Dopaminergic Influence Over Hippocampal Synaptic Plasticity and Function

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Keywords: Dopamine; Hippocampus; Mesolimbic; Ventral tegmental area; Nucleus accumbens; Long-term potentiation; Memory

The hippocampal formation is an important center for spatial and episodic memories. In the most simplified terms, multi-sensory information from the entorhinal cortex enters the dentate gyrus and begins a trisynaptic loop through the CA3 subfield and then to the CA1 subfield of the hippocampus. While the neuronal connections involved are primarily excitatory and inhibitory, there is neuromodulatory innervation of the hippocampus arising from cholinergic and noradrenergic centers. The medial septum provides cholinergic and GABAergic input to the hippocampus, and the consensus is that this regulates theta oscillations that contribute to mechanisms of both plasticity and memory [1]. It has also been demonstrated that the locus coeruleus provides a second source of neuromodulation via noradrenergic afferents to the hippocampus [2]. The most common anatomical marker for both norepinephrine and dopamine (DA) synthesis is Tyrosine Hydroxylase (TH), which does not distinguish between the two neurotransmitters. Thus, there is not a clear consensus regarding the extent of direct dopaminergic (DA) innervation from the Ventral Tegmental Area (VTA). Several lines of evidence suggest that DA neurotransmission influences hippocampal plasticity [3,4] and function [5], but some recent work questions whether these effects arise from direct dopaminergic afferents or from co-release of DA from noradrenergic fibers within the hippocampus [6]. Here we will discuss the discrepancy arising from several different approaches, and how two viable hypotheses of dopaminergic influence over hippocampal function have arisen.

There have been a number of studies supporting the functional role of dopaminergic D1/D5 receptors that are expressed in the hippocampus. Immunohistochemistry has revealed that these receptors are expressed in the dentate gyrus, CA1, and CA3 of the hippocampal formation [7], and on excitatory neurons [8]. DA enhances the excitability of hippocampal neurons by decreasing the calcium activated potassium conductance, thereby reducing the after hyper polarization of the action potential [9]. Further, inhibition of D1-type receptors prevented nicotine-induced in vivo synaptic potentiation measured in the dentate gyrus [10]. In addition, the amplitude of the dendritic action potential is enhanced by D1/D5 neurotransmission [11]. Recordings from hippocampal brain slices showed that D1/D5 receptor neurotransmission supports induction of late phase long term potentiation in CA1 synapses, an effect that is dependent upon protein synthesis [12]. Furthermore, it was shown that D1/D5 neurotransmission is important for the consolidation or persistence of long term memories [5,13,14].

Despite these varied forms of anatomical and functional evidence supporting the importance of D1/D5 receptor signaling in the hippocampus, the anatomical projections from known dopaminergic centers are relatively sparse. In 1978, Moore and Bloom [15] published a review of Substantia Nigra Compacta (SNc) and Ventral Tegmental Area (VTA) injections, and they make no mention of the hippocampus. However, one year later they presented strong evidence of noradrenergic projections to the hippocampus [2]. Since then, two groups have used either retrograde or anterograde labeling to establish projections from the VTA to the hippocampus [16-18]. Anterograde tracing from the VTA demonstrated projections to the stratum oriens of the dorsal CA1, broad innervations of ventral CA1, and sparser projections to the CA3 and dentate gyrus. However, only a minority of the VTA neurons that project to the hippocampus are dopaminergic, with one estimate of TH-co-labeled projections being as low as 6% [18], and between 10-18% in others [16,17]. Retrograde tracing combined with immunofluorescence from the CA1 indicated that dopaminergic VTA projections are mainly from the peribrachial pigmented nuclei of the VTA [16]. Modern molecular techniques may revise or confirm these early estimates of VTA dopaminergic innervation of the hippocampus.

One factor that complicates the interpretation of dopaminergic innervation of the hippocampus is that DA is the precursor to norepinephrine, and the rate-limiting enzyme for the synthesis of both catecholamines is Tyrosine Hydroxylase (TH). Early approaches used injections of 6-hydroxydopamine (6-OHDA) specifically into either the locus coeruleus or VTA to lesion TH-containing neurons. Using this chemical lesion, it was shown that hippocampal DA levels were markedly reduced following injections into the VTA but not when the injections were into the substantia nigra [19] or the locus coeruleus [20].

