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Review

Glutamatergic medications for the treatment of drug and behavioral addictions

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ABSTRACT

Historically, most pharmacological approaches to the treatment of addictive disorders have utilized either substitution-based methods (i.e., nicotine replacement or opioid maintenance) or have targeted monoaminergic or endogenous opioidergic neurotransmitter systems. However, substantial evidence has accumulated indicating that ligands acting on glutamatergic transmission are also of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling. The purpose of this review is to summarize the pharmacological mechanisms of action and general clinical efficacy of glutamatergic medications that are currently approved or are being investigated for approval for the treatment of addictive disorders. Medications with effects on glutamatergic transmission that will be discussed include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. We conclude that manipulation of glutamatergic neurotransmission is a relatively young but promising avenue for the development of improved therapeutic agents for the treatment of drug and behavioral addictions.

Contents

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1. Introduction

Drug addiction, defined by the American Psychiatric Association as *substance dependence* (American Psychiatric Association, 2002), has numerous maladaptive psychological and behavioral manifestations including: loss of control over drug intake, taking drugs in greater quantities than intended, repeated unsuccessful attempts at quitting or reducing drug use, continued drug use despite negative consequences, and the emergence of drug-specific symptoms of tolerance and/or withdrawal. In addition to numerous intangible humanistic factors such as the disruption of families and interpersonal relationships, social dysfunction, and loss of life, the socioeconomic burden that drug addiction places on society is enormous (Cartwright, 2008; Gilson and Kreis, 2009; Malliarakis and Lucey, 2007; Rehm et al., 2009; Spanagel, 2009; Thavorncharoensap et al., 2009). In recent years it has become evident that the neural substrates underlying addiction to drugs of abuse overlap considerably with those of non-drug "behavioral" addictions (i.e., pathological gambling, pornography/internet addiction, etc.) (Grant et al., 2010a).

To date, medications that have been developed to aid in the treatment of addictive disorders have shown only moderate success. Known barriers that compromise the efficacy of medication-based approaches to treatment to addiction disorders include poor medication compliance, adverse side effects, safety issues, variable medication responses within treatment groups, poor integration of medication management into psychosocial or cognitive-behavioral therapies, inaccessibility to medications or adequate health care, and relapse following discontinuation of the therapeutic medication (Koob et al., 2009; Montoya and Vocci, 2008; O'Brien, 2008; Ross and Peselow, 2009; Zahm, 2010). While numerous medications of various classes that have been approved for other medical conditions are currently being investigated as potential aids in the treatment of addictive disorders, the only medications approved specifically for the treatment thus far in the United States are varenicline, buproprion, and nicotine replacement therapies for smoking cessation, long-acting opioids (i.e., methadone or buprenorphine) for opiate dependence, and disulfiram, naltrexone, and acamprosate for alcohol dependence. No medications to aid in the treatment of addiction to cocaine, methamphetamine, or marijuana are currently approved, nor are any approved for the treatment of behavioral addictions.

The purpose of the present review is to provide a summary of the pharmacological mechanisms of action and general clinical efficacy of medications acting on glutamatergic transmission in the treatment of addictive disorders. These medications include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. It should be noted that many of these medications have mechanisms of action that include multiple neurotransmitter systems, and perhaps with the exception of D-cycloserine, none is known to selectively target glutamatergic transmission or specific glutamate receptors. However, there is a strong body of preclinical evidence arising from over two decades of animal studies suggesting a critical role for glutamate transmission and glutamate receptors in drug reward, reinforcement, and relapse (Bird and Lawrence, 2009; Bowers et al., 2010; Gass and Olive, 2008; Kalivas et al., 2009; Moussawi and Kalivas, 2010; Olive, 2009, 2010; Reissner and Kalivas, 2010; Tzschentke and Schmidt, 2003; Uys and LaLumiere, 2008). For an overview of glutamatergic transmission and glutamate receptors, the reader is referred to the review by Sanacora in the current issue (*publisher – please insert correct page numbers here*). In addition, the small but growing body of literature on the use of these medications to treat behavioral addictions such as compulsive gambling, and studies on this topic will also be reviewed.

2. Glutamatergic medications for the treatment of substance use disorders

2.1. Acamprosate

2.1.1. Mechanism of action

Acamprosate (calcium acetylhomotaurine) is derived from homotaurine, a nonspecific γ-aminobutyric acid (GABA) agonist. The molecule is N-acetylated to facilitate penetration across the blood–brain barrier, and is formulated as a calcium salt to increase absorption of the compound from the gastrointestinal tract. Despite these chemical modifications, its overall bioavailability remains poor (i.e., <20%) and requires doses in the range of 2–3 g per day to demonstrate efficacy. Many pharmacological mechanisms of action of acamprosate have been proposed, but the first studies suggesting that acamprosate exerts its actions through glutamatergic mechanisms were reported by =Zeise et al. (1990, 1993). These investigators showed that acamprosate reduced the excitation of neuronal firing evoked by iontophoretic application of L-glutamate onto cortical neurons in vivo, and inhibited excitatory postsynaptic potentials (EPSPs) evoked by glutamate and N-methyl-D-aspartate (NMDA). Additional evidence for a NMDA antagonist-like mechanism of action of acamprosate came from studies demonstrating that this compound antagonizes NMDA-evoked excitatory postsynaptic currents (EPSCs) in hippocampal neurons (Rammes et al., 2001) and up-regulates NMDA receptor subunit expression in a similar fashion to that observed following treatment with the non-competitive NMDA antagonist MK-801 (Putzke et al., 1996; Rammes et al., 2001). However, some investigators have found no effect of acamprosate on NMDA-mediated synaptic transmission in the CA1 region of the hippocampus (Popp and Lovinger, 2000), while others have found that acamprosate actually potentiates NMDA receptor function in the CA1 region of the hippocampus (Madamba et al., 1996) and in the nucleus accumbens (Berton et al., 1998). Despite these inconsistent electrophysiological findings, binding studies have confirmed an interaction of acamprosate with the spermidine-, glutamate- and/or MK-801-sensitive binding site of the NMDA receptor (al Qatari et al., 1998; Harris et al., 2002; Naassila et al., 1998), and as such acamprosate is often referred to nonspecifically as an "NMDA modulator" (Fig. 1). Although the precise molecular target(s) of acamprosate are still not firmly established (Kiefