

# Cognitive Enhancement

Pharmacologic, Environmental  
and Genetic Factors



Edited by

**Shira Knafo**  
**César Venero**



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# Cognitive Enhancement

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## Pharmacologic, Environmental and Genetic Factors

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# Dedication

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This book is dedicated to the memory of my dear sister Naama Ruth Yemini (Knafo), who loved life, but passed away in 2014 at 47.

The editors dedicate this book to their families and to patients suffering from cognitive impairment and their families, in the hope that the continued advance of research will soon produce a remedy to their suffering.

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# What is Cognitive Enhancement?

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## Abstract

“Cognitive enhancement” is commonly associated with drug use or the use of devices to improve cognition, technologies that have on the whole been established in laboratory animals or through a history of use in humans. In this chapter we aim to clarify the concept underlying “cognitive enhancement” and to provide a brief overview of the current use of this term in the academic literature, distinguishing the strategies to enhance cognitive function under normal conditions and the therapeutic strategies aimed at overcoming cognitive impairment. In addition, we will briefly review the various approaches to cognitive enhancement later described in this book.

## Keywords

Brain power; Cognitive enhancement; Life style; Technology; Therapy

## General Definition of Cognitive Enhancement

The term “cognitive enhancement” is currently associated with a wide range of existing, emerging, and visionary biomedical technologies that intend to improve the cognitive status of animals and human beings. As such, it offers the promise (or threat) of drastically changing the lives of citizens. Among the technologies proposed for use in humans are drugs that boost “brain power,” neuroimplants that may interface with computers or artificial means of augmenting cognition, neurostimulation technologies to alleviate pain and control mental focus, and highly sophisticated prosthetic applications to provide specialized sensory input or mechanical output (e.g., [STOA, 2009](#)). Most of these technologies have either been established in animal models (e.g., [Warwick, 2008](#)) or they have already been used in humans (e.g., [Dubljevic, 2013a](#)). In this chapter, we will clarify what is meant by the term “cognitive enhancement” as it is currently used in the academic literature and provide an overview of the different issues addressed in this book.

In the most general sense, cognitive enhancement can be considered as the improvement of performance related to cognitive tasks. The term “cognitive enhancement” is usually used without clarifying any of the nuances associated with its meaning, yet it refers to a wide range of practices and assumptions that impinge on other concepts. Indeed, this term is often defined distinctly in different spheres, and for example, public health and epidemiological studies usually describe the use of drugs for cognitive enhancement as the “non-medical use of prescription drugs,” “drug misuse,” or even “drug abuse” (e.g., [De Santis et al., 2008](#); [Franke et al., 2010](#)). On the other hand, contributions in the interdisciplinary bioethics literature regarding cognitive enhancement (e.g., [Harris, 2011](#)), as well as in neuroscientific (e.g., [Greely et al., 2008](#)) and clinical journals ([Larrieviere et al., 2009](#)), generally

have a more positive attitude toward the effects of cognitive enhancers, as reflected in their preferred examples (coffee, education, etc.).

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## Different Classes of Cognitive Enhancement

The general definition of cognitive enhancement is usually articulated by its proponents, and although chiefly considered through the application of medical tools, it may involve a wider range of approaches (e.g., computer technology, education, etc.). For example, “cognitive enhancement” is commonly considered to be applied in healthy individuals, although this term has also been used historically in Alzheimer’s research (see [Chapter 9](#)) and in research into neuropsychiatric illnesses involving cognitive impairment, such as schizophrenia and depression (see [Chapter 10](#)). In the latter pathologies, cognitive enhancement clearly refers to possible *therapeutic* interventions to improve the memory or cognitive function of patients. Thus, it is a term that is often used nonspecifically and sometimes, academic contributions consider both contexts together. This makes the normative implications harder to define and, to some extent, may confuse the specific scientific questions underlying both these contexts. That is why “general improvement in cognitive performance” is sometimes differentiated from “maintenance of cognitive performance” and from “augmented cognitive performance.”

## Lifestyle Use versus Therapeutic Use of Cognitive Enhancers

In a more technical sense, cognitive enhancement could be defined as the use of pharmaceutical drugs (see [Chapters 3](#) and [11](#)) or devices (see [Chapters 11](#) and [12](#)) for non-health-related improvement of cognition. This definition has the virtue of dissociating contexts that are socially encouraged from those that are legitimately discouraged or even prohibited. The preventive, curative, rehabilitative, and compensatory uses of pharmaceutical drugs and devices are important elements in meeting health needs. By contrast, the use of medical means to gain competitive advantage is an issue that might cause social problems (please refer to [Chapter 13](#) in which ethical issues are discussed) and, as such, the distinction between therapy and enhancement is largely context dependent.

