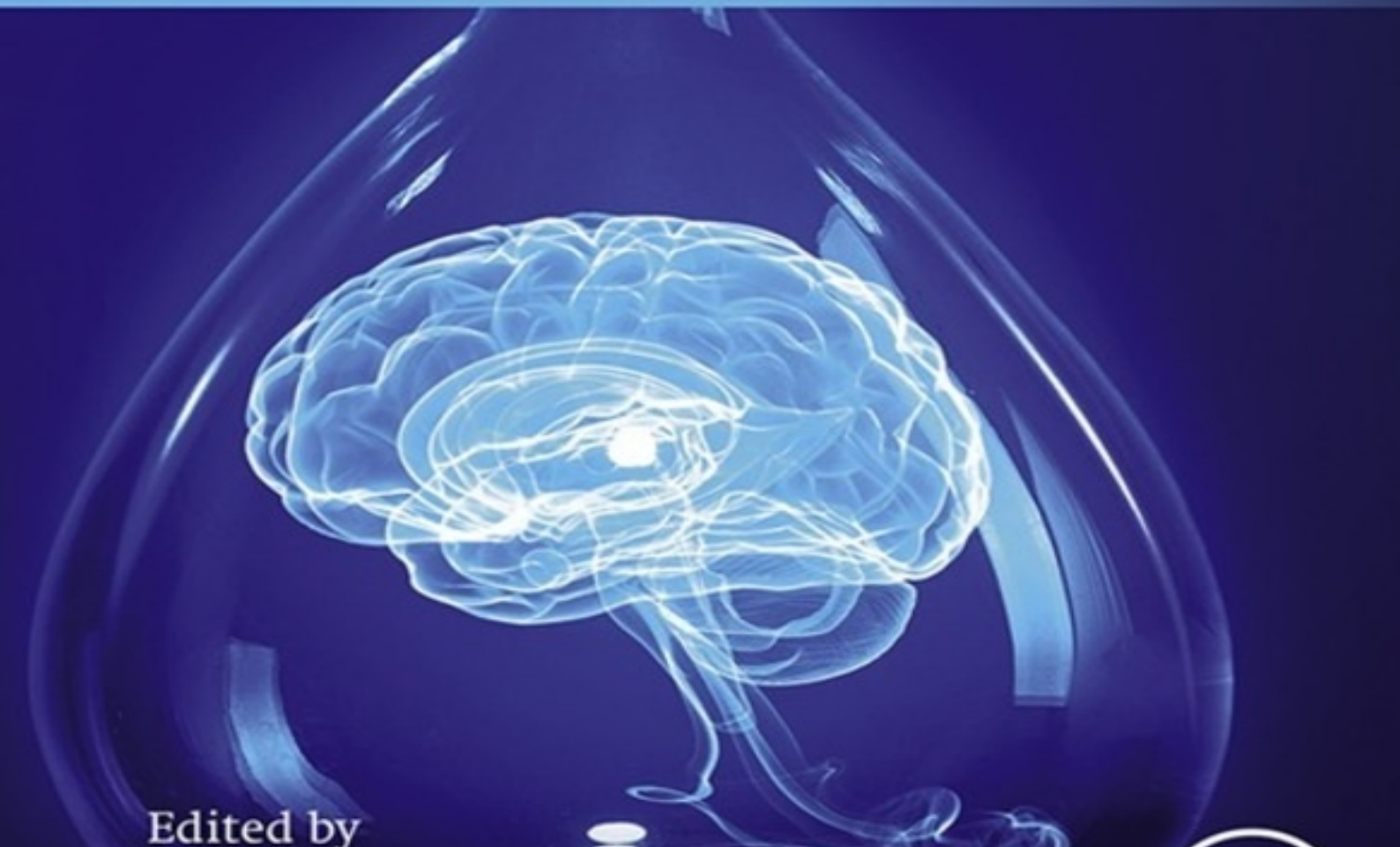
Cognitive Enhancement

Pharmacologic, Environmental and Genetic Factors



Edited by
Shira Knafo
César Venero

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Pharmacologic, Environmental and Genetic Factors

Editors

Shira Knafo

Unidad de Biofísica CSIC, UPV/EHU, Campus Universidad del País Vasco, and IkerBasque, Basque Foundation for Science, Basque Country, Spain

César Venero

Psychobiology Department, Faculty of Psychology, Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain

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Dedication

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.

