Through the Looking Glass: Differential Noradenergic Modulation of Prefrontal Cortical Function

Amy F.T. Arnsten

Section of Neurobiology, Yale Medical School, New Haven, CT, USA

For Simon

Ghosts rising off the lake
In to moonlight
In between
Never so alive

Norepinephrine (NE) facilitates the functioning of many brain areas, often by increasing “signals” relative to “noise”. In most brain regions, NE enhances neural processing through actions at beta and alpha-1 adrenergic receptors. This review will provide a brief overview of the receptor mechanisms influencing subcortical and posterior cortical functions and contrast these actions with the very different mechanisms by which NE modulates the working memory functions of the prefrontal cortex (PFC; Fig. 1).

**BETA- AND ALPHA-1-ADRENOCEPTOR STIMULATION ENHANCE POSTERIOR CORTICAL AND SUBCORTICAL FUNCTIONS**

NE has widespread effects on arousal state, stimulus processing, and plasticity including long-term memory consolidation. Most of these NE actions involve beta adrenergic mechanisms, although alpha-1 receptor stimulation also has important effects on excitability and cortical plasticity. In contrast, alpha-2 receptor stimulation often impairs stimulus processing and plasticity. This review provides a very brief synopsis of this research.

**Arousal**

NE profoundly modulates the state of alertness through a variety of actions, many of which involve stimulation of beta adrenergic receptors. Beta adrenergic receptor stimulation in the cortex produces an awake state by potently blocking spike frequency adaptation by reducing a potassium current, I_{	ext{ADP}} (reviewed in McCormick et al., 1991). In the thalamus, application of NE suppresses rhythmic burst activity and switches neurons to a single-spike firing mode, capable of transmitting information. This effect reflects a beta receptor-mediated enhancement of a hyperpolarization-activated cation current, IH, and an alpha-1 receptor-mediated suppression of a resting leak potassium current, IKL (ibid). Buzsaki and colleagues (1991) have shown that stimulation of alpha-1 receptors in the thalamus elicits an alert state, whereas stimulation of postsynaptic alpha-2 receptors produces sedation. Activation of the EEG in the cortex and hippocampus can also be produced by beta adrenergic stimulation in the medial septal nucleus (Beridge et al., 1996; Berridge & Foote, 1996).
Fig. 1: The neurochemical needs of the PFC appear to be "upside down and backwards" from those of posterior cortical and subcortical structures. See text for details.
Stimulus processing

It has long been appreciated that NE enhances the “signal/noise” processing of sensory stimuli (Foote et al., 1975; Segal & Bloom, 1976; Waterhouse et al., 1998). Waterhouse and colleagues (Waterhouse et al., 1980; Waterhouse et al., 1981; Mouradian et al., 1991) dissected the receptor mechanisms underlying these effects and found that beta adrenergic receptor stimulation can enhance inhibitory responses, whereas alpha-1 adrenergic receptor stimulation can enhance excitatory responses. Such effects have been observed in a variety of brain regions, including auditory and somatosensory cortices, cerebellum, and hippocampus. For example, the receptive field properties of auditory cortical neurons are sharpened through an alpha-1 receptor mechanism (Manunta & Edeline, 1997), whereas the visual field properties of cerebellar neurons are modulated by a beta receptor mechanism (Moises et al., 1990).

Long term memory consolidation

Beta receptor stimulation plays a critical role in long-term memory consolidation, particularly in the amygdala. Memory enhancement by emotional events is thought to occur through epinephrine release in the periphery and through beta adrenergic receptor stimulation in the amygdala (reviewed in Cahill & McGaugh, 1996). Thus, infusion of beta adrenergic antagonists into the amygdala impairs long-term memory consolidation, whereas infusion of a beta adrenergic agonist improves memory consolidation (ibid). Recent findings suggest that alpha-1 adrenergic mechanisms may facilitate beta adrenergic effects (Ferry et al., 1999). In contrast, alpha-2 receptor stimulation impairs memory consolidation, and the alpha-2 agonist, clonidine, is used as an amnestic agent in basic research (Genkova-Papazova et al., 1997).

