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Adrenergic Pharmacology and Cognition: Focus on the Prefrontal Cortex

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Abstract

Norepinephrine (NE) has widespread projections throughout brain, and thus is ideally positioned to orchestrate neural functions based on arousal state. For example, NE can increase "signal/noise" ratio in the processing of sensory stimuli, and can enhance long-term memory consolidation in the amygdala and hippocampus through actions at α-1 and β adrenoceptors. Over the last 20 years, NE has also been shown to play a powerful role in regulating the working memory and attention functions of the prefrontal cortex (PFC). Moderate levels of NE released under control conditions strengthen prefrontal cortical functions via actions at post-synaptic α-2A adrenoceptors with high affinity for NE, while high levels of NE release during stress impair PFC cortical functions via α-1 and possibly β-1 receptors with lower affinity for NE. Thus, levels of NE determine whether prefrontal cortical or posterior cortical systems control our behavior and thought. Understanding these receptor mechanisms has led to new, intelligent treatments for neuropsychiatric disorders associated with PFC dysfunction.

Keywords

norepinephrine; adrenoceptor; frontal lobe; working memory; guanfacine; prazosin; clenbuterol; betaxolol; cAMP; protein kinase C

1. Introduction: Functions of the Prefrontal Cortex and Their Relevance to Mental Illness

The cognitive functions of the prefrontal cortex (PFC) are arguably the most advanced in our cognitive repertoire, and likely the most vulnerable to disruption. PFC circuits have the unique ability to represent information that is no longer in the environment- even in the face of distraction and to use this "representational knowledge" to guide behavior, thought and affect. This process is often referred to as "working memory". Working memory is thought to arise from networks of PFC pyramidal cells with shared properties engaged in recurrent excitation. These networks are thought maintain task relevant information during the delay period when stimuli are no longer present in the environment (Goldman-Rakic, 1995; see Figure 1). During this period that follows cue presentation, prefrontal neurons show increased firing rate in association with a specific location in the visual field where the cue was presented (i.e. 90° vs 45 °; Figure 1). The ability of PFC neuronal networks to keep task-relevant information 'online' in the form of delay-related firing is thought to represent the physiological basis of working memory. These firing patterns are tuned by GABAergic inputs, and by proper catecholamine

modulation (Rao et al., 2000; Constantinidis et al., 2002). Optimal PFC network firing allows the regulation of attentional focus, the inhibition of inappropriate motor responses, and planning for the future.

Deficits in PFC function are evident in most neuropsychiatric disorders (indeed, the term "psychiatric" may be synonymous with PFC dysfunction), and they are amongst the most prominent cognitive problems with normal aging (Nielsen-Bohlman & Knight, 1995; Schacter et al., 1996; Albert, 1997; Chao & Knight, 1997). Even in young, so-called "normal" individuals, PFC cognitive abilities fluctuate, eroding when we are fatigued or when we are exposed to uncontrollable stress. Even mild uncontrollable stressors have been shown to impair PFC working memory functions in both humans and animals (reviewed in Arnsten, 2000a). Furthermore, stress can precipitate or exacerbate many neuropsychiatric disorders. For example, stress has been linked to the onset of schizophrenic symptoms (Breier et al., 1991; Dohrenwend et al., 1995), and to the precipitation of manic episodes in patients with bipolar disorder (Hammen & Gitlin, 1997). Chronic uncontrollable stress is used as a model of depression, and even an acute, traumatic stress can induce Post-Traumatic Stress Disorder (PTSD), a syndrome associated with overactive amygdala and impaired PFC function (Bremner, 2002). Thus, it is critical that we understand how the PFC is modulated, and how modulation changes with age and with stress. Many neurotransmitters (glutamate, GABA) and neuromodulators (e.g. dopamine, serotonin, acetylcholine) contribute to PFC cognitive functioning in critical ways (reviewed in Arnsten & Robbins, 2002). This review focuses on the mechanisms by which NE influences PFC functions, as the field has achieved a surprising consistency, and is directly relevant to the treatment of neuropsychiatric disorders.

2. Background on Norepinephrine

The noradrenergic neurons arise from the locus coeruleus (LC) within the brainstem and their terminals project to many different brain regions, including the PFC (Arikuni & Ban, 1978; Gerfen & Clavier, 1979; Morrison et al., 1979; Morrison et al., 1982; Porrino & Goldman-Rakic, 1982). There is a reciprocal relationship between the PFC and the LC, as the PFC provides one of the few higher cortical inputs back to the LC neurons (Arnsten & Goldman-Rakic, 1984; Sara & Herve-Minvielle, 1995; Jodo et al., 1998). Within the monkey PFC, noradrenergic fibers target both deep and superficial layers of the cortex (Lewis & Morrison, 1989). NE released by these fibers interacts with three families of adrenergic receptors: the α1, the α2 and the β receptors (1-3).

NE has highest affinity for the α2 receptors, which consist of three subtypes: the α2A, the α2B and the α2C. The α2A, and to a lesser extent the α2C, are found pre-synaptically on NE cells and terminals, while all three subtypes are found post-synaptically (MacDonald et al., 1997). The α2A receptor is the most common subtype found in the PFC, however, there are low levels of α2C receptors as well (Aoki et al., 1994; Aoki et al., 1998a). Binding studies suggest that α2 receptors are most concentrated in superficial layers in primate PFC (Goldman-Rakic et al., 1990), although electron microscopic (EM) analyses also see receptors in deep layers. These studies have found α2A receptors, among other cellular locations, over post-synaptic densities on dendritic spines in the primate PFC (Aoki et al., 1994; Aoki et al., 1998a). α2 receptors are generally coupled to G_i proteins (Duman & Nestler, 1995; Ramos et al., 2006a), which can reduce intracellular cyclic adenosine monophosphate (cAMP) production by inhibiting some adenylyl cyclase isoforms (Figure 2).

NE has lower affinity for α1 adrenergic receptors, of which there are three subtypes: the α1A, the αB, and the α1D (Hieble et al., 1995). The α1A and α1D are most prominent in rodent PFC (Pieribone et al., 1994; Day et al., 1997). Receptor binding studies of primate PFC have shown that α1 receptors are concentrated in superficial layers (Goldman-Rakic et al., 1990), similar

to α2 receptors. However, in contrast to the α2 subtype, the subcellular localization of these receptors is not yet known. α1 Receptor stimulation has been found to enhance excitatory processes in many brain regions, particularly in the somatosensory cortex (Waterhouse et al., 1981; Mouradian et al., 1991). α1 receptors are generally coupled to G_q proteins, and can thus activate phospholipase C and phosphotidyl inositol intracellular signaling, resulting in activation of protein kinase C (PKC) and the release of intracellular calcium via inositol 1, 4, 5-triphosphate (Duman & Nestler, 1995; Birnbaum et al., 2004; see Figure 2).