Contributors

Daniel L. Alkon, Blanchette Rockefeller Neurosciences Institute, Rockville, MD, USA

Mathew Blurton-Jones
Department of Neurobiology & Behavior, University of California Irvine, Irvine, CA, USA
Sue and Bill Gross Stem Cell Research Center, University of California Irvine, Irvine, CA, USA
Institute for Memory Impairments and Neurological Disorders, University of California Irvine, Irvin
CA, USA

Roi Cohen Kadosh, Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

Jonathan E. Draffin, Centro de Biología Molecular Severo Ochoa, Consejo Superior de Investigaciones Científicas/Universidad Autónoma de Madrid, Madrid, Spain

Martin Dresler
Max Planck Institute of Psychiatry, Munich, Germany
Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmege
Netherlands

Veljko Dubljević
Neuroethics Research Unit, Institut de Recherches Cliniques de Montréal (IRCM)
Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada
International Centre for Ethics in the Sciences and Humanities, University of Tübingen, Germany

Jose A. Esteban, Centro de Biología Molecular Severo Ochoa, Consejo Superior de Investigacione
Científicas/Universidad Autónoma de Madrid, Spain

Natalie R.S. Goldberg, Department of Neurobiology & Behavior, University of California Irvine, Irvine, CA, USA

Inbal Goshen, Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem, Israel

Michael T. Heneka
Department of Neurology, Clinical Neuroscience Unit, Universitätsklinikum Bonn, Bonn, Germany
German Center for Neurodegenerative Disease (DZNE), Bonn, Germany

Tsuneya Ikezu, Laboratory of Molecular NeuroTherapeutics, Departments of Pharmacology & Experimental Therapeutics and Neurology, Boston University School of Medicine, Boston, MA, USA

Shira Knafo, Unidad de Biofísica, CSIC, UPV/EHU, Universidad del País Vasco, Ikerbasque, The Basque Foundation for Science, Leioa, Spain

Yong-Seok Lee, Department of Life Science, College of Natural Science, Chung-Ang University,

Seoul, Republic of Korea

Chung Yen Looi, Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

Yanir Mor, Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem, Israel

Thomas J. Nelson, Blanchette Rockefeller Neurosciences Institute, Morgantown, WV, USA

Ciaran M. Regan, School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Belfield, Dublin, Ireland

Dimitris Repantis, Charité Universitätsmedizin, Department of Psychiatry, Berlin, Germany

Anat Shapir, Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem, Israel

Miao-Kun Sun, Blanchette Rockefeller Neurosciences Institute, Morgantown, WV, USA

César Venero, Faculty of Psychology, Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain

CHAPTER 1

What is Cognitive Enhancement?

Veljko Dubljević[1,2,3], César Venero[4], and Shira Knafo[5] [1]Neuroethics Research Unit, Institut de Recherches Cliniques de Montréal (IRCM), Montréal, Canada [2]Department of Neurology and Neurosurgery, McGill University, Montreal, Canada [3]International Centre for Ethics in the Scienc and Humanities, University of Tübingen, Germany [4]Faculty of Psychology, Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain [5]IKERBASQUE, Molecular Cognition Laboratory, Unidad de Biofísica CSIC-UPV/EHU, Campus Universidad del País Vasco, Leioa, Spain

