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Evaluation of Noradrenergic α2a Agonist Guanfacine and Direct Electrical Stimulation on Enhancement of Working Memory and Cognitive Deficits in the Patients with Alzheimer's Disease

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Abstract

Recent works show the critical role of working memory deficits as a clinical and preclinical marker of Alzheimer's disease (AD). The prefrontal cortex (PFC) is among the most evolved brain regions, contributing to our highest order cognitive abilities. It regulates behavior, thought, and emotion using working memory. Many cognitive disorders involve impairments of the PFC. Alzheimer's disease adversely effects working memory performance. The α2A-adrenoceptor agonist guanfacine improves working memory performance in humans. Recent research has found that the noradrenergic α2A agonist guanfacine can improve PFC function by strengthening PFC network connections via inhibition of cAMP-potassium channel signaling in postsynaptic spines. Guanfacine is a sympatholytic drug now being used to treat a variety of PFC cognitive disorders.

The aim of this study is to review the efficacy of treatment with noradrenergic α2A agonist guanfacine and direct electrical stimulation on enhancing working memory and cognitive deficits in the patients with AD. We searched in medical databases with articles dated from 1974 to 2017.The results provided very promising ground on enhancement of working memory and cognitive deficits upon using guanfacine and PFC stimulation in AD patients. This study sheds light on the subject and suggests that more detailed future studies may be warranted to further investigate the ability of noradrenergic α2a agonist guanfacine and direct electrical stimulation on enhancement of working memory and cognitive deficits in AD patients.

Keywords: Noradrenergic α2A agonist guanfacine; Direct electrical stimulation; Working memory; Cognitive deficits; Alzheimer's disease

Introduction

Cognitive disorders are among the most challenging and disturbing ailments. They can alter who a person is, limit his or her success in school or work, interfere with friendships, impair the ability to care for themselves and others, and disrupt the lives of families and loved ones. Cognitive disorders involve dysfunction of the most highly evolved cortical regions, the association cortices, with particular vulnerabilities in the prefrontal cortex (PFC). The PFC is among the most evolved brain regions, contributing to our highest order cognitive abilities. It regulates behavior, thought, and emotion using working memory. Many cognitive disorders involve impairments of the PFC. Alzheimer's disease (AD) adversely effects working memory performance. In patients with AD, a continual functional decline is often seen. The decline often begins with the patient's inability to remember past events in time. As the disease progresses, cognitive decline continues with patients losing the ability to perform many activities of daily living.

Cognitive deficits associated with AD are known to result from decreases in acetylcholine within the cholinergic system of the medial septal area, which projects to the hippocampus. It is obvious that advances in treatment options for age associated cognitive decline and AD are needed to improve the lack of memory function associated with them. One potential approach to treatment of Alzheimer's might involve the pharmacological norepinephrine agonist, guanfacine, which has been shown to increase learning and memory in human studies. Accordingly, guanfacine administration might aid in improving long-term memory impairments seen in age associated cognitive decline and AD.

The α2A-adrenoceptor agonist guanfacine improves working memory performance in humans. Recent research has found that the noradrenergic α2A agonist guanfacine can improve PFC regulation of behavior, thought, and emotion by strengthening PFC

network connections via inhibition of cAMP-potassium channel signaling in postsynaptic spines [1]. Based on these discoveries in animals and humans, guanfacine is a sympatholytic drug now being used to treat a variety of PFC cognitive disorders. The PFC guides thought, actions, and emotion using representational knowledge [2,3]. Allowing us to marry the past to the future using working memory [4,5]. Arnsten and Jin [6]. Documented that guanfacine may be useful for a breadth of PFC cognitive disorders. The aim of this study is to review the efficacy of treatment with noradrenergic α2A agonist guanfacine and direct electrical stimulation on enhancing working memory and cognitive deficits in the patients with AD. We searched in medical databases with articles dated from 1974 to 2017.