Finally, NE has lowest affinity for β adrenergic receptors. There are three subtypes of β receptors: β1 (localized in heart), β2 (localized in lung), and β3 (localized in stomach), and all are found in the central nervous system as well (Insel, 1993). These subtypes are differentially expressed in various regions of the brain, with β1 receptors in higher concentrations in the adult rat cortex compared to the other receptor subtypes (Rainbow et al., 1984; Nicholas et al., 1993; Summers et al., 1995). β Receptors are densest in the intermediate layers of the PFC (Goldman-Rakic et al., 1990), where thalamic inputs are concentrated. Moreover, these receptors have been identified in high concentration in the monkey PFC (Goldman-Rakic et al., 1990; Aoki et al., 1998b). EM studies of monkey PFC have localized β2 receptors on dendritic spines (presumably of PFC pyramidal neurons) and on GABAergic interneurons (Aoki et al., 1998b). Electrophysiological studies of somatosensory cortex have shown that β receptors can potentiate GABAergic processes (Waterhouse et al., 1980). As GABA has a key influence on tuning of PFC neuronal response (Rao et al., 2000; Constantinidis et al., 2002), similar effects in PFC would be of great interest. Finally, many β receptors are found on glia, where they have multiple actions including reducing the uptake of glutamate (Hansson & Ronnback, 1991) and regulating glucose availability (Fillenz & Lowry, 1998; Fillenz et al., 1999). In general, β receptors are coupled via G_s to adenylyl cyclase, increasing cAMP signaling (Ordway et al., 1987; Duman & Nestler, 1995; Ferry et al., 1999a; Zhang et al., 2005; see Figure 2).

3. Activity Patterns of the Locus Coeruleus

LC neurons fire in accordance to arousal state, and the attentional interest of the animal (Foote et al., 1980). LC cells are silent during REM sleep, and increase their firing rate with increasing state of arousal. During alert waking, LC cells are in a so-called “phasic” state, with low levels of spontaneous firing and bursts of firing to stimuli that are of interest to the animal (Rajkowski et al., 1998; Aston-Jones et al., 1999). In contrast, when animals are stressed or anxious the cells enter a “tonic” state, with very high levels of spontaneous activity and less phasic activity to stimuli (ibid). The interaction between arousal state and information processing was observed in monkeys performing a continuous performance task where they had to distinguish the correct target stimuli and ignore distracting stimuli (ibid). When the monkey was alert and attentive, LC cells were in a “phasic” state, and fired to the targets but not the distractors. In contrast, when the animal was either drowsy or stressed it made errors, and the LC cells responded to the distractors with less response to the targets. It is tempting to speculate that the PFC regulates appropriate LC responding during the phasic, alert state, as it would be one of the few brain regions that contacts the LC with higher order information. The importance of NE and LC firing to attention regulation has been appreciated for a long time. Depletion of forebrain NE in rats leads to distractibility and attentional deficits in a variety of paradigms (Carli et al., 1983; Cole & Robbins, 1992).

4. The Effects of Norepinephrine on Prefrontal Cortex Function

4.1. Catecholamine depletion of the PFC dramatically impairs function

The pioneering study of Brozoski and colleagues was the first to demonstrate that catecholamines play a critical role in the modulation of the spatial working memory functions

of the PFC (Brozoski et al., 1979). Dopamine (DA) and NE depletion in the PFC was produced by infusion of the catecholamine neurotoxin, 6-hydroxy-dopamine (6-OHDA), into the dorsolateral PFC of monkeys. Animals with large catecholamine depletion of the PFC were as impaired similar to those with PFC ablations, highlighting the critical role of catecholamine modulatory influences. The effect of catecholamine depletion was specific to the cognitive functions of the PFC, since animals were not impaired on performance of a non-PFC task, visual pattern discrimination. Although the Brozoski study focused on the importance of DA to PFC function, as monkeys with large NE depletion and small DA depletion did not show deficits, it is now appreciated that both catecholamines are important to PFC function. Hence, it is likely that both must be substantially depleted to produce marked impairment in chronic studies. The Brozoski study has been replicated in rats with 6-OHDA lesions of the medial PFC (Simon, 1981), and in marmosets with 6-OHDA lesions to the dorsolateral PFC (Roberts et al., 1994; Collins et al., 1998). More recently, studies in marmosets have shown that 6-OHDA lesions of the dorsolateral PFC impair the ability to acquire an attentional set, a related function of this brain region (Crofts et al., 2001).

Spatial working memory deficits with preserved visual discrimination function have also been observed with global catecholamine depletion. For example, systemic, chronic reserpine treatment depletes monoamines and impairs spatial working memory performance without altering visual discrimination performance in young adult monkeys (Cai et al., 1993). Furthermore, aged monkeys and rats with naturally-occurring catecholamine depletion exhibit prominent spatial working memory deficits and generally spared performance on discrimination tasks (Bartus et al., 1978; Luine et al., 1990). In both young (Sahakian et al., 1985) and aged (Luine et al., 1990) rats, cognitive performance correlates with levels of PFC catecholamines. Pharmacological studies in aged animals and young, depleted animals indicate that PFC working memory function can be restored by administering compounds that mimic NE actions at α2 adrenergic receptors (Arnsten & Goldman-Rakic, 1985; Cai et al., 1993).

4.2. α2 Improves PFC function

4.2.1. α2 Agonists restore PFC functions in catecholamine-depleted animals: evidence for post-synaptic actions Studies in rodents, monkeys and humans have all shown that NE has an important beneficial influence on spatial working memory performance through its actions at α2 adrenergic receptors. Young monkeys with working memory impairment induced by local PFC (Arnsten & Goldman-Rakic, 1985) or global (Cai et al., 1993) catecholamine depletion are greatly improved by systemic treatment with α2 agonists such as clonidine and guanfacine. The beneficial effects of α2 agonists have also been observed in aged monkeys (Arnsten & Goldman-Rakic, 1985; Arnsten et al., 1988; Rama et al., 1996) and aged rats (Carlson et al., 1992; Ramos et al., 2006a) with naturally-occurring catecholamine loss. α2 Agonists also improve working memory performance in intact, young monkeys, but at higher doses than those needed to improve aged or depleted animals (Franowicz & Arnsten, 1998). Improvements with α2 agonists can be reversed with α2, but not α1, antagonists, and α2 antagonists by themselves impair PFC function, consistent with an α2 receptor mechanism (Arnsten & Goldman-Rakic, 1985). α2 Agonists have been shown to improve working memory for both visuo-spatial (Arnsten et al., 1988) and visuo-feature (Jackson & Buccafusco, 1991) cues, suggesting enhancement of both dorsolateral and ventrolateral PFC function.