Abstract

"Cognitive enhancement" is commonly associated with drug use or the use of devices to improve cognition, technologies th have on the whole been established in laboratory animals or through a history of use in humans. In this chapter we aim to clar the concept underlying "cognitive enhancement" and to provide a brief overview of the current use of this term in the acaden literature, distinguishing the strategies to enhance cognitive function under normal conditions and the therapeutic strateg aimed at overcoming cognitive impairment. In addition, we will briefly review the various approaches to cognitive enhanceme 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, emergin and visionary biomedical technologies that intend to improve the cognitive status of animals ar human beings. As such, it offers the promise (or threat) of drastically changing the lives of citizen 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, ne brain stimulation technologies to alleviate pain and control mental focus, and highly sophisticate 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) they have already been used in humans (e.g., Dubljevic, 2013a). In this chapter, we will clarify what meant by the term "cognitive enhancement" as it is currently used in the academic literature ar provide an overview of the different issues addressed in this book.

In the most general sense, cognitive enhancement can be considered as the improvement performance related to cognitive tasks. The term "cognitive enhancement" is usually used witho clarifying any of the nuances associated with its meaning, yet it refers to a wide range of practices ar assumptions that impinge on other concepts. Indeed, this term is often defined distinctly in differe spheres, and for example, public health and epidemiological studies usually describe the use of drug for cognitive enhancement as the "non-medical use of prescription drugs," "drug misuse," or eve "drug abuse" (e.g., De Santis et al., 2008; Franke et al., 2010). On the other hand, contributions in th interdisciplinary bioethics literature regarding cognitive enhancement (e.g., Harris, 2011), as well in neuroscientific (e.g., Greely et al., 2008) and clinical journals (Larriviere et al., 2009), general

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

Different Classes of Cognitive Enhancement

The general definition of cognitive enhancement is usually articulated by its proponents, and althoug chiefly considered through the application of medical tools, it may involve a wider range approaches (e.g., computer technology, education, etc.). For example, "cognitive enhancement" commonly considered to be applied in healthy individuals, although this term has also been us historically in Alzheimer's research (see Chapter 9*)* and in research into neuropsychiatric illness involving cognitive impairment, such as schizophrenia and depression (see Chapter 10). In the pathologies, cognitive enhancement clearly refers to possible *therapeutic* interventions to improve t memory or cognitive function of patients. Thus, it is a term that is often used nonspecifically an sometimes, academic contributions consider both contexts together. This makes the normativ implications harder to define and, to some extent, may confuse the specific scientific questio underlying both these contexts. That is why "general improvement in cognitive performance" sometimes differentiated from "maintenance of cognitive performance" and from "augmente 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 dru (see Chapters 3 and 11) or devices (see Chapters 11 and 12) for non–health-related improvement cognition. This definition has the virtue of dissociating contexts that are socially encouraged fro those that are legitimately discouraged or even prohibited. The preventive, curative, rehabilitative, a compensatory uses of pharmaceutical drugs and devices are important elements in meeting heal needs. By contrast, the use of medical means to gain competitive advantage is an issue that mig cause social problems (please refer to Chapter 13 in which ethical issues are discussed) and, as suc 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 peop realized the potential of certain technologies, they began to consider the conceptual differenc between, say, vaccination and enhancement. That is not to say that new technologies have blurred th boundary themselves; rather, our attitude has shifted from taken-for-granted to the need to explai This is why it is useful to set apart the concept of enhancement that explicitly excludes medical nee from the *therapeutic* uses of the same technology (i.e., preventive, curative, rehabilitative, a compensatory). In this sense, it is also useful to clarify the extent of moral unease felt abo 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 detrimental per se but it might cause social problems if unregulated, the appropriate response is son form of discouragement (see Dubljevic, 2013a,b).