The concept of therapy was taken to be fairly unproblematic for a long time, yet once people realized the potential of certain technologies, they began to consider the conceptual differences between, say, vaccination and enhancement. That is not to say that new technologies have blurred the boundary themselves; rather, our attitude has shifted from taken-for-granted to the need to explain. This is why it is useful to set apart the concept of enhancement that explicitly excludes medical needs from the *therapeutic* uses of the same technology (i.e., preventive, curative, rehabilitative, and compensatory). In this sense, it is also useful to clarify the extent of moral unease felt about enhancement and the appropriate regulatory response of the state (see [Dubljevic, 2012a,b](#) for a long argument). For example, when a given technology or social practice is not yet proved to be detrimental per se but it might cause social problems if unregulated, the appropriate response is some form of discouragement (see [Dubljevic, 2013a,b](#)).

However, notions other than cognitive enhancement have also been used to capture the concept of nonmedical drug use to improve performance. For example, “lifestyle use” of drugs may in part reflect pharmaceutical drug use that does not correspond to a medical condition or need in the traditional sense of the term but rather, to the demand for greater performance or a modified lifestyle. It may be claimed that references to the use of cognitive enhancement in the scientific literature

obscure a longer history of nonmedical drug use to enhance performance. Indeed, a group of Australian authors ([Bell et al., 2012](#)) argued that the use of drugs for enhancement may even cross the border of illegal drug use (e.g., cocaine and amphetamines). This consideration adds normative implications as prohibition would be the assumed regulatory response, which might not be fully justifiable on judicial grounds. For this reason, the use of medical drugs to enhance cognitive function by healthy adults, such as Adderall (amphetamine) and Ritalin (methylphenidate, see [Chapter 11](#)), and devices such as those involving transcranial direct current stimulation (tDCS, see [Chapter 12](#)), has to be dissociated from both the therapeutic drug use and the leisure use of illegal substances.

## The Aspects of Cognition Being Enhanced

A further issue is to understand exactly what is improved by cognitive enhancement (i.e., what capacity). The naive and undifferentiated term “cognitive enhancement” (as well as more popular terms for such enhancers, such as “smart drugs”) suggests that the use of said stimulants generally improves cognition, or even IQ. However, it is important to note that current evidence is contradictory with respect to the possible “enhancement” caused by currently available cognitive enhancers (see e.g., [Ilieva et al., 2013](#)). This has led some to conclude that the label “cognitive enhancement” may be a misnomer (see [Vrecko, 2013](#)). Accordingly, much like a drug undergoing clinical trials cannot properly be called a “treatment” or “therapy” before its effectiveness has been proved, prescription stimulants should not be called “cognitive enhancers” until there is scientific proof that they actually increase cognitive function or IQ. Many of the “smart drugs” have not been tested in the same way with the same rigor for enhancement as they were for the original therapeutic applications (see [Chapters 9, 10, and 11](#)), and recent reviews have highlighted the limited evidence supporting claims of enhancement (see, e.g., [Repantis et al., 2010](#)). Obviously, we need a stricter definition of specific aspects of cognitive enhancement. Improved cognitive function (such as IQ, working memory, etc.) for which there is currently insufficient evidence, should be referred to as “augmented cognitive performance” and, as such, distinguished from “maintained cognitive performance.” “Maintained cognitive performance” refers to the prolongation of normal cognitive activity and a dampening of the effects of fatigue and sleep deprivation, for which there is strong evidence (see, e.g., [Estrada et al., 2012](#); [Lagarde, 1995](#)).

“General improved performance” has been analyzed as a descriptive that can be applied to cognitive enhancement, and it has been rejected as unspecific, since it does not distinguish even the therapeutic use of drugs and devices. On the one hand, “augmented cognitive performance” can be applied to healthy adults using drugs or devices to improve general IQ, working memory, or accuracy of recall, thereby achieving significantly better levels of cognitive functioning. On the other hand, “maintained cognitive performance” refers to the use of drugs or devices that serve to maintain normal levels of cognitive activity for longer periods of time, while reducing the impairment associated with fatigue and sleep deprivation. While the evidence supporting the former remains somewhat controversial, current “cognitive enhancers” undoubtedly provide such maintenance effects, although some issues regarding safety remain unclear.

