFC assumes a relatively greater role than hippocampus in GR-
mediated feedback, while the hippocampus mediates corticosteroid actions primarily through MR activation.

Studies examining the effects of medial PFC lesions on HPA function have also yielded significant results, although the direction of observed changes may be anatomically specific. In the study of Diorio et al. (1993), thermal lesions of anterior cingulate/prelimbic cortex were found to significantly increase plasma ACTH and corticosterone responses to restraint stress, an effect consistent with removal of a negative feedback site. As with the effect of PFC corticosterone implants, this lesion effect was specific to restraint, but not ether stress, possibly indicating that systemic or physiological stressors may activate the HPA axis by direct (brainstem) pathways, while the PFC is involved in situations requiring higher levels of processing or assessment of coping strategies. A recent study by Brake et al. (2000a) has reported similar lesion effects on HPA function. In this case, the effects of early postnatal damage to medial PFC were investigated by lesioning rat pups (Day 7) with ibotenic acid. As adults, these animals also showed a significant exaggeration of the plasma corticosterone response to a 20 min restraint stress. Cortical damage in these animals was confined to the most medial aspects of the dorsal prelimbic and anterior cingulate cortex.

In a study which examined the effects of more ventral medial PFC lesions (infralimbic cortex), it was found that ibotenic acid lesions suppress restraint stress-induced plasma corticosterone responses (Sullivan and Gratton, 1999a). This effect was particularly pronounced when neuroendocrine profiles were assessed after a repeated stress protocol (on the last of five daily restraint sessions). The lesions of this study included variable damage to the more dorsal prelimbic and anterior cingulate regions, the extent of which was not correlated with stress-related measures. Given that lesions always included infralimbic cortex, it appears that the lesion effects of this more ventral region may supercede those of more dorsal sites. This is a notion with some anatomical and functional support. In regard to autonomic regulation, it has been suggested that the prelimbic region exerts its effects by acting as a conduit of limbic inputs to infralimbic cortex, which was described as a visceral motor cortex (Cechetto and Saper, 1990). The infralimbic region is better positioned to directly influence numerous key structures involved in regulating both autonomic and neuroendocrine responses to stress. While direct projections to PVN are reportedly sparse, there are strong projections to adjacent hypothalamic areas, along with brainstem and limbic nuclei which directly influence PVN activity (Hurley et al., 1991; Takagishi and Chiba, 1991; Terreberry and Neafsey, 1987; Jodo et al., 1998).

The above studies suggest that while more dorsal regions of medial PFC normally act to inhibit HPA axis function (as does the hippocampus), the ventral or infralimbic area of medial PFC plays a facilitating role in activating the HPA axis, perhaps especially so when mounting an appropriate response to a previously experienced stressor. This is not the first example of a functional dissociation between dorsal and ventral regions of PFC in the rat. A number of behavioral and stress-related processes are differentially regulated by these subregions of PFC (e.g, Morgan and LeDoux, 1995; Doherty and Gratton, 1996; Jinks and McGregor, 1997; Pierce et al., 1998; Tzschentke and Schmidt, 2000).
An activational role in HPA modulation by the ventromedial PFC is consistent with the finding that electrical stimulation in this area increases plasma corticosterone in the rat, an effect mediated by lateral hypothalamic inputs to PVN (Feldman and Conforti, 1985). Also of interest in this context is an early study in human patients undergoing limbic leucotomy surgery, where electrical stimulation of ventral (orbital) frontal cortex, but not cingulate, was found to increase plasma levels of ACTH without affecting growth hormone or luteinizing hormone secretion (Frankel and Jenkins, 1975). The ventromedial PFC of humans is also essential for mounting appropriate autonomic responses to cortically processed stimuli, as selective bilateral damage eliminates this capacity (Damasio et al., 1990; Damasio, 1994). The ability of such patients to activate the HPA axis however, has not been reported, although one might predict this ability to be compromised as well.