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

obscure a longer history of nonmedical drug use to enhance performance. Indeed, a group Australian authors (Bell et al., 2012) argued that the use of drugs for enhancement may even cross t border of illegal drug use (e.g., cocaine and amphetamines). This consideration adds normativ implications as prohibition would be the assumed regulatory response, which might not be ful justifiable on judicial grounds. For this reason, the use of medical drugs to enhance cognitive functio by healthy adults, such as Adderall (amphetamine) and Ritalin (methylphenidate, see Chapter 11), devices such those involving transcranial direct current stimulation (tDCS, see Chapter 12), has to b 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., wh capacity). The naive and undifferentiated term "cognitive enhancement" (as well as more popul terms for such enhancers, such as "smart drugs") suggests that the use of said stimulants general improves cognition, or even IQ. However, it is important to note that current evidence is contradicto with respect to the possible "enhancement" caused by currently available cognitive enhancers (se e.g., Ilieva et al., 2013). This has led some to conclude that the label "cognitive enhancement" may b a misnomer (see Vrecko, 2013). Accordingly, much like a drug undergoing clinical trials cann properly be called a "treatment" or "therapy" before its effectiveness has been proved, prescriptio stimulants should not be called "cognitive enhancers" until there is scientific proof that they actual 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 (s Chapters 9, 10, and 11), and recent reviews have highlighted the limited evidence supporting claims enhancement (see, e.g., Repantis et al., 2010). Obviously, we need a stricter definition of specif 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 cognitiv performance" and, as such, distinguished from "maintained cognitive performance." "Maintaine cognitive performance" refers to the prolongation of normal cognitive activity and a dampening of th effects of fatigue and sleep deprivation, for which there is strong evidence (see, e.g., Estrada et a 2012; Lagarde, 1995).

"General improved performance" has been analyzed as a descriptive that can be applied to cognitiv enhancement, and it has been rejected as unspecific, since it does not distinguish even the therapeut use of drugs and devices. On the one hand, "augmented cognitive performance" can be applied healthy adults using drugs or devices to improve general IQ, working memory, or accuracy of recal thereby achieving significantly better levels of cognitive functioning. On the other hand, "maintaine cognitive performance" refers to the use of drugs or devices that serve to maintain normal levels cognitive activity for longer periods of time, while reducing the impairment associated with fatigu and sleep deprivation. While the evidence supporting the former remains somewhat controversia current "cognitive enhancers" undoubtedly provide such maintenance effects, although some issu 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 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 assess claims of improved cognition. Since the benefits of cognitive enhancers should by definitio not involve the response to a clear pathology, lesion, or identified behavioral or mental heal problem, establishing the basal measures to evaluate the effects of enhancement is likely to l somewhat controversial. The studies carried out to date have examined the enhancement of exta neuropharmaceuticals (see Ilieva et al., 2013; Repantis et al., 2010) and brain stimulation technique such as transcranial magnetic stimulation (Luber and Lisanby, 2013) and tDCS (Dockery et al., 200 see Chapter 12), through the performance of specific tasks in controlled laboratory settings. Howeve critics point out that these tasks do not fully capture the effects on the more general capaciti underlying them or on other tasks (see Iuculcano and Cohen Kadosh, 2013; Ranisch et al., 201 Vrecko, 2013) and that cognitive enhancers should (also) be examined in the context of real-wor performance.

Possible Risks in the Use of Cognitive Enhancers

The nonspecific term "cognitive enhancement" has an in-built positive connotation that diver attention from the possible short-term and long-term risks or the side effects associated with usi drugs or devices to stimulate the brain for non-medical reasons and without any relevant knowledge supervision. Drugs such as ampakines (see Chapter 3) might augment cognitive performance in t sense of increasing general IQ, working memory or more accurate recall, yet perhaps they will n work in humans (Goff et al., 2008). Furthermore, these drugs might produce some side effects, or th may be harmless (Goff et al., 2008). Indeed, even "maintained cognitive performance" rais important ethical issues, depending on the potential side effects of the substances (or devices) us (see Dubljevic, 2012b; Ranisch et al., 2013; and Chapter 13). The issue of whether new "cogniti enhancers" are harmless like coffee or dangerous like amphetamines can only be resolved on research into the effects of new drugs (or devices) has delivered robust and reliable finding 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 loo in depth at a number of the traditional and cutting-edge technologies that are currently studied a 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 a therefore unlikely to be tested on human beings. Nevertheless, they provide precious insight into t 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 enhance is to identify the pathways involved in learning and memory, and to test activators specific to the pathways. In a second, often used approach, pathways leading to synaptic loss or cell death a identified and inhibited. A third approach described in this chapter relies on the activation of norm cell repair mechanisms to restore lost synapses.

