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Clinical Neuroscience Research 5 (2005) 147–150

Clinical Neuroscience Research

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New directions pharmacotherapy for addiction or can we forget to be addicted?

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Abstract

Addiction is characterized by an uncontrollable drive to obtain drugs and reduced drive to seek biological rewards. These behavioral changes result from enduring neuroplasticity in brain circuits that underlie motivation and the initiation of adaptive behaviors. In most cases, the pharmacological treatments have been only modestly successful or failed to alter the cardinal features of addiction. However, recent advances in the neurobiology of synaptic plasticity, and in particular plasticity elicited in animal models of addiction, provide novel potential pharmacological targets for treating addicts. Since addiction results from pathological forms of neuroplasticity, it is proposed that targeting and normalizing these adaptations may more effectively ameliorate the behaviors that characterize addiction than current pharmacotherapies.

Keywords: Addiction; Relapse; Cocaine; Prefrontal cortex; Glutamate; Dopamine; Neuroplasticity

1. Introduction

Drug addiction is defined by two key criteria, the irresistible drive to obtain drug and a decreased drive for natural reward [1]. The fact that these characteristics can remain after years of drug abstinence indicates enduring neuroplastic adaptations in the brain resulting from a combination of repeated drug use, learned associations with the pharmacological effects of drugs of abuse, and genetic vulnerability to drug-induced neuroplasticity [2]. While still incomplete, there is a maturing body of knowledge on the cellular mechanisms mediating long-term alterations in the strength of the synaptic transmission, including changes in synapse morphology, transmitter release and postsynaptic signaling [3–5]. Using this literature as a guide, recent studies have begun to elucidate the cellular mechanisms of the enduring neuroplasticity associated with animal models of addiction, in particular cocaine addiction [6,7].

Conventional treatments for addiction have arisen from knowledge of the acute pharmacology of the drug (e.g. dopamine and opioid-related drugs), or serendipitous observations of modest efficacy when treating psychiatric disorders that are co-morbid with addiction (e.g. anti-depressants, antianxiety drugs) [2]. Alternatively, certain drugs, such as indirect and direct GABA agonists (e.g. anticonvulsants, muscle relaxants) have proven modestly effective in some studies, probably by virtue of a general reduction in motivational drive [8,9]; although enduring drug-induced adaptations in GABA transmission may also be targeted by GABAergic drugs [10]. Thus, for the most part, current treatments for drug addiction do not target the underlying biological pathology, which probably resides in enduring neuroplastic changes in excitatory transmission, including both the regulation of glutamate release by other transmitters, as well as adaptations within the glutamatergic synapse. In as much as addiction is the result of neuroplasticity arising from a complex interplay between drug pharmacology, environmental associations made with the drug and the genetic vulnerability, examining the cellular mechanisms of neuroplasticity in general, and in particular those elicited by repeated use of drugs of abuse could yield potential pharmacotherapies that target the biological pathology mediating addiction. Indeed, by targeting and ameliorating the neurobiological pathology that underlies addictive behavior, it may be possible for addicts to forget to be addicted.

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1566-2772/$ - see front matter
doi:10.1016/j.cnr.2005.08.010

2. Reported findings and analysis of topics

2.1. Where to look in the brain for relevant addiction-related neuroplasticity

Neuroimaging studies provide the most relevant information regarding the brain regions most likely involved in addiction, in particular those brain circuits mediating the initiation of drug-seeking and relapse. While the imaging literature is reviewed in detail elsewhere, it is now clear that among the prime candidates are allocortical regions such as the amygdala, and prefrontal regions such as the ventral orbital cortex and anterior cingulate cortex [1]. All of these regions send dense glutamatergic projections to the limbic portions of the basal ganglia, in particular the nucleus accumbens [11]. Thus, neuroimaging drug addicts in unstimulated conditions reveals a general reduction in metabolic activity and blood flow in the prefrontal cortex, but after being challenged with stimuli that induce craving, these same areas show a marked enhancement in activity.

In animal models of drug-seeking, more detailed evaluations of the neural circuitry underlying the initiation of craving and relapse are possible [12]. Employing these models has confirmed the clinical neuroimaging studies and verified critical involvement of glutamate release in the pathway from the prefrontal cortex to the nucleus accumbens, as well as regulation of the prefrontal cortex by dopamine transmission [13]. Thus, blocking glutamate receptors in the accumbens or dopamine receptors in the prefrontal cortex inhibits the initiation of drug-seeking in animal models, marking the prefrontal—accumbens pathway as a strong candidate site for identifying relevant neuroplastic changes that may mediate relapse to drug-seeking.