The discrepancy between the importance of functional D1/D5 neurotransmission in the hippocampus and the evidence for sparse direct VTA projections to the hippocampus lead to two plausible hypotheses. The first is that sparse dopaminergic neurons projecting to the hippocampus may have fewer DA transporters, and other catecholamine transporters have a role in dopamine clearance [21]. Therefore, the low levels of released DA are not cleared rapidly and, thus, remain in the synapse longer. The resulting “volume transmission” of DA is then able to influence synaptic events on a longer time scale [22].

The second hypothesis is that locus coeruleus noradrenergic projections may also release dopamine [23,24]. A recent study provides evidence in support of this second hypothesis, demonstrating that amphetamine produces dopamine-dependent changes in hippocampal synaptic plasticity, and in this case the DA is derived from locus coeruleus noradrenergic terminals [6]. Synaptic plasticity is a proxy or indicator for changes in neural function, and changes in hippocampal plasticity are thought to underlie changes in learning and memory. The CA1 subfield of the hippocampus is the final field of the trisynaptic hippocampal loop, and it is crucial for forming a cognitive spatial...
and temporal map [25,26]. CA1 synaptic plasticity can be measured by stimulating Shaffer collateral axons from the CA3 subfield and measuring the synaptic responses where the Shaffer collateral axons make synapses in the CA1 subfield. In support of the hypothesis that noradrenergic/norepinephrine (NE) terminals also release DA, Smith and Greene [6] recorded from the stratum radiatum of hippocampal slices and stimulated the Shaffer collaterals, and they demonstrated that amphetamine modulates the slope of the field Excitatory Post-Synaptic Potential (EPSP) via local D1/D5 neurotransmission, and not via β-adrenergic receptors. Then, they injected adeno-associated virus specifically designed to silence TH, into either the locus coeruleus or VTA. When they silenced TH in the LC, but not the VTA, the authors blocked amphetamine-enhanced plasticity of CA1 neurons. Based on this evidence, Smith and Greene suggested that amphetamine blocks the vesicular packing of DA in terminals, and the resultant accumulation of presynaptic DA results in reverse transport through NE transporters. While their techniques and experiments are alluring, their approach suggests that locus coeruleus neurons mainly release DA under the influence of amphetamine, which does not explain why D1/D5 receptors seem to be functionally influential even in absence of amphetamine [5,7,13,27].

A corollary to this hypothesis that DA is released from adrenergic terminals is that specific locus coeruleus projections to the hippocampus may lack dopamine β-hydroxylase, which catalyzes the conversion of DA to norepinephrine. Thus, what are thought to be norepinephrine terminals are actually functioning as DA terminals [28]. A recent paper highlighted the type of techniques required to investigate this issue. Transgenic mice were generated that specifically expressed dopamine β-hydroxylase gene promoter [29]. In these mice the trans-synaptic tracer was transferred across the synapses from all locus coerules to the hippocampus, but the density of direct DA innervations is still low, even a small amount of innervation can produce a current hypothesis, and that work will likely extend presently held concepts. It is likely that sparse, diffuse dopaminergic projections from the VTA innervate the hippocampus. Because the density of DA transporters is low, even a small amount of innervation can produce a DA signal that spreads from the release sites and influences synaptic events. In addition, under a least some circumstances norepinephrine terminals produce a DA signal dependent of the activity of fibers from the locus coeruleus.

Acknowledgments

The authors are supported by grants from the National Institutes of Health, NIDA DA09441 and NINDS NS21229, and by the Cancer Prevention and Research Institute of Texas, and by the Diana Helis Henry Medical Research Foundation through its direct engagement in the continuous active conduct of medical research in conjunction with Baylor College of Medicine and the project, Genomic, Neural, Preclinical Analysis for Smoking Cessation, and the Cancer Program.

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