Beta adrenergic mechanisms also contribute to memory consolidation in the hippocampus. For example, it has long been appreciated that NE enhances long-term potentiation (LTP) in the mossy fiber-CA3 synapse, via a beta adrenergic mechanism (Hopkins & Johnston, 1988). Indeed, beta receptor stimulation in the dentate gyrus can actually induce LTP, even in the absence of high-frequency stimulation (Lacaille & Harley, 1985; Bramhan et al., 1997; Chaulk & Harley, 1998). Alpha-1 receptor stimulation appears to contribute as well, although these effects are not as long lasting (Chaulk & Harley, 1998). Beta adrenergic stimulation appears to be particularly important for the late phase of memory consolidation (Roullet & Sara, 1998; Sara et al., 1999), which is thought to involve a cAMP/protein kinase A (PKA) signaling pathway in the hippocampus (Bevilaqua et al., 1997; also see below). Stimulation of NE cells facilitates memory retrieval through a beta receptor mechanism (Devauges & Sara, 1991), and these receptor mechanisms are also critical for memory reactivation (Przybalskiew et al., 1999). Beta adrenergic mechanisms also appear to facilitate long-term memory consolidation in the entorhinal and parietal cortices (Ardenghi et al., 1997). Alpha-1 adrenergic mechanisms appear to have a weaker, but nonetheless beneficial, effect on memory consolidation (Puumala et al., 1998) and on long-term potentiation in the hippocampus (Pussinen & Sirviö, 1998). In contrast to the beneficial effects of beta and alpha-1 adrenergic receptor stimulation, administration of alpha-2 adrenergic agonists either has no effect or impairs memory tasks, such as the Morris water maze, that depend on hippocampal functioning (Sirvio et al., 1991) or attentional orienting tasks that depend upon the parietal cortex in primates (Witte & Marrocco, 1997).

More recently, several lines of research suggest that long-term memory consolidation is accomplished through the activation of several intracellular signaling pathways, including protein kinase C (PKC), PKA, MAP kinase, and CAM kinase II (for example, Paylor et al., 1991; Abeliovich et al., 1993; Bach et al., 1995; Abel et
As beta receptors are generally positively coupled to the cAMP/PKA signaling pathway via Gs proteins, it is likely that NE enhances long-term memory processes via beta adrenergic stimulation of PKA (for example, Bevilaqua et al., 1997). In contrast, alpha-2 receptors are generally coupled to Gi proteins that reduce cAMP/PKA signaling. Thus, alpha-2 receptor stimulation may impair long-term memory consolidation through both pre-synaptic mechanisms (reducing catecholamine release) and post-synaptic mechanisms (reducing PKA activation).

**Plasticity**

In addition to its beta adrenergic influences on LTP in the hippocampus, NE has been shown to modulate plasticity in the visual (Bear & Singer, 1986) and somatosensory (Levin et al., 1988) cortices. An interaction between noradrenergic and cholinergic mechanisms appears to be critical for plasticity of the visual cortex during development, permitting shifts in ocular dominance columns (Bear & Singer, 1986). In the adult brain, NE alpha-1 mechanisms are important for modulating long-term depression (LTD) in visual cortical neurons (Kirkwood et al., 1999). In contrast, alpha-2 receptor stimulation weakens LTD, and this was thought to occur through presynaptic reductions in NE release (ibid). The authors speculated that NE modulation of LTD may have a critical modulatory influence on plasticity of receptive fields in the adult brain and during development.