An additional possibility which emerges from the above animal studies, is that the hippocampus (and dorsomedial PFC) may exert their negative feedback regulation of HPA activity, at least in part through modulation of infralimbic outputs. The ventral hippocampus and particularly the subiculum exert inhibitory tonic regulation over HPA function (Herman et al. 1995, 1998), which is mediated by outputs through the fimbria–fornix (Herman et al., 1992), and which reach the PVN via relays through the bed nucleus of the stria terminalis (Cullinan et al., 1993). The fimbria–fornix however, also contains a significant projection of hippocampal and subicular fibers to ventral prelimbic and infralimbic PFC (Swanson, 1981; Conde et al., 1995; Carr and Sesack, 1996), which undoubtedly modulate cortical outputs as well. Still other investigators, employing fimbria–fornix lesions and carefully controlled handling and blood sampling procedures, have seriously challenged the role of hippocampal involvement in HPA feedback regulation at all, stressing the importance of extrahippocampal structures (Bradbury et al., 1993).

Many details remain to be unraveled in this story. Anatomical networks involved in HPA regulation, as opposed to individual structures, need to be carefully characterized as they are likely to differ with varying stress modalities and experiential histories. As well, the electrophysiological and cellular actions of corticosteroids within the PFC under a variety of conditions, need to be elucidated so that we can better understand their effects on neuronal communication, both within PFC subregions and between hippocampus and PFC. It is suggested that the PFC will continue to be revealed as an important player in HPA regulation, particularly as one ascends the evolutionary ladder, where the integration of higher mental or psychological processes with stress physiology and somatic states, assumes an ever increasing relevance for both physical and mental health.

3. Cerebral laterality, stress and prefrontal function

A number of animal studies in recent years have shown the medial PFC to exhibit functional hemispheric asymmetries. This is especially true in the context of stressful or highly emotional situations and predominantly involve the mesocortical DA system (e.g., Carlson et al. 1991, 1993; Sullivan and Szechtman, 1995). HPA activity
in the rodent has also been related to cerebral asymmetries. Both leftward turning behavior and left paw preference are associated with significantly elevated stress-induced increases in ACTH and corticosterone (LaHoste et al., 1988; Neveu and Moya, 1997), suggesting that at some level, right brain dominance is associated with heightened HPA responsivity.

In the study of Sullivan and Gratton (1999a), the effects of left and right unilateral lesions of infralimbic cortex on corticosterone levels were examined (in addition to bilateral lesions). It was found that right side lesions alone suppressed stress-induced corticosterone responses to an identical extent as bilateral lesions. Conversely, left side lesions did not differ from shams, indicating that an intact right PFC is necessary to mount a maximal HPA stress response. In an attempt to understand the additional consequences of such lesions, the same animals were later subjected to a longer cold-restraint stress, for the purpose of assessing gastric stress ulcer formation as a physiological index of coping ability. Lesions dramatically reduced this autonomic mediately mediated measure of stress pathology, and again the effect was lateralized entirely to the right PFC. It could be said that these animals fail to fully perceive the “stressfulness” of the situation, and/or fail to integrate the stress-related sensory inputs with the appropriate autonomic and neuroendocrine outputs. As a point of interest, the stress-induced plasma corticosterone response was not significantly related to stress ulcer pathology in acutely stressed animals, however in repeatedly (5 times) restrained rats, a significant positive relationship emerged between these measures. This may suggest that while the HPA response to acute stress does not predict susceptibility to stress pathology, the (in)ability to habituate or adapt to repeated mild stress does predict vulnerability to the pathological effects of more formidable stressors.

As a behavioral complement to the above physiological effects, selective infralimbic lesions of the right, but not left PFC, were found to result in an anxiolytic profile, as assessed by increased time spent on the open arms of an elevated plus maze (Sullivan and Gratton, 1999b). Such findings support the view that the right ventromedial PFC is an important site for the integration of neuroendocrine and autonomic activity with the behavioral states normally associated with stressful or anxiety-provoking situations.

Asymmetrical lesion effects have also been reported when the predominantly inhibitory mesocortical DA inputs to the medial PFC are compromised, as 6-hydroxydopamine lesions of the right, but not left PFC, significantly exaggerate stress ulcer development (Sullivan and Szechtman, 1995). This indicates that i) the mesocortical DA system normally plays an adaptive role in protecting against the pathological effects of stress and ii) while the right medial PFC is required for the normal (optimal) activation of physiological stress responses, disinhibition or excessive activity in this region is maladaptive and confers an increased vulnerability to stress-related pathology. DA metabolism in the right medial PFC has also been associated with successful escape performance following uncontrollable footshock stress, suggesting that DA in this area facilitates behavioral coping strategies (Carlson et al., 1993). Additionally, Berridge et al. (1999) have demonstrated that animals placed in a stressful, brightly lit novel environment, exhibit a right-sided increase in PFC
DA metabolism. However, when allowed to perform a coping behavior (chewing an inedible object), which attenuates HPA activity, the lateralized DA increase is also diminished. This may indicate that as the stressfulness of a situation is reduced, so too is the intrinsic activity of the right PFC and its need for DAergic modulation.