Having understood the signaling pathways that globally modulate learning and memory, it essential to uncover the specific molecular and synaptic events mediating cognitive functio Accordingly, sophisticated molecular and electrophysiological tools are described in Chapter 3 bas 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 chapt also describes how synthetic compounds specifically engineered to boost synaptic transmission a plasticity positively affect cognitive capacity in a variety of experimental paradigms. Although th routine use of these drugs in humans is still a long way off, experiments in animals are encouragi and represent the first essential step for the selection of drugs for clinical trials. Together, Chapters and 3 provide valuable insights into the molecular mechanisms believed to induce cognitiv enhancement and how this knowledge can be used to develop new, mechanism-based drugs for use healthy humans or in individuals suffering from cognitive impairment. Nonetheless, drugs are n necessarily the optimal approach to enhance cognitive function.

Chapter 4 describes how control over the environment may represent a more physiological approac to cognitive enhancement, focusing on how the incredible plasticity of the brain is used to evol behaviors that accommodate the inherent uncertainty and probabilistic nature of the environment. Th plasticity requires a constant interaction between the genome and the environment, whereby the latt regulates the cell signals and functions that control gene expression. Such epigenetic mechanism represent ideal devices, as many transcription factors control neuronal structure and functio supporting the interplay between hippocampal and neocortical assemblies necessary for the formatio and modification of new and existing representations.

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

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

Chapter 7 describes another innovative approach that has become popular in the past decad Optogenetics is a method that permits real-time control of genetically defined neuronal populatio using light-sensitive proteins. This chapter shows how optogenetic tools can be used to gain ne insights into the way in which memories are formed, saved, and extracted. The incorporation optogenetic tools into the field of learning and memory has led to an important increase in o understanding of the networks underlying complex cognitive processes. Hence, this chapter focuses o 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. explains how multipotent stem cells within the adult brain play a critical role in cognition and t strategies to favor neural stem cell populations within key brain regions that are being developed enhance cognition in rodents. The relationship between neural stem cells and cognition in the health aging, and pathological brain and the molecular mechanisms by which stem cells may exert the effects on learning and memory are also addressed. Moreover, the brain's capacity for plasticity ar regeneration is reviewed, along with the potential role of endogenous neurogenesis and stem ce transplantation to augment this capacity.

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

Chapter 10 reviews different pharmaceutical treatments approved by the Food and Dru Administration to reverse or ameliorate neurocognitive deficits frequently found in sever neuropsychiatric disorders or those being tested in clinical trials. Crucially, cognitive deficits are times a core feature of such disorders. The chapter focuses on pharmacological treatments th effectively improve some aspects of cognition in certain neuropsychiatric illnesses, includin attention-deficit/hyperactive disorder, schizophrenia, bipolar disorder, posttraumatic stress disorde and depression.

Chapter 11 summarizes empirical data on the approaches to enhance cognitive capabilities humans using pharmaceuticals, nutrition, physical exercise, sleep, meditation, mnemonic strategie computer training, and brain stimulation. This chapter also describes the drugs that are currently bein used in patients suffering from Alzheimer's disease. Unfortunately, antidementia drugs offer onl minor benefits in cognitive function and none of them seem to have disease-modifying properties. Th mixed evidence for the efficacy of many pharmaceutical drugs currently used for cognitiv enhancement is summarized, while a growing body of evidence for several nonpharmacologic interventions indicates reliable cognition-enhancing effects. In this respect, Chapter 12 provid valuable data on the use of noninvasive brain stimulation for cognitive enhancement, such as tDC The evidence of the safety, beneficial impacts, and cost-benefit ratio of these techniques at th 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 on efficient cognitive enhancers are developed for human use. It starts by describing possible scenari that may currently sound unrealistic yet that serve to reflect on the danger of unregulated use cognitive enhancers. This chapter explains why and how authorities should strictly control th prescription of cognitive enhancers, adapting state laws to these new technologies.

