

# 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- $\kappa$ B):** 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 (PPAR $\gamma$ ):** 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.

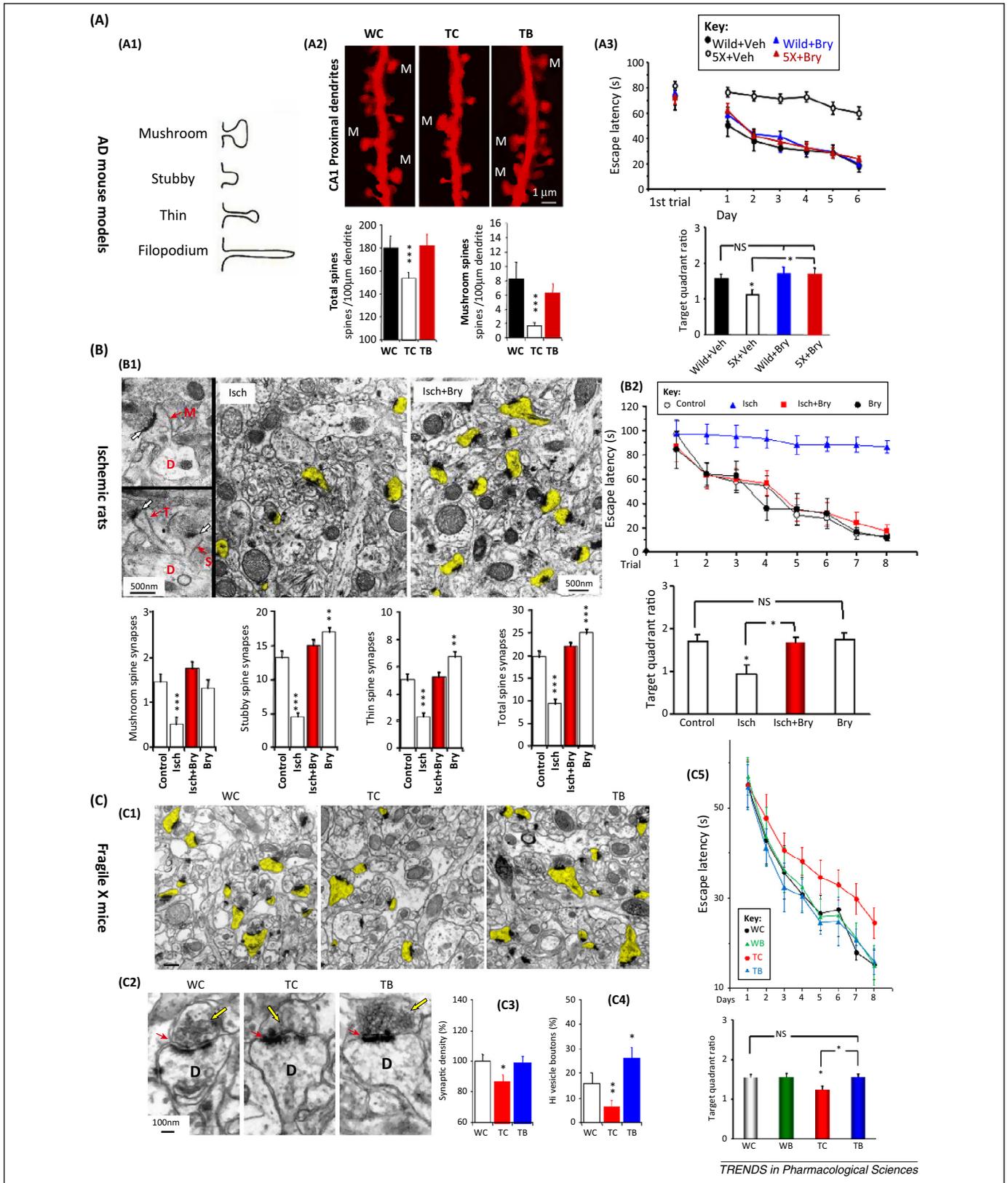
**Telomerase reverse transcriptase (TERT):** a catalytic subunit of the enzyme telomerase, which lengthens telomeres in DNA strands by adding nucleotides of a TTAGGG sequence to their ends.

**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<sup>2+</sup> 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 PKC $\epsilon$ -selective inhibitor  $\epsilon$ V1-2 blocks recognition memory, through either pre- or post-training administration, in rats [31]. PKC isozymes such as PKC $\epsilon$  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]. PKC $\epsilon$  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. PKC $\epsilon$  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 *Hermisenda*, spatial learning and memory, conditioned



**Figure 1.** Examples of the effects of a protein kinase C (PKC) activator on hippocampal synapses and spatial learning and memory (water maze) impairments due to memory disorders. (A) Bryostatin-1 protects the Alzheimer’s disease (AD) animal models Tg2576 and 5XFAD mice against the loss of postsynaptic dendritic spines and synapses in the hippocampal CA1 area [39]. The therapeutic effects of bryostatin-1 on the synapses and spatial learning and memory (a modified Morris Water Maze task, two training trials/day for 6 days, followed by a memory recall task) are consistent in both AD models [39], although only some data are illustrated here for simplicity. Consistent schematic drawings (A1) and confocal images (A2 top) show different shapes of dendritic spines and filopodia, examined at an age of 5 months with Dil confocal microscopy (after 2.5 months’ treatment). A2 bottom panels show the total spines and mushroom spines in the various groups, with a significant reduction in both numbers, and a rescue effect by bryostatin-1. The synaptic protection is accompanied by a recovery of spatial learning and memory. A similar synaptoprotective effect is also observed in 5XFAD mice, accompanied by rescued spatial learning ( $F_{3,611} = 25.472, P < 0.001$ ; A3 top) and memory ( $F_{3,31} = 3.428, P < 0.05$ ; A3 bottom [39]). Abbreviations: WC, wild type with vehicle; TC, Tg2576 mice with vehicle; TB, Tg2576 mice with bryostatin-1; 5X, 5XFAD mice; Veh, vehicle; Bry, bryostatin-1. (B) Chronic

(Figure legend continued on the bottom of the next page.)

avoidance, learning and memory of eye-blink conditioning, olfactory discrimination learning, contextual fear memory, and drug-associated reward memory.

### Common signaling pathways in memory disorders

There are many types of memory disorder: AD, vascular dementia, Parkinson's disease (PD) dementia, Huntington's disease (HD), frontotemporal dementia (FTD), memory impairments due to TBI, mental retardation, depression, alcohol-related dementia, and Creutzfeldt–Jakob disease. Several pathological mechanisms have been implicated in memory disorders, including formation and accumulation of neurotoxic substances, oxidative/vascular stress, inflammation, protein degradation, and mitochondrial dysfunction. While these factors can certainly damage synaptic and cognitive functions, it remains unsettled, in most cases, whether they are the cause or the consequence of primary and/or secondary damage.

Synaptic deficits, including synaptic impairment, synaptic loss, and impaired capacity of synapses to meet memory demands, underlie various memory disorders (Table 1). Memory disorders such as AD are accompanied by deficits in BDNF and PKC [37]. BDNF levels are lower in the brains of AD [38], PD [39], and HD [40] patients. Vascular memory impairment is associated with increased BDNF activity in the surviving neural structures, perhaps as a compensatory response [41]. However, the endogenous mechanism is not sufficient to overcome the injury, and memory can be rescued by further enhancement of BDNF activity with PKC activation [41].

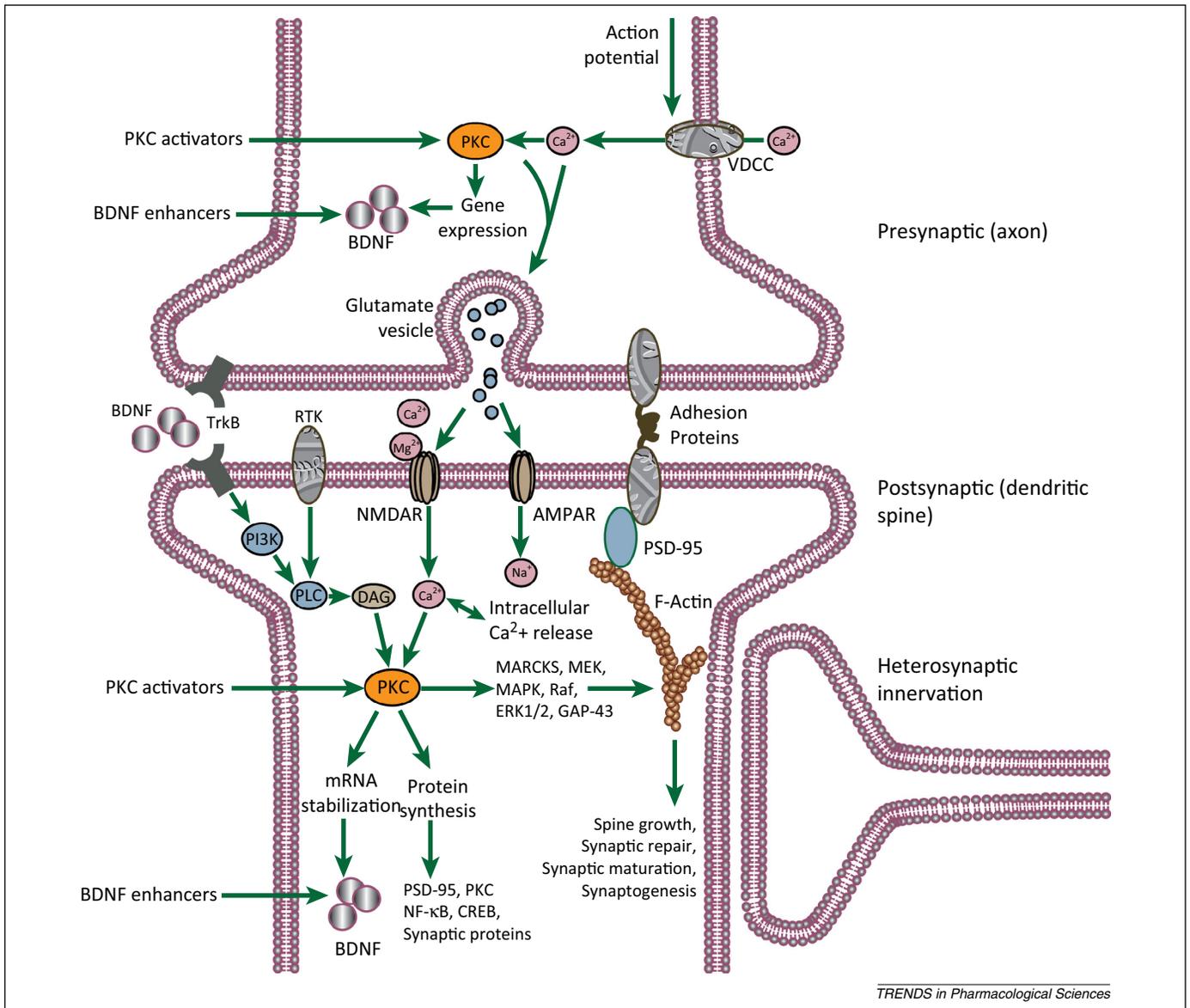
Synaptic dysfunction occurs as a core feature of memory disorders (Table 1) including AD, vascular dementia, depression-related behavioral and cognitive deficits, mental retardation, TBI, PD, HD, and FTD. The common feature of synaptic involvement in memory disorders can be best illustrated with AD, the most common form of memory disorder. AD affects over 5 million Americans and 35 million people worldwide [42]. Less than 1% of cases are genetically determined and develop clinical symptoms before the age of 65 years [43]. The disorder is characterized by  $\beta$ -amyloid (A $\beta$ ) plaques and neurofibrillary tangles. The plaques also activate microglia and induce the release of associated inflammatory factors [44] at late stages of the disorder. A $\beta$  is well known to decrease ATP, resulting in reactive oxygen species (ROS) generation in the mitochondria and cell apoptosis [45]. These pathological features

could serve as perfect 'disease-modifying' targets for therapeutics, except for two problems. One is that plaque loads do not correlate well with functional impairment in AD. The other is that agents that reduce the amyloid plaque pathology do not produce the expected disease-modifying effects on cognition (see [46] and below). The formation of neurofibrillary tangles is another pathological feature of AD [47]. When hyperphosphorylated, tau, a microtubule-associated protein, is unable to bind to microtubules, which become unstable and disintegrate. The unbound tau aggregates and forms neurofibrillary tangles. Although neurofibrillary tangles correlates somewhat more closely with cognitive impairment in AD than plaques, evidence from transgenic mice shows that neurofibrillary tangles do not necessarily impair neuronal function [48]. A recent study in an animal model of AD showed that cognitive improvement coincided with reduced levels of synaptotoxic A $\beta$  oligomers without removal of deposited amyloid plaques [49]. Synaptic dysfunction, by contrast, is an early feature of AD, perhaps before A $\beta$  deposition [50,51]. Loss of dendritic spines and synapses correlates well with cognitive decline in AD, more closely than the loss of neurons [52,53]. The synaptic dysfunction in AD, similar to many other memory disorders, is associated with loss of synaptogenic action of PKC $\epsilon$  and its protective effects against neurotoxic factors [27,37]. PKC $\epsilon$  levels are significantly lower in the hippocampal and temporal pole areas of AD brains [54]. Interestingly, a miRNA, miR-206, is at an aberrantly high level in the brains of AD Tg2576 mice [55] and could be involved in the pathogenesis of AD by suppressing BDNF expression.

### Universal memory therapeutics

With brain injury and without pharmacological help, cognitive functions largely depend on the capacity of the brain to repair and/or to compensate for injury [56]. Currently, the four FDA-approved drugs (donepezil, galantamine, rivastigmine, and memantine) available for AD treatment provide symptomatic, short-term benefit only [57] and no specific treatments are available for other memory disorders. Phase III trials of active and passive A $\beta$  immunization have failed to demonstrate any cognitive benefits [58] in AD patients.  $\gamma$ -Secretase inhibitors such as semagacestat and avagacestat impair memory in mice [59] and worsen cognition scores in AD patients [60,61], although a  $\gamma$ -secretase modulator, AS2715348, is reported to reduce

bryostatin-1 rescues synapses in the dorsal hippocampal CA1 area and spatial learning and memory from cerebral ischemia-induced damage (9 days after the last bryostatin-1 dose of a 5-week treatment and about 7 weeks after a cerebral ischemic/hypoxic event comprising two-vessel occlusion and 5% O<sub>2</sub> for about 14 min, a global ischemic-hypoxic insult that caused lasting damage to the hippocampus and spatial learning performance [41]). B1: Changes in axospinous synapses in the stratum radiatum of the hippocampal CA1 area. The left-side electron micrographs show the ultrastructures of mushroom (M), stubby (S), and thin (T) spines, branching from the dendritic shaft (D). The heads of these dendritic spines form synapses (white arrows) with presynaptic axonal boutons that contain presynaptic vesicles. Right electron micrographs show the densities of dendritic spines (yellow highlight) in cerebral ischemia with and without bryostatin-1. The bottom panel shows quantification of the different types and total number of synapses observed. Cerebral ischemia reduces mushroom spine synapses and other types of spine in the hippocampal CA1 area and the synaptic impairment is rescued by the treatment. B2: Spatial learning (water maze, two training trials/day for 8 days;  $F_{3,255} = 31.856$ ;  $P < 0.001$ ; top) and memory recall ( $F_{3,31} = 6.181$ ,  $P < 0.005$ ; bottom) tests reveal a dramatic learning and memory impairment in the ischemic group, rescued by the bryostatin-1 treatment. Abbreviations: Bry, bryostatin-1; Isch, cerebral ischemia. (C) Bryostatin-1 protects adult fragile X mice from synaptic loss of hippocampal CA1 pyramidal cells and memory impairment. Reproduced, with permission, from [37]. Fragile X mice (FVB.129P2-*Pde6b*<sup>+</sup> *Tyr*<sup>fl-ch</sup> *Fmr1*<sup>tm1Cgr/J</sup>) do not express fragile X mental retardation protein (FMRP), a selective RNA-binding protein that regulates the translation of dendritic mRNAs. The lack of FMRP alters signal processing at synapses and impairs synaptic maturation. The drug treatment began when the mice were aged 2 months and lasted for 13 weeks; data (training and brain samples) were collected 10 days after the last dose. C1: Electron microscopy (EM) of the stratum radiatum in the right dorsal hippocampal CA1 area. Dendritic spines are highlighted in yellow. C2: EM at higher magnification shows dendritic spines forming synapses (red arrows) with presynaptic axonal boutons that contain presynaptic vesicles (yellow arrows). Bryostatin-1 prevents the loss of synaptic density (C3) and presynaptic vesicle concentration (C4). C5: Spatial learning (water maze, two training trials/day for 8 days;  $F_{3,623} = 5.214$ ,  $P < 0.001$ ; top) and memory recall ( $F_{3,38} = 3.016$ ,  $P < 0.05$ ; bottom) tests reveal a significant learning and memory impairment in the fragile X mice, rescued by bryostatin-1 treatment. Abbreviations: WC, wild type with vehicle; WB, wild type with bryostatin-1; TC, fragile X mice with vehicle; TB, fragile X mice with bryostatin-1. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .



TRENDS in Pharmacological Sciences

**Figure 2.** Synaptic protein kinase C (PKC)–brain-derived neurotrophic factor (BDNF) signaling pathway and potential memory therapeutics. The pyramidal cells in the hippocampal CA1 area receive glutamatergic and heterosynaptic innervation (such as cholinergic, catecholaminergic, and GABAergic). When an information-carrying signal (action potential) reaches the axon terminal (presynaptic), neurotransmitters are released and activate postsynaptic receptors and ion channels in the membranes. Recent findings indicate that associated learning triggers essential synaptic responses involving PKC, BDNF, and calcium/calmodulin-dependent protein kinase (CaMK) in the underlying neural networks. The interactions among PKC, synaptic transmission,  $\text{Ca}^{2+}$  signaling (through voltage-dependent calcium channels, NMDR receptors, and intracellular release from the endoplasmic reticulum), and BDNF induce sustained activity of mitogen-activated protein kinase (MAPK) kinase (MEK), MAPK, Raf, extracellular signal-regulated kinase (ERK) 1/2, growth associated protein 43 (GAP-43), and HuD, leading to increased transcription of PKC, increased expression and translation of BDNF and of postsynaptic density protein 95 (PSD-95), and F-actin expansion. Myristoylated alanine-rich C-kinase substrate (MARCKS), a filamentous (F) actin crosslinking protein, binds calmodulin, actin, and synapsin, and is a PKC substrate. F-actin expansion is important to spine growth, synaptic repair and maturation, and synaptogenesis. Adhesion molecules such as cadherin are also involved. PKC is also activated by increased activity of BDNF [through tyrosine kinase B (TrkB), phosphatidylinositol 3-kinase (PI3K), phospholipase C (PLC), and diacylglycerol (DAG)] and of receptor tyrosine kinase (RTK), which activates PLC, and  $\text{Ca}^{2+}$ . PKC also interacts with mRNA-binding proteins such as HuD to stabilize mRNA. Memory disorders impair the function of these signaling proteins and can be rescued by PKC activators and BDNF enhancers, which exhibit pharmacological profiles of universal therapeutics for memory disorders.

cognitive deficits in Tg2576 mice [62]. These drug trial failures may stem from the narrow view that AD is either a cholinergic or an amyloid disease. Blockade of  $\text{A}\beta$  should normalize memory functions, but did not. Tauopathy of AD remains a tough target with few pharmacological options. In addition, it has been shown that neurofibrillary tangles do not necessarily impair neuronal function in AD transgenic mice [48].

However, all memory disorders are characterized by synaptic dysfunction (Table 1). It would be greatly beneficial to patients if synaptic and cognitive functions could be restored to meet memory demands, as a

disorder-modifying treatment in terms of cognition. Although it has not been studied whether the loss of synaptic capacity is part of the pathology of some memory disorders, such treatments that target synaptic efficacy may be more effective in terms of cognition, even if synaptic dysfunction may be only one important element of the underlying pathophysiology.

#### Adult synaptogenesis and synaptic repair

Downregulated PKC–BDNF signaling and increased  $\text{A}\beta$  pathology in AD brains may constitute a vicious cycle in which the two events synergistically promote synaptic

**Table 1. Synapses, memory disorders, and memory therapeutics**

Memory disorder	Disease model	Synapses and memory	Therapeutic	Refs
AD	AD brain	Loss of dendritic spines and synapses correlates best with cognitive decline	–	[52,53]
	Tg2576 mice	Synaptic loss and impaired synaptogenesis Impaired memories (spatial and recognition)	Bryostatin-1: Restored synaptogenesis, spatial learning and memory Stem cells (bone marrow-derived mononuclear cells): Restored recognition memory	[37] [93]
	5XFAD mice	Synaptic loss and impaired synaptogenesis Impaired spatial learning and memory	Bryostatin-1: Restored synaptogenesis, spatial learning and memory	[37]
	ApoE4 knock-in hAPP <sub>FAD</sub> mice	Impaired GABAergic synaptic innervation Impaired spatial learning and memory	Stem cells: Restored GABAergic synaptic innervation, spatial learning and memory	[92]
Stroke – cerebral ischemia	Focal	Loss of neural structure and synapses	Bryostatin-1: Reduced lesion volume and improved spatial learning and memory	[72]
	Global cerebral ischemia – rats	Synaptic loss and impaired synaptogenesis Impaired spatial learning and memory	Bryostatin-1: Restored synaptogenesis and spatial learning and memory Transcranial magnetic stimulation: Improved spatial learning and memory	[41,73] [82]
Fragile X syndrome	Fragile X mice	Synaptic loss, impaired synaptogenesis, synaptic maturation Impaired spatial learning and memory	Bryostatin-1: Restored synaptogenesis, synaptic maturation, and spatial learning and memory	[75]
Depression-related memory impairment	Induced immobility – rats	Synaptopathy and spatial learning and memory deficits	Bryostatin-1 and BDNF: Antidepressive effects, restored spatial learning and memory	[76,117,118]
	Patients	Depression and cognitive deficits	Transcranial magnetic stimulation: Improved cognition	[119]
TBI	Induced mild TBI – mice	Synaptopathy and spatial learning and memory deficits	Bryostatin-1: Restored synaptic integrity and spatial learning and memory Low-level laser therapy: Improved spatial learning and memory	[74] [84]
PD	Induced PD – monkeys, matured neurons – mice	Reduction in synaptic innervation, synaptopathy	Stem cells (human adipose-derived mesenchymal stem cells): Improved motor function	[98,120,121]
HD	Induced HD – mice and rats	Dendritic spine and synaptic loss	Stem cells (induced pluripotent stem cells): Improved spatial learning and memory	[99,122]
FTD	FTD brain Mouse model	Synaptic dysfunction	–	[123,124]
Alcohol-associated dementia	Rat model	Impaired spatial memory	Stem cells (bone marrow mesenchymal stem cells): Restored spatial memory	[100]

