Review

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Towards universal therapeutics for memory disorders

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Evidence is accumulating that many memory disorders, including those due to neurodegenerative diseases, traumatic brain injury (TBI), vascular disease, or abnormal brain development, share common features of memory-related pathology. Structural and functional deficits of synapses are at the core of the underlying pathophysiology, constituting a critical point of convergence in memory disorders. Memory therapeutics that target synaptic loss and dysfunction – that is, to slow, halt, or reverse progression of the disorders at the level of synapses, via synaptogenic molecular cascades such as those of protein kinase C (PKC) and brain-derived neurotrophic factor (BDNF) – possess universal therapeutic value for many forms of memory disorder. They may be useful either as standalone interventions for patients with memory disorders or as adjuncts to drugs that target the underlying pathology.

Aging and memory disorders

Age drives memory decline and increases brain vulnerability to injuries, resulting in various forms of memory disorder. The term 'memory disorder' is defined here as any forms of memory abnormality, including memory impairment and dementia. Human memory, particularly memory that can be recalled in appropriate contexts, has quantifiable characteristics and, in many cases, has generality across many mammalian and nonmammalian species. Classical conditioning, for example, has been shown to have the same defining behavioral characteristics and common underlying mechanisms in snails, insects, rabbits, rodents, and, potentially, humans [1]. Although considerable progress in understanding the molecular mechanisms of brain disorders has been made in recent decades, the scientific knowledge so far has not translated into effective therapeutics for memory disorders [2,3].

As life expectancy is increasing every year, a greater fraction of the world population is expected to suffer from memory disorders, potentially leading to an exhaustion of human and financial resources in the near future. This gloomy outlook is exacerbated by the lack of effective therapeutics for any type of memory disorder. Now is the time, therefore, for new mechanistic strategies to bring more effective therapeutics to the clinic for patients with memory disorders [4]. In this review we focus on the potential of therapeutic agents that target the formation of newly matured synapses and the restoration of synaptic function as universal therapeutics for memory disorders. Evidence is accumulating that these agents are effective in many types of memory disorder (Figure 1). The involvement of PKC and BDNF in memory therapies is particularly emphasized.

Synapses and common memory biology

Human experience comprises associative memories that encode relationships in time, space, and content. All types of associative learning and memory, including classical conditioning, fear conditioning, olfactory discrimination learning, and spatial maze learning, are activated by combinations of sensory stimulation patterns and, despite their diversity, involve common molecular and synaptic mechanisms.

It is well recognized that the activity of molecular pathways in associative learning dramatically changes the structure and operation of neural networks, especially of synapses. Synapses, which permit a neuron to pass a chemical or electrical signal to another cell, are dynamic and their plasticity is at the core of associative memory [5,6]. Dynamic changes occur in brain structures such as the hippocampus and related cortices and represent the cognitive capacity (see Glossary) of the individual. The hippocampus, whose network and synapses have been intensively studied, comprises neuroanatomical convergence networks for processing associative (relational/declarative) memory, binding information into associative memories [7,8], and linking cortical modules during memory retrieval [9] in rodents and humans. Synaptic dysfunction in the hippocampus has thus been found to be responsible for various types of memory deficit. Although it can still be debated which particular form of neuroplasticity could be defined as the molecular mechanism of memory, it is well known that not only acquisition of memory but also memory reconsolidation involves the restructuring of synapses [5,10], supported by both protein synthesis and protein degradation mechanisms [11–14].

Learning and memory depend on synaptic efficacy as well as the number of synapses and their operation [15]. Both are dynamic: they may change dramatically in shape, density, and operation in response to memory demands and are vulnerable to injuries. Information-dependent synaptic strengthening and remodeling involve various interacting signaling pathways (Figure 2), including calcium, protein kinase C (PKC) isozymes, diacylglycerol