Therapeutic Effects of Guanfacine on Cognitive Disorders

PFC microcircuits interconnect on dendritic spines, where they excite each other via glutamate release onto N-methyl-D-aspartate receptors [7]. These synaptic connections appear to be the target of many neuron modulatory systems, which can dynamically increase or decrease the strength of connections to coordinate cognitive capacity with arousal state [7,8]. For example, intracellular calcium and cAMP signaling can open potassium channels to rapidly weaken a network connection and reduce cell firing [9-11]. Alpha-2 adrenergic receptors are localized next to these potassium channels on spines, and α-2A agonists, such as guanfacine, inhibit cAMP signaling, close these potassium channels and strengthen PFC connectivity [9]. These enhancing effects have now been observed in humans [12]. and have been observed as enhanced PFC activity in imaging studies of humans [13,14]. In 2010, Arnsten [8]. showed that α-2A agonists are generally safe and the stimulation of postsynaptic α-2A receptors on PFC dendritic spines strengthens PFC network connections by inhibiting cAMP and closing ion channels that hyperpolarize the spine and reduce network firing.

Importantly, the α-2A agonist guanfacine can enhance dorsolateral PFC function. Noradrenergic α2A agonist guanfacine inhibits norepinephrine release, cAMP-signaling and HCN potassium channel function, which in turn is thought to normalize the balance of norepinephrine and dopamine between the amygdala and PFC (i.e., the PFC–amygdala axis), thus reducing stress reactivity and improving cognitive function. In animals and humans, the behavioral effects of adrenergic agents are presumed to involve neuron modulation of the PFC, consistent with the demonstrated actions of dopaminergic agents. In a study conducted in 2017, Sandiego et al. [15]. evaluated the effect of treatment with noradrenergic α2A agonist guanfacine on dopaminergic tone in tobacco smokers and their finding was indicative of an overall increase in dopamine levels after 3 weeks of guanfacine treatment. Alpha-2 adrenergic agonists, such as guanfacine, may be particularly helpful in patients with symptoms of PFC dysfunction, such as impaired working memory.

The noradrenergic system, and specifically, α2 adrenergic receptors, plays an important role in cognitive functions such as memory, learning and attention [16]. and this is particularly true in the PFC [17]. Pharmacological manipulation of this system for improvement of attention and memory has received considerable attention [18]. Alpha-2A agonists, such as guanfacine, is also being tested in adult PFC cognitive disorders, and has been found to be helpful in patients recovering from parietal cortex strokes [19]. or encephalitis [20]. Where strengthened PFC abilities are thought to facilitate attention and cognition. Guanfacine is also being tested in normal elderly subjects, as PFC cognitive abilities decline early in the aging process in humans [21]. Alpha-2 adrenergic receptor agonists have been suggested as potential therapeutics for a variety of cognitive disorders including "normal" age-related cognitive decline, pathological memory disorders and attention deficit disorder [22].

Beneficial effects of α-2 adrenergic agonists on attention and working memory have been reported in a variety of animal models [23]. In particular, the noradrenergic agonists guanfacine and clonidine have been proposed as potential therapeutic agents for treating age-related cognitive problems as well as certain conditions (e.g., attention-deficit/hyperactivity disorder, schizophrenia, Parkinson's disease) that present with cognitive disturbances [24,25]. It has been shown that guanfacine can also improve working memory in patients with schizotypal disorder with cognitive deficits resembling those in schizophrenia [26]. And it improves PFC function and metabolism in patients with some forms of epilepsy [13]. In addition, Abela and Chudasama [27]. examined the effect of local ventral hippocampus infusions of guanfacine and other neuron pharmacological agents on behavioral decisions that involve a trade-off between reward size and delay and their results provided the first evidence that guanfacine may derive its clinical benefits through hippocampus stimulation, via α2A-adrenergic receptors. However, there are few studies which have used noradrenergic α2A agonist guanfacine to enhance working memory in the patients with AD.

