Perspective

Implication of 14-3-3ζ-BDNF pathway in long-lasting memory enhancement and the rescue from memory deficits

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Intact memory function is critical for carrying out daily life activities, such as managing finances, remembering to take medications, driving in familiar environments, remembering a grandchild’s birthday, and learning to use a new computer. However, memory deficits not only accompany normal aging but are also comorbid with many psychiatric, neurological, and neurodegenerative diseases. Intellectual disability, autism, attention deficit disorder, learned helplessness, schizophrenia, and depression all have memory deficit components, as do Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and other neurodegenerative diseases (Khan et al., 2014). Therefore, a large proportion of the human population is affected by this brain disorder. In addition, according to the US Census Bureau and Eurostat estimations, the aged population (individuals over the age of 65 years) will double within three decades. Thus, the number of persons with memory deficits is expected to increase drastically, as is the social and economic burden associated with their treatment and care. Cognition-enhancing pharmacological agents are viewed as a strategy for treating memory deficits or slowing the effects of aging on memory function. Some of the most thoroughly studied examples of memory enhancers are partial agonists of the N-methyl-D-aspartic acid receptor, D-cycloserine and D-serine; synthetic amphetamine that allow glutamate to exert a prolonged effect on α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors; and stimulant drugs that inhibit monoamine reuptake, including amphetamines (Adderall), methylphenidate (Ritalin) and modafinil (Provigil); and donepezil (Aricept), which was designed to inhibit the enzyme acetylcholinesterase, which is responsible for degrading acetylcholine. These agents and other memory enhancers that have been studied to date have failed to produce consistent and invariable effects across various types of memory and have shown limited to no effect on memory deficits. Recently, we discovered that the expression of regulator of G protein signaling 14 of 414 amino acids (RGS1414) in the brain not only induced memory enhancement of multiple types of memory but also was sufficient for the rescue of recognition, spatial, and temporal memory, which are kinds of episodic memory that are primarily affected in patients or individuals with memory dysfunctions, in rodent models of aging and Alzheimer’s disease (López-Aranda et al., 2009; Masmudi-Martin et al., 2019; Navarro-Lobato et al., 2021). This RGS1414-mediated memory enhancement was facilitated through an increase in 14-3-3ζ activity (Navarro-Lobato et al., 2021).

14-3-3ζ is a multifunctional protein that belongs to a conserved family of 14-3-3 proteins, and it is widely expressed in the mammalian brain. This protein family is one of the major constituents of the brain, accounting for almost 1% of total cytosolic proteins. 14-3-3ζ interacts with many proteins and intercedes in several biological functions, and it has been implicated in aging and several neurological diseases, including Alzheimer’s disease and schizophrenia (Fan et al., 2019). The first evidence that 14-3-3ζ is related to memory was found in Drosophila melanogaster, where the leonardo gene, a homolog of vertebrate 14-3-3ζ, is abundantly expressed in mushroom body neurons. Mutant Drosophila that lacked the leonardo gene showed a significant decrease in the capacity for olfactory memory but not for olfactory sensory (Mooij et al., 1997). Similarly, mice lacking the 14-3-3ζ gene showed a decrease in their learning and recall abilities compared to their wild-type siblings (Xu et al., 2015). A novel object recognition test revealed that these mutant mice had no preference between familiar objects and novel objects, and they exhibited defects in discrimination index. A cross-maze escape task showed an increased escape latency and a reduced accuracy in arm choice in these mice. Moreover, a conditional rescue study of the behavioral phenotype in Drosophila mutants further suggested an acute requirement of 14-3-3ζ in both learning and memory (Philip et al., 2001). Altogether, the findings from these studies in mice and Drosophila suggest that an increase in 14-3-3ζ could rescue animals from memory deficits. Accordingly, we found that RGS1414-mediated long-lasting memory enhancement was mediated through the upregulation of 14-3-3ζ, which caused a boost in brain-derived neurotrophic factor (BDNF) protein levels and an increase in neuronal structural plasticity (Navarro-Lobato et al., 2021). Furthermore, 14-3-3ζ gene knockdown caused a complete loss of memory enhancement and an increase in BDNF protein and neuronal structural plasticity. These observations suggest that 14-3-3ζ-mediated structural plasticity is an essential step in RGS1414-induced memory enhancement and that RGS1414 exerts its function primarily through the regulation of 14-3-3ζ (Navarro-Lobato et al., 2021).

14-3-3ζ protein forms a complex with receptor for activated C kinase 1 (RACK1) and is then transported to the nucleus, where it binds to exon IV of BDNF and promotes the transcription of the BDNF gene (Neasta et al., 2012). Thus, 14-3-3ζ regulates the transcription of the BDNF gene in a manner that is different from the cyclic adenosine monophosphate-response element binding-BDNF pathway, which is susceptible to the activation of Ras/extracellular regulated protein kinases 1/2, cyclic adenosine monophosphate/protein kinase A and calmodulin kinase intracellular signaling, and the specific contribution of the 14-3-3ζ-BDNF pathway to BDNF-assigned biological functions has not been described. High 14-3-3ζ protein levels in RGS1414-treated animals are expected to facilitate the transport of RACK1 to the nucleus and thus increase BDNF transcription. In line with the same idea, animals treated with RGS1414 showed high mRNA and protein levels, and similar to the 14-3-3ζ gene, the deletion of the BDNF gene completely abolished the increase in neuronal structural plasticity and memory enhancement (Navarro-Lobato et al., 2021). Therefore, an increase in BDNF after the upregulation of 14-3-3ζ and the complete loss in structural plasticity and memory enhancement after BDNF gene deletion suggest that 14-3-3ζ mediates the effect of RGS1414 through the regulation of BDNF signal via the 14-3-3ζ-BDNF pathway (Figure 1). It is well documented in the literature that both the mRNA and protein levels of BDNF are significantly reduced during normal aging and in Alzheimer’s disease. We found that treatment with RGS1414 not only rescued memory in rodent models of aging and Alzheimer’s disease but also prevented memory deficits (Masmudi-Martin et al., 2019; Navarro-Lobato et al., 2021). Therefore, the rescue from memory deficits in rodent models of aging and Alzheimer’s disease was likely due to the activation of the 14-3-3ζ-BDNF pathway and the restoration of BDNF function.