The relationship between HPA function and mesocortical DA asymmetry was further explored by monitoring changes in extracellular DA in left and right medial PFC by in vivo voltammetry (Sullivan and Gratton, 1998). In response to the psychological or emotional stress of predator odor exposure, individual left/right asymmetries in PFC DA activation were strongly correlated with stress-induced plasma corticosterone profiles, such that right-biased DA responses were associated with heightened HPA activation. Such an asymmetrical relationship was not observed however, in response to a mild physical stressor (two min tail pinch), suggesting that stressor specificity is also important in the expression of prefrontal asymmetries. Taken together with the adaptive role of DA described above, it is suggested that the mesocortical DA system of the right brain represents a “high level” coping system, particularly in individuals predisposed to HPA hyperfunction or deficient feedback regulation.

Similar patterns of frontal asymmetry and HPA activity have been described in the rhesus monkey. In electroencephalographic (EEG) studies monitoring activity over the left and right frontal cortex, it was found that animals with extreme right frontal activity had significantly elevated levels of plasma cortisol, the predominant corticosterone in the primate (Kalin et al., 1998). Behaviorally, these animals displayed intense defensive responses and highly fearful behavior, all of these characteristics being stable over time. The same pattern of frontal EEG asymmetry is also associated with increased cerebrospinal fluid levels of corticotropin-releasing hormone (CRH) at all ages examined, ranging from 4 to 52 months (Kalin et al., 2000). These findings suggest that excessive or extreme right frontal activity is a trait feature of a highly anxious or stressed individual, which may predispose to a variety of stress-related pathologies or tissue damage associated with prolonged exposure to high levels of glucocorticoids.

Frontal brain asymmetries in EEG activity have also been studied extensively in humans and related to emotional states and affective styles (for review, see Davidson, 1998). Even from very early ages, left-biased frontal activity is associated with approach behaviors and positive affect, while right-biased individuals display more withdrawal, shyness and defensive behavior. The human brain has long been recognized as being lateralized with respect to emotional processing, with the right hemisphere being dominant in this regard, particularly for negative emotional states (e.g., Gainotti, 1983; Robinson et al., 1984; Wittling and Roschmann, 1993). A series of recent studies has concluded that the right hemisphere in humans is also dominant in the activation and coordination of physiological stress responses, both autonomic and neuroendocrine (Wittling, 1997; Henry, 1997). It has also been reported that reversals of a normally right-sided asymmetry in the activation of cortisol secretion, appear to be associated with an increased incidence of a variety of pathologies (Wittling and Schweiger, 1993). While the latter studies do not allow for the localization of these effects, the evidence presented thus far strongly implicates the PFC.
Moreover, it has recently been postulated that the ventral prefrontal (orbital) region of the right hemisphere, represents the apex of a system which generates stress-regulating coping strategies, and which is importantly regulated by the mesocortical DA system (Schore 1996, 1997). Early social experience is said to impact significantly on the maturation of this system, abnormalities of which predispose to a variety of psychiatric disorders. It is thus not surprising that so many psychiatric conditions are associated with prefrontal dysfunction, suboptimal activation/suppression of the HPA axis and impaired coping ability.