2.2. Cellular changes in the prefrontal cortex that mediate drug-seeking

The prepotent involvement of dopamine transmission in the prefrontal cortex in initiating drug-seeking indicates that cellular plasticity in dopamine receptors or receptor signaling may be a relevant site of intervention. Notable in this regard is a marked reduction in signaling through dopamine D2 receptors in animals withdrawn from cocaine administration. This reduction arises from a decrease in G protein coupling as a result of the cocaine withdrawal mediated rise in a G protein binding protein called AGS3 [14]. When the content of this protein is elevated, there is a selective decrease in signaling through receptors that couple with Giα. Thus, while the cocaine-induced increase in AGS3 markedly decreases the efficacy of D2 receptor signaling, it is without effect on D1 receptor coupling. Based upon a recent analysis and modeling of data in the literature [15], this relative increase in D1 signaling in prefrontal cortex would be predicted to focus behavior on very strong, motivationally relevant stimuli, and reduce responding for other stimuli. In addicts, drug-associated stimuli provide particularly strong motivational incentive as a result of constant pairing of the stimuli with drug-induced dopamine release [16], and the relative increase in D1 signaling would be hypothesized to focus behavioral output initiated drug-related stimuli (e.g. drug-seeking). If this hypothesis were true, returning the levels of AGS3, and correspondingly D2 receptor signaling, to normal should prevent the initiation of drug-seeking in animal models. Using an antisense oligonucleotide strategy, the levels of AGS3 in the prefrontal cortex of cocaine withdrawn rats were restored to normal values, and the ability of a cocaine priming injection to induced drug-seeking was abolished [14]. Drug-seeking could then be restored by removing the mRNA block and allowing AGS3 to return to its cocaine-induced elevated levels. These data point to targeting a specific protein, AGS3, in treating the tendency of addicts to focus inordinate amounts of behavioral drive on drug-seeking and relapse to drug-taking. Given the physiological model of dopamine regulation of prefrontal cortex outlined by Seamans and Yang [15], reversing AGS3 would be expected to facilitate the ability of an addict to behaviorally orient towards non-drug related rewards and incentives.

2.3. Cellular changes in the nucleus accumbens that mediate drug-seeking

Glutamate release into the nucleus accumbens from the prefrontal cortex is necessary to initiate drug-seeking in animal models of relapse [6]. Thus, there is a large release of synaptic glutamate in the accumbens that initiates drug-seeking, and studies have shown that this release arises in part from neuroplasticity in the proteins that regulate the release probability of synaptic glutamate. Notably, adaptations have been measured in the group II metabotropic glutamate receptors (mGluR2/3) that function as inhibitory autoreceptors, and in the cystine–glutamate exchanger which provides extracellular glutamatergic tone to mGluR2/3 [17,18]. As a result of these cellular adaptations, there is a reduction in presynaptic inhibitory tone on the release of glutamate, and when prefrontal cortical neurons send action potentials to the nucleus accumbens there is an increased probability of releasing glutamate [19]. Importantly, restoring tone on the mGluR2/3 receptors, either by increasing cystine–glutamate exchange or by administering a mGluR2/3 agonist, inhibits the reinstatement of drug-seeking in animals withdrawn from cocaine self-administration [18,20]. Recently, a small clinical trial in cocaine addicts was conducted using *N*-acetylcysteine to activate cysteine–glutamate exchange [21]. In this trial, *N*-acetylcysteine was shown to be beneficial at reducing arousal and self-reported cocaine craving induced by cocaine-associated visual stimuli. Thus, directly targeting pathological alterations in the presynaptic regulation of glutamate

release in the accumbens prevented drug-seeking in animal models and was shown somewhat effective at reducing craving in cocaine addicts in a small double-blind clinical trial.

In the in vitro neuroplasticity literature, there has been a primary emphasis on changes in postsynaptic signaling and dendritic architecture induced by changing synaptic activity [3,4]. Similarly, recent studies indicate that postsynaptic changes in glutamate synapses may be critical sites of clinically relevant neuroadaptation in addiction. For example, there are marked dendritic dysmorphisms in the nucleus accumbens produced by the repeated administration of opioids and psychostimulants [22,23]. These morphological changes may be the result of neuroplastic changes in three proteins found in relatively high abundance in the postsynaptic membrane of excitatory synapses, including PSD-95, Homer and F-actin. While the levels of PSD-95 and Homer1bc are reduced after withdrawal from cocaine, the level of F-actin is increased [24–26]. The reduction in PSD-95 was associated with increased synaptic and behavioral plasticity induced by cocaine, while the reduction in Homer has been linked to a number of alterations in postsynaptic signaling, presynaptic glutamate release, as well as cocaine-induced behaviors [24,27]. Similarly, the increase in F-actin was associated with the expression of motor plasticity produced by repeated cocaine administration [26], and given the important role of actin in the formation and retraction of dendritic spines [28], increased F-actin is hypothesized to underlie the drug-induced dendritic dysmorphisms. While none of these proteins has yet been examined in animal models of drug-seeking, all three constitute potential targets for the development of drugs that may ameliorate pathological neuroplasticity associated with addiction.

3. Discussion

A number of cellular changes are outlined above that appear to regulate drug-seeking behavior in animal models of addiction. Moreover, one adaptation, the reduction in cystine–glutamate exchange, has been targeted in a small clinical trial with cocaine addicts which documents potential therapeutic benefit. This latter clinical trial benefited from the off-label use of *N*-acetylcysteine, a drug currently used to restore glutathione levels in situations such as in treating acetaminophen overdose [29]. In contrast, the other potentially important neuroadaptations identified in preclinical studies were targeted with rather exotic mechanisms and delivery systems not currently available for clinical use (e.g. viral transfection, membrane permeability fusion proteins, antisense oligonucleotide infusions). Given that most of the proteins identified are intracellular proteins, the ability to target these sites in a clinically acceptable manner is currently remote, and highlights the critical need for developing safe mechanisms for delivering compounds to intracellular compartments if we are to ameliorate psychiatric disorders that involve neuroplastic adaptations.

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