## Are Today’s “Cognitive Enhancers” Truly Efficient?

It is currently not easy to define improvement in cognition. For an individual interested in enhancement, the effect depends on the expectations of a subjective improvement in performance

real-life settings, whereas a regulatory review body usually requires controlled laboratory settings to assess claims of improved cognition. Since the benefits of cognitive enhancers should by definition not involve the response to a clear pathology, lesion, or identified behavioral or mental health problem, establishing the basal measures to evaluate the effects of enhancement is likely to be somewhat controversial. The studies carried out to date have examined the enhancement of executive functions by neuropharmaceuticals (see [Ilieva et al., 2013](#); [Repantis et al., 2010](#)) and brain stimulation techniques such as transcranial magnetic stimulation ([Luber and Lisanby, 2013](#)) and tDCS ([Dockery et al., 2008](#); see [Chapter 12](#)), through the performance of specific tasks in controlled laboratory settings. However, critics point out that these tasks do not fully capture the effects on the more general capacities underlying them or on other tasks (see [Iuculcano and Cohen Kadosh, 2013](#); [Ranisch et al., 2013](#); [Vrecko, 2013](#)) and that cognitive enhancers should (also) be examined in the context of real-world performance.

## Possible Risks in the Use of Cognitive Enhancers

The nonspecific term “cognitive enhancement” has an in-built positive connotation that diverts attention from the possible short-term and long-term risks or the side effects associated with using drugs or devices to stimulate the brain for non-medical reasons and without any relevant knowledge or supervision. Drugs such as ampakines (see [Chapter 3](#)) might augment cognitive performance in the sense of increasing general IQ, working memory or more accurate recall, yet perhaps they will not work in humans ([Goff et al., 2008](#)). Furthermore, these drugs might produce some side effects, or they may be harmless ([Goff et al., 2008](#)). Indeed, even “maintained cognitive performance” raises important ethical issues, depending on the potential side effects of the substances (or devices) used (see [Dubljevic, 2012b](#); [Ranisch et al., 2013](#); and [Chapter 13](#)). The issue of whether new “cognitive enhancers” are harmless like coffee or dangerous like amphetamines can only be resolved once research into the effects of new drugs (or devices) has delivered robust and reliable findings, something to which this book will contribute.

## A Journey through this Book

After defining the possible meanings of cognitive enhancement in its multiple forms, this book looks in depth at a number of the traditional and cutting-edge technologies that are currently studied and employed in experimental animals and sometimes, in humans. Unlike traditional approaches (e.g. enriched environment, [Chapter 4](#)), most of the innovative approaches are invasive and they are therefore unlikely to be tested on human beings. Nevertheless, they provide precious insight into the avenues of current research that may lead to future modes of enhancement.

As described in [Chapter 2](#), one of the most common approaches to develop new cognitive enhancers is to identify the pathways involved in learning and memory, and to test activators specific to these pathways. In a second, often used approach, pathways leading to synaptic loss or cell death are identified and inhibited. A third approach described in this chapter relies on the activation of normal cell repair mechanisms to restore lost synapses.

Having understood the signaling pathways that globally modulate learning and memory, it is essential to uncover the specific molecular and synaptic events mediating cognitive function. Accordingly, sophisticated molecular and electrophysiological tools are described in [Chapter 3](#) based on the idea that facilitating synaptic plasticity may eventually lead to better cognitive function,

result that can be achieved by manipulating the activity of neurotransmitter receptors. This chapter also describes how synthetic compounds specifically engineered to boost synaptic transmission and plasticity positively affect cognitive capacity in a variety of experimental paradigms. Although the routine use of these drugs in humans is still a long way off, experiments in animals are encouraging and represent the first essential step for the selection of drugs for clinical trials. Together, [Chapters 1 and 3](#) provide valuable insights into the molecular mechanisms believed to induce cognitive enhancement and how this knowledge can be used to develop new, mechanism-based drugs for use in healthy humans or in individuals suffering from cognitive impairment. Nonetheless, drugs are not necessarily the optimal approach to enhance cognitive function.