Figure 1 | A diagram of 14-3-3ζ-brain-derived neurotrophic factor (BDNF) pathway.
This diagram shows the steps leading to RGS1414-mediated increase in BDNF. 14-3-3ζ binds to receptor for activated C kinase 1 (RACK1) and help to shuttle from cytoplasm to nucleus, where 14-3-3ζ-RACK1 complex interacts with exon IV of BDNF and promotes its transcription. Increase in BDNF induces neuronal structural plasticity, which in turn, facilitates memory enhancement and causes rescue from memory deficits. RGS1414: regulator of G protein signaling 14.

BDNF has been shown to play crucial roles in neuronal growth and branching and the formation of synaptic connections and is essential for long-term memory (Kowiański...
In our study, a surge in BDNF was observed within a week of RGS14 treatment; however, object recognition memory enhancement was first detected after 18 days of treatment (Masmudi-Martin et al., 2019). Therefore, we believe that the increase in BDNF initially induced neuronal structural plasticity through neuronal arborization and the generation of new synapses, which then enforced the reorganization of neuronal circuit connectivity. This improved circuitry could have served as a structural substrate for the memory-enhancing effect of RGS14. Furthermore, we found that in pyramidal neurons, branching was more dominant in dendrites (structures that receive innervations from other brain areas), whereas in nonpyramidal neurons, branching was prevalent in cell body neurites (structures that are involved in local circuits). In addition, we found that the increase in neuronal arborization generated an approximately twofold increase in the spine number of both types of neurons. An increase in the spine number of such a scale in both types of neurons is expected to cause synaptic reorganization in local (nonpyramidal) as well as in dendrites interconnected to other brain areas (pyramidal) synaptic networks. Our results indicate that circuit reorganization occurred within 20 days of the treatment because further neuronal arborization was undetectable beyond this period, and this was the period when high activity in the 14-3-3-BDNF pathway was observed. There was no difference in neuronal arborization between 20 days and 60 days of treatment (Navarro-Lobato et al., 2021). In addition, low activity in the 14-3-3-BDNF pathway after 60 days of treatment coincided very well with inactivity in neuronal arborization. Therefore, the memory-enhancing effect appears to emerge when novel connections are established and neuronal circuits are reorganized. The increase in neuronal circuitry could thus promote more efficient memory-related information processing and facilitate memory formation in the brain. Similarly, it has been shown that long-term memory formation is critically associated with synaptic remodelling, including synaptic growth (Hebsher et al., 2019). Memory is processed through interconnected brain circuits that are formed by the participation of distinct brain areas, and memory deficits occur as a consequence of reduced activity within these circuits. Consistent with this observation, poorer performance in patients with memory deficiency has been shown to be associated with decreased functional activity in neural networks (Daselaar et al., 2004). Therefore, a permanent structural change through neuronal arborization and synaptic reorganization could promote memory enhancement by uplifting activity in the interconnected neuronal networks. Sustained activity in these circuits could thus enhance the memory storage capacity in animals and the rescue and prevention of memory deficits in aging rats and Alzheimer’s disease mice.

The activation of 14-3-3 specifically induces BDNF-mediated structural plasticity and synaptic reorganization, which in turn facilitates memory functions in the brain. Our results indicate that high 14-3-3-BDNF pathway activity was essential for structural plasticity. However, low levels of 14-3-3-BDNF pathway activity observed 60 days after RGS14 treatment, which remained significantly higher than those control animals, seemed to be essential for the maintenance of memory functions. Sustained activity in the 14-3-3-BDNF pathway might have arrested the awaited deterioration of the neuronal networks and prevented memory deficits in rodent models of aging and Alzheimer’s disease. In contrast, reduced expression of the 14-3-3 gene, as observed in aging and Alzheimer disease, increased the vulnerability of these neuronal networks to deterioration. Thus, an adequate level of 14-3-3-BDNF pathway activity is essential for the maintenance of synaptic vigor, the well-being of neuronal circuits and normal memory functions. Furthermore, the 14-3-3-BDNF pathway regulates BDNF levels in a very different manner than the cyclic adenosine monophosphate-response element binding-BDNF pathway, which requires external signals/stimuli for activation. In contrast, 14-3-3 could perpetuate autocrine BDNF signaling through its receptor TrkB by activating the 14-3-3-BDNF pathway in the absence of external signals/stimuli, such as during sleep. It is likely that the 14-3-3-BDNF pathway might serve as an internal mechanism for the consistent BDNF supply required for the maintenance of synaptic structures and related neuronal networks in the brain, and reduced activity in this pathway could lead to the deterioration of these structures. Intact synaptic structures and related neuronal networks are crucial for adequate execution of memory functions. Thus, an adequate level of 14-3-3 is crucial for the continuous supply of BDNF needed for synaptic well-being, at least during one-third of our daily life. Altogether, our findings indicate that the 14-3-3-BDNF pathway might play a fundamental role in the maintenance of the memory system in the brain. A moderate activation of the 14-3-3-BDNF pathway is not only adequate for remediation against memory deficits but also useful as a memory enhancer for long-term effects on memory.

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