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Review

Therapeutic potential of histaminergic compounds in the treatment of addiction and drug-related cognitive disorders

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HIGHLIGHTS

- Addictive drugs cause cognitive deficits that compromise treatment outcome.
- Histamine H_3R antagonists/inverse agonists have cognition enhancing properties.
- H_3R blockade can attenuate the rewarding effects of opioids and alcohol.
- Several H_3R antagonists/inverse agonists have proven to be safe in humans.
- H_3R inverse agonists may be useful for the treatment of drug addiction.

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ABSTRACT

Addiction is a behavioral disorder characterized by the compulsive seeking and taking of drugs despite serious negative consequences. In particular, the chronic use of drugs impairs memory and cognitive functions, which aggravates the loss of control over drug use and complicates treatment outcome. Therefore, cognitive enhancers targeting acetylcholine have been proposed to treat addiction. Interestingly, histamine H_3 receptor (H_3R) antagonists/inverse agonists stimulate acetylcholine transmission in different brain areas, facilitate memory in animal models and can reverse learning deficits induced by drugs such as scopolamine, dizocilpine and alcohol. Moreover, several studies found that compounds capable of activating the histaminergic system generally decrease the reinforcing effects of drugs, namely alcohol and opioids, in preclinical models of addiction. Finally, several H_3R antagonists/inverse agonists increase histamine in the brain and have proven to be safe in humans. However, no studies have yet investigated the therapeutic potential of cognitive enhancing H_3R antagonists/inverse agonists in the treatment of addiction in humans. The present review first describes the impact of addictive drugs on learning processes and cognitive functions that play an important role for addicts to remain abstinent. Second, our work briefly summarizes the relevant literature describing the function of histamine in learning, memory and drug addiction. Finally, the potential therapeutic use of histaminergic agents in the treatment of addiction is discussed. Our review suggests that histaminergic compounds like H_3R antagonists/inverse agonists may improve the treatment outcome of addiction by reversing drug-induced cognitive deficits and/or diminishing the reinforcing properties of addictive drugs, especially opioids and alcohol.

Contents

1. Introduction 358
2. Addictive drugs impair cognitive processes 358
   2.1. Cognitive processes related to hippocampal activity 358
   2.2. Cognitive processes dependent on prefrontal cortex function 359
3. Histaminergic drugs improve cognitive processes 360
   3.1. Cognitive processes related to hippocampal activity 360
   3.2. Cognitive processes dependent on prefrontal cortex function 361

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4. Therapeutic potential of histaminergic compounds in the treatment of drug addiction 361
4.1. Histamine and cognitive deficits induced by drugs 361
4.2. Histamine and the rewarding properties of drugs 362
5. Clinical implications and future directions 363
Acknowledgements 364
References 364

1. Introduction

Drug addiction is characterized by the loss of control of drug consumption despite the occurrence of serious negative consequences [1]. Relapse represents a major issue in this disorder since it refers to the sudden resumption of drug taking in addicts that were abstinent for long periods. Numerous studies have demonstrated that specific associative learning processes play a central role in drug relapse. Through these learning processes, the stimuli or cues present in the environment where the drug is consumed progressively gain control over behavior and can precipitate relapse in humans and in animal models of addiction [1,2]. Cognitive therapies are based on the view that drug addicts must learn to resist the control that drug-associated stimuli can take over behavior and eventually cause relapse. In other words, when drug-associated stimuli elicit cravings in addicts, they need to actively inhibit behaviors leading to drug consumption. What complicates the treatment of drug addiction is that many addictive drugs such as psychostimulants, opioids and alcohol impair cognitive functions essential to remain abstinent [3,4]. Therefore, drugs with cognitive enhancing properties, such as cholinergic, glutamatergic or noradrenergic compounds, have been proposed to treat drug addiction [5–8]. Interestingly, histamine has been shown to improve learning and memory processes, in part by modulating the release of acetylcholine in relevant brain areas [9,10]. In this regard, several histamine H_3 receptor (H_3R) antagonists/inverse agonists capable of activating histaminergic neuron activity facilitate learning in animal models and can reverse learning deficits induced by drugs such as scopolamine and dizocilpine [11]. Importantly, some of these histaminergic compounds have already been scheduled for testing in humans [12–14]. In addition to its effect on cognitive function, activation of the histaminergic system generally decreases the reinforcing properties of addictive drugs such as alcohol and opioids [15]. However, to date, no studies have investigated the therapeutic potential of H_3R antagonists/inverse agonists to treat drug dependence in human addicts.