To summarize, this book contains a vast amount of information regarding traditional and moder strategies aimed at enhancing cognitive function, both in animals and humans. The editors made a effort to make this book accessible to the general public, although some of the chapters may be mo scientifically oriented than others. Nevertheless, the general goal of this book is to bring together th 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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CHAPTER 2

Signaling Pathways Involved in Cognitive Enhancement

Thomas J. Nelson[1], *Miao-Kun Sun*[1], *and Daniel L. Alkon*[2] [1]Blanchette Rockefeller Neurosciences Institute, Morgantown, WV, USA [2]Blanchette Rockefeller Neurosciences Institute, Rockville, MD, USA

Abstract

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

Keywords

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

Introduction

Cognitive enhancement is a general strategy for treating the effects of conditions involving cogniti 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, whi not necessarily effecting a cure, can improve the quality of life for patients suffering such condition In a broad sense, however, cognitive enhancement also includes pharmacological and other means f increasing memory and cognitive capacity, targeting both cognitive disorders and normal mentatio Such drugs would be valuable even if effective treatments for specific disorders are eventually foun because arresting disease progression at a late stage of a neurodegenerative disease would be marginal value without some way of enhancing normal cognitive function and repairing th accumulated injuries to synaptic pathways and networks.

One approach to finding cognitive enhancers is to identify the molecular signaling pathways learning and memory and search for compounds that activate the relevant components of the pathwa These targets could include protein kinases, cell surface receptors, neural signaling mechanism components of synaptic transmission, or enzymes anywhere along the signaling pathway. Th approach could also involve stimulating enzymes involved in neurotransmitter synthesis, enhanci 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 synapt

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

In this chapter, we will review the signaling pathways involved in these two approaches. For eac approach, we will consider potential therapeutic agents that act on these pathways, mainly sma 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 direct activate mechanisms of memory and cognition and those that act indirectly by affecting performan or by activating stress mechanisms. Acute stress produces a generalized activation of neuronal activi and profound biochemical changes that can enhance (McGaugh and Roozendaal, 2002) or impa (Wang et al., 2013; Eagle et al., 2013; Lee et al., 2013) memory encoding and formation. Thus, stres and agents that induce stress, may be thought of in certain contexts as cognitive enhancers. F example, fear stress activates the basolateral complex in the amygdala, which is critically involved the storage of conditioned fear memories, but not spatial or declarative memories. Animals subjecte to threatening stimuli show increases in phospho-ERK2 (extracellular signal-related kinase 2) in th amygdala, which is associated with reduced inhibitory control of GABAergic interneurons, resultin in increased neuronal excitability (Martijena and Molina, 2012).