dysfunction, leading to eventual neurodegeneration. Restoring synaptic function should be a useful therapy for AD and can be achieved through activation of PKC and/or enhancement of BDNF activity (Figure 2). Increasing the brain levels of neurotrophic factors such as BDNF [63], glial cell-derived neurotrophic factor (GDNF) [64], ciliary neurotrophic factor (CNTF)-derived peptidergic compounds [65], bone morphogenetic protein 9 [66], and insulin-like growth factors [67] has been reported to reverse AD-like pathology and other memory impairments and to promote dendritic spine formation, with increased BDNF activity being the common feature associated with the therapeutic impact. Overexpression of GDNF upregulates BDNF and preserves spatial learning and memory in 10-month-old 3xTg-AD mice, without significant reduction in amyloid and tau pathology [64]. The results are consistent with some early reports that transplantation of neuronal

stem cells in 3xTg-AD mice [68] and BDNF gene delivery in APP+PS1 mice [69] rescued synaptic plasticity deficits and cognitive impairment without significant alteration in A $\beta$  and Tau pathology. Similar therapeutic effects of BDNF have been observed with treatment after disease onset in transgenic mice [70], indicating that synaptic repair can be obtained without direct amyloid reduction. However, the difficulties of delivering BDNF or other important synaptic growth factors such as nerve growth factor (NGF) should not be underestimated.

PKC activators can also increase BDNF expression [37]. One benefit of PKC activators is their impacts on both the pathology and pathophysiology of AD, in that activation of PKC not only restores neurotrophin levels, synapses in the hippocampus, and cognitive functions (Figure 1) but also reduces amyloid formation and apoptosis in several mouse models of AD [37].

The same BDNF–PKC-based therapeutic agents are effective in other memory disorders such as vascular dementia, TBI, mental retardation, and depression-related memory deficits (Table 1). Vascular dementia is a form of cognitive dysfunction caused by cerebrovascular disease, without any known effective cure. Bone marrow mesenchymal stem cells (BMSCs) cotransfected with NGF and telomerase reverse transcriptase (TERT) can produce significant improvement in learning and memory in vascular-demented rats [71]. Bryostatin-1, a PKC $\epsilon$  and  $\alpha$  activator, rescues cognitive functions from cerebral ischemia in adult rats (Figure 1) and improves survival and reduces ischemic brain injury in aged rats after acute focal ischemic stroke [72]. It restores synaptic capacity of the hippocampus following cerebral ischemia [73] and protects against the loss of presynaptic synaptophysin and postsynaptic spinophilin after mild TBI in mice [74]. Bryostatin-1 has also been found to restore blood–brain barrier integrity after blast-induced TBI [28]. Adult fragile X mice, a model of the fragile X syndrome, have impaired synaptic regulation in the hippocampus and deficits in performing spatial learning and memory tasks. Similar therapeutic effects of bryostatin-1 on hippocampal synapses and spatial learning and memory have also been obtained in these retardation mice (Figure 1) [75]. Its therapeutic effects on depression make it a suitable treatment for depression-related memory impairment (Table 1), since it targets both the pathology (depression) and the associated synaptic dysfunction (pathophysiology) [76].