**Differential Regulation of Working Memory Functions of the Prefrontal Cortex**

In contrast to the posterior cortices and subcortical structures, the cognitive processes of the PFC appear to be unaffected by beta

**Fig. 2:** Alpha-1, but not beta receptor stimulation in the PFC impairs working memory function. Intra-PFC infusion of the beta agonist, isoproterenol, has no effect on delayed alternation performance in rats. In contrast, intra-PFC infusion of the alpha-1 agonist, phenylephrine, induces working memory deficits that are reversed by co-infusion of the a0-1b antagonist, urapidil. Results represent mean ± S.E.M. percent correct on the delayed alternation task. VEH = vehicle; ISO = isoproterenol (0.1 ug/0.5µl); PE = phenylephrine (0.1µg/0.5µl); URA = urapidil (0.01µg/0.5µl); *significantly different from vehicle + vehicle; †significantly different from phenylephrine + vehicle (adapted from Arnsten et al., 1999).
stimulation, and are impaired by alpha-1 receptor stimulation. Thus, the neurochemical needs of the PFC appear to be “upside down and backwards” from that of the rest of the brain (Fig. 1).

**PFC functions**

The PFC expands greatly in primates and is critical for guiding behavior, using working memory (Goldman-Rakic, 1987). As working memory is constantly updated, the memories may be called up from long-term storage or from more recent buffers. The PFC uses these representations to guide behavior effectively, freeing the organism from its dependence on the environment, inhibiting inappropriate responses or distractions, and allowing us to plan and organize effectively (Robbins, 1996). The PFC regulates attention, inhibiting responses to irrelevant stimuli by gating stimulus processing in sensory cortices (Knight et al., 1989; Yamaguchi & Knight, 1990) and by sustaining attention to relevant stimuli, particularly over long delays (Chao & Knight, 1997; Wilkins et al., 1987). Animals or humans with lesions to the PFC can exhibit poor attention regulation, disorganized behavior, hyperactivity, and impulsivity (Stuss et al., 1994).

**Beta adrenergic mechanisms**

Evidence to date indicates that beta adrenergic mechanisms have little influence on the working memory functions of the PFC. Neither systemic administration (Arnsten & Goldman-Rakic, 1985) nor intra-PFC infusion (Li & Mei, 1994) of the beta adrenergic antagonist, propranolol, alters working memory performance in monkeys. Similarly, infusion of the beta adrenergic agonist, isoproterenol (0.1 µg/0.5 µL) into the medial PFC in rats has no effect on working memory performance in a T maze (Fig. 2). More detailed studies with selective beta 1 or beta 2 agents may produce different results, but current evidence suggests little involvement of beta adrenoceptor mechanisms in PFC function.

**Alpha-2 adrenergic mechanisms**

Although beta adrenergic receptors appear to have little influence on working memory, stimulation of post-synaptic alpha-2 adrenergic receptors has marked beneficial effects on PFC function (Fig. 3). Alpha-2-adrenoceptor agonists, such as clonidine, guanfacine, or meditomidine, administered either systemically (Arnsten & Goldman-Rakic, 1985; Arnsten et al., 1988; Carlson et al., 1992; Rama et al., 1996; Franowicz & Arnsten, 1998) or directly into the PFC (Tanila et al., 1996; Arnsten, 1997; Mao et al., 1999) improve working memory performance in monkeys (Fig. 3A) and in rats. Guanfacine has also been shown to enhance the performance of an object reversal task, a test of response inhibition that depends upon the functional integrity of the orbital PFC (Fig. 3B; Steere & Arnsten, 1997). The effects are blocked by co-administration of alpha-2 antagonists, such as yohimbine, which by themselves impair working memory performance (Arnsten & Goldman-Rakic, 1985; Li & Mei, 1994). Thus, intra-PFC infusion of an alpha-2, but not a beta or alpha-1 antagonist, produces a delay-related impairment in working memory performance in monkeys (Li & Mei, 1994). Evidence indicates that alpha-2 agents alter working memory through actions at post-synaptic alpha-2 receptors. For example, alpha-2 agonists are more potent and more efficacious in animals with catecholamine depletion (Arnsten & Goldman-Rakic, 1985; Cai et al., 1993). Evidence also suggests that the alpha-2A receptor subtype is likely to be the receptor underlying beneficial effects on working memory, from pharmacological profiles (Arnsten et al., 1988; Arnsten & Leslie, 1991; Rama et al., 1996), and from results in mice with genetically altered alpha-2 receptors (Franowicz et al., 1998; Tanila et al., 1999). The cognitive-enhancing effects of alpha-2 agonists can be completely dissociated from their sedating and hypotensive actions (Arnsten et al., 1988), which most likely occurs in different brain regions. Alpha-2 agonist-enhancing effects are particularly prominent under
conditions of high interference or distraction, conditions that require PFC function for optimal performance (Jackson & Buccafusco, 1991; Arnsten & Contant, 1992).