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

Glucocorticoid receptor agonists administered to the medial prefrontal cortex also enhance memo by effects on the noradrenergic system via G-protein coupled receptors that do not involve changes DNA synthesis (Barsegyan et al., 2010). As with catecholamines, cAMP-dependent protein kinase the proximate biochemical mediator of stress signaling (Schwabe et al., 2012). Although the amygda is not a storage site for spatial or declarative memories, glucocorticoid receptor stimulation in th basolateral amygdala can affect spatial memory via its neuronal projections to the hippocampus. Th cognitive enhancement effect of stress may also be due in part to increased exclusion of unrelate information (Henckens et al., 2009). It is important to mention, though, that stress reduc glutamatergic transmission and glutamate receptor surface expression in the prefrontal pyramid neurons (Wei et al., 2013), and also alters the production and survival of new neurons in th hippocampus (Schoenfeld and Gould, 2012). Stress also reduces levels of BDNF (Masi and Brovedan 2011), leading to a reduction of synaptic growth. These findings imply that stress has numero 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 bee known that calcium and other cations are involved in the signaling pathways of learning. Alkon an Rasmussen (1988) proposed a cellular model of cell activation that involved spatially discre responses to a stimulus mediated by calcium. Alkon et al. (1982) also identified changes in membra potassium currents during the retention of associative learning in the marine invertebrate *Hermissend crassicornis*. From these and many other experiments, it was clear that ion channels were critical 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 an memory. Bank et al. (1988) identified an increase in PKC in crude membrane fractions of CA hippocampus prepared from rabbits subjected to rabbit classical eyelid conditioning. This w correlated with focal increments of [^{3}H]phorbol-12,13-dibutyrate binding (Olds et al., 1989 Increased phosphorylation of PKC substrates was found following associative learning *Hermissenda* (Neary et al., 1981; Nelson et al., 1990). PKC was also found to regulate A-typ potassium channels, which had previously been associated with classical conditioning in *Hermissend* (Alkon et al., 1982) and rabbits (Alkon et al., 1988; Etcheberrigaray et al., 1992). Activation of PK with bryostatin 1 enhances learning and memory, while at the same time increasing the numbers mushroom spines, perforated postsynaptic densities, and double-synapse presynaptic bouto associated with spines. Ro 31-8220, an inhibitor of PKC, prevents these effects (Hongpaisan an Alkon, 2007). PKC activation was found to induce the synthesis of other proteins when given sever days before training (Alkon et al., 2005). This protein synthesis greatly decreased the number

training events required for memory acquisition in *Hermissenda* and prolonged retention from 7 m

to over 1 week, indicating a markedly reduced threshold for long-term consolidation.

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

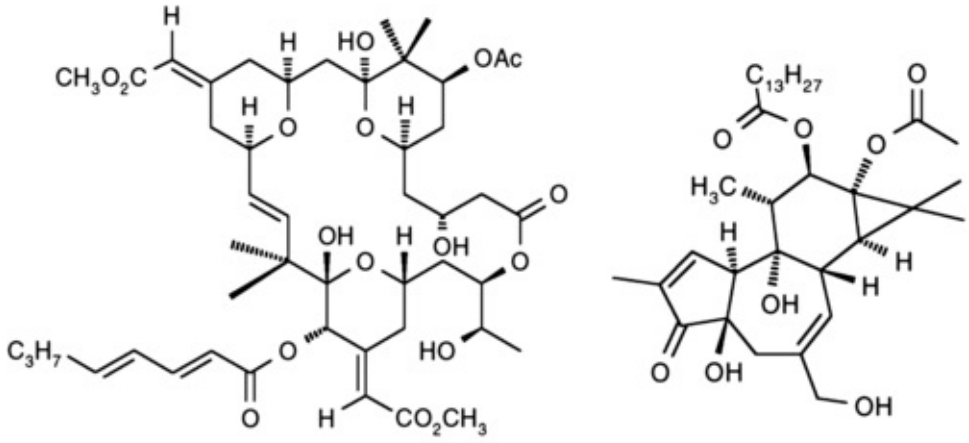
Bryostatin, phorbol esters, and similar PKC activators, such as ingenol and picologs, bind to t C1A and C1B domains on PKC (DeChristopher et al., 2012; Nelson and Alkon, 2009). The natur ligand for C1 domains is 1,2-diacylglycerol (Blumberg et al., 2008). Conventional PKC isoforms (βI, βII, and γ), and novel PKC isoforms (δ, ε, η, and θ) also possess a C2 domain, which bin phosphatidic acid and phosphatidylserine (Corbalán-Garcia et al., 2003; Conesa-Zamora et al., 200 These lipids have been implicated in neurite outgrowth and spine formation (Ammar et al., 201 Shirai et al., 2010), and artificial ligands of the PKC C2 domain, such as DCP-LA, have been shown restore mature mushroom spine synapses and prevent memory loss in aging rats (Hongpaisan et a 2013).

