Pharmacology, Biochemistry and Behavior 99 (2011) 113–115

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Editorial

Cognitive enhancers for the treatment of neuropsychiatric disorders: Clinical and preclinical investigations

In 2003, NIH outlined the Roadmap for Medical Research, an ambitious plan with the explicit goal to identify and support crosscutting and translational research agenda in the health sciences (Zerhouni, 2003). This roadmap encourages investigators to form close working relationships among basic and applied clinical sciences in order to identify and support crosscutting research objectives. The current issue on *Cognitive Enhancers for the Treatment of Neuropsychiatric Disorders: Clinical and Preclinical Investigations* is consistent with the NIH Roadmap initiative. We were fortunate to be able to recruit some of the foremost experts from various disciplines, ranging from basic, preclinical, and clinical areas, to review the current state of cognitive enhancers.

The appropriate application of cognitive-enhancing therapeutic drugs requires careful consideration of a broad spectrum of issues ranging from drug selection to dosing schedule, behavioral target, and the need for adjunct medications. Clinical trial and human laboratory studies currently are testing several lead compounds, and preclinical research is in the process of discovering new drug targets for cognitive enhancement. This special issue is dedicated to these endeavors as they apply to a variety of neuropsychiatric disorders. Content is divided into three sections: I. Basic Aspects of Cognitive Enhancement; II. Cognitive Enhancers in Preclinical Models of Neuropsychiatric Disorders; and III. Clinical Use of Cognitive Enhancers for Neuropsychiatric Disorders.

Section I begins with a lead article by Gary Lynch, Linda Palmer and Christine Gall that defines the problem, highlights controversies, and touches on ethical issues concerning the use of cognitive enhancers. The authors propose a three-category system for classifying cognitive enhancers and distinguish among agents that operate primarily on psychological state, through a specific neurobiological mechanism, or via the generation of new cognitive capabilities. A major translational theme that is explored is how to integrate animal and human studies on cognitive enhancement. The authors conclude their review by proposing that more empirical research is necessary to fully understand the consequences for society of introducing cognitive enhancers into healthy as well as diseased individuals. Three additional reviews on general topics of relevance to cognitive enhancement complete section I. The first of these by Tanya Wallace, Theresa Ballard, Bruno Pouzet, Wim Riedel and Joseph Wettstein concerns drug targets for cognitive enhancement. Several drug categories, including cholinergic, glutamatergic, serotonergic and dopaminergic agonists and antagonists, histamine H_3 antagonists, GABA A-α5 inverse agonists, glycine transporter inhibitors, and phosphodiesterases inhibitors are under investigation and in different stages of preclinical and clinical development. Of key importance for pro-cognitive effects of various agents is receptor subtype specificity, though it remains difficult to predict which drug targets will be most beneficial to patients. The authors conclude that as the detrimental effects on attention, learning, memory and executive processes differ across the various disorders, it is probable that future effective drugs will be directed towards a different molecular mechanism in each disorder. Next is a review by Edward Levin, Philip Bushnell and Amir Rezvani that focuses on attention-modulating effects of cognitive enhancers. Animal models (e.g., 5-choice serial reaction time task, signal detection task, and novel object recognition test) have been used to better understand the neuronal mechanism of attention and to develop new therapeutic treatments for attentional impairment. These models are used together with genetic, lesion, pharmacological and behavioral models of attentional impairment. Among the agents that improve attention in preclinical models are stimulants, nicotinic agonists, and histamine H_3 receptor antagonists. The authors caution that dose–effect functions need to be carefully assessed in testing drug effects on attentional function in animal models because all drugs which improve attention have an inverted U-shaped dose–effect function in which either lower or higher than optimal doses are less effective. In concluding remarks, the authors note that animal models of attention are valuable tools in developing novel attentional improving drugs and will become more valuable as the models continue to improve. Lastly, a review by Rafael Roesler and Nadja Schröder concerns memory-modulating effects of cognitive enhancers. Events involved in memory consolidation can be thought of as signifying either "core" mechanisms critical for synaptic modifications (e.g., glutamate receptor activation, CREB activation, and protein synthesis) or "modulatory" mechanisms critical for regulating memory strength (e.g., release of stress hormones, activation of noradrenergic and dopaminergic neuronal pathways). Focus of the review is on the latter and the authors suggest that research on the development of cognitive enhancers based on memory modulation should take into consideration the critical role of neurochemical systems within the basolateral amygdala in mediating enhancement of memory. The authors also point out that neuropeptides constitute a major class of signaling molecules within the brain and play a role in regulating learning and memory. As technology improves for the efficient delivery of peptidergic molecules to the brain, new targets for memory enhancement may emerge.

