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Adrenergic pharmacology and cognition: Focus on the prefrontal cortex

Brian P. Ramos, Amy F.T. Arnsten *

Department Neurobiology, Yale Medical School, New Haven, CT 06520-8001, USA

Abstract

Norepinephrine (NE) has widespread projections throughout the 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

Abbreviations: 6-OHDA, 6-hydroxy-dopamine; ADHD, attention-deficit hyperreactivity disorder; cAMP, cyclic adenosine monophosphate; DA, dopamine; DBH, dopamine beta hydroxylase; EM, electron microscopic; LC, locus coeruleus; NE, norepinephrine; PFC, prefrontal cortex; PKC, protein kinase C; PTSD, post-traumatic stress disorder; rCBF, regional cerebral blood flow.

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* Corresponding author.
E-mail address: AMY.ARNSTEN@YALE.EDU (A.F.T. Arnsten).

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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 Fig. 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°; Fig. 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

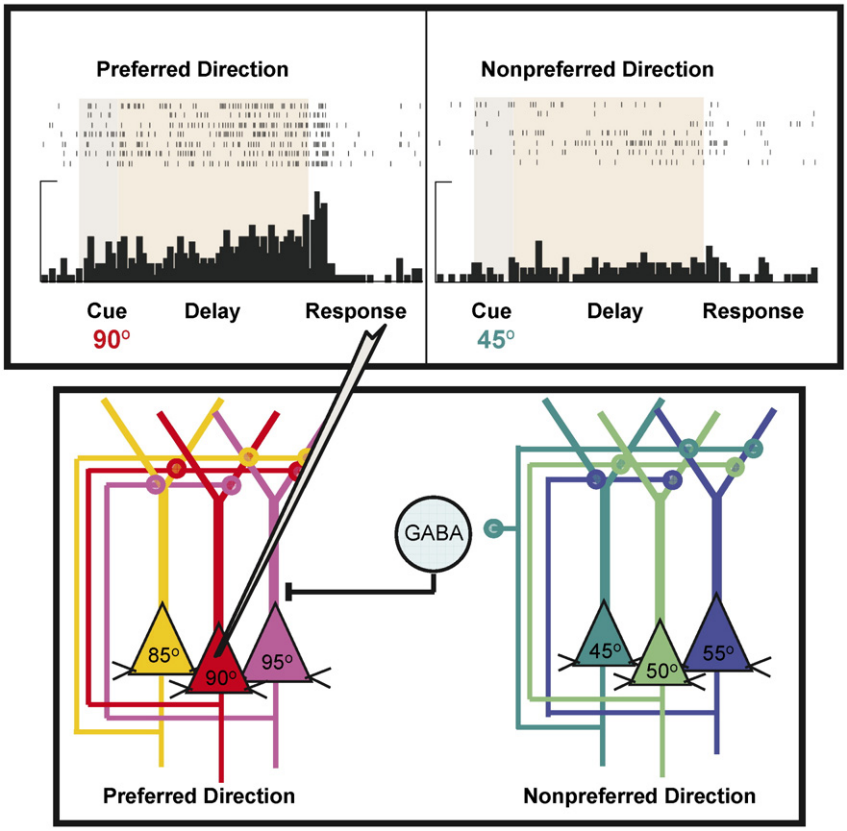

Fig. 1. The cellular basis of spatial working memory. (**A**) A neuron with spatially tuned persistent activity during the delay period of a spatial working memory task. Data from Dr. Min Wang. (**B**) Schematic representation of PFC networks of pyramidal cells that represent the cellular basis of working 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 nonpreferred directions enhance spatial tuning by inhibiting firing to nonpreferred directions. Adapted from Goldman-Rakic, 1995.