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Glossary

Apolipoprotein E (ApoE): combines with lipids in the body to form lipoproteins, which package cholesterol and other fats and carry them through the bloodstream. There are at least three alleles of the *APOE* gene (e2, e3, and e4); *APOE4* is linked to early-onset AD.
Bone marrow mesenchymal stem cells (BMSCs): multipotent stromal cells that can differentiate into various cell types.
Brain-derived neurotrophic factor (BDNF): promotes the survival of neurons by playing a role in their growth, maturation (differentiation), and maintenance.
cAMP response element-binding protein (CREB): a cellular transcription factor. It binds to DNA to increase or decrease downstream genetic transcription.
Ciliary neurotrophic factor (CNTF): promotes neurotransmitter synthesis and neurite outgrowth in certain types of neuron, including astrocytes.
Cognitive capacity: the overall amount of information one's brain is capable of handling at a particular moment. Age- or disorder-related decline in cognitive ability has been linked to deficits in synaptic communication, restricting the capacity of signal processing and impairing memory formation and recall. When the brain structure and plasticity are insufficient to support cognitive performance, the capacity also suffers [116].
Cyclin-dependent kinase 5 (Cdk5): involved in neuronal maturation and migration.
Damage-associated molecular pattern molecules (DAMPs): released by stressed cells, triggering an inflammatory response.
Diacylglycerol (DAG): functions as a second messenger in many cellular processes.
Extracellular signal-regulated kinases: (ERKs): part of signaling cascades that transmit signals from many extracellular agents to regulate cellular processes.
Fragile X syndrome: an inherited genetic syndrome with a spectrum of intellectual disabilities. It is associated with CGG trinucleotide-repeat expansion, affecting the *Fragile X mental retardation 1* (*FMR1*) gene on the X chromosome, leading to failure to express fragile X mental retardation protein (FMRP), a protein required for normal neural development and synaptic function.
Glial cell-derived neurotrophic factor (GDNF): promotes the survival and differentiation of many types of neuron, including dopaminergic neurons.
Growth associated protein 43 (GAP-43): a PKC substrate and a crucial component in neuronal growth/development, axonal regeneration, and learning-associated neuroplasticity.
Hypoxia inducible factor 1 (HIF-1): plays an essential role in cellular responses to hypoxia.
Low-density lipoprotein receptor-related protein 1 (LRP1): forms a receptor in the plasma membrane of cells and is involved in lipid homeostasis and intracellular signaling.
Metaplasticity: an important regulator of learning rules. The current plasticity of a synapse depends on its previous history of activity. Metaplasticity thus refers to the plasticity of synaptic plasticity, or the synaptic 'state' of plasticity.
Myristoylated alanine-rich C-kinase substrate (MARCKS): a filamentous, actin crosslinking protein.
Neuroplasticity: a term that encompasses synaptic plasticity, non-synaptic plasticity, and structural plasticity. Synaptic plasticity is usually about the strength of the synaptic connections while non-synaptic plasticity involves modification of neuronal excitability in the axon, dendrites, and cell body. Structural plasticity refers to changes in physical structures as a result of learning, such as network reorganization, neurogenesis, synaptic remodeling, and synaptogenesis.
Nuclear factor kappa B (NF-κB): a protein complex that is involved in cellular responses to various stimuli, including processes of memory formation and synaptic plasticity. It controls DNA transcription.
Peroxisome proliferator-activated receptor gamma (PPARγ): a regulator of fatty storage and glucose metabolism in cells. Its enhancement in activity has been shown to decrease insulin resistance.
Synaptic injury: the functional operation and structural maintenance of synapses involve many molecular signal pathways and active synthesis of proteins. These pathways and regulatory mechanisms may be impaired, affecting synaptic function. Synaptic injury includes structural and operational injuries and may occur in various forms, such as insufficient/excessive transmitter synthesis or release, impaired maturation and/or ability to change the shapes and numbers of spines and synapses in response to memory demands, and dysfunction in the induction and maintenance of synaptic plasticity.
Telomerase reverse transcriptase (TERT): a catalytic subunit of the enzyme telomerase, which lengthens telomeres in DNA strands by adding nucleotides of a TTAGGG sequence to their ends.
Tumor necrosis factor (TNF): a cytokine that is best known for its effect in tumor regression.

(DAG), ryanodine II receptors (regulating intracellular calcium release), and mRNA-stabilizing factors, which are activated during associative learning [16,17]. Molecules such as PKC and ryanodine II receptors are endogenously activated during the associative learning and memory process [17]. These molecular events, in turn, activate synaptogenic pathways that are critical for associative learning. The synaptogenic pathways involve neurotrophins [18] such as BDNF, nerve growth factor, neurotrophin-3, and other signaling molecules. BDNF, a well-known synaptogenic molecule, enhances synaptic transmission, facilitates synaptic plasticity, and promotes synaptic growth in developing and adult brains. It is specifically required for activity-dependent maintenance of the mature spine phenotype [19] and appears to mediate exercise-induced improvement in spatial learning and memory [20]. It may directly facilitate consolidation of existing synapses and the formation of new synapses [21].

The *BDNF* transcript contains exon I and exon IV. Exon I-specific transcripts, with neuronal localization predominantly in the soma, respond mostly to L-type voltage-dependent Ca^{2+} signals [22]. Exon IV-specific transcripts, with neuronal localization in dendrites and soma [23], respond to *N*-methyl-D-aspartate (NMDA) receptor activation and the pan-histone deacetylase inhibitor valproic acid [24]. Administration of valproic acid appears to improve verbal memory in high-grade glioma patients [25] or to alleviate memory deficits in Alzheimer's disease (AD) model mice [26]. Thus, various signaling molecules are involved in shaping the 'hardware' – the architecture (the network and synaptic connection) – and the 'software' – the operation of synapses, including the glutamatergic signaling pathway, the PKC [11,15] signaling pathway, the cAMP response element-binding protein (CREB) pathway, and miRNAs (Figure 2). Evidence is accumulating, for instance, that through interaction with other molecules PKC plays an essential role in the regulation of synaptic and memory functions [27–30]. The PKCε-selective inhibitor εV1-2 blocks recognition memory, through either pre- or post-training administration, in rats [31]. PKC isozymes such as PKCε are involved in synaptic and memory functions at several levels. First, their activation leads to post-translational modification of synaptic proteins (Figure 2), including neurotransmitter receptors. Phosphorylated PKC substrates [myristoylated alanine-rich C-kinase substrate (MARCKS) and growth associated protein 43 (GAP-43)] bind F-actin and are pivotal in growth cone guidance and synaptic formation. Second, PKCs regulate transcriptional activity and local protein synthesis in synapses through mRNA availability [18]. PKCε activators increase phosphorylation of MARCKS and activation of the non-receptor protein tyrosine kinase protein Src, Raf, and, finally, extracellular signal-regulated kinase (ERK) 1/2. PKCε binds through its regulatory domain onto several SH2 and SH3 Src domains, activating Src [31,32]. Src regulates, through phosphorylation, several synaptic proteins important for learning and memory [33], including F-actin-binding proteins, and ionotropic receptors and their surface expression, and appears to be critically involved in synaptic plasticity and metaplasticity (Figure 2) [33–35]. Evidence has been provided that formation of associative memories requires hippocampal metaplasticity [36]. It is unsurprising that roles of PKC in synaptic and cognitive regulation are 'universal' and not restricted by a particular type of memory (see [16] for a review), including Pavlovian conditioning of *Hermissenda*, spatial learning and memory, conditioned