Section II provides a preclinical perspective on the use of cognitive enhancers for schizophrenia and other psychotic disorders, Alzheimer's disease and age-related memory decline, attention deficit hyperactivity disorder, fear and anxiety, and substance use disorders. The basis for this choice of disorders stems from the fact that these present with co-occurring neurocognitive changes. These changes are central to many of the maladaptive behaviors that characterize each disorder. Segev Barak and Ina Weiner tackle the issue of cognitive enhancers for schizophrenia through preclinical research. Typically, this research involves first treating

0091-3057/$ – see front matter
doi:10.1016/j.pbb.2011.02.006

an animal with a schizophrenia-mimetic drug (e.g. phencyclidine, scopolamine or amphetamine), and then comparing the effects of putative cognitive enhancers or antipsychotic drugs on several tasks considered to measure cognitive processes/domains that are disrupted in schizophrenia (the five choice serial reaction time task, sustain attention task, working and/or recognition memory, reversal learning, attentional set-shifting, latent inhibition and spatial learning and memory). Given that these models do not distinguish between the effects of cognitive enhancers and antipsychotic drugs, the authors conclude that there is a need to search for models that can differentiate between the actions of these two classes of drugs and several suggestions are offered. The review by Alvin Terry, Patrick Callahan, Brandon Hall and Scott Webster examines Alzheimer's disease and age-related memory decline. The currently available therapies designed to improve cognition in this domain are limited by modest efficacy, adverse side effects, and their effects on cognitive function are not sustained over time. In the development of pro-cognitive drugs for Alzheimer's disease and other forms of dementia, preclinical research mainly has utilized general behavioral tasks (e.g., radial arm maze, Morris water maze, Y-maze, passive avoidance, and delayed matching-to position) in animals genetically modified (e.g., ApoE knockout mice and 3xTG-AD mice), given lesions (e.g., in the nucleus basalis), administered drugs (e.g., scopolamine) or tested in old age. Several categories of drugs show pro-cognitive effects in these preclinical models and include novel cholinergic-based strategies, phosphodiesterases inhibitors, histamine H_3 receptor antagonists, and a variety of serotonin-based strategies. The authors present the idea that because Alzheimer's disease is a complex illness, a multiple drug target approach to therapy may be necessary. Use of single drugs with multiple actions would simplify the therapeutic regimen and improve compliance. Among the candidate therapeutics with these properties are Ladostigil (a brain specific inhibitor of MAO-A and MAO-B), Dimebolin (affects cholinergic, histaminergic, glutamatergic and serotonergic systems among other properties), and JWS-USC-75-IX (AchE inhibitor, M_2 autoreceptor antagonist). Amy Arnsten and Steven Pliszka review the relevance, from animal studies, of catecholamine influences on prefrontal cortical function for treatment of attention deficit hyperactivity disorder (ADHD). The critical role of postsynaptic α_{2A}-adrenoceptor and dopamine D_1-receptor activation for stronger prefrontal cortex regulation of attention, behavior, and emotion is highlighted. The authors conclude that improved understanding of catecholamine actions in the prefrontal cortex has led to new treatments for ADHD (e.g., guanfacine).

In contrast to daily treatment regimens with cognitive enhancers for schizophrenia, Alzheimer's disease and ADHD, the approach taken for the treatment of fear and anxiety or substance use disorders relies on isolated dosing with these agents in the context of cue-based extinction, an analog of exposure therapy in people. Gary Kaplan and Katherine Moore review the use of cognitive enhancers in animal models of fear extinction. The animal research literature is rich in its demonstration of cognitive-enhancing agents that alter fear extinction, including agents that act on GABAergic, glutamatergic, cholinergic, adrenergic, dopaminergic, and cannabinoid signaling pathways. The rationale behind this approach is that cognitive-enhancing therapeutics would facilitate extinction learning, a process that alters the association between conditioned fear cues and conditioned fear responses. Of note are findings to suggest that epigenetic mechanisms and neurotrophic factors may represent novel therapeutic targets for enhancing fear extinction (e.g., modification of brain-derived neurotrophic factor [BDNF] expression). The authors conclude that greater precision in our understanding of the effects of cognitive enhancers on functional and structural plasticity will result in the development of new and effective pharmacological approaches in fear extinction that may translate to exposure therapies for anxiety-related disorders. The use of cognitive enhancers for facilitating drug cue extinction in animal models is reviewed by Bríd Nic Dhonnchadha and Kathleen Kantak. Given the success of exposure therapy combined with a cognitive enhancer for reducing anxiety disorders, it is anticipated that this approach will prove more efficacious than exposure therapy alone in preventing relapse in individuals with substance use disorders. There is an abundance of evidence using preclinical animal models for improved treatment outcome for drug addiction (e.g. alcohol, amphetamine, cocaine, and heroin) when explicit extinction training is conducted in combination with acute dosing of a cognitive-enhancing therapeutic drug (e.g., glycine site agonists and transporter inhibitors, cystine-glutamate exchanger activators, and metabotropic glutamate receptor activators). The authors discuss the several factors that may be important to consider for successful translation of these findings to human substance abusers.