4. Relevance for psychopathological states

Intuitively, it would seem that the conditions most directly associated with impaired coping ability, heightened sensitivity to stress and dysfunction of stress regulatory systems, are the depressive and anxiety disorders. Both classes of disorders exhibit significant alterations in HPA function. Depressive disorders are commonly associated with increased CRH activity, persistent elevations in basal cortisol and deficient feedback regulation, as reflected by failure of dexamethasone to suppress cortisol levels (Barden et al., 1995; Plotsky et al., 1998; Wong et al., 2000). Across the spectrum of anxiety disorders many changes have been described including elevated cortisol (in many but not all cases), inadequate termination of stress responses, sensitization of HPA activity and dissociation of neuroendocrine and central autonomic regulation (Bandelow et al., 2000a,b; Uhde et al., 1994; Henry, 1997; Yehuda, 2000). Despite considerable heterogeneity in specific features of the above disorders, the phenomenological similarities in terms of stress sensitivity and impaired coping ability, suggest that at a general level, such disorders should exhibit a pathological imbalance favoring right-sided prefrontal activity. This, in fact, appears to be the case, with depressive conditions demonstrating predominantly left-sided PFC hypofunction, and anxiety disorders right-sided PFC hyperfunction.

Depressed states have been associated with left frontal brain damage (Gainotti, 1983; Robinson et al., 1984), subnormal EEG activation (Schaffer et al., 1983; Henriques and Davidson, 1991; Davidson, 1998), hypometabolism and volumetric reductions in left ventromedial PFC (Martinot et al., 1990; Teneback et al., 1999; Drevets et al., 1997). An intriguing series of recent studies using transcranial magnetic stimulation (TMS) highlights the importance of prefrontal asymmetries in depression. By varying the frequency of magnetic stimulation, the neural activity or cerebral metabolism of underlying cortical tissue can either be stimulated (rapid frequencies) or suppressed (low frequencies). Significant antidepressant effects have been reported either from rapid rate TMS over the left PFC (George et al., 1997; Pascual-Leone et al., 1996) or from low frequency TMS over the right PFC (Klein et al., 1999; Menkes et al., 1999). In other words, facilitating left PFC or suppressing right PFC function is beneficial. Despite the local (external) application of the magnetic pulses, widespread functional networks are affected, as lasting metabolic changes are induced in inferior (ventral) prefrontal and associated limbic structures (Teneback et al., 1999). Significantly, improvements in depression ratings following
TMS, as with other successful antidepressant treatments, were associated with normalization of the dexamethasone suppression test, implying that proper HPA feedback regulation had been restored (Pridmore, 1999).

Electrophysiological and metabolic evidence supports the notion of excessive activation of right frontal systems in anxious states. Social phobics show exaggerated right-sided anterior cortical activation, when anticipating an anxiety-provoking situation (Davidson et al., 2000). Similarly, right-biased frontal brain asymmetries of EEG activity characterize panic disorder patients (Wiedemann et al., 1999). Panic disorder patients also exhibit reduced binding to GABA-(A)-benzodiazepine receptors, with the most prominent decrease being in the right orbitofrontal cortex, implying that disinhibition of this region may be integral to heightened stress sensitivity or pathological fear (Malizia et al., 1998). Preliminary evidence also suggests that low frequency TMS over the right frontal region may be beneficial in post-traumatic stress disorder, by normalizing right frontal and paralimbic hyperactivity (McCann et al., 1998).

The notion of normalizing imbalances of prefrontal function in stress-related psychopathology must be considered central to successful therapies (e.g., Menkes et al., 1999). Inherent in this notion is the fact that both left and right sides must play important, yet complementary, roles. While the present paper has emphasized the role of the right PFC, given its more direct control of stress-regulatory systems, animal studies have revealed that the left cortex actively inhibits the emotional expression of the right (Denenberg, 1981; Denenberg et al., 1986). Other studies in the rat have suggested that stress initially activates the left medial PFC, followed by the right, when the stress is prolonged or uncontrollable (Carlson et al. 1991, 1993). Such a role for the left PFC has recently been conceptualized as preventing small stressors from becoming big stressors (Sullivan and Szechtman, 1995). This may be especially relevant for the left PFC deficits seen in depressed patients, where small stressors indeed become overwhelming. Future studies in this area will need to clarify the nature of interhemispheric interactions between left and right PFC, and identify the systems most responsible for maintaining optimal functional balances.