Working Memory in Patients with Alzheimer's Disease

While the PFC is not the only brain region where cognitive functions are processed, a majority of human imaging studies indicate the PFC as the main site of working memory processing [28]. The concept of working memory was initially proposed by Baddeley & Hitch [29] and developed by Baddeley [30]. Working memory was defined as comprising a number of different subsystems, each related to the specific nature of the information to be processed. It is characterized by the assumption that short-term storage of information must be considered as part of a more complex system involved in the execution of a specific task. The information is stored in the working memory as long as necessary and the structure need not be defined only in terms of the dichotomy between short- and long-term information storage. Recent works show the critical role of working memory deficits as a clinical and preclinical marker of AD. Kessels et al. [31].

examined verbal working memory in both cognitively unimpaired older people and mild cognitive impairment and AD

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patients and their findings showed that working memory deficits are already present in patients with mild cognitive impairment and worsen in AD patients, suggesting that working memory should be assessed as part of neuropsychological testing. Despite the fact that some authors [32] have questioned a primary function of working memory in mind operations, the working memory approach assumes that the system is involved in all cases when some information must be temporarily maintained and processed, and thus is capable of performing virtually all types of cognitive task-thought, verbal comprehension, or mental imagery. Recent works evince the critical role of visual short-term memory short-term memory binding deficits as a clinical and preclinical marker of AD.

These studies suggest a potential role of posterior brain regions in both the neurocognitive deficits of Alzheimer's patients and short-term memory binding in general. Decamp et al. [33] investigated the effects of the alpha-2 adrenoceptor agonist guanfacine on attention and working memory in aged non-human primates trained to perform an attention task with no working memory component and a spatial working memory task with minimal attention demands. Their findings showed that guanfacine may have a preferential effect on some aspects of attention in normal aged monkeys and in doing so may also improve performance on some working memory tasks that have relatively high attention demands [33]. Moreover, Tharp [34] evaluated the effects of the norepinephrine agonist, guanfacine, on scopolamine-induced memory impairments in the rat and the results from his study indicated that guanfacine may be effective at improving memory impairments caused by decreased acetylcholine function as seen in AD.

Therapeutic Effects of Direct Electrical Stimulation on Cognitive Deficits

Electrical stimulation has been used both for clinical purposes and to causally probe brain mechanisms. Previous evidence of electrical currents spreading through white matter along well defined functional circuits indicates that visual working memory mechanisms are sub served by a specific widely distributed network. In a study conducted by Birba et al. [35] in 2017, the authors evaluated the enhanced working memory binding by direct electrical stimulation of the parietal cortex and their findings showed that that direct stimulation of the parietal cortex induced a selective improvement in short-term memory. Cheng et al. [36] investigated whether transcranial direct current stimulation (tDCS) would enhance the effects of working memory training in older adults with mild neurocognitive disorder due to AD, but they could not reach a conclusion in this regard. However, in 2015, Nikolin et al. [37] showed that high definition tDCS to the left dorsolateral PFC facilitates the rate of verbal learning and improved efficiency of working memory may underlie performance effects and this method has potential for enhancing cognitive functioning. Although working memory training programs consistently result in improvement on the trained task, benefit is typically short-lived and extends only to tasks very similar to the trained task (i.e., near transfer).

It is possible that pairing repeated performance of a working memory task with brain stimulation encourages plasticity in brain networks involved in working memory task performance, thereby improving the training benefit. In 2016, Trumbo et al. [38] investigated the working memory performance via tDCS and their results suggested that working memory training paired with brain stimulation may result in cognitive enhancement that transfers to performance on other tasks, depending on the combination of training task and tDCS parameters used. Brunoni and Vanderhasselt [39] performed a systematic review and meta-analyses on non-invasive brain stimulation studies assessing the n-back task, which is a reliable index for working memory and their findings showed that repetitive transcranial magnetic stimulation of the dorsolateral PFC significantly improved all measures of working memory performance whereas tDCS significantly improved the response time, but not the percentage of correct and error responses. In review conducted in 2017, Papagno [40] studied cognitive functions by means of direct electrical stimulation and reported that direct electrical stimulation has relevant advantages in detecting the neural correlates ofcognitive functions and itallows studying brain connectivity.

Conclusion

Only a few studies in the literature have evaluated noradrenergic α2a agonist guanfacine and direct electrical stimulation on enhancement of working memory and cognitive deficits in the patients with AD. This study sheds light on the subject and suggests that more detailed future studies may be warranted to further investigate the ability of nor adrenergic α2a agonist guanfacine and direct electrical stimulation on enhancement of working memory and cognitive deficits in AD patients.

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