[Chapter 4](#) describes how control over the environment may represent a more physiological approach to cognitive enhancement, focusing on how the incredible plasticity of the brain is used to evolve behaviors that accommodate the inherent uncertainty and probabilistic nature of the environment. This plasticity requires a constant interaction between the genome and the environment, whereby the latter regulates the cell signals and functions that control gene expression. Such epigenetic mechanisms represent ideal devices, as many transcription factors control neuronal structure and function supporting the interplay between hippocampal and neocortical assemblies necessary for the formation and modification of new and existing representations.

Moving on to an approach that is only possible in rodents, [Chapter 5](#) describes genetic engineering technologies to produce transgenic mice. This is a commonly used method to study cognitive function at distinct levels, ranging from molecules to behaviors. This chapter analyzes how negative genetic manipulations cause behavioral deficits in mutant animals, while cognitive functions are enhanced in some such transgenic mice. The phenotype of these mice is summarized, along with the signaling pathways affected by the genetic manipulation. This overview of “smart” transgenic mice reveals that cognitive enhancement can be achieved by altering the regulation of molecules involved in cell signaling events, shifting this from the receptors at the cell surface to the transcription factors in the nucleus of neurons. Understanding the mechanisms of memory enhancement is therefore an important tool to elucidate the basic mechanisms underlying learning and memory, as well as to develop treatments for cognitive disorders.

This book also contains three chapters describing cutting-edge experimental technologies that are currently being employed to enhance cognitive functions in rodents. [Chapter 6](#) describes how recovering cognitive function through viral gene therapy has become feasible in the last decade. This approach involves delivering genes of interest into the specific brain region to either protect neurons or to enhance neural regeneration, thereby promoting cognitive function. The chapter focuses on adeno-associated virus (AAV) vectors, those most widely used in basic research and that are currently being tested in clinical trials to treat neurodegenerative disorders. This chapter delves into the background of the AAV vector system, as well as analyzing successful candidate transgenes that enhance neurogenesis and hippocampal function, and it describes their application in cognitive enhancement.

[Chapter 7](#) describes another innovative approach that has become popular in the past decade. Optogenetics is a method that permits real-time control of genetically defined neuronal populations using light-sensitive proteins. This chapter shows how optogenetic tools can be used to gain new insights into the way in which memories are formed, saved, and extracted. The incorporation of optogenetic tools into the field of learning and memory has led to an important increase in our understanding of the networks underlying complex cognitive processes. Hence, this chapter focuses on how optogenetics can be used for memory generation and cognitive enhancement.

[Chapter 8](#) describes another cutting-edge technology, to date used only in a laboratory setting. It explains how multipotent stem cells within the adult brain play a critical role in cognition and the strategies to favor neural stem cell populations within key brain regions that are being developed to enhance cognition in rodents. The relationship between neural stem cells and cognition in the healthy aging, and pathological brain and the molecular mechanisms by which stem cells may exert their effects on learning and memory are also addressed. Moreover, the brain's capacity for plasticity and regeneration is reviewed, along with the potential role of endogenous neurogenesis and stem cell transplantation to augment this capacity.

[Chapter 9](#) describes the cognition-enhancing manipulations overcoming the cognitive deficits related to Alzheimer's disease. Unfortunately, in most cases the strategies that have proved successful in rodents tend to fail in human beings. Examples of manipulations are described, and the possible causes of failure are analyzed. A significant part of this chapter is dedicated to clinical trials in Alzheimer's patients that failed to recapitulate the positive effects found in rodents. In some cases, the failure of the treatment can be easily traced, as when the treatment produced significant side effects. However, in most cases, there is no ready explanation for failure.

[Chapter 10](#) reviews different pharmaceutical treatments approved by the Food and Drug Administration to reverse or ameliorate neurocognitive deficits frequently found in several neuropsychiatric disorders or those being tested in clinical trials. Crucially, cognitive deficits are sometimes a core feature of such disorders. The chapter focuses on pharmacological treatments that effectively improve some aspects of cognition in certain neuropsychiatric illnesses, including attention-deficit/hyperactive disorder, schizophrenia, bipolar disorder, posttraumatic stress disorder, and depression.

