

## **Neurotransmitters and neuromodulators involved in learning and memory**

**Laxminarayana Kurady Bairy\*, Suresh Kumar**

Department of Pharmacology,  
RAK College of Medical  
Sciences, RAK Medical and  
Health Sciences University, Ras  
al Khaimah, United Arab  
Emirates

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**\*Correspondence to:**

Dr. Laxminarayana Kurady  
Bairy,  
Email: [klbairy@gmail.com](mailto:klbairy@gmail.com)

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### **ABSTRACT**

Learning and memory being highly specialized process of human brain involves complex interaction between neurotransmitters and cellular events. Over the years, the understandings of these processes have been evolving from psychological, neurophysiological, and pharmacological perspectives. The most widely appraised model of learning and memory involves attention, acquisition, storage and retrieval. Each of these events involve interplay of neurotransmitters such as dopamine, acetylcholine, norepinephrine, N-methyl-d-aspartic acid, gamma-aminobutyric acid, though preponderance of specific neurotransmitter have been documented. The formation of long-term memory involves cellular events with neuroplasticity. Further, dopamine is documented to play crucial role in the process of forgetting. Understanding of the processes of learning and memory not only facilitates drug discovery, but also helps to understand actions of several existing drugs. In addition, it would also help to enhance psychological interventions in children with learning disabilities. Thus, the review intends to summarize role of neurotransmitters and neuromodulators during different phases of learning and memory.

**Keywords:** Learning, Memory, Attention, Neurotransmitters, Neuromodulators

### **INTRODUCTION**

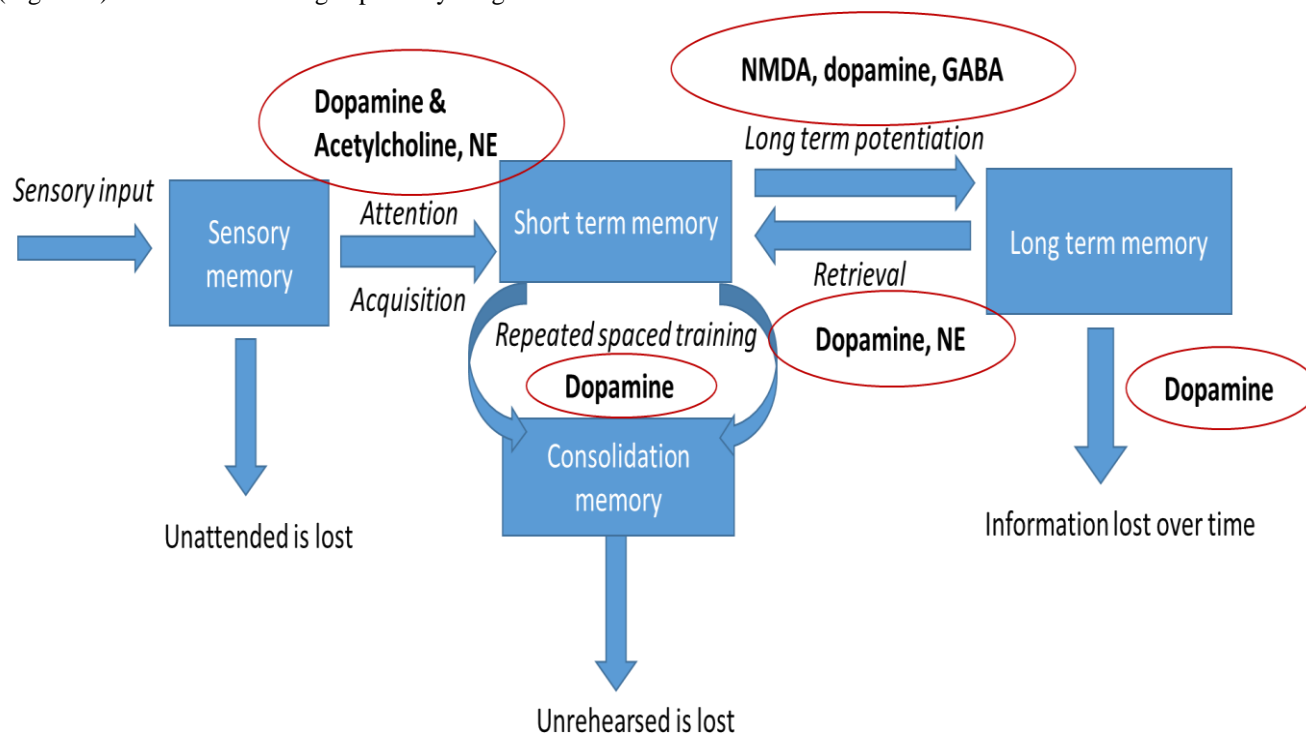
Learning and memory are the most fundamental and highly specialized functions of the brain. Learning is defined as “the process whereby knowledge is created through the transformation of experience” which involves experiencing, reflecting, concept formation, testing hypothesis again leading to experience.<sup>1</sup> Memory refers to a change in behavior caused by an experience and learning is a process by which memory is acquired. Atkinson et al proposed the well-documented model for memory processes in 1968.<sup>2</sup> The model delineates the basic short and long-term memory process along with causes of forgetting. Then the evidence gathered for molecular basis of short and long-term memory. It was reported that short-term memory involves covalent