#### *Cranial stimulation, physical exercise, and environmental enrichment*

Cranial stimulation is a potential universal therapy for memory-related disorders. Partially due to the lack of effective pharmacological therapeutics for treating dementia, efforts have been made to investigate novel therapeutics such as deep brain stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. Deep brain stimulation involves minimally invasive surgical implantation of electrodes for delivering electrical impulses to specific parts of the brain [77]. Evidence has been provided that deep brain stimulation in mice, refined by selective blockade of dopamine D1 receptors, normalizes synaptic transmission [78]. Improvement in cognitive function has been observed in AD [79] and PD [80] patients after deep brain stimulation. However, there is a lack of solid evidence demonstrating that it can be disease modifying [81] and patients who undergo the therapy need the insertion of electrodes into the brain tissues. Hippocampal stimulation might cause an acute depolarization block, disrupting memory formation and recall [77]. Transcranial stimulation has attracted much interest recently for its noninvasive nature and potential benefits. Transcranial magnetic stimulation [7], for instance, could protect rats against vascular dementia [82] and treat depression-related cognitive impairment in humans (Table 1). It enhances some sequential memory encoding but disrupts other memory encoding [81]. Not yet studied, however, is its impact on memories from the past; that is, memories that have been previously stored in the brain. By targeting the cortical–hippocampal networks, activity in the

networks can be enhanced with electromagnetic stimulation in humans, resulting in enhanced associative memory persisting for approximately 24 h after stimulation [7,83]. Low-level laser (light) therapy has been shown to reduce neuronal death after TBI and improve spatial learning and memory at 4 weeks [84]. The therapy uses red or near-infrared light, the photons of which are absorbed by the cellular respiratory chain to increase ATP and modulate ROS, leading to activation [85] of BDNF signal pathways, neurogenesis, synaptogenesis, and transcription factors.

Along this line is also the evidence that physical exercise [86,87] and environmental enrichment [88–90] can enhance memories and reduce memory impairments, most likely through an enhancement of BDNF activity (Figure 2). The benefits appear unrestricted by the type of memory disorder, but their maximally achievable impact on memory disorders remains to be defined.

#### *Stem cells*

Stem cells, including embryonic stem cells, induced pluripotent stem cells, and tissue-derived stem cells, have the potential of integrating into the existing brain network of the host [91,92]. Stem cell therapy is more than just regenerating injured cells or tissues: one major impact derives from its induction of endogenous repair activity in cells and synapses. Stem cell transplantation has been shown to improve cognition in AD models [93], with or without A $\beta$  accumulation [94], and other types of memory disorder [71]. The mechanism may involve neurotrophic factors secreted by the stem cells to increase synaptic density and modulate neuroplasticity and neurogenesis [94–96].

So far, many studies have reported therapeutic effects of stem cells for various memory disorders, such as AD models [93,97], PD models [98], HD models [99], alcohol-associated dementia [100], and vascular dementia [71], showing their potential as a universal therapeutic for memory disorders. Studies are needed to fine-tune the appropriate conditions for their clinical usage and limit their undesired impact (such as abnormal growth, misdirected growth, immune reaction, and long-term behavioral changes).

#### *Other potential universal memory therapeutics*

Besides BDNF, many other neuronal repair pathways could serve as targets for universal brain therapeutics. Apolipoprotein E (ApoE) is a critical signal for synaptogenesis and synaptic maturation [101]. ApoE/cholesterol complex released from astrocytes is taken up through low-density lipoprotein receptor-related protein 1 (LRP1) and activates PKC $\epsilon$  synthesis in neurons [102], thereby activating PKC-dependent neuronal repair pathways. ApoE4 is a risk factor for many neurodegenerative diseases as well as stroke and focal ischemia. Amyloid plaques are found in 100% of patients with two apoE4 alleles [103]. ApoE functions as a cholesterol transport protein and is a potent signal for synaptogenesis and neurorepair. In the E4 variant, these functions are partially lost; ApoE4 may also have toxic properties independent of A $\beta$ , including an ability to trigger inflammatory cascades [103]. ApoE2 carriers have lower risk for AD but increased risk for

cerebral amyloid angiopathy [104]. Thus, a universal therapeutic acting downstream of ApoE signaling could counteract the loss of function in patients with one or two E4 alleles.