[Chapter 11](#) summarizes empirical data on the approaches to enhance cognitive capabilities in humans using pharmaceuticals, nutrition, physical exercise, sleep, meditation, mnemonic strategies, computer training, and brain stimulation. This chapter also describes the drugs that are currently being used in patients suffering from Alzheimer's disease. Unfortunately, antidementia drugs offer only minor benefits in cognitive function and none of them seem to have disease-modifying properties. The mixed evidence for the efficacy of many pharmaceutical drugs currently used for cognitive enhancement is summarized, while a growing body of evidence for several nonpharmacologic interventions indicates reliable cognition-enhancing effects. In this respect, [Chapter 12](#) provides valuable data on the use of noninvasive brain stimulation for cognitive enhancement, such as tDCS. The evidence of the safety, beneficial impacts, and cost-benefit ratio of these techniques at the individual and societal level are discussed in detail, along with the mechanisms and physiologic effects of tDCS and its effects on human cognition.

The final chapter of this book ([Chapter 13](#)) summarizes the ethical issues that may arise once efficient cognitive enhancers are developed for human use. It starts by describing possible scenarios that may currently sound unrealistic yet that serve to reflect on the danger of unregulated use of cognitive enhancers. This chapter explains why and how authorities should strictly control the prescription of cognitive enhancers, adapting state laws to these new technologies.

To summarize, this book contains a vast amount of information regarding traditional and modern strategies aimed at enhancing cognitive function, both in animals and humans. The editors made an effort to make this book accessible to the general public, although some of the chapters may be more scientifically oriented than others. Nevertheless, the general goal of this book is to bring together the bulk of information available in this field, in the hope that this will eventually help scientists develop new, more efficient approaches to treat cognitive impairment.

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# Signaling Pathways Involved in Cognitive Enhancement

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## Abstract

Cognitive enhancement is a general strategy for treating the effects of neurological injury or neurodegeneration by enhancing or preserving normal synaptic pathways, while not necessarily affecting the underlying disease. One approach to identifying cognitive enhancers is to identify pathways involved in learning and develop activators specific for that pathway. Potential candidates include brain-derived neurotrophic factor, protein kinase C, and neurosteroid pathways. A second approach is to activate normal cellular repair mechanisms to restore lost synapses or inhibit pathways leading to synaptic loss or cell death. In this chapter, we discuss some of the pathways that are known to be important in learning and memory, and describe some novel small-molecule drugs that may be of use as cognitive enhancers.

## Keywords

Apolipoprotein E; Brain-derived neurotrophic factor (BDNF); Bryostatins; Dendritic spine; Ephrin; Insulin; Learning; Memory; Neurosteroids; Protein kinase C; Rho GTPases; Stress

## Introduction

Cognitive enhancement is a general strategy for treating the effects of conditions involving cognitive impairment such as traumatic brain injury, Down syndrome, and neurodegenerative diseases (e.g. Alzheimer's disease). The goal of cognitive enhancement therapy is to develop treatments that, while not necessarily effecting a cure, can improve the quality of life for patients suffering such conditions. In a broad sense, however, cognitive enhancement also includes pharmacological and other means for increasing memory and cognitive capacity, targeting both cognitive disorders and normal mentation. Such drugs would be valuable even if effective treatments for specific disorders are eventually found because arresting disease progression at a late stage of a neurodegenerative disease would be of marginal value without some way of enhancing normal cognitive function and repairing the accumulated injuries to synaptic pathways and networks.

One approach to finding cognitive enhancers is to identify the molecular signaling pathways involved in learning and memory and search for compounds that activate the relevant components of the pathway. These targets could include protein kinases, cell surface receptors, neural signaling mechanisms, or components of synaptic transmission, or enzymes anywhere along the signaling pathway. This approach could also involve stimulating enzymes involved in neurotransmitter synthesis, enhancing the contacts between pre- and post-synaptic proteins, or inducing the maturation of synapses.

A second approach is to activate normal neuronal repair mechanisms in order to restore synaptic

pathways that have been lost. Again, this depends on understanding the signaling pathways and how they interact. An example would be a drug that induces the formation of new synapses. This approach is potentially more powerful, because it can be directed toward reversing the underlying neurodegeneration rather than simply stimulating a signaling pathway.

In this chapter, we will review the signaling pathways involved in these two approaches. For each approach, we will consider potential therapeutic agents that act on these pathways, mainly small molecule drugs, along with their potential benefits and drawbacks.