The aim of the present review is to present evidence supporting that histaminergic compounds could be useful to treat drug addiction by reversing cognitive disorders caused by the chronic use of drugs and by decreasing their reinforcing properties. First, we will present an overview of the cognitive processes that are affected by the prolonged intake of drugs of abuse. Second, we will inform the reader about the studies showing that activation of the histaminergic system improves memory and decreases reinforcement processes. In addition, we will summarize the brain mechanisms through which histamine affects memory and drug reward. Finally, the therapeutic potential of H_3R antagonists/inverse agonists in the treatment of addiction will be discussed.

2. Addictive drugs impair cognitive processes

The chronic consumption of addictive drugs causes neurobiological alterations affecting multiple brain regions that eventually lead to cognitive and behavioral impairments. In the present review, we will focus on neuronal deficits in the hippocampus and prefrontal cortex because these cortical areas underlie cognitive processes particularly important for addicts to remain abstinent [3,4]. In addition, in the following section, we will present evidence showing that histaminergic compounds exert their cognitive enhancing properties through the modulation of neural activity in these two brain regions. Table 1 proposes an overview of the cognitive deficits caused by chronic drug consumption in animal models of cognition and confronts the results with data obtained with histaminergic compounds.

2.1. Cognitive processes related to hippocampal activity

Learning and memory processes play an important role in the strategies addicts have to develop to remain abstinent. In particular, the former drug user must constantly be able to remind himself that the consumption of drugs is excluded even if he is under stress or in the presence of drug-related cues causing intensive craving [2]. The hippocampus supports multiple forms of memories, such as acquisition and retrieval of spatial and declarative memory and associations between stimuli [16]. These memory processes depend in part on molecular mechanisms of neuroplasticity, namely long term potentiation (LTP), which is mediated by the activation of glutamate AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and NMDA (N-methyl-D-aspartate) receptors in hippocampal CA1 neurons. Accordingly, facilitation of excitatory transmission in the hippocampus has been shown to account for the cognition enhancing properties of pharmacological compounds [17]. The integrity of this brain structure is essential for the former drug addict to store and retrieve information necessary to cope with situations that can trigger relapse. Unfortunately, virtually all addictive drugs interfere with hippocampal activity. In a recent study, Gould et al. showed that nicotinic acetylcholine receptor agonists like varenicline can improve working memory in rhesus monkeys with a history of cocaine self-administration and this amelioration was mediated, at least in part, through nicotinic receptors located in the hippocampus [18]. Consequently, former drug abusers could benefit from the cognitive enhancement induced by activation of the hippocampal network in order to maintain abstinence.

Repeated cocaine intake induces various hippocampus-related deficits that have been extensively reviewed by Canales [19]. From a neurocognitive point of view, cocaine abusers, even when abstinent, show deficits in a variety of verbal tasks, as well as in working memory and visuo-spatial tests [20–22]. In animals, chronic cocaine treatment leads to impaired object recognition and induces deficits in the Morris water maze task [23,24]. Performance in spatial learning tasks like the Morris maze highly depends on the functional integrity of the hippocampus and more specifically the cholinergic septohippocampal pathway [16,25]. Interestingly, in a recent study, maladaptive changes in cholinergic neurotransmission have been observed in the prefrontal cortex, hippocampus and amygdala of cocaine-addicted subjects, suggesting a role for acetylcholine in the cognitive deficits observed after chronic cocaine