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# Effect of Stress on Prefrontal Cortex Function

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**Stress is the major epigenetic factor that contributes to the etiology, pathophysiology, and treatment outcome of most psychiatric disorders. Understanding the mechanisms by which stress contributes to these processes can have important implications for improving therapeutic outcome. Considering that a dysfunctional prefrontal cortex has been implicated in many psychiatric disorders, such as schizophrenia and mood disorders, delineating mechanisms by which stress affects prefrontal cortex (PFC) function is critical to our understanding of the role of stress in influencing the disease process. This paper will review recent mechanistic information about the effects of stress on dopamine and glutamate neurotransmission in the PFC.**

*Keywords:* Dopamine; Glutamate; Prefrontal cortex; Microdialysis;

## INTRODUCTION

It is generally accepted that an interplay between genes and environment influences the presentation of most major psychiatric disorders, including major depression and schizophrenia. Understanding the epigenetic and environmental factors that contribute to the development of these disorders is becoming a major focus of biomedical research. Environmental factors in this context generally refers to exposure to "stress" or conditions where the individual experiences physical or psychological strain. Stress, in addition to contributing to the development of the disorder, contributes to exacerbation of acute symptoms, recurrence or relapse after a period of remission, and failure to respond to pharmaco- and psychotherapy. Thus, understanding the mechanism by which stress influences normal brain function is fundamental to understanding the contribution of environmental factors to the disease process.

Functional neuroimaging and postmortem studies suggest that a dysfunctional prefrontal cortex (PFC) is a primary culprit in stress-sensitive psychiatric disorders such as schizophrenia (Weinberger *et al.*, 1986), mood disorders (Rajkowska *et al.*, 1999; Stoll *et al.*, 2000; Drevets, 2001) and addiction (Volkow and Fowler, 2000). PFC, and in particular glutamatergic and dopaminergic afferents to this region are exquisitely sensitive to stress. Therefore, understanding the contribution of stress to dopamine and glutamate-mediated processes in normal versus disrupted PFC can not only provide insights to the fundamental pathophysiology of these disorders but may also suggest novel treatment strategies.

## Effects of Acute Stress on Dopamine and Glutamate Efflux in the Prefrontal Cortex

It has been known for decades that dopamine neurotransmission in the PFC and subcortical limbic regions such as the nucleus accumbens (NAc) are activated in response to aversive stimuli (Abercrombie *et al.*, 1989; Sorg and Kalivas 1991; Piazza and Le Moal 1998; Di Chiara *et al.*, 1999; Morrow *et al.*, 2000; Feenstra *et al.*, 2001). However, though the effect of stress on the turnover of monoamine neurotransmitters was studied almost as soon as analytical methods made it possible to measure brain levels of these compounds (Sepping *et al.*, 1977; Axelrod and Reisine, 1984), few studies have examined the effect of stress on glutamate levels. This is in part due to the fact that until the early 1980s,

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glutamate was not recognized as a neurotransmitter. Furthermore, involvement of glutamate in protein synthesis, and other non-neuronal physiological processes, questioned the relevance of measures of tissue content of glutamate to neurotransmission. Utilizing microdialysis in awake freely moving animals, we made the observation that restraint stress increases the extracellular glutamate levels in the PFC, NAc, and hippocampus (Lowy *et al.*, 1993; Moghaddam, 1993). The increases in glutamate levels were significantly higher in the medial PFC than that observed in other regions (Moghaddam, 1993). Similar results were found with other physical (Bagley and Moghaddam, 1997) and pharmacological (Karreman and Moghaddam, 1996b) stressors. These studies provided the first *in vivo* evidence that stress increases the neuronal release of glutamate in a regionally selective manner.