## Stress as a Cognitive Enhancer

One challenge in classifying cognitive enhancers is to discriminate between substances that directly activate mechanisms of memory and cognition and those that act indirectly by affecting performance or by activating stress mechanisms. Acute stress produces a generalized activation of neuronal activity and profound biochemical changes that can enhance (McGaugh and Roozendaal, 2002) or impair (Wang et al., 2013; Eagle et al., 2013; Lee et al., 2013) memory encoding and formation. Thus, stress and agents that induce stress, may be thought of in certain contexts as cognitive enhancers. For example, fear stress activates the basolateral complex in the amygdala, which is critically involved in the storage of conditioned fear memories, but not spatial or declarative memories. Animals subjected to threatening stimuli show increases in phospho-ERK2 (extracellular signal-related kinase 2) in the amygdala, which is associated with reduced inhibitory control of GABAergic interneurons, resulting in increased neuronal excitability (Martijena and Molina, 2012).

Although not completely understood, in general, the release of catecholamines and glucocorticoids following sympathetic nervous system activation enhances memory consolidation through a variety of mechanisms, while at the same time interfering with memory retrieval. Catecholamines such as norepinephrine influence the amygdala via the  $\beta$ -adrenoreceptor, which is coupled to adenylyl cyclase and cyclic adenosine monophosphate (cAMP) synthesis. cAMP acts through cAMP-responsive element-binding protein (CREB) and induces the synthesis of a number of genes, including brain-derived neurotrophic factor (BDNF) and c-fos, and promotes synaptic growth. Because of this, a large industry has arisen to search for drug compounds that can activate the CREB pathway (Scott et al., 2002).

Glucocorticoid receptor agonists administered to the medial prefrontal cortex also enhance memory by effects on the noradrenergic system via G-protein coupled receptors that do not involve changes in DNA synthesis (Barsegyan et al., 2010). As with catecholamines, cAMP-dependent protein kinase is the proximate biochemical mediator of stress signaling (Schwabe et al., 2012). Although the amygdala is not a storage site for spatial or declarative memories, glucocorticoid receptor stimulation in the basolateral amygdala can affect spatial memory via its neuronal projections to the hippocampus. The cognitive enhancement effect of stress may also be due in part to increased exclusion of unrelated information (Henckens et al., 2009). It is important to mention, though, that stress reduces glutamatergic transmission and glutamate receptor surface expression in the prefrontal pyramidal neurons (Wei et al., 2013), and also alters the production and survival of new neurons in the hippocampus (Schoenfeld and Gould, 2012). Stress also reduces levels of BDNF (Masi and Brovedani, 2011), leading to a reduction of synaptic growth. These findings imply that stress has numerous detrimental effects and must be regarded with caution.

# Biochemical Signaling Pathways in Learning

A fundamental property of cognitive enhancers is the ability to facilitate learning. It has long been known that calcium and other cations are involved in the signaling pathways of learning. [Alkon and Rasmussen \(1988\)](#) proposed a cellular model of cell activation that involved spatially discrete responses to a stimulus mediated by calcium. [Alkon et al. \(1982\)](#) also identified changes in membrane potassium currents during the retention of associative learning in the marine invertebrate *Hermissenda crassicornis*. From these and many other experiments, it was clear that ion channels were critically involved in learning. One protein that affects ion channels is protein kinase C (PKC).

## Protein Kinase C

Early research with marine invertebrates identified PKC as a central component of learning and memory. [Bank et al. \(1988\)](#) identified an increase in PKC in crude membrane fractions of CA1 hippocampus prepared from rabbits subjected to rabbit classical eyelid conditioning. This was correlated with focal increments of [<sup>3</sup>H]phorbol-12,13-dibutyrate binding ([Olds et al., 1989](#)). Increased phosphorylation of PKC substrates was found following associative learning in *Hermissenda* ([Neary et al., 1981](#); [Nelson et al., 1990](#)). PKC was also found to regulate A-type potassium channels, which had previously been associated with classical conditioning in *Hermissenda* ([Alkon et al., 1982](#)) and rabbits ([Alkon et al., 1988](#); [Etcheberrigaray et al., 1992](#)). Activation of PKC with bryostatin 1 enhances learning and memory, while at the same time increasing the numbers of mushroom spines, perforated postsynaptic densities, and double-synapse presynaptic boutons associated with spines. Ro 31-8220, an inhibitor of PKC, prevents these effects ([Hongpaisan and Alkon, 2007](#)). PKC activation was found to induce the synthesis of other proteins when given several days before training ([Alkon et al., 2005](#)). This protein synthesis greatly decreased the number of training events required for memory acquisition in *Hermissenda* and prolonged retention from 7 months to over 1 year, indicating a markedly reduced threshold for long-term consolidation.

