

## **Cognitive Enhancement Strategies**

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A decline in memory and cognitive function is a natural aspect of aging. In addition, cognitive deficits are comorbid with many mental disorders and neuronal diseases in humans. Mental retardation, autism, attention deficit disorder and schizophrenia, as well as neurodegenerative diseases including Alzheimer's and Parkinson's diseases all feature prominent deficits in cognitive abilities.

Cognitive enhancement is viewed as a strategy to treat these diseases, or to slow age-related decline of brain function. The development of cognition-enhancing drugs is, therefore, the focus of a considerable research effort. Recent advances in the understanding of the molecular mechanisms underlying learning and memory are providing a significant impetus for the research into cognitive enhancers (Bibb et al., 2010). Most approaches target neuronal processes that have been critically implicated in cognitive functions. Various neuronal processes, including neurotransmission, intracellular signaling, synaptic remodeling, protein transcription and translation, are all essential for cognition. In fact, manipulation of several molecular mechanisms governing these processes has been found to enhance memory functions.

As outlined in this chapter, virtually all of these neuronal processes are fundamentally regulated via protein phosphorylation. Modulators of the phosphorylation machinery therefore represent a valid drug target for cognitive enhancement. In particular, protein kinases and phosphatases involved in the signal transduction of the second messengers  $\text{Ca}^{2+}$  and cAMP appear to be particularly promising targets. For example, postsynaptic increases in  $\text{Ca}^{2+}$  levels induced by NMDA receptor stimulation, and subsequent activation of  $\text{Ca}^{2+}$ -dependent signal pathways have been unequivocally identified as critical for learning and memory (Lee & Silva,

2009). Consistently, molecular modifications that boost expression of the NMDA receptor subunit, NR2B, have been associated with enhanced mnemonic functions in several genetically modified mouse models (Tang et al., 1999). Attenuation of NR2B degradation through knockout of CDK5 enhances synaptic plasticity and cognition in mice (Hawasli et al., 2007).

Comparable to  $\text{Ca}^{2+}$  signaling, production of cAMP and subsequent induction of downstream signaling pathways are integral mechanisms underlying cognition. It is well established that increases in cAMP level are beneficial for memory functions. Indeed, a classical example of a pharmacological cognitive enhancer, rolipram, exerts its effect by increasing cAMP levels via the inhibition of phosphodiesterase 4 (PDE4), an enzyme that metabolizes cAMP (see Ch. 21). Similarly, overexpression of adenylyl cyclase, the enzyme synthesizing cAMP, results in learning and memory improvement in mice (Wang et al., 2004). Memory enhancement achieved via mechanisms that increase cAMP levels always depend upon the involvement of cAMP-dependent protein kinase (PKA). This central role of PKA in cognitive enhancement is underscored by evidence that modulators of PKA activity themselves have been linked to memory improvements.

$\text{Ca}^{2+}$ - and cAMP-induced activation of protein kinases is counterbalanced via protein phosphatases, and reduction in phosphatase activity has been associated with learning and memory enhancement. For example, inhibition of PP1 via the expression of inhibitor-1 improved memory formation (Genoux et al., 2002). The memory was also strengthened when the inhibition of PP1 was induced after learning, indicating an endogenous role of PP1 in counteracting memory formation. Comparably, decreasing the function of the  $\text{Ca}^{2+}$ -dependent phosphatase PP2B (also called calcineurin) facilitates synaptic plasticity and learning, whereas elevating its activity leads to disruption of these processes (Malleret et al., 2001).

The processes downstream of the  $\text{Ca}^{2+}$  and cAMP signaling cascades are still not well understood. One perspective is that ultimately the protein kinases and phosphatases stimulated by  $\text{Ca}^{2+}$  and cAMP converge onto transcription factors. In this way, they regulate expression of rate-limiting proteins needed to stabilize activity-dependent synaptic changes and thus memory. Consistently, transcription factors, including cyclic-AMP response element binding protein (CREB), are found to be integral for higher mental functions. Increases in levels of CREB activity consistently result in memory enhancements as seen in experiments with CREB overexpression (Matynia et al., 2002). Moreover, learning and memory improvements observed in mice overexpressing CaMKIV, a  $\text{Ca}^{2+}$ -dependent protein kinase, could be associated with increases in CREB phosphorylation and thus CREB activation (Wu et al., 2008; Fukushima et al., 2008).

Even though it may sound utopian, the use of memory-boosting substances to overcome cognitive deficits is in itself not a novel concept. Psychostimulants, such as caffeine and nicotine, have been used to alter mental states since ancient times. However, only now it is known that they affect cognitive performance via influencing, directly or indirectly, cAMP signaling. Other cognitive drugs, such as methylphenidate and amphetamines are commonly prescribed to treat attention disorders. These compounds modulate the responses of several key neurotransmitters in the brain, thereby affecting cAMP signaling. Nevertheless, most cognitive deficits cannot be addressed by such stimulants and more effective and refined therapeutic strategies are needed. To identify suitable targets for the development of cognition-enhancing drugs, further progress in our understanding of the molecular basis of cognition will be paramount.

### **References**

Bibb, J. A., Mayford, M. R., Tsien, J. Z., & Alberini, C. M. (2010). Cognition enhancement

strategies. *Journal of Neuroscience*, 30(45), 14987–14992.

Fukushima, H., Maeda, R., Suzuki, R., Suzuki, A., Nomoto, M., & Toyoda, H., et al. (2008). Upregulation of calcium/calmodulin-dependent protein kinase IV improves memory formation and rescues memory loss with aging. *Journal of Neuroscience*, 28(40), 9910–9919.

Genoux, D., Haditsch, U., Knobloch, M., Michalon, A., Storm, D., & Mansuy, I. M. (2002). Protein phosphatase 1 is a molecular constraint on learning and memory. *Nature*, 418(6901), 970–975.

Hawasli, A. H., Benavides, D. R., Nguyen, C., Kansy, J. W., Hayashi, K., & Chambon, P., et al. (2007). Cyclin-dependent kinase 5 governs learning and synaptic plasticity via control of NMDAR degradation. *Nature Neuroscience*, 10(7), 880–886.

Lee, Y. S., & Silva, A. J. (2009). The molecular and cellular biology of enhanced cognition. *Nature Reviews Neuroscience*, 10(2), 126–140.

Malleret, G., Haditsch, U., Genoux, D., Jones, M. W., Bliss, T. V., & Vanhoose, A. M., et al. (2001). Inducible and reversible enhancement of learning, memory, and long-term potentiation by genetic inhibition of calcineurin. *Cell*, 104(5), 675–686.

Matynia, A., Kushner, S. A., & Silva, A. J. (2002). Genetic approaches to molecular and cellular cognition: A focus on LTP and learning and memory. *Annual Review of Genetics*, 36, 687–720.

Tang, Y. P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., & Zhuo, M., et al. (1999). Genetic enhancement of learning and memory in mice. *Nature*, 401(6748), 63–69.

Wang, H., Ferguson, G. D., Pineda, V. V., Cundiff, P. E., & Storm, D. R. (2004). Overexpression of type-1 adenylyl cyclase in mouse forebrain enhances recognition memory and LTP. *Nature Neuroscience*, 7(6), 635–642.

Wu, L. J., Zhang, X. H., Fukushima, H., Zhang, F., Wang, H., & Toyoda, H., et al. (2008).

Genetic enhancement of trace fear memory and cingulate potentiation in mice overexpressing Ca<sub>v</sub>2/calmodulin-dependent protein kinase IV. *The European Journal of Neuroscience*, 27(8), 1923–1932.