modification of preexisting protein and long-term memory requires long-term processes such as gene expression.<sup>3</sup> Now, it has been shown that short-term memory and long-term memory involve independent and separate mechanisms with specific interactions.<sup>4</sup> Further, various types of memory depend on the integrated activity of several brain sites and involve more than one receptor or post-receptor mechanisms.<sup>5</sup>

Neuromodulators including acetylcholine (Ach), monoamines, amino acids, lipids, peptides and neurotrophins have been involved in most of the behavioural traits including arousal, sleep, motivation, emotions and memory. Among neurotransmitters, in learning and memory Ach and glutamate have been widely studied. Current evidence also suggests various

other neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine, serotonin and norepinephrine (NE), as well as various neuropeptides to memory (Figure 1). The monoaminergic pathways regulate both

short term and long-term memory through cAMP/protein kinase A-mediated signaling in CA1 of hippocampus, the entorhinal cortex and the parietal cortex.<sup>6</sup>



**Figure 1: Overview of major neurotransmitters and their role in memory. A modified model of memory formation, storage, and retrieval originally proposed by Atkinson et al with the most probable neurotransmitters involved being shown in the oval marking.<sup>2</sup>**

NMDA: N-methyl-D-aspartate; NE: Norepinephrine; GABA: Gamma-Aminobutyric acid.

Further gathering evidence suggest that most neurons release one or more classical neurotransmitter and one or more neuropeptides.<sup>7</sup> Thus neuromodulator circuits involve dual transmitters. The literature also reveal that release of these transmitters may be from same vesicle, (co-release) separate vesicles in the same terminals, (co-transmission) or separate terminals of neurons, as in case of Ach and GABA.<sup>8</sup>

### CHOLINERGIC SYSTEM

Numerous animal studies have linked Ach to learning and memory. The role of cholinergic pathways in memory is utilized for use of centrally acting cholinergic agents in treatment of Alzheimer's disease. Cholinergic agonists such as physostigmine accentuates memory formation, whereas cholinergic antagonists such as scopolamine significantly impairs acquisition and retention of memory.<sup>9</sup> Both muscarinic and nicotinic receptors are involved in encoding of new memories. Further Ach is showed to augment encoding of memories in response to sensory stimuli. This is brought by not only enhancement of afferent to cortical areas but also by inhibition of excitatory feedback activity. Increased excitatory afferent

in by nicotinic stimulation and inhibition of feedback is mediated by presynaptic muscarinic receptors.<sup>10</sup>

Wisman et al provided the platform for understanding differential role of dopamine and Ach in learning and memory. These neural interactions possibly explains the cognitive dysfunction on Parkinson's disease. The study showed convergence of both mesocorticolimbic dopamine pathway with forebrain cholinergic neurons to neocortex and hippocampus in modulating learning and memory.<sup>11</sup> The dopamine-depletion in ventral tegmental area resulted in impaired memory storage and/or recall, but cholinergic lesions alone in hippocampal region did not impair memory in all test paradigms. However, when both dopamine and Ach were depleted, animals were impaired in the working memory task, suggesting that the convergence of both these systems was crucial for acquisition of spatial memory.<sup>11</sup>