One of the important mechanistic implications of PFC glutamate activation by stress is that it may play an integral role in mediating stress responses in other systems that have traditionally been implicated in psychiatric disorders. One example is the dopamine system, which has been implicated strongly in schizophrenia (Carlsson, 1978) and addictive disorders (Wise and Rompre, 1989; Piazza *et al.*, 1996; Breiter *et al.*, 1997; Koob and Nestler, 1997; Childress and O'Brien, 2000). In the rodent, dopamine afferents to the PFC originate primarily from the ventral tegmental area (VTA) and terminate in prelimbic and infralimbic regions of the PFC (Berger *et al.*, 1976; Van Eden *et al.*, 1987). The PFC and the VTA are densely innervated by glutamatergic afferents from cortical and basal ganglia regions (Divac *et al.*, 1978; Conde *et al.*, 1995). Morphological and pharmacological studies suggest that glutamatergic projections to the PFC and to the VTA regulate dopamine neuronal activity and release (Chergui *et al.*, 1993; Wang and French, 1993; 1995; White, 1996; Paquet *et al.*, 1997) and terminal dopamine release in the PFC (Jedema and Moghaddam, 1996). On the basis of these findings, it may be postulated that dopaminergic activation in the PFC during stress may be regulated by glutamatergic inputs that are also activated during these conditions. Indeed, pharmacological manipulation of glutamate systems modifies cortical dopamine activation in response to stress (Kalivas *et al.*, 1989; Morrow 1993; Jedema and Moghaddam, 1994; Enrico *et al.*, 1998; Feenstra *et al.*, 1998). Specifically, blockade of both *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subtypes in the VTA, as well as AMPA receptors in the PFC, inhibits the activation of dopamine release in the PFC in response to stress (Kalivas *et al.*, 1989; Jedema and Moghaddam, 1994; Enrico *et al.*, 1998; Takahata and Moghaddam, 2000) suggesting that activation of glutamatergic neurotransmission within the VTA and/or the PFC is necessary for stress-induced activation of cortical dopamine. Similarly, systemic pretreatment with glutamate receptor antagonists attenuates the dopamine response to stress (Kalivas *et al.*, 1989; Serrano *et al.*, 1989; Keefe *et al.*, 1993a,b; Morrow 1993; Westerink *et al.*, 1997) indicating that activation of mesoaccumbens neurons by stress results from an increase in glutamate neurotransmission in the VTA. In addition, these data suggest that glutamatergic dysregulation at the cortical or midbrain level may be a preceding factor in abnormal cortical dopamine neurotransmission in a disease state.

While most studies have pointed to the VTA as the primary site for the glutamatergic regulation of dopamine during stress (Kalivas *et al.*, 1989; Rossetti and Wise, 1996; Enrico *et al.*, 1998; Takahata and Moghaddam, 1998), several observations suggest that the PFC may actually be the primary site of this regulation. First, blockade of AMPA receptors in the PFC was more effective in inhibiting the cortical dopamine response to stress than was blockade of these receptors in the VTA (Takahata and Moghaddam, 1998). Second, glutamate projections to the VTA primarily arise from the PFC (Oades and Halliday, 1987; Sesack *et al.*, 1989) and recent morphological studies have indicated that these cortical afferents synapse onto dopamine neurons that project back to the PFC (Carr and Sesack, 2000).

Another important aspect of the PFC's dopaminergic and glutamatergic response to stress is that these responses appear to be necessary for normal activation of dopamine in the NAc, a region which is thought to be critical for regulation of goal-directed behavior (Taylor and Robbins, 1986; LeMoal and Simon, 1991; Salamone, 1991; Kelley, 1999). Recent studies from our lab suggest that reduction of efferent glutamatergic activity in the PFC not only prevented the stress-induced activation of dopamine release in the NAc, but it produced a significant decrease in basal dopamine release during exposure to stress. This observation suggests that during stressful conditions, glutamatergic efferents from the PFC attenuate the actions of an inhibitory (most likely GABA) influence on dopamine neurons. Specifically, glutamate afferents to the NAc primarily arise from limbic regions that are highly responsive to stress. These include the PFC, ventral hippocampus, thalamus, and basolateral nucleus of the amygdala. These projections may work in concert in