Other agents that may be potentially effective as universal memory therapeutics include the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist rosiglitazone [105,106], histone deacetylase inhibitors, and disruptors of cyclin-dependent kinase 5 (Cdk5)-dependent NMDA receptor subtype 2B (NR2B) phosphorylation [107]. Cdk5-dependent NR2B phosphorylation decreases NR2B's surface levels and thus attenuates synaptic transmission. Histone acetylation and deacetylation are enzymatically controlled by histone acetyltransferases (addition of acetyl groups to lysine residues on N-terminal histone tails) and histone deacetylases. Most of the memory disorders, including aging-related memory impairment, seem to be accompanied by decreased histone acetylation [106]. PPAR $\alpha$  agonism facilitates recruitment of PPAR $\gamma$  to activated, phosphorylated ERK (pERK) during cognitive enhancement in Tg2576 mice [105]. The PPAR $\alpha$  agonist fenofibrate has been found to protect vessels and neurons against vascular impairment of cognition [108]. PPAR $\gamma$  agonists have been shown to reduce M2 activation and cytokine release in a mouse model of progressive PD [109]. However, several large-scale clinical trials did not show efficacy of PPAR $\gamma$  agonism for AD dementia [110]. It is unclear what underlies the failure. In addition, rosiglitazone has been banned in the EU for the increased risk of heart attack. Targeting cannabinoid transmission in the brain, such as enhancing endocannabinoid-mediated synaptic disinhibition [111], may have therapeutic value against AD [111] and depression-related cognitive dysfunction [112]. However, the use of cannabinoid receptor activators is limited by their abuse potential.

Microglia, the immune cells of the nervous system, normally exert a protective role in the brain by clearing debris and toxins by phagocytosis. They also participate in activity-dependent synaptic pruning. However, once cell injury occurs, microglia transform into their motile, so-called amoeboid state known as the M1 phenotype. The activated microglia respond to injury by activation of hypoxia inducible factor 1 (HIF-1) and nuclear factor kappa B (NF- $\kappa$ B), which leads to secretion of cytokines and neurotoxic mediators including interleukin-12, tumor necrosis factor alpha (TNF- $\alpha$ ), superoxide, matrix metalloproteases, and nitric oxide, which can exacerbate neuronal injury. ATP can also be released and contributes to the release of toxic cytokines by binding to purinergic receptors. Excessive microglial activation occurs in memory disorders, including AD [113]. Thus, another type of universal therapeutic might be to suppress microglial activation altogether, to administer specific purine receptor antagonists, or to find a way to switch the microglia to the more benevolent, repair-oriented M2 phenotype, in which microglia secrete wound-healing factors such as interleukin-10 and neurotrophic factors [114].

One way to accomplish this might be by blocking Toll-like receptors (TLRs), extracellular receptors on microglia and perivascular macrophages that are critical for microglial activation. TLRs bind to various substances,

known as damage-associated molecular pattern molecules (DAMPs), which are released by dying cells [115]. DAMPs may include hyaluronan, heat shock proteins, RNA, and single-stranded DNA. One TLR antagonist in development is eritoran, which is being investigated for the treatment of sepsis. TLRs can also be inhibited by PPAR $\gamma$ . Thus, the neuroprotective effect of PPAR $\gamma$  agonists such as rosiglitazone (discussed above) may rely in part on their ability to interfere with TLR signaling.

### Concluding remarks

Memory disorders involve structural and functional changes in the network underlying cognition. Increasing evidence indicates that synaptic loss and dysfunction is a key pathophysiological hallmark of memory disorders, if not part of their underlying pathology. So far, all efforts to develop therapies targeting specific AD-related pathways have failed in clinical trials of late-stage AD [48]. Many agents have also been tried against other memory disorders, without great success. The ineffectiveness of the agents for memory disorders may result from the concept of targeting pathology, right or wrong, rather than the pathophysiology. Targeting the disease pathology, even if right, may not necessarily bring significant improvement in memory functions if the brain cannot recover the synaptic functions by itself. Dementia and memory impairment have been recognized as the consequence of synaptic failure and deficits. Disease-modifying therapeutics should aim for brain network repair, especially synaptic repair and regeneration. Directly targeting synaptic efficacy with pharmaceutical agents may bring effective rescue to many types of memory disorder. PKC and synaptic growth factors such as BDNF are not only associated with synaptic regulation but also with the synaptic replacement that appears at the core of the disease-modifying therapeutics. Pharmacological agents that act on the PKC and synaptic growth factor pathways are promising as universal therapeutics for memory disorders, while the potential of brain stimulation and stem cells as therapeutics for multiple types of memory disorder needs more intensive investigation. The universal therapeutics may be used either as standalone interventions for patients with memory disorders when pathology is undefined or when antipathological agents are ineffective or as adjuncts in addition to drugs that target the underlying pathology directly.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tips.2015.04.004>.

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