Section III presents the clinical perspective on the use of cognitive enhancers for neuropsychiatric disorders. Donald Goff, Michele Hill, and Deanna Barch review the literature on treating cognitive impairment in schizophrenia. Given the degree of cognitive impairment in patients with this debilitating disorder, the search for cognitive-enhancing agents is of particular importance. In their review, the authors examine agents that target the dopaminergic, glutamatergic, GABAergic, serotonergic, and/or the cholinergic system. Unfortunately, the empirical evidence for the efficacy of these agents has been generally disappointing. The authors call for novel paradigms that promote neuroplasticity (as exemplified by recent work with cognitive remediation) and neuroprotection (as exemplified by recent work with neurosteroids, antioxidants, and anti-inflammatory agents). Age-related cognitive deficits, Alzheimer's disease, and mild cognitive impairment are other obvious targets for cognitive enhancers. The review by Julie Dumas and Paul Newhouse presents a model that integrates cognitive aging with data from functional neuroimaging studies of aging and psychopharmacological manipulations of the cholinergic system. The authors propose that age-related changes in cognition are linked to cholinergic dysfunction and that cholinergic compensation causes alterations in task-related brain activity. It is suggested that the wide range of response to treatment seen in dementia patients may be due to variations in cholinergic deficit. Several recommendations for future studies are provided. The contribution by Cinnamon Bidwell, Joseph McClernon, and Scott Kollins reviews the role of cognition enhancers in the treatment of ADHD. The authors highlight the complexity of the multidimensional construct we refer to as *cognition* in the context of ADHD. In addition, they examine at depth both pharmacological (e.g., stimulants, atomoxetine, guanfacine, and nicotinic agonists) and non-pharmacological (e.g., working memory training and neurofeedback) methods aimed at improving cognitive processes in people with ADHD. Given that most clinical studies examining the effects of cognitive enhancers have limited the time course of investigation to acute effects, the authors suggest that there is considerable need for more sustained and systematic assessment of how cognition-enhancing interventions impact longer term functioning in those with ADHD.

The review by Stefan Hofmann, Anu Asnaani, Cassidy Gutner, and Michael Otto highlights the complexity of cognitive processes as they relate to anxiety disorders. Although cognitive behavioral therapy (CBT) is clearly an effective treatment for anxiety disorders, a sizeable number of patients remain symptomatic after the intervention. Combining conventional anxiolytic medication with CBT has led to disappointing results. More promising results have been reported when combining CBT with cognitive enhancers. Some of the agents that are reviewed include D-cycloserine, methylene blue, catecholamines (dopamine and norepinephine), yohimbine, modafinil, endocannabinoids, cortisol, and nutrients and botanicals (omega-3 fatty acids, caffeine, and nicotine). Of these agents, D-cycloserine appears to hold the most promise. The authors also put forth a hypothesis that the efficacy of exposure-based treatments can be enhanced with non-pharmacological strategies (e.g., aerobic exercise) that increase hippocampal BDNF, a marker of neuroplasticity. This may be particularly important for the treatment of anxiety disorders where there is a dysregulation of BDNF. Finally, the review by Kathleen Brady, Kevin Gray, and Bryan Tolliver examines cognitive enhancers for the treatment of substance use disorders. The review points to the importance of enhancing inhibitory

control and improving executive function to reduce attentional bias to drug-related cues when treating substance use disorders. Although the field is still at an early stage, preliminary studies suggest that cholinergic, noradrenergic, and glutamatergic agents show some promise for reducing craving. Notably, glutamatergic agents (e.g., D-cycloserine) may benefit substance use disorders by accelerating extinction of responses to drug-related cues. Agents that have anticonvulsant, anti-inflammatory or neuroprotective effects also may have pro-cognitive effects in addicts. The authors conclude that studies focused on combining cognitive-enhancing agents with specific psychosocial therapies to investigate potential synergistic effects are warranted.

In sum, the current special issue on cognitive enhancers is a snapshot of the current field across various disciplines. From these collective reviews, the similarity is striking in the drug targets that have been examined and those that have been proposed across multiple neuropsychiatric disorders. One possibility is that the discovery of safe and effective cognitive-enhancing therapeutic drugs resulting from research in one domain of investigation would seamlessly translate to the treatment of a variety of neuropsychiatric disorders that present with neurocognitive deficits. Also striking is the view from various disciplines that pharmacotherapy combined with non-pharmacological approaches that induce neuroplasticity may offer greater improvements for cognitive enhancement than either treatment alone. With these considerations in mind, our hope is that this special issue will stimulate further translational research and collaborations across various disciplines, consistent with the NIH Roadmap initiative.

Reference

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