An example of a prefrontal functional imbalance in the opposite direction can be found with attention–deficit/hyperactivity disorder (ADHD). Anatomical and functional deficits in right-sided prefrontal–striatal circuitry are correlated with symptomatology (Castellanos, 1997), and a right-sided defect in prefrontal DA transmission has been postulated in ADHD neuropathology (Heilman et al., 1991). While ADHD is almost never examined from the perspective of stress physiology, a recent study demonstrated that ADHD subjects with persistent forms of the disorder, are clearly deficient in the ability to mount a normal cortisol increase in response to a stressful situation (King et al., 1998). Such an effect would be expected from a right prefrontal deficit and recent animal studies add further support to this view. Based on the significant association between birth complications and ADHD (Milberger et al., 1997), it has been reported that perinatal anoxia in the rat leads not only to long-lasting behavioral hyperactivity, but a dramatically lateralized right PFC deficit in DA transmission, and a significant blunting of the stress-induced increase in plasma corticosterone (Brake et al., 2000b; Boksa et al., 1996).
Yet another scenario emerges with schizophrenia. In this case, subjects are commonly characterized by the lack of development of normal cerebral asymmetry (e.g., Petty, 1999; James et al., 1999). Not unlike ADHD subjects, schizophrenics show a complete blunting in the cortisol response to psychosocial stress (public speaking), with no deficit in the cortisol response to physical (exercise) stress, and appear to have an otherwise intact HPA axis (Jansen et al. 1998, 2000). The inability of cortically-processed stressful inputs to activate the HPA axis, may reflect the loss of a normally dominant right prefrontal system. This also suggests that the prefrontal maturation deficits proposed in schizophrenia and ADHD (Weinberger, 1987; Castellanos, 1997) may lead to secondary defects in normal HPA activation, thus robbing individuals of a much needed glucocorticoid-mediated coping system and exacerbating characteristic “executive” deficits particularly in challenging situations.

Finally, the present discussion is not without implications for substance abuse disorders. While few clinical studies in this area have systematically examined the issue of cerebral laterality, prefrontal abnormalities have been related to substance abuse. Chronic cocaine abuse is associated with dysfunction in orbitofrontal and anterior cingulate regions (e.g., Bolla et al., 1998), and chronic alcoholics as well, show significant metabolic deficits in medial frontal regions (e.g., Samson et al., 1986). In cocaine addicts, however, craving has been specifically related to both activation of right orbitofrontal cortex (Volkow et al., 1999) and left prefrontal regions (Maas et al., 1998). Again, recent animal studies have demonstrated the lateralized regulation of drug self-administration. It was shown that lesioning the DAergic inputs to the left and right medial PFC, respectively, increases and decreases voluntary ethanol consumption in the rat (Nielsen et al., 1999a). In intact animals, prefrontal DA asymmetries were also related to ethanol consumption (Nielsen et al., 1999b). Similarly, cocaine self-administration is positively correlated with DA metabolism in the left medial PFC, but negatively correlated with the DA metabolism in right medial PFC (Glick et al., 1994). Conversely, DA metabolism in the right, but not left medial PFC, is positively related to morphine intake (Glick et al., 1992). It was suggested that inherent asymmetry in prefrontal function, may well predispose an individual to abuse one class of drug over another. Similarly, certain psychopathological states or stressful experience may also increase vulnerability to abuse particular drugs in an attempt to “self-medicate.” Certainly, stress is a potent factor in triggering reinstatement of drug-seeking behavior (Erb et al. 1996, 1998). Given the asymmetric role of the PFC, both in stress regulation and drug self-administration, future studies incorporating all of these factors should greatly facilitate our understanding of the complex underpinnings of substance abuse disorders.

5. Summary

It is now clear that the PFC of the rat is involved in both driving the stress-induced activation of the HPA axis, and in mediating negative feedback regulation in times of stress. The medial PFC integrates a wide variety of inputs in order to effect an optimal level of HPA functioning, a necessary component of good coping ability. The
right PFC most directly modulates stress-regulatory circuits, although an appropriate balance of activity between the hemispheres appears essential in achieving such optimal levels of function. Excessive, deficient, or abnormally lateralized PFC activity, disrupts this equilibrium, and is associated with numerous forms of psychopathology. It is hoped that future studies will reveal in greater detail both the mechanisms by which PFC influences various aspects of HPA function, and the consequences of glucocorticoid action within the PFC. It will also be essential to understand the genetic and early environmental factors which determine patterns of prefrontal functional asymmetries, the particular systems which mediate such asymmetries, and potential means of modifying maladaptive patterns of asymmetry. Such knowledge would go far in our understanding of psychopathological states associated with dys-function of stress-regulating systems.

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