Most studies of NE modulation of PFC function have used working memory tasks, but a few animal studies have shown effects on PFC tasks that challenge attention regulation and behavioral inhibition. For example, α2 agonists are particularly effective at enhancing working memory during distracting conditions (Jackson & Buccafusco, 1991;Arnsten & Contant, 1992), a finding consistent with earlier studies showing that forebrain NE depletion increases distractibility (Carli et al., 1983). Clonidine and guanfacine have been shown to improve

attentional regulation, behavioral inhibition and planning in humans as well (see below). A recent study by Chamberlain et al. suggested that NE is more sensitive in modulating lateral compared to orbital PFC function (Chamberlain et al., 2006). In this study, atomoxetine, a NE reuptake blocker, enhanced response inhibition, but had no significant effect on a probabilistic learning task dependent on the orbital PFC, a region regulated more by serotonin (Clark et al., 2005; Chamberlain et al., 2006). The latter study may help explain why higher doses of guanfacine are required to improve performance of an object reversal task associated with orbital PFC function (Steere & Arnsten, 1997).

4.2.2. α2 Agonists improve via the A-subtype—The greater the loss of NE, the lower the dose of α2 agonist needed to improve PFC performance (Franowicz & Arnsten, 1999), a pattern consistent with drug actions at supersensitive, post-synaptic receptors. Pharmacological profiles further indicate that the α2A receptor subtype may be the most critical for cognitive enhancement (see (Arnsten et al., 1996) for review). For example, the α2A selective agonist, guanfacine, is the most effective compound in enhancing working memory without side effects (Arnsten et al., 1988; Rama et al., 1996). Guanfacine is about ten times weaker than clonidine in inhibiting firing of the NE cell bodies in the LC or in decreasing NE release (Engberg & Eriksson, 1991), but is 10-100 times more potent in improving working memory in aged monkeys (Arnsten et al., 1988). Studies in genetically-altered mice emphasize the importance of the α2A receptor subtype, as mice with a mutation of the α2A subtype no longer show beneficial effects on working memory after guanfacine treatment (Franowicz et al., 1998), while knockout of the α2C subtype has no effect on the response to another alpha-2 adrenergic agonist, dexmedetomidine (Tanila et al., 1999). Although knockout of the α2C receptor had no effect on working memory, it does seem to be related to the modulation of other NE-associated behaviors. Interestingly, knockout of the α2C subtype diminished the response to stress in classic tests of depression (i.e. forced swim test), suggesting that α2C receptor blockade may be useful for treating stress-related psychiatric disorders such as depression (Sallinen et al., 1999).

4.2.3. α2 Adrenergic agonists improve PFC, but not nonPFC, cognitive functions —Although α2 agonists improve the performance of tasks that challenge the PFC, they often have little beneficial effect under conditions that do not challenge the PFC. For example, these drugs have no effect or impair the spatial reference memory functions of the hippocampus (Sirviö et al., 1991), the visual feature discrimination memory functions of the inferior temporal cortex (Arnsten & Goldman-Rakic, 1985; Steere & Arnsten, 1997),the visual feature recognition memory functions of the perirhinal cortex (Arnsten & Goldman-Rakic, 1990), and the covert visual-spatial attention shifting functions of the parietal cortex (Witte & Marrocco, 1997). Thus, the beneficial effects of α2 agonists are relatively specific to PFC functions.

4.2.4. Evidence for actions in the PFC—A number of studies in rodents and monkeys demonstrate that α2 compounds act directly in the PFC to alter working memory function. As with systemic injection, direct infusion of α2 antagonists, but not α1 or β antagonists, into the dorsolateral PFC produces a delay-related impairment in spatial working memory (Li & Mei, 1994), demonstrating that endogenous NE stimulation of α2 receptors in the PFC is critical to working memory performance. Infusions of the α2 antagonist, yohimbine, into dorsolateral PFC also impaired impulse control (Ma et al., 2003) and induced locomotor hyperactivity (Ma et al., 2005), thus producing a profile of behavioral disinhibition. Conversely, intra-PFC infusion of α2 agonists improved working memory performance in either young (Mao et al., 1999) or aged monkeys (Arnsten, 1997), or aged rats (Tanila et al., 1996; Ramos et al., 2006a).

Imaging studies in monkeys are also consistent with α2 adrenergic mechanisms enhancing PFC function. We have observed increased regional cerebral blood flow (rCBF) in the dorsolateral

PFC of monkeys treated with guanfacine prior to performing a spatial working memory task (Avery et al., 2000). Guanfacine improved working memory performance and increased rCBF in the PFC surrounding the principal sulcus, the same region essential for spatial working memory function (Goldman & Rosvold, 1970). In contrast, guanfacine had no effect on rCBF in the auditory association cortex (superior temporal cortex), a region not involved in task performance (Avery et al., 2000). These results are consistent with imaging studies in humans treated with guanfacine (see below).

4.2.5. Effects on PFC neurons—Electrophysiological studies have observed parallel findings at the cellular level. Iontophoresis of the α2 antagonist, yohimbine, reduced delay-related activity in PFC neurons of monkeys performing spatial working memory tasks (Sawaguchi, 1998; Li et al., 1999). Conversely, systemic clonidine administration enhances delay-related firing in PFC cells, and this effect is reversed by iontophoretic application of yohimbine (Li et al., 1999). Similar results have recently been observed with guanfacine (Wang et al., 2006). Clonidine and guanfacine increase delay-related firing for the preferred direction, but have little effect on firing for nonpreferred spatial directions, thus enhancing spatial tuning during the delay period (ibid). Thus, NE actions at α2A receptors in PFC have powerful effects on delay-related firing, the presumed neuronal substrate of working memory function (see introduction above). It is possible that the beneficial effects of α2 receptor stimulation occur on dendritic spines, as α2A receptors have been localized on the post-synaptic membranes of spines in monkey PFC (Aoki et al., 1994; Arnsten et al., 1996).

4.2.6. Second messenger actions—α2 adrenergic receptors are commonly coupled to G_i proteins which inhibit adenylyl cyclase/cAMP pathways (Duman & Nestler, 1995; see Figure 2). As activation of the adenylyl cyclase/cAMP pathway seems to impair PFC function (Taylor et al., 1999; Ramos et al., 2003), inhibition of this intracellular signaling pathway may contribute to the beneficial effects of α2 agonists on PFC cognitive function. Indeed, recent evidence demonstrated that treatments that increase cAMP signaling block guanfacine's beneficial effects in both aging rats and monkeys (Ramos et al., 2006a). For example, in rats, a dose of Sp-cAMPS (a compound that mimics cAMP) that has no effect on its own completely reversed guanfacine's enhancing effects. Similar effects were observed in monkeys using rolipram, a drug that inhibits the phosphodiesterases that normally catabolize cAMP, thus leading to an increase in endogenous levels of cAMP. The enhancing effects of guanfacine were significantly reduced by co-administration of rolipram, using a low dose that had no effect on task performance on its own (ibid). Thus, guanfacine's beneficial effects on working mediated appear to be mediated via inhibition of cAMP signaling in the PFC. Recent electrophysiological studies in monkeys are consistent with this hypothesis (Wang et al., 2006).