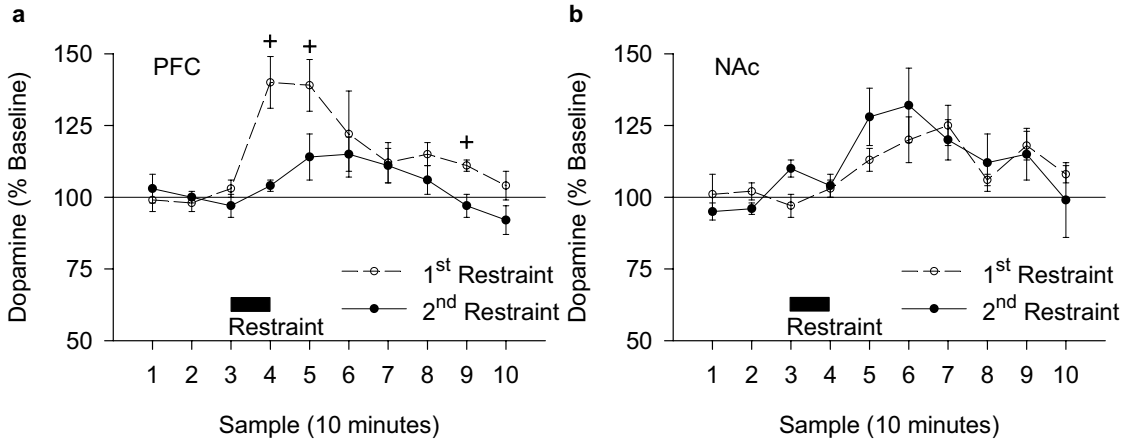


FIGURE 1 Dopamine release was measured in the (a) PFC and (b) NAc of awake rats ($n$=5) during two sequential (3 hours apart) exposures to acute (10 min duration) restraint stress. The second period of restraint stress produced greater dopamine release in the PFC but not in the NAc, compared to dopamine release during the first exposure to restraint stress. Dopamine release was measured by *in vivo* microdialysis and HPLC. Adapted from figure in Jackson and Moghaddam, *J. Neurochem.* 2004.

the NAc to influence the activity of medium spiny GABAergic output neurons, which are a principal source of GABA projections to the VTA (Nauta *et al.*, 1978; Domesick, 1981; Mogensen *et al.*, 1983). Concomitant activation of hippocampal and PFC inputs has been shown to increase the activity of NAc output neurons (O'Donnell and Grace, 1995; Grace, 2000), which can in turn lead to an increase in the GABAergic tone on dopamine neurons in the VTA. This mechanism would provide an inhibitory influence on dopamine neurons during conditions such as stress where the PFC is co-activated with the hippocampus. However, during stress this inhibition must be counteracted by an excitatory influence since the net effect of stress is an increase, albeit small in magnitude, in NAc dopamine release. Based on the present observation, it appears that the PFC provides this excitatory influence. The PFC, in addition to innervating the NAc, is a major source of glutamatergic input to the VTA and may be in a position to directly stimulate dopamine neurons. However, recent morphological studies have indicated that PFC efferents synapse onto GABA neurons, and not dopamine neurons, that project to NAc (Carr and Sesack, 2000). This suggests that the PFC does not directly stimulate the activity of mesoaccumbens DA neurons, and may in fact tonically inhibit these neurons (Takahata and Moghaddam, 2000). During stress, the PFC may indirectly stimulate dopamine neurons through stress-induced activation of its projections to regions such as the habenula and the pedunculopontine tegmentum (PPT) that also innervate the VTA (Phillipson, 1979; Oades and Halliday, 1987; Herbert *et al.*, 1997). Another excitatory mechanism may involve a PFC-mediated disinhibition of dopamine neurons: activation of mesoaccumbens GABA neurons that receive direct input from the PFC (Carr and Sesack, 2000) may in turn inhibit the activity of GABAergic projections from NAc to the VTA. This latter influence may be especially important for counteracting the direct stimulatory effects of the hippocampus and PFC on NAc output neurons. Thus, by taking PFC "off line" during stress, the indirect inhibitory influence of other regions such as the hippocampus (or amygdala) on dopamine neuronal activity may prevail and result in a net inhibition of accumbal dopamine release.