Indeed, protein synthesis had long been recognized as essential for long-term memory acquisition. Much of the protein synthesis that occurs during learning occurs locally in neuronal dendrites, which confer specificity to associative memories ([Jiang and Schuman, 2002](#); [Govindarajan et al., 2011](#)).

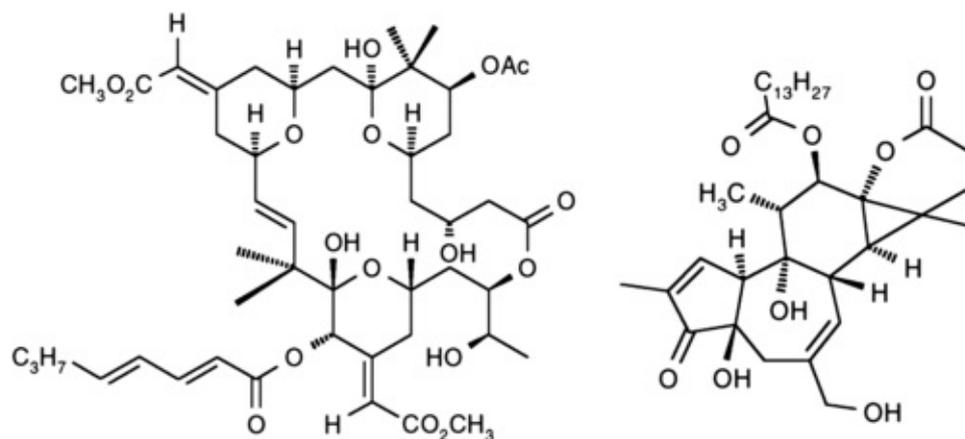
Bryostatin, phorbol esters, and similar PKC activators, such as ingenol and picologs, bind to the C1A and C1B domains on PKC ([DeChristopher et al., 2012](#); [Nelson and Alkon, 2009](#)). The natural ligand for C1 domains is 1,2-diacylglycerol ([Blumberg et al., 2008](#)). Conventional PKC isoforms ( $\beta$ I,  $\beta$ II, and  $\gamma$ ), and novel PKC isoforms ( $\delta$ ,  $\epsilon$ ,  $\eta$ , and  $\theta$ ) also possess a C2 domain, which binds phosphatidic acid and phosphatidylserine ([Corbalán-García et al., 2003](#); [Conesa-Zamora et al., 2001](#)). These lipids have been implicated in neurite outgrowth and spine formation ([Ammar et al., 2011](#); [Shirai et al., 2010](#)), and artificial ligands of the PKC C2 domain, such as DCP-LA, have been shown to restore mature mushroom spine synapses and prevent memory loss in aging rats ([Hongpaisan et al., 2013](#)).

In conventional PKC isoforms, the C2 domain participates in calcium binding ([Steinberg, 2008](#)). Along with the C1 domain, the C2 domain is not unique to PKC but is also found in many other proteins ([Kim et al., 2003](#)), including proteins involved in synaptic vesicle exocytosis, such as synaptotagmin ([Martens, 2010](#); [Südhof and Rizo, 1996](#)). C1- and C2-like domains are found in the sequences of many

proteins involved in synaptic enhancement or neurotransmitter release. Thus, both classes of PKC activators may also have strong non-PKC effects on synaptic vesicle release and, hence, produce cognitive enhancement.

## Other C1-Domain Proteins

PKC is not the only protein that possesses a C1 domain. Many other proteins bind 1,2-diacylglycerol and possess homologous domains, including Rat sarcoma guanyl releasing protein 1 (Lorenzo et al., 2000) and the Mammalian Uncoordinated (Munc)-13 family proteins (Wojcik and Brose, 2007). These proteins are all located in neurons and participate in dendritic growth and synaptic vesicle release, and thus cannot be overlooked as potential neurological targets for bryostatin and similar cognitive enhancers.



Bryostatin 1 and phorbol ester (phorbol-12-myristate-13-acetate, PMA)

Like PKC, Munc13 has multiple isoforms. The Munc13-3 isoform is found primarily in the cerebellum granule and Purkinje cells, where it regulates motor learning. The more abundant Munc13-1 isoform, which is expressed throughout the brain, is particularly interesting as a potential target for cognitive enhancers, because it is a synaptic vesicle protein, colocalizing with the presynaptic marker synaptophysin (Augustin et al., 2001), and thus is well positioned to change synaptic efficiency. Basbaum et al. (2007) found that phorbol dibutyrate binding to Munc 13 lowers the energy barrier for synaptic vesicle fusion. Diacylglycerol and phorbol esters augment neurotransmitter release in hippocampal neurons; Munc13, and not PKC, is the protein responsible for this effect (Rhee et al., 2002).