4.2.7. Clinical relevance—Recent studies with α2 agonists in healthy humans and patients with PFC disorders have found surprising similarity to basic studies in animals. Earlier studies had focused on clonidine, a suboptimal drug due to its potent inhibition of LC firing, prominent side effect profile, and high affinity for imidazoline I1 receptors. Clonidine usually has mixed effects on PFC functions in healthy young adults, presumably due to competing pre- vs. post-synaptic effects and dose limitations from sedative and hypotensive side effects (Coull, 1994; Jakala et al., 1999a). However, improvement with clonidine has been observed in patient groups with PFC deficits and likely alterations in PFC catecholamines. For example, clonidine improved performance of memory recall and the Stroop interference task in patients with Korsakoff's amnesia, and was most effective in those with the greatest signs of NE loss (Mair & McEntree, 1986). Clonidine has also been shown to improve memory recall and performance of the Trails B behavioral inhibition task in schizophrenic patients (Fields et al., 1988). Clonidine improves spatial working memory in Parkinson's patients with presumed

catecholamine depletion in the PFC (Riekkinen & Riekkinen, 1999a). One recent study has shown that clonidine can even improve working memory in patients with Alzheimer's Disease (Riekkinen & Riekkinen, 1999b), although previous studies have not shown benefit (Mohr et al., 1989).

Imaging studies in humans generally support findings from animal research. Studies using low doses of clonidine in normal adults generally show a picture of impaired attention and emerging sedation associated with imaging changes in thalamus and parietal cortex (Coull et al., 1997). These findings are consistent with an older study showing clonidine impaired attentional orienting (Clark et al., 1987), a function dependent on parietal lobe function (Posner et al., 1984). These findings reinforce the notion that posterior cortex and most subcortical structures are impaired by α2 receptor stimulation. However, a different picture emerges when higher doses of clonidine are given to patients with presumed NE loss, or when guanfacine is used. For example, administration of higher doses of clonidine to Korsakoff's patients increased regional cerebral blood flow in frontal lobe, and the increased blood flow in the left PFC correlated with improved verbal fluency performance (Moffoot et al., 1994). A more sophisticated analysis also suggests that clonidine can have important modulatory effects on higher cortical function. Clonidine has also been shown to increase the effective connectivity between the LC, parietal cortex and PFC during an attentional task, while decreasing connectivity during rest (Coull et al., 1999). More recently, guanfacine has been shown to increase regional cerebral blood flow in the frontal lobe of healthy adults as measured by PET imaging (Swartz et al., 2000). These studies reinforce the idea that α2 receptor stimulation often impairs the functioning of most brain regions, and that the PFC is exceptional in its beneficial influence from α2A receptor stimulation.

A superior profile has been observed with the more selective α2A agonist, guanfacine. Guanfacine has been shown to improve working memory, planning and paired associates learning tasks in healthy young adults (Jakala et al., 1999a;Jakala et al.,1999b), although this effect was not replicated in a study of younger, healthy subjects (Muller et al., 2005). However, guanfacine has been shown to be very effective in patients with PFC dysfunction.

Much research with α2 agonists has focused on patients with attention-deficit hyperactivity disorder (ADHD), a disorder with prominent PFC dysfunction. Early studies demonstrated that clonidine can improve symptoms of ADHD (Hunt et al., 1985), but serious hypotensive and sedative side effects have limited its use. Current studies have turned to the more selective α2A agonist, guanfacine. Guanfacine has been shown to be effective in three open label trials (Chappell et al., 1995; Horrigan & Barnhill, 1995; Hunt et al., 1995; Boon-yasidhi et al., 2005). In addition, two placebo controlled trials have come to similar results (trial in ADHD adults, guanfacine favorable to dexedrine, Taylor & Russo, 2001; trial in ADHD children with tics, guanfacine improved tics and ADHD symptoms, Scahill et al., 2001). In addition to having therapeutic effects on standard rating scales, guanfacine has been shown to improve performance of PFC tasks such as the Stroop (Taylor & Russo, 2001, guanfacine superior to dexedrine) and the Connors CPT which assesses vigilance, working memory and behavioral inhibition (Scahill et al., 2001). These published findings are consistent with clinical reports that guanfacine reduces impulsivity (ibid), a sign of improved PFC function. Interestingly, susceptibility to ADHD has been associated with a Taq IA polymorphism of the dopamine beta hydroxylase (DBH) gene (Smith et al., 2003; Tang et al., 2006). DBH catalyzes the conversion of dopamine to norepinephrine, and this polymorphism results in lower DBH activity. Thus, patients with ADHD may have less endogenous activation of α2 receptors and benefit from treatment with an α2 agonist such as guanfacine.

Guanfacine may also be useful in treating PFC dysfunction in other types of patients. It has been tested in patients with schizophrenia (Friedman et al., 1999), and more recently in subjects

with schizotypal disorder where it normalized cognitive performance on a Connors CPT (McClure, 2006). Guanfacine is also being tried in patients with mild traumatic injury to the PFC (McAllister et al., 2004), and in PTSD (Horrigan, 1996). Thus, this is a rare instance where basic research has led to a treatment for neuropsychiatric dysfunction.

4.3. α1 Impairs PFC function

4.3.1. High levels of NE impair working memory function via α1 receptor stimulation—New evidence indicates that high concentrations of NE impair PFC function through activation of α1 adrenergic receptors. NE has higher affinity for α2A than α1 receptors (α2A receptors: 56 nM, O'Rourke et al., 1994; α1 receptors: 330 nM, Mohell et al., 1983). Thus, it is likely that low levels of NE (e.g. under basal or nonstress conditions) preferentially engage α2 receptors and improve PFC function, while during conditions of high NE release, α1 receptors would become engaged and override the effects of α2 receptor stimulation. It is well established that high levels of NE are released in the PFC during stress exposure (e.g. Finlay et al., 1995; Goldstein et al., 1996), and recent evidence suggests that these high NE levels stimulate α1 receptors and impair PFC function (Birnbaum et al., 1999). Thus, stress-induced cognitive deficits were blocked by infusion of the α1 receptor antagonist, urapidil, into the PFC prior to cognitive testing (Birnbaum et al., 1999). Infusions of urapidil had no effect under nonstress conditions (ibid), presumably due to little endogenous NE α1 receptor stimulation during nonstressful conditions.