### DOPAMINERGIC SYSTEM

The role of dopamine is not only as a precursor of noradrenaline but in certain areas of brain it itself acts as a neurotransmitter. Several studies have inferred that reduced dopamine function is associated with cognitive impairments, which is associated with several

neurodegenerative disorders.<sup>12</sup> Dopaminergic neurotransmission is shown to be essential for retrieving acquired information from long-term storage in the striatum.<sup>13</sup> The data suggest involvement of both D1 and D2 receptors in nucleus accumbens is required for consolidation of spatial memory.<sup>14</sup> Further dopamine is attributed to motivation and reward related declarative memory.<sup>15</sup> However, D3 receptor antagonism is shown to enhance memory, attention and learning by increasing release of Ach and disinhibition of dopamine neurons projecting to prefrontal cortex.<sup>16</sup> Further dopamine neurons also have active role in forgetting olfactory memories. Thus dopamine is linked with both memory acquisition through dDA1 signaling and forgetting through dopamine receptor DAMB signaling.<sup>17</sup> The dopamine-depletion in ventral tegmental area resulted in impaired memory storage and/or recall, inferring the role of dopamine in both the processes.<sup>11</sup> (Figure 1) Recently, there is evidence to indicate role of dopamine in memory consolidation following training. The disinhibition of dopaminergic neurons were demonstrated during memory consolidation through spaced training in *Drosophila*.<sup>18</sup>

### GLUTAMATERGIC PATHWAY

The excitatory amino acid glutamate is the most abundant amino acid transmitter in the central nervous system (CNS) involved in learning and memory. Glutamate's role in memory is primarily concerned with long-term potentiation (LTP), a mechanism of memory storage. LTP is a model of the synaptic and cellular events that may underlie memory formation first described by Bliss et al (Figure 1).<sup>19</sup>

Among the glutamatergic receptors, N-methyl d-aspartate (NMDA) is the most important receptor involved in generation of LTP. Further, it is showed that LTP decay is an active process involving NMDA receptor activation. Thus blocking NMDA receptors prevents LTP decay.<sup>20</sup> Nitric oxide acts as a messenger and plays an adjuvant role in mediating synaptic changes.<sup>21</sup> Drugs modulating on glutamate or NMDA receptors and thereby LTP are being explored to improve learning and memory. The role of NMDA in LTP is further supported by the study which explained ethanol induced complete blockade of LTP by both NMDA inhibition and  $\gamma$ -aminobutyric acid A (GABA-A) activation at area CA1 of hippocampus (Figure 1).<sup>22</sup>

### GABAERGIC SYSTEM

GABA is the primary inhibitory neurotransmitter in the CNS, distributed abundantly in the brain regions involved in learning and memory. The GABA-A activation is one of the mechanism of alcohol induced LTP block, which prevents the transfer of information from being short-term memory to long-term memory (Figure 1).<sup>22</sup> The data regarding GABA B also show its role in several learning and memory tests and synaptic plasticity.<sup>23</sup> However, both inotropic GABA A and metabotropic (GABA B)

receptors play crucial role in stable development of conditioned inhibition.<sup>24</sup>

### NOREPINEPHRINE SYSTEM

Several animal studies have demonstrated that memory formation associated with emotional arousal results from an activation of beta-adrenergic stress hormone systems, during and after an emotional event.<sup>25</sup> It has also been shown that both NE and dopamine are involved in the prefrontal area and affect the prefrontal-dependent working memory. NE is also found to interact with ACh and both act together to affect some types of memory.

Propranolol was demonstrated to impair emotionally charged memories, while having no effect on neutral ones.<sup>26</sup> Further beta-receptors have been found on both amygdala and hippocampus, which are respectively involved in acquisition (encoding) and retrieval (recall) and of emotional memories.<sup>27</sup> Thus, beta-receptors are critical in processing of emotionally charged memories.

### SEROTONERGIC SYSTEM

Deficiency of 5-HT in regions such as hippocampus can impair memory.<sup>28</sup> 5-HT interacts with its receptors and has a role in tasks of passive avoidance retention, and LTP. It also improves spatial memory in the Morris water maze task. Further, serotonergic system may also involve in modulation of synaptic plasticity and sensory input reorganization.<sup>29</sup>

The data suggest interaction of serotonergic transmission with release of several neurotransmitters such as Ach, dopamine, GABA and glutamate. In addition, seven distinct serotonin receptors found in brain have been shown to alter in its function in cognitive decline. Serotonergic neurons are also implicated in formation of amyloid, which is characteristic of degenerative disease such as Alzheimer's disease.<sup>30</sup>