Whichever protein is responsible, C2-domain activators such as DCP-LA and DCP-LA methyl ester produce beneficial morphological and behavioral effects, indicating potential value as cognitive enhancers (Hongpaisan et al., 2011, 2013). In Tg2576 and 5XFAD transgenic mice, often used as models for familial Alzheimer's disease, DCP-LA prevents synaptic loss and cognitive deficits (Hongpaisan et al., 2011). Bryostatin has similar effects (Hongpaisan et al., 2011, 2013; Sun and Alkon, 2005).

## PKC Substrates

Many PKC substrates are also involved in cognitive and learning pathways. One is Myristoylated Alanine-Rich C-Kinase Substrate (MARCKS), an acidic membrane-bound protein. Phosphorylation

MARCKS by PKC inhibits its association with actin and with the plasma membrane, reducing its ability to crosslink F-actin, and triggering dendritic spine destabilization (Calabrese and Halpain, 2005). PKC-induced spine destabilization can be prevented by creating a nonphosphorylatable MARCKS mutant. Dendritic spines are highly dynamic; over 80% of the F-actin in spines turns over every minute (Koleske, 2013). Thus, PKC, in conjunction with signaling molecules that promote stabilization, may be preferentially involved in the early stages of dendritic restructuring during development, or during adulthood when dendritic spines have largely stabilized.

Another PKC substrate important in cognitive function is GAP-43, a growth cone-associated protein that is essential for neurite outgrowth. Like MARCKS, GAP-43 interacts with actin filaments. After phosphorylation by PKC, GAP-43 promotes the stabilization of long filaments (He et al., 1997). PKC activation increases the level of autophosphorylated CaMKII and promoted association with NMDA receptors, possibly through phosphorylation of calmodulin-binding proteins such as neuromodulin (Yan et al., 2011), indicating overlap of their signaling pathways, but there is little evidence of an in vivo physiological direct phosphorylation. Although not fully understood, these interactions between signaling kinases such as CaMKII and PKC and cytoskeletal proteins such as actin modify the geometry of dendritic spines, and thereby directly change the function and connectivity of the neuronal networks responsible for cognition.

## Structural Proteins

Dendritic spines are the primary site of excitatory input on most principal neurons. Their size, shapes, and numbers change during aging, memory formation, and neurodegenerative disease progression. The mature so-called mushroom spines are formed from an enlargement of thin spines during synaptic enhancement. The stability of these spines suggests, to many investigators, their involvement in long-term memory (Bourne and Harris, 2007). If so, an effective memory therapy should restore the brain's capacity to form mushroom spines.

As mentioned above, changes in structural proteins, particularly actin, play an important role in cognitive enhancement. A cytoskeletal change in dendritic spines is the most well established candidate for the biochemical localization of memory (Hotulainen and Hoogenraad, 2010; Kasai et al., 2010). The rearrangement of the actin cytoskeleton is instrumental in synaptic maturation and memory (Hotulainen and Hoogenraad, 2010). Spine length and morphology are modified by learning and profoundly affect synaptic transmission. Defects in dendritic spine cytoskeleton are observed in patients with mental retardation (Newey et al., 2005), traumatic brain injury (TBI) (Gao et al., 2011) and Alzheimer's disease (Perez-Cruz et al., 2011). Thus, it is no surprise that many cognitive enhancers modify the actin cytoskeleton either directly or indirectly.

## Rho GTPases

Reorganization of structural proteins is effected in part by small GTP-binding proteins, which bind and hydrolyze GTP. Perhaps the most important of these are the Rho GTPases. Rho is the name for a family of small GTPases that regulate the actin cytoskeleton, including RhoA, Rac1, and Cdc42 (Ridley, 2006). Rac1 and Cdc42 are important for spine formation and growth, whereas RhoA is important for spine loss (Newey et al., 2005). Rho proteins are therefore instrumental in regulating synaptogenesis (Tolias et al., 2011).

The activity of Rho family proteins is modulated by a number of proteins called guanine nucleotide

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