4.3.2. Evidence for actions in the PFC—The effects of stress on working memory performance can be mimicked by infusion of an α1 adrenergic receptor agonist into the PFC. Infusions of the α1 agonist, phenylephrine, into the PFC in rats markedly impaired working memory performance (Arnsten et al., 1999). This impairment was reversed by co-infusion of the α1 receptor, antagonist, urapidil, (ibid), consistent with actions at α1 receptors. Similar effects have been observed in monkeys, where infusions of phenylephrine into the dorsolateral PFC produced a marked, delay-related impairment in working memory performance (Mao et al., 1999). 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). Thus, high levels of NE release in the PFC may engage α1 receptors and impair PFC working memory function. Interestingly, most effective antipsychotic medications, including the new "atypical" neuroleptics, have potent α1 blocking properties (Baldessarini et al., 1992). Although most previous attention has focused on the sedating effects of these α1 blocking properties, the current data suggest that α1 blcockade may have therapeutic effects as well.

4.3.3. Effects on PFC neurons—Iontophoresis of the α1 agonist, phenylephrine, onto PFC neurons suppressed delay-related firing in monkeys performing a spatial working memory task (Birnbaum 2004). The suppression in firing was most evident for the preferred direction, thus resulting in an erosion of spatial mnemonic tuning. These results are the opposite of what was observed with α2 agonists, consistent with the behavioral findings.

4.3.4. Second messenger actions—α1 Adrenergic receptors are commonly coupled to the phosphotidyl inositol/PKC intracellular pathway via G_q proteins (Duman & Nestler, 1995; see Figure 2). Evidence to date suggests that α1 receptor stimulation impairs PFC function through activation of this second messenger pathway. For example, both the α1 adrenergic agonist, phenylephrine, and pharmacological stressor, FG7142 (increases catecholamine release), can increase PKC enzymatic activity in the membrane fraction of prefrontal cortical slices (Birnbaum et al., 2004). 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).

However, lithium can alter other second messenger pathways. Therefore, more recent studies in animals have focused on agents which selectively target molecules in the phosphotidyl inositol/PKC cascade. For example, intra-PFC infusion of the PKC inhibitors, chelerythrine or NPC15437, blocked the detrimental effects of α1 agonists and/or stress (Birnbaum et al., 1999). Similar results have been reported by Dash and colleagues, whereby performance of an aversive working memory task was improved by infusion of PKC inhibitors into the rat PFC (Runyan et al., 2005). Systemic administration of the PKC inhibitor, chelerythrine, also protects working memory in monkeys (Birnbaum et al., 2004). Interestingly, electrophysiological recordings showed that the suppression of delay-related firing induced by iontophoresis of phenylephrine was prevented by co-iontophoresis of chelerythrine (ibid). These results are consistent with activation of the phosphotidyl inositol/PKC pathway underlying α1 receptor-mediated impairment of PFC cognitive function at a behavioral, biochemical, and physiological level.

4.3.5. Clinical relevance—This basic research is highly relevant to PTSD, and may also have direct relevance to bipolar disorder and schizophrenia.

In humans as well as animals, traumatic stressors likely lead to excessive NE release and α1 adrenergic receptor engagement. The animal research suggests that high levels of α1 receptor stimulation should weaken PFC inhibitory functions (see above) and strengt'hen amygdala function (Ferry et al., 1999b), the profile observed in PTSD. Thus it has been very compelling that α1 receptor blockade with prazosin has been shown to lessen symptoms of PTSD in patients with combat (Raskind et al., 2000; Raskind et al., 2003) or civilian (Taylor & Raskind, 2002; Taylor et al., 2006) PTSD. It has also been helpful in treating elderly patients with longstanding PTSD (Peskind et al., 2003). Together, these studies suggest that α1 receptor blockade strengthens the inhibitory functions of the PFC function and thus lessens intrusive thoughts and flashbacks that are cardinal symptoms of this disorder.

The finding that excessive activation of PKC impairs PFC function also has relevance to bipolar disorder and schizophrenia. Bipolar disorder is associated with excessive levels and overactivity of PKC, and most effective treatments for mania (e.g. lithium, valproic acid) reduce the activity of the phosphotidyl inositol/PKC cascade (Manji & Lenox, 1999). The antiestrogen, tamoxifen, has PKC-blocking properties at high doses, and proof of concept studies suggest that this compound can be helpful in bipolar disorder (Bebchuk et al., 2000; Kulkarni et al., 2006). The successful use of atypical antipsychotics is likely related to the α1 and 5HT2A-blocking properties of these compounds, as both of these receptors activate the PKC signaling pathway. Recent gene array and genetic studies suggest that overactive PKC may also contribute to schizophrenia. RGS4 is a molecule that inhibits PKC signaling, and its levels are greatly reduced in the PFC of patients with schizophrenia, and may be genetically linked to schizophrenia and bipolar disorder (Mirnics et al., 2001; Prasad et al., 2004; Erdely et al., 2006), although see (Lipska et al., 2006; Talkowski et al., 2006). Thus, disinhibited PKC signaling may contribute to these psychotic disorders, and may worsen during stress exposure. It is hoped that more selective PKC inhibitors may have more rapid and powerful effects in treating psychotic disorders.

4.4. β Receptors

4.4.1. Opposing effects of β1 and β2?—β Adrenergic receptor stimulation has been known to play a critical role in long-term memory consolidation in the amygdala and hippocampus. For example, infusion of β adrenergic antagonists into the amygdala impairs, whereas infusion of a β adrenergic agonist improves memory consolidation (reviewed in (Cahill & McGaugh, 1996). Similarly, β receptor stimulation in the dentate gyrus can induce long-term potentiation (Lacaille & Harley, 1985; Chaulk & Harley, 1998) and is involved in

the late phase of memory consolidation in the hippocampus (Roullet & Sara, 1998; Sara et al., 1999). In contrast, previous studies had observed no effect on the working memory functions of the PFC when β1 and β2 receptors were blocked with the mixed β1/β2 antagonist, propanolol. For example, neither microinjection of propanolol into the PFC (Li & Mei, 1994), nor systemic administration of propanolol (Arnsten & Goldman-Rakic, 1985) altered PFC function in monkeys. This lack of effect is surprising as β receptors have been identified in high concentration in the monkey PFC (Goldman-Rakic et al., 1990; Aoki et al., 1998b). However, different results are obtained when selective β adrenergic drugs are used that target specific receptor subtypes. Indeed, a recent study showed that endogenous activation of β1 receptors, as can occur with stress, impairs PFC cognitive function (Ramos et al., 2005). In this study, infusion of the β1 adrenergic antagonist, betaxolol, improved working memory performance in both rats and monkeys (ibid). The effect of betaxolol seen in the latter study contrasts with the effects described above in the amygdala where infusion of a β adrenergic antagonist impairs memory consolidation.

In contrast, recent evidence from our lab suggests that β2 receptors have beneficial effects on working memory. Stimulation of β2 receptors with clenbuterol significantly, yet modestly, enhances working memory function in aging animals (Ramos et al., 2006b). The enhancement with clenbuterol is similar to its effects in the amygdala and hippocampus. For example, McGaugh and colleagues have demonstrated that β2 receptor stimulation within the amygdala immediately after training enhances performance in an inhibitory avoidance task (Introini-Collison et al., 1991; Ferry & McGaugh, 1999). Thus, clenbuterol could be one of the few agents to produce global cognitive improvement. β2 receptor stimulation could produce generalized improvement by enhancing glucose availability through influences on astrocytes.

Finally, the influence of β3 receptor stimulation on PFC function has yet to be studied. There are high levels of β3 receptor mRNA in rat cortex (Summers et al., 1995), indicating that this should be a direction for future research.

4.4.2. Second messenger actions—In contrast to α2 adrenergic receptors, β receptors can be coupled to G_s which can lead to an increase in cAMP levels (Figure 2). Previous research has shown that increasing cAMP levels impairs PFC function in both young and aged animals (Taylor et al., 1999;Ramos et al., 2003). Thus, β1 receptors, like DA D1 receptors, may impair PFC cognitive function via this intracellular pathway during conditions of high catecholamine release (i.e. stress). Similar to β1 receptors, β2 receptors can also couple to G_s proteins. Indeed, activation of β2 receptors in the cortex increases levels of cAMP (Ordway et al., 1987). Moreover, this increase in cAMP is significantly reduced by the β2 antagonist, ICI 118551 (ibid). Similarly, in the amygdala, β2 receptors modulate memory storage by a direct coupling to adenylyl cyclase and influencing cAMP formation (Ferry et al., 1999a). A recent study by O'Donnell and colleagues suggests that clenbuterol's antidepressant effects are also via increased cAMP signaling in cortical neurons (Zhang et al., 2005). Taken together, clenbuterol's effects on working memory performance may be via activation of this pathway. The fact that both β receptors can couple to the same pathway, but have opposite effects suggests different sites of action. Future studies should compare β1 vs β2 receptors' subcellular localization within the PFC and examine whether or not activation of a cAMP-dependent signaling mediates the effects of these receptors in the PFC.

4.4.3. Clinical relevance—β Adrenergic receptor blockers such as propranolol are being tested immediately post-trauma in the hopes of alleviating the development of PTSD (Vaiva et al., 2003). Studies in animals suggest that this drug treatment may prevent amygdala-induced enhancement of the traumatic memories, but may not strengthen PFC inhibitory abilities. Specific blockade of the β1 receptor subtype may provide a more powerful therapeutic effect because this strategy strengthens the PFC and could weaken amygdala function. Thus, unlike

propanolol, betaxolol may prove useful in treating established PTSD as has been suggested previously (Ramos et al., 2005).

Previous evidence suggests that the effects of clenbuterol could result from β receptors' ability to enhance the breakdown of glycogen and the export of glucose from astrocytes to increase local cerebral blood flow (Fillenz et al., 1999).Since glucose metabolism has been found to be decreased in the frontal and temporal lobes of aged humans and monkeys (De Santi et al., 1995; Eberling et al., 1997; Noda et al., 2002), the effects of clenbuterol could be important for the elderly population with prefrontal cortical deficits. Interestingly, age-related memory impairment can be reversed by administration of glucose or epinephrine, which binds preferentially to β receptors (Korol & Gold, 1998). Thus, β2 receptor activation may be particularly relevant in the aged population where reduced glucose metabolism may be contributing to prefrontal cortical deficits. However, to our knowledge, no study has examined the effects of β2 receptors in human cognition and thus it is hard to speculate as to clenbuterol's clinical efficacy. Despite the initial positive findings with β adrenergic agonists in rats and monkeys, it is still too early to have this basic research translated into the clinic.

5. Comparison with Other Brain Regions: Why the Qualitative Differences?

The PFC successfully guides behavior under nonstressful conditions when we feel in control. However, there is abundant evidence that the PFC goes 'off-line' during stress. Our emerging picture suggests that the PFC may be modulated differently than other than brain regions, and that the neurochemical conditions that are optimal for PFC are suboptimal for posterior cortical and subcortical regions, and vice versa. NE seems to play an important role in this 'neurochemical switch' (reviewed in Arnsten, 2000b; Arnsten, 2000a). NE regulation of the PFC is "upside down and backwards" from much of the rest of the brain. Thus, NE stimulation of α2 adrenergic receptors enhances PFC functions but impairs many posterior cortical functions, while stimulation of α1 and/or β receptors enhances posterior cortical functions but impairs or has no effect on PFC function. As NE has higher affinity for α2 than α1 or β receptors (see above), lower levels of NE release during non-stressed conditions may preferentially engage α2 receptors and facilitate PFC regulation of behavior, while high levels of NE release during stress may engage α1 and β1 receptors, taking the PFC "off-line" but providing areas such as the amygdala, hippocampus, sensory/motor cortices and cerebellum with a more optimal neurochemical environment. This may have survival value, allowing more habitual or reflexive mechanisms to control behavior during dangerous conditions (Figure 3). However, this differential neurochemical regulation may render the PFC particularly vulnerable to dysfunction in our daily lives, and in a wide variety of neuropsychiatric disorders, particularly under conditions of repeated or uncontrollable stress. Finally, the enhancement of amygdala or hippocampal function could be important to improve the recollection of memories with strong survival value and thus help to be better equipped for similar, future experiences. However, as is the case of PTSD, overactivation of these traumatic memories can have very deleterious effects in our daily lives.

6. Noradrenergic biology: Peripheral versus Central Effects

A parallel to this process can be observed in the peripheral nervous system. Noradrenergic neurons contribute to the stress response in the periphery via the sympathetic nervous system, and epinephrine is released by the adrenal medulla. As can be seen in Figure 3, increases in epinephrine or norepinephrine can increase heart rate (via β1 receptors), enhance pulmonary function (via β2 receptors), and increase blood pressure (via α1 and β receptors) to increase the amount of oxygenated blood being delivered to striated muscle for the fight and flight response. At the same time, norepinephrine and epinephrine reduce digestive function via β3 receptors, as one can "stop digesting lunch in order to not become someone else's lunch". Thus,

in the periphery, norepinephrine orchestrates physiological functions to switch us from a nonstress to a stressful state. A similar orchestration appears to occur in the central nervous system, where the PFC is the thoughtful, “digestive” organ that is strengthened by moderate levels of NE and shut off by stressful levels of NE release, while the sensor-motor and affective regions of brain are enhanced by higher levels of NE.

7. Conclusion

Understanding adrenergic pharmacology of PFC helps to develop therapeutic agents for mental illness. Indeed, symptoms such as poor concentration, impulsivity, working memory impairment, and inappropriate behaviors are common in mental illness and are thought to reflect PFC dysfunction. Furthermore, psychiatric disorders are influenced by stress, which, as has described above, impairs PFC cognitive function. For example, schizophrenia and affective disorder are often exacerbated or precipitated by stress exposure (reviewed in (Mazure, 1995). The current review described how stress can increase the release of catecholamines in both peripheral and central nervous systems, with a focus on NE’s effects on the PFC via its different adrenergic receptor subtypes (α1, α2, and β). α2 Receptors regulate working memory in a beneficial way during non-stressful moments, whereas α1 or β1 are engaged during stress to impair prefrontal cortical function. Moreover, many psychiatric disorders such as schizophrenia (Baldessarini et al., 1992), anxiety disorders such as PTSD (Krystal et al., 1996; Bremner et al., 1997; Southwick et al., 1997a; Southwick et al., 1997b), bipolar disorder (Post et al., 1973; Schildkraut, 1974; Young et al., 1994), and dementia (Gottfries et al., 1983; Lawlor et al., 1995; Elrod et al., 1997) are associated with high levels of NE turnover. Currently, adrenergic receptors, particularly the α1 and α2 receptor subtypes, are targets for the treatment of PTSD and ADHD, respectively. With further research, the β receptors may become part of the treatment repertoire for diseases with PFC dysfunction. Hence, greater understanding of the effects of norepinephrine on PFC function will greatly benefit the field of neuropsychiatry and could lead to better treatments for various mental illnesses.

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Abbreviations

PFC
prefrontal cortex

NE
norepinephrine

LC
locus coeruleus

EM
electron microscopic

cAMP
cyclic adenosine monophosphate

PKC protein kinase C

DA dopamine

6-OHDA 6-hydroxy-dopamine

rCBF regional cerebral blood flow

ADHD attention-deficit hyperreactivity disorder

DBH dopamine beta hydroxylase

PTSD post-traumatic stress disorder

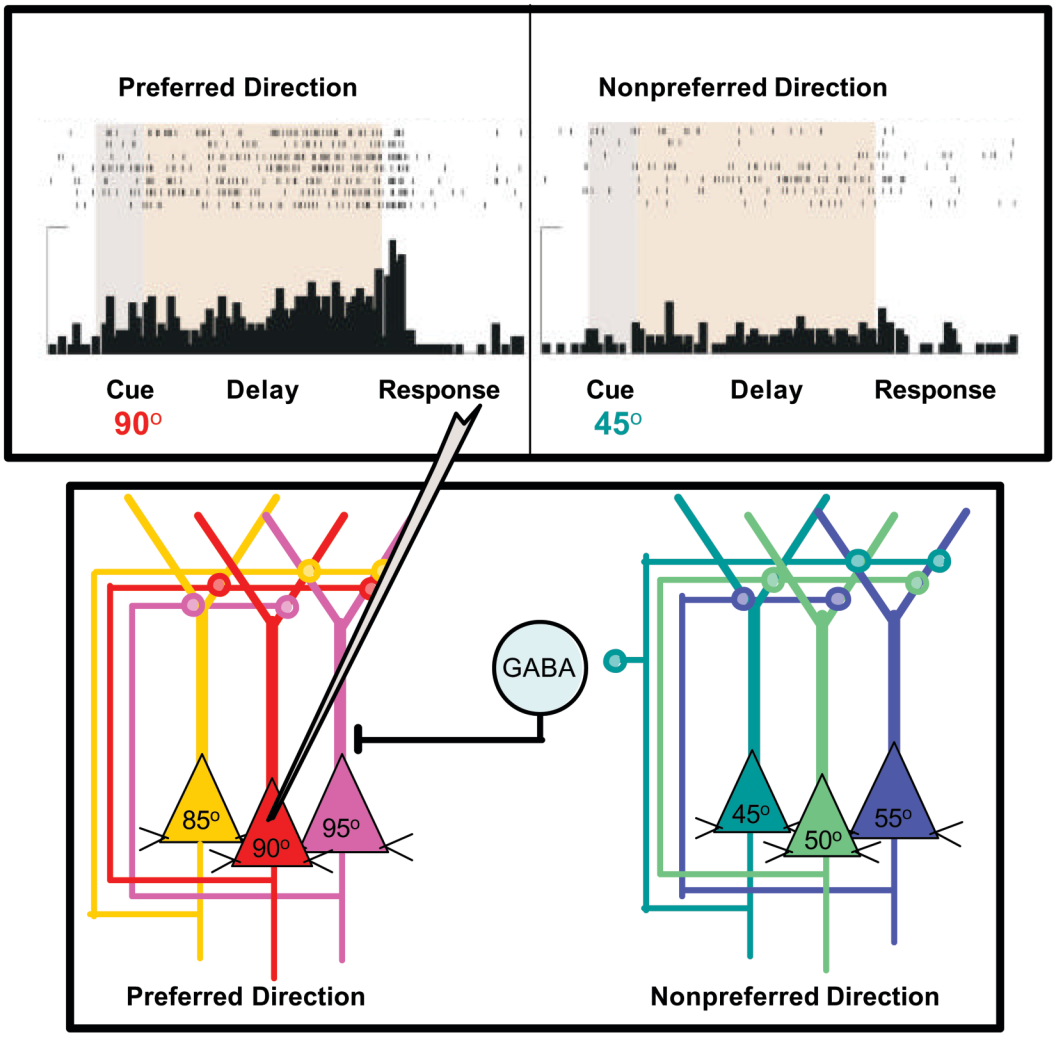

Figure 1.

The cellular basis of spatial working memory. **(A)** A neuron with spatially tuned persistent activity during the delay period of a spatial working memory task. Data from Dr. Min Wang. **(B)** Schematic representation of PFC networks of pyramidal cells that represent the cellular basis of working memory. Networks with shared mnemonic properties (preferred direction) engage in recurrent excitation to maintain information (increase in firing rate) during the delay period in the absence of environmental stimuli. GABAergic interneurons activated by networks firing to non-preferred directions enhance spatial tuning by inhibiting firing to nonpreferred directions. Adapted from Goldman-Rakic.

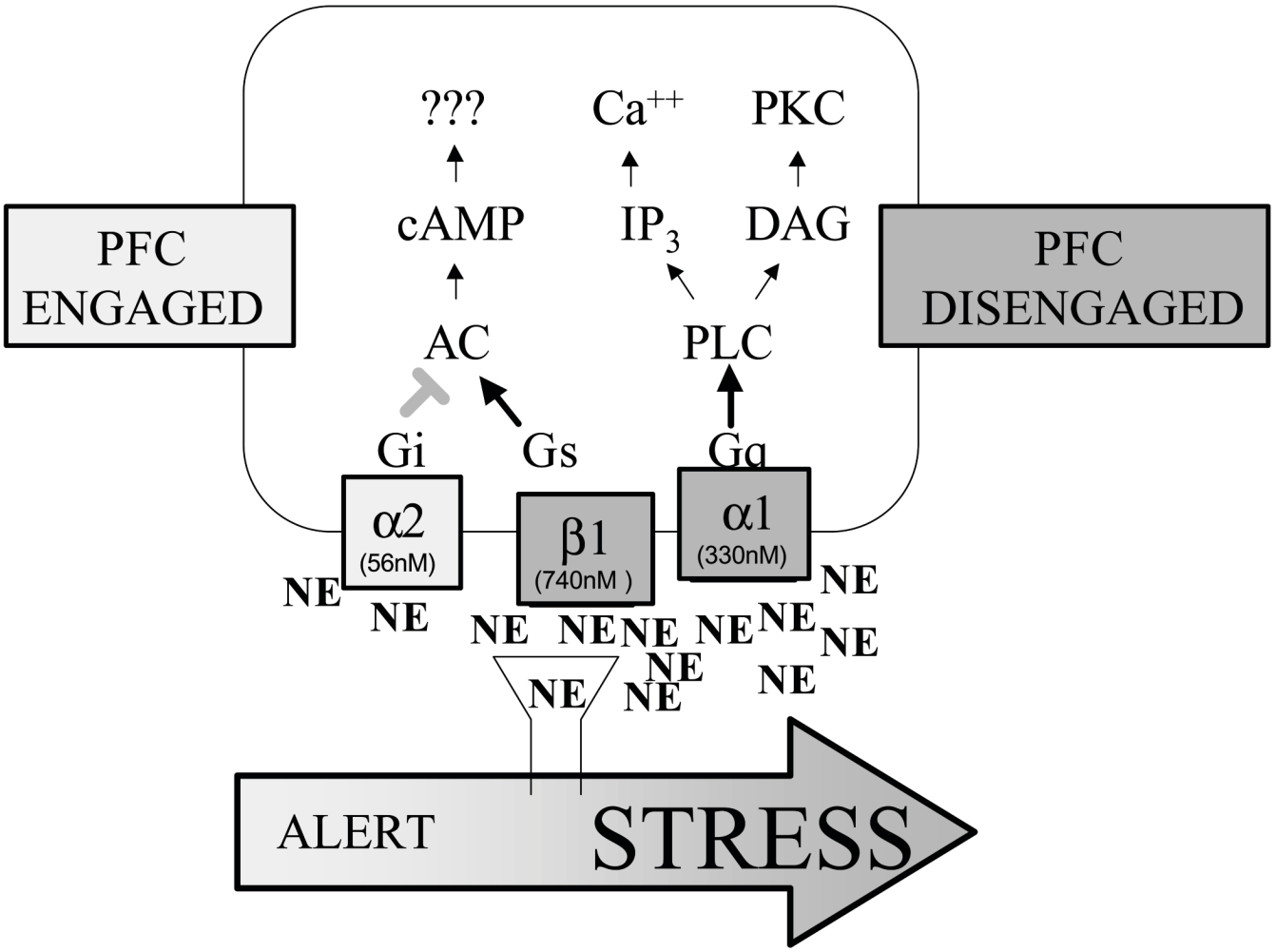

Figure 2.

Norepinephrine (NE) released in the PFC activates different intracellular signaling pathways through distinct adrenoceptors with varying affinities for NE. PFC cognitive function is enhanced by moderate levels of NE engaging post-synaptic α2A receptors with high affinity for NE, while high levels of NE impair PFC cognitive function by engaging α1 and β1 receptors with lower affinity for NE. AC, adenylyl cyclase; LC, locus coeruleus; PLC, phospholipase C; DAG, diacylglycerol.

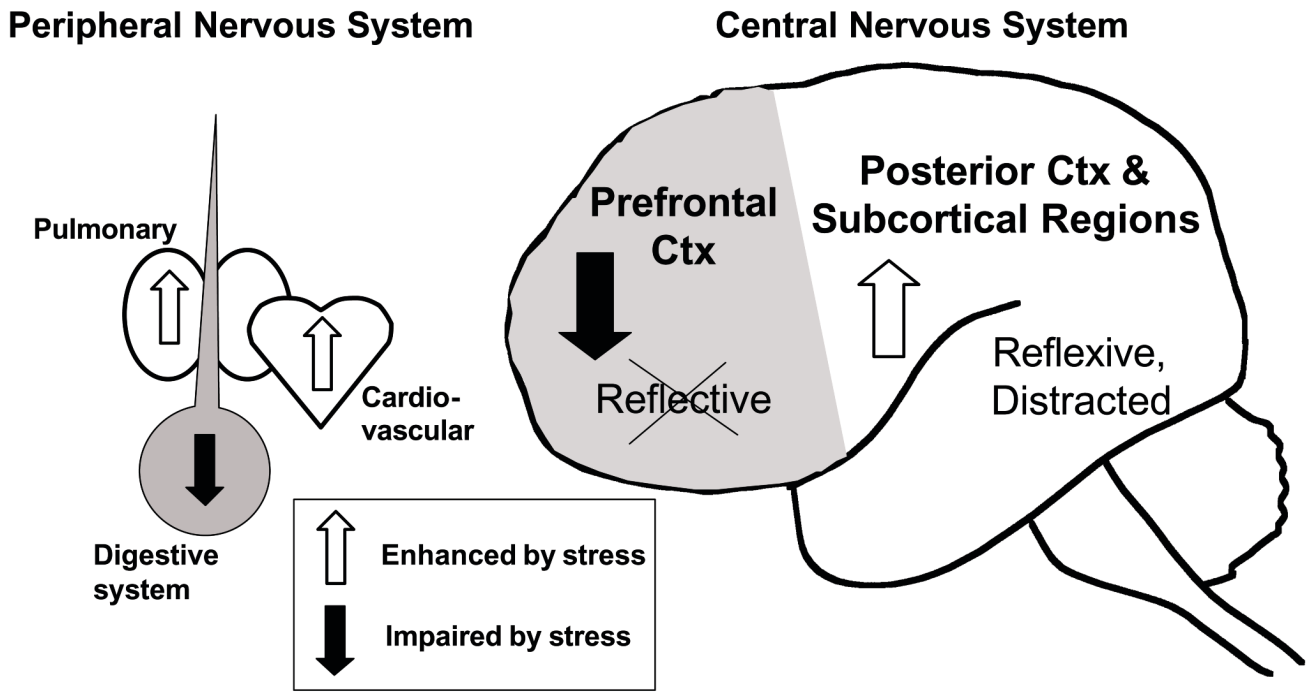

Figure 3.

Differential effects of the adrenergic system on peripheral versus central nervous systems. Epinephrine is released into blood by the adrenal gland in response to stress. NE is released by the sympathetic nervous system and throughout most of brain. Turning off PFC control of behavior during stress may have survival value under conditions of danger by switching control of our behavior from a slow, “reflective” region to more reflexive and instinctual brain areas. However, shutting off the PFC may make us more vulnerable to neuropsychiatric illness.