The importance of drug actions in the PFC for working memory enhancement has recently been confirmed in electrophysiological studies of monkeys performing working memory tasks.

Delay-related firing, namely, an increased rate of firing during the delay period relative to spontaneous activity, is thought to reflect the cellular basis of working memory function (Funahashi et al., 1989). Iontophoresis of the alpha-2 antagonist, yohimbine, onto PFC neurons reduces delay-related firing (Sawaguchi, 1998; Li et al., 1999). Conversely, systemic administration

![Diagram of Alpha-2 receptor stimulation effects on working memory and response inhibition](image)

Fig. 3: Alpha-2 receptor stimulation enhances working memory and response-inhibition functions of the PFC. A. The alpha-2A agonist, guanfacine, improves spatial working memory performance in aged monkeys. The improvement with guanfacine is reversed by the alpha-2 antagonist, idazoxan (adapted from Arnsten et al., 1988). B. Guanfacine improves response inhibition as measured by reversal of object discrimination performance; the improvement is reversed by the alpha-2 antagonist, idazoxan (adapted from Steere & Arnsten, 1997). For both graphs, results represent mean ± S.E.M. change from saline. SAL = saline, GFC = guanfacine, IDA = idazoxan, *significantly different from saline, **significantly different from guanfacine.
of the alpha-2 agonist, clonidine, increases delay-related activity, and this enhancement is reversed by iontophoresis of yohimbine onto the PFC neuron (Li et al., 1999). Taken together, the results at the cellular and behavioral level indicate that NE actions at alpha-2 receptors in PFC play an important role in facilitating working memory function.

Accumulating evidence indicates that the beneficial effects of alpha-2 agonists on PFC function in animals extend to humans as well. Earlier literature showed that the alpha-2 agonist, clonidine, could improve PFC deficits in patients with Korskoff's amnesia (Mair & McEntree, 1986) or with Attention Deficit Hyperactivity Disorder (ADHD; Hunt et al., 1985), but the side effects of this agent have limited its clinical use. Interestingly, clonidine improves memory and Trails B performance in schizophrenic patients (Fields et al., 1988), suggesting that the PFC deficits in this disorder may respond to alpha-2 agonist stimulation. Similarly, a recent study has shown that clonidine can improve word fluency and working memory in Alzheimer's patients (Riekkinen & Riekkinen, 1999), and researchers have suggested that alpha-2 agonists may provide an important adjunctive therapy in Alzheimer's disease (Haroutunian et al., 1990). The effects of clonidine in healthy young adults have been more complex. Higher doses that are thought to improve PFC function were often not given to normal individuals because of problematic side effects, and studies using lower clonidine doses have shown mixed effects on cognitive function (Coull, 1994; Coull et al., 1995; Jakala et al., 1999a; Jakala et al., 1999b). Imaging studies with clonidine showed enhanced frontal function in Korsakoff's patients (Moffoot et al., 1994), but studies of normal individuals with lower doses of clonidine generally showed changes in the thalamus that are likely to be related to the sedating actions of clonidine (Coull et al., 1997). Recent studies in humans of the more selective alpha-2A agonist, guanfacine, have been more successful in enhancing PFC function, with fewer side effects, similar to studies in animals. Guanfacine improves working memory and other PFC functions in young adults (Jakala et al., 1999a; Jakala et al., 1999b). Guanfacine has been shown to improve ADHD symptoms and PFC task performance in both open label (Chappell et al., 1995; Horrigan & Barnhill, 1995; Hunt et al., 1995) and controlled trials (F. Taylor, personal communication; L. Scahill, personal communication), and is now being tested in other PFC cognitive disorders. Thus, alpha-2A receptor stimulation may have therapeutic effects in disorders with PFC cognitive deficits.