### HISTAMINE

The histaminergic neurons are closely associated with sleep-wake cycle, water intake, motor activity, and nociception.<sup>31</sup> Histaminergic system have been shown to influence emotional memory encoding, consolidation, and retrieval.<sup>32</sup> Evidence also point the association of histamine in influencing NMDA induced hippocampal LTP through histamine receptors.<sup>33</sup> Further, histamine also can directly activate NMDA receptor by binding to the polyamine modulatory site.<sup>34</sup> The evidence also suggest role of histamine 2 receptors in late phase of NMDA induced LTP and related cognitive domain.<sup>35</sup>

### NITRIC OXIDE

Nitric oxide or cGMP pathway is involved in synaptic plasticity and neurotransmitter release.<sup>36</sup> Nitric oxide as an intracellular messenger enhances glutamine-NMDA

mediated synaptic plasticity.<sup>37</sup> It is also involved through activation of cAMP- response element binding protein and other interlinked signaling cascades such as calcium/calmodulin-dependent protein kinase II and mitogen-activated protein kinases.<sup>38</sup> Further, cGMP pathway is also linked with cyclic nucleotide gated (CNG) channel and hyperpolarisation activated cyclic nucleotide gated (HCN) channels.<sup>36</sup> Thus making these as potential targets in degenerative conditions associated with cognitive decline.

## ENDORPHINS

Dynorphins and nociceptin are documented to be of prime role in hippocampal learning, memory and neuroplasticity.<sup>39</sup> It was reviewed that endorphins mediate learning process especially in association with stress.<sup>40</sup> The importance of opioids in learning is recently emphasized by studies, which again showed its role in aversive learning. The study documented the complex role of brain nociceptin and its receptor nociceptin opioid peptide (NOP) in regulating processing of aversive events and related emotional memory in mice.<sup>41</sup> Similarly, NOP receptor agonism has been shown to impair memory consolidation in contextual fear and passive avoidance paradigms.<sup>42</sup> Nociceptin or orphanin FQ (N/OFQ) and its receptor NOP is also implicated for interactions with glutamatergic, cholinergic and NE neurotransmission thus becoming a promising target for future drug development in learning and memory.

## ENDOCANNABINOIDS

The lipid neuromodulator endocannabinoids play pivotal role in development of brain.<sup>43</sup> Both natural and synthetic cannabinoids (CB) influence the learning and memory retention by acting on CB receptors. Anandamine or N-arachidonylethanolamine, first reported endocannabinoid play the role of intercellular messenger. CB receptor (CB1 R) activation in astrocytes leads to increased glutamate release. Further, it is reported that co-release of glutamate and NO by astrocytes induces LTP.<sup>44</sup> The preclinical data have demonstrated the ability of CB agonists to impair cognition. The CB compounds through both CB1 and CB2 receptors could impair or facilitate learning and memory by various mechanisms. The type of compound, route, dosage and memory task tested determined its action in these models.<sup>45</sup>

## BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor (BDNF), a key neurotrophin is involved in synaptic plasticity by inducing dendritic growth and remodelling. BDNF is shown to facilitate LTP, a long-lasting augmentation of connection between two neurons when they are repeatedly activated.<sup>46</sup> BDNF is also reported for its role in exercise-induced neuroplasticity there by, facilitating motor learning and rehabilitation post-stroke.<sup>47</sup> However,

resistance training also facilitated neuroplasticity in another randomized controlled trial.<sup>48</sup>

## OTHER NEUROMODULATORS

Galanin is a neuropeptide attributed for hippocampal learning and memory.<sup>39</sup> Several other peptides such as somatostatin, cortistatin, tachykinin, vasoactive intestinal polypeptide, calcitonin gene related peptide, neuropeptide Y and pituitary adenylate cyclase activating polypeptide have also been shown to play an important role in learning and memory.<sup>49</sup> Similarly, neurotrophic factors such as nerve growth factor, and neurotrophins have been shown to affect memory via modulation of cholinergic and glutaminergic systems.<sup>50</sup> In addition, Vitamin D have shown to be associated with the brain function by aiding neurons in synaptic plasticity.<sup>51</sup> The early evidence also indicate Vitamin D linkage with extracellular matrix and perineuronal nets to modulate plasticity. Further, Vitamin D is also involved in regulation of neurotransmitters and ion channels such as L-type voltage gated calcium channels.<sup>51</sup>

## CONCLUSION

The neurotransmission with regard to memory formation, storage and retrieval involves numerous neurotransmitters importantly dopamine, Ach, NE, NMDA, GABA. However, long-term memory involves synaptic plasticity. The interactions between neurons are not strictly restricted to single neurotransmitter as recent evidence suggests co-release and co-transmission of many neurotransmitters.

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