Although high intensity stimulation of the PFC has been shown to increase dopamine release in the NAc (Taber and Fibiger, 1995; Karreman and Moghaddam, 1996a), during basal (tonic) conditions or electrical stimulation at physiological frequencies we primarily observe an inhibitory influence of PFC on mesoaccumbens dopamine neurons (Jackson and Moghaddam, 2000; Takahata and Moghaddam, 2000). Thus, the present observation of a facilitatory influence of PFC on accumbal dopamine release is somewhat specific to stress since a different mode of influence of PFC over NAc dopamine release is observed under basal conditions. A decrease in NAc dopamine release has been observed in rats exposed to chronic stress (Imperato *et al.*, 1993; Gambarana *et al.*, 1999). This decrease has been suggested to be of mechanistic relevance to depression because it occurs in animals that display "escape deficit" and is reversed by treatment with the antidepressant drug imipramine (Gambarana *et al.*, 1999). Our finding suggests that the reduced activity of mesoaccumbens dopamine neurons in animal models of depression may have resulted from reduction in the

efferent activity of the PFC. This mechanism is consistent with a plethora of clinical findings suggesting reduced neuronal (and glial) density, and decreased metabolic activity and blood flow, in the PFC of patients with depressive disorders (Rajkowska *et al.*, 1999; Stoll *et al.*, 2000). The present finding may also be relevant to the mechanisms by which stress can lead to reinstatement of drug taking (relapse) in addicts. This consequence of stress has generally been attributed to a "priming" effect whereby the supposed increase in dopamine release during stress mimics the activation of dopamine release elicited by drugs of abuse (Shaham and Stewart, 1995; Erb *et al.*, 1996; Ahmed and Koob, 1997). However, if, according to recent animal research (Lu *et al.*, 1999) and human imaging studies (Volkow *et al.*, 1999), addiction may involve reduced efferent activity in some subregions of the PFC, exposure to stress would decrease accumbal dopamine output below basal levels, potentially producing an exacerbated dysphoric state that leads to reinstatement of drug taking in order to normalize basal dopamine.

### Effects of Repeated Stress on PFC Activity

Chronic exposure to stress modifies the effect of subsequent stressors on dopamine release (Imperato *et al.*, 1993; Cabib and Puglisi-Allegra, 1996; Cuadra *et al.*, 1999; Moore *et al.*, 2001). Our recent results suggest a different pattern of response adaptation in dopamine release in PFC vs. NAc. Specifically, while the first exposure to restraint produced a robust increase in dopamine release in the PFC, a second exposure three hours later led to significantly attenuated dopamine release (FIG. 1A). This adaptive response was specific to the PFC in that in these same animals, the increase in NAc dopamine release was similar in response to first and second restraint procedures (FIG. 1B).

Relatively few studies, have studied the effects of repeated stress on the output of glutamate neurons. We have observed there was a progressive reduction in the increase in glutamate efflux in response to repeated stress that was specific to the PFC. Collectively, these findings suggest that glutamate and dopamine output in the PFC may play a role in the neurochemical adaptation of this region to stress.

## CONCLUSION

Anomalies in dopaminergic and glutamatergic activity in the PFC may have a profound effect on the function of these regions and, therefore, play a major role in the adverse effects of stress in psychiatric disorders that have traditionally been associated with cortical dysfunction. An underlying pathophysiology in the PFC may produce a state whereby the nature of the dopamine stress response is modified in a manner that can directly contribute to development or exacerbation of symptoms. Thus, an understanding of the mechanisms that contribute to the stress-reactivity of dopamine and glutamate neurotransmission in the PFC may have implications for delineating the underlying biological vulnerability to develop some psychiatric disorders.

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