**Alpha-1 adrenergic mechanisms**

In contrast to the beneficial effects of alpha-2 receptors, recent studies suggest that alpha-1 adrenoceptor stimulation markedly impairs PFC function. In rats, infusions of the alpha-1 agonist, phenylephrine, into the PFC produced large deficits in working memory performance (Fig. 2; Arnsten et al., 1999). This impairment was reversed by the co-infusion of the alpha-1 receptor antagonist, urapidil, consistent with actions at alpha-1 receptors. Similar effects have been observed in monkeys performing the delayed response task, a test of spatial working memory that is dependent on the dorsolateral PFC surrounding the principal sulcus (Mao et al., 1999). Infusions of phenylephrine produced a delay-related impairment in working memory performance. Infusions were most effective in the caudal two-thirds of the principal sulcal cortex (ibid), the cortical region most tightly associated with spatial working memory performance in monkeys (Goldman & Rosvold, 1970).

Alpha-1 receptors are generally coupled to the phosphotidyl inositol/PKC intracellular pathway via Gq proteins (Duman & Nestler, 1995), and evidence to date suggests that alpha-1 receptor stimulation impairs PFC function through the activation of this second messenger pathway. For example, the cognitive impairment induced by phenylephrine infusions into the rat PFC can be
completely reversed by pretreatment with a dose of lithium, known to suppress phosphotidyl inositol turnover (Arnsten et al., 1999). These data may have special relevance to bipolar disorder, a disorder commonly treated with lithium and associated with increased NE turnover. Lithium, however, can alter other second messenger pathways; thus, current studies in animals are focusing on agents that selectively target molecules in the phosphotidyl inositol/PKC cascade. For example, intra-PFC infusion of the PKC inhibitor, chelerythrine, appears to block the detrimental effects of alpha-1 agonists (S. Birnbaum & A. Arnsten, unpublished). The results are consistent with the activation of the phosphotidyl inositol/PKC pathway underlying alpha-1 receptor-mediated impairment of PFC working memory function. These findings contrast with those of studies showing that long-term memory consolidation is enhanced by activating PKC signaling pathways in such brain regions as the hippocampus (for example, Abeliovich et al., 1993). The finding that alpha-1 receptor stimulation impairs PFC function is likely to be relevant to the PFC cognitive deficits observed in rats, monkeys, and humans that are exposed to uncontrollable stress. Even relatively mild stressors can impair working memory and other PFC functions (reviewed in Arnsten & Goldman-Rakic, 1998). Although most of this research has focused on the role of high levels of dopamine-receptor stimulation in the stress response, NE is also released in the PFC during stress exposure (Finlay et al., 1995; Goldstein et al., 1996). Recent results demonstrate that NE alpha-1 receptor mechanisms also contribute to stress-induced working memory deficits, as intra-PFC infusion of the alpha-1 antagonist, urapidil, protected performance from the detrimental effects of stress (Birnbaum et al., 1999). It is likely that during stress exposure, NE and dopamine mechanisms synergize to take the PFC “off-line”. Recent results suggest that dopamine may impair working memory performance via the activation of D1 receptors (Zahrt et al., 1997) that are coupled to the cAMP/PKA pathway (Taylor et al., 1999). Thus, whereas the activation of PKA and PKC intracellular signaling pathways in posterior cortical and subcortical areas may enhance long-term memory consolidation, in PFC these pathways appear to impair working memory processes.