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

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

Other C1-Domain Proteins

PKC is not the only protein that possesses a C1 domain. Many other proteins bind 1,2-diacylglycer and possess homologous domains, including Rat sarcoma guanyl releasing protein 1 (Lorenzo et a 2000) and the Mammalian Uncoordinated (Munc)-13 family proteins (Wojcik and Brose, 2007). The proteins are all located in neurons and participate in dendritic growth and synaptic vesicle release, ar thus cannot be overlooked as potential neurological targets for bryostatin and similar cogniti 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 th cerebellum granule and Purkinje cells, where it regulates motor learning. The more abundant Munc1 1 isoform, which is expressed throughout the brain, is particularly interesting as a potential target f cognitive enhancers, because it is a synaptic vesicle c, colocalizing with the presynaptic mark synaptophysin (Augustin et al., 2001), and thus is well positioned to change synaptic efficiency. Bas et al. (2007) found that phorbol dibutyrate binding to Munc 13 lowers the energy barrier for synapt vesicle fusion. Diacylglycerol and phorbol esters augment neurotransmitter release in hippocamp 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 est produce beneficial morphological and behavioral effects, indicating potential value as cogniti enhancers (Hongpaisan et al., 2011, 2013). In Tg2576 and 5XFAD transgenic mice, often used models for familial Alzheimer's disease, DCP-LA prevents synaptic loss and cognitive defici (Hongpaisan et al., 2011). Bryostatin has similar effects (Hongpaisan et al., 2011, 2013; Sun an Alkon, 2005).

PKC Substrates

Many PKC substrates are also involved in cognitive and learning pathways. One is Myristoylate 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 i ability to crosslink F-actin, and triggering dendritic spine destabilization (Calabrese and Halpai 2005). PKC-induced spine destabilization can be prevented by creating a nonphosphorylatab MARCKS mutant. Dendritic spines are highly dynamic; over 80% of the F-actin in spines turns ov every minute (Koleske, 2013). Thus, PKC, in conjunction with signaling molecules that promo stabilization, may be preferentially involved in the early stages of dendritic restructuring duri development, or during adulthood when dendritic spines have largely stabilized.

Another PKC substrate important in cognitive function is GAP-43, a growth cone-associated prote that is essential for neurite outgrowth. Like MARCKS, GAP-43 interacts with actin filaments. Aft phosphorylation by PKC, GAP-43 promotes the stabilization of long filaments (He et al., 1997). PK activation increases the level of autophosphorylated CaMKII and promoted association with NMD receptors, possibly through phosphorylation of calmodulin-binding proteins such as neuromodul (Yan et al., 2011), indicating overlap of their signaling pathways, but there is little evidence of ar physiological direct phosphorylation. Although not fully understood, these interactions betwe signaling kinases such as CaMKII and PKC and cytoskeletal proteins such as actin modify th geometry of dendritic spines, and thereby directly change the function and connectivity of th 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 disea progression. The mature so-called mushroom spines are formed from an enlargement of thin spin during synaptic enhancement. The stability of these spines suggests, to many investigators, the involvement in long-term memory (Bourne and Harris, 2007). If so, an effective memory therap should restore the brain's capacity to form mushroom spines.

As mentioned above, changes in structural proteins, particularly actin, play an important role cognitive enhancement. A cytoskeletal change in dendritic spines is the most well establishe candidate for the biochemical localization of memory (Hotulainen and Hoogenraad, 2010; Kasai et a 2010). The rearrangement of the actin cytoskeleton is instrumental in synaptic maturation ar memory (Hotulainen and Hoogenraad, 2010). Spine length and morphology are modified by learnin and profoundly affect synaptic transmission. Defects in dendritic spine cytoskeleton are observed 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 cognitiv 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 bin and hydrolyze GTP. Perhaps the most important of these are the Rho GTPases. Rho is the name for family of small GTPases that regulate the actin cytoskeleton, including RhoA, Rac1, and Cdc4 (Ridley, 2006). Rac1 and Cdc42 are important for spine formation and growth, whereas RhoA important for spine loss (Newey et al., 2005). Rho proteins are therefore instrumental in regulatin synaptogenesis (Tolias et al., 2011).

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

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