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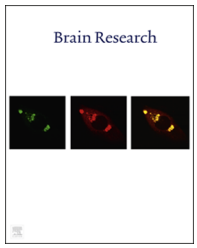

Review

Norepinephrine versus dopamine and their interaction in modulating synaptic function in the prefrontal cortex

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ABSTRACT

Among the neuromodulators that regulate prefrontal cortical circuit function, the catecholamine transmitters norepinephrine (NE) and dopamine (DA) stand out as powerful players in working memory and attention. Perturbation of either NE or DA signaling is implicated in the pathogenesis of several neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), schizophrenia, and drug addiction. Although the precise mechanisms employed by NE and DA to cooperatively control prefrontal functions are not fully understood, emerging research indicates that both transmitters regulate electrical and biochemical aspects of neuronal function by modulating convergent ionic and synaptic signaling in the prefrontal cortex (PFC). This review summarizes previous studies that investigated the effects of both NE and DA on excitatory and inhibitory transmissions in the prefrontal cortical circuitry. Specifically, we focus on the functional interaction between NE and DA in prefrontal cortical local circuitry, synaptic integration, signaling pathways, and receptor properties. Although it is clear that both NE and DA innervate the PFC extensively and modulate synaptic function by activating distinctly different receptor subtypes and signaling pathways, it remains unclear how these two systems coordinate their actions to optimize PFC

Abbreviations: AC, adenylate cyclase; ADHD, attention deficit hyperactivity disorder; Akt, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, Cyclic adenosine monophosphate; DA, dopamine; DAG, diacylglycerol; DAT, dopamine transporter; DARPP-32, dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; FS, fast-spiking; GABA, gamma-aminobutyric acid; GSK-3, glycogen synthase kinase-3; IP3, inositol 1,4,5-trisphosphate; LC, locus coeruleus; LTP, long-term potentiation; mEPSCs, miniature excitatory postsynaptic currents; mPFC, medial prefrontal cortex; NE, norepinephrine or noradrenaline; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartic acid; PFC, prefrontal cortex; PKA, protein kinase A; PKC, protein kinase C; PLC, Phospholipase C; PP2A, protein phosphatase-2A; PTSD, posttraumatic stress disorder; PV, parvalbumin; RGS, regulators of G protein signaling; VTA, ventral tegmental area

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function for appropriate behavior. Throughout this review, we provide perspectives and highlight several critical topics for future studies.

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Contents

1. The roles NE and DA play in regulating prefrontal synaptic function

The prefrontal cortex (PFC) is well-known for its role in numerous cognitive and executive functions, such as attention, working memory, decision making, and inhibitory control. PFC dysfunction has long been recognized as a central feature of many psychiatric disorders, including schizophrenia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and drug addiction. PFC-associated cognitive deficits are largely resistant to current treatment approaches, and greater cognitive deficits often predict worse functional outcomes. Thus, it is critical to understand the molecular and cellular influences that modulate PFC function in order to develop intelligent medications for related psychiatric disorders.

The catecholamine neurotransmitters norepinephrine (NE) and dopamine (DA) stand out as two powerful players in regulating PFC-dependent functions. Given that disruption of the excitation/inhibition balance in the PFC has been associated with many aforementioned psychiatric disorders such as schizophrenia (Krause et al., 2013; Lisman, 2012; Winterer and Weinberger, 2004; Yizhar et al., 2011) and ADHD (Moll et al., 2003; Pouget et al., 2009; Won et al., 2011), the individual actions as well as cooperative effects of both transmitters on synaptic transmission, intracellular signaling, and neuronal integration within immature and mature PFC circuitry are thus critical for the execution of prefrontal functions. How NE and DA, individually or synergistically, activate their respective receptors and the effects this on prefrontal functioning at the cellular, physiological, and behavioral level has been well-studied and reviewed in the past (Arnsten, 2011; Arnsten and Pliszka, 2011; Arnsten et al., 2015a; Arnsten et al., 2012b; Berridge and Waterhouse, 2003; Berridge and Arnsten, 2013, 2008; Clark and Noudoost, 2014; Puig et al., 2014; Ramos and Arnsten, 2007; Seamans and Yang, 2004; Spencer et al., 2015; Tritsch and Sabatini, 2012). Nevertheless, recent compelling evidence demonstrates that the functional interaction between NE and DA exerts powerful biological effects by activating converging synaptic pathways in PFC circuitry; however this interaction has yet to be well characterized. In the scope of this review, we will focus on the synergistic interactions of NE and DA on synaptic signaling in the PFC. This interaction serves as another level of study that will significantly improve our understanding of how these two catecholamine neurotransmitters modulate prefrontal functions.

Catecholaminergic projections to the cerebral cortex stem from two main sources, NE neurons of the locus coeruleus (LC) in the brainstem and DA neurons of the ventral tegmental area (VTA) in the midbrain. The PFC is a main cortical target of both NE and DA innervations (Knable and Weinberger, 1997; Ramos and Arnsten, 2007) with both neuronal systems modulating PFC activity in addition to memory and attentional performance. Overall noradrenergic fibers target the entire cerebral cortex with a more even distribution, whereas dopaminergic fibers are more restricted, having significantly more innervations in the PFC than in other cortical regions such as the primary visual and auditory cortex or somatosensory and motor cortex (Agster et al., 2013). In addition, laminar differences exist between NE and DA distributions within the PFC; noradrenergic fibers innervate both superficial and deep layers of the cortex, while dopaminergic fibers exhibit a regional variations in laminar pattern (Lewis and Morrison, 1989; Lewis et al., 2001; Nomura et al., 2014; Williams and Goldman-Rakic, 1993).

Recent morphological evidence demonstrates the presence of synaptic complexes formed by axospinous contacts, where dendritic spines of prefrontal cortical pyramidal neurons appear to be a common target of both noradrenergic and