ADAPTIVE VALUE OF PFC DYSFUNCTION DURING STRESS

Although PFC cognitive functions are often essential for successful organization of high order behavior, under certain conditions, for example acute danger, when it may be adaptive to “shut down” these complex, reflective operations and to allow more automatic or habitual responses, dependent on posterior cortical and subcortical structures, to control our behavior (Arnsten, 1998; Arnsten & Goldman-Rakic, 1998). Studies of the effects of stress on higher cognitive functioning in humans have illustrated that many of the cognitive abilities that are now associated with the PFC are impaired by exposure to stress (Hockey, 1970; Broadbent, 1971; Hartley & Adams, 1974), particularly when the subject feels no control over the stressor (for example see Glass et al., 1971), whereas highly trained or prepotent responses can actually improve with stress (Broadbent, 1971). Possibly, many of these changes in performance during stress result from increased catecholamine release during stress exposure. Increased catecholamine release during stress is thought to be triggered by the amygdala, which projects to the catecholamine cells (Goldstein et al., 1996). Increased catecholamine release during stress may enhance the functions of the posterior cortices and many subcortical areas through actions at beta and/or alpha-1 receptors, while impairing prefrontal cortical function through actions at alpha-1 receptors. For example, increased catecholamine release during stress would enhance our long-term memory of an aversive event so that we might avoid it in the
future, and this enhanced memory consolidation would likely involve increased beta-receptor stimulation in the amygdala (Cahill et al., 1994) and in the hippocampus (Packard & Teather, 1998). Increased catecholamine release during stress might also alter attentional regulation, allowing attention to be “captured” by prominent stimuli in the environment. For example, in his study of humans exposed to loud noise stress, Hockey (1970) showed that stress (a) narrows the focus of attention onto salient signals, but (b) makes attention more labile (namely, impaired ability to sustain attention). These changes in attentional regulation may occur by (a) beta/alpha-1 receptor enhancement of signal processing in sensory cortices, and (b) alpha-1 receptor impairment of PFC, respectively. This hypothesis is consistent with the affinity of NE for the adrenergic receptors (Fig. 4). NE has a much higher affinity for alpha-2A than for alpha-1 or beta-1 receptors.

**Fig. 4:** NE has higher affinity for alpha-2A receptors (O'Rourke et al., 1994) than for alpha-1 receptors (Mohell et al., 1983) or beta receptors (Pepperl & Regan, 1994). Thus, lower, basal levels of NE release may engage alpha-2A receptors and facilitate PFC function, while high levels of NE release during stress may be needed to engage alpha-1 receptors and impair PFC function. Conversely, high levels of NE engaging alpha-1 and beta receptors would enhance the functions of the amygdala, hippocampus, and posterior cortices.
beta receptors. Thus, lower levels of NE release (during normal waking, for example) may engage alpha-2 receptors and enhance the PFC regulation of behavior. During stress, however, higher levels of NE would be released, engaging alpha-1 receptors and impairing PFC function while enhancing the abilities of the posterior cortices and subcortical structures through actions at beta and/or alpha-1 receptors. This neurochemical “switch” may be helpful under many conditions, for example, during dangerous circumstances that require rapid responding to stimuli in the environment, but may be problematic when PFC regulation of behavior is required. For example, such a switch would be maladaptive under stressful conditions, such as a very difficult math exam, where salient stimuli (for example, voices outside the window) often must be ignored, and attention must be sustained on less compelling stimuli (for example, the math exam). The discovery of neurochemical mechanisms that actively impair PFC function may help to explain why deficits in PFC function are prevalent in most neuropsychiatric disorders, and why such disorders are often precipitated or exacerbated by exposure to stress (Mazure, 1995).

In summary, a balance may exist between the anterior versus posterior cortical systems in the control of our behavior. The tipping of this “seesaw” may depend upon our perceived state of the environment, which is then reflected by the levels of NE release. Simply stated, PFC regulation of behavior may prevail when we perceive ourselves as safe and NE release is modest, whereas posterior cortical and subcortical systems may prevail when we perceive ourselves to be in danger and NE release is high. The tipping of this balance may be accomplished by the differential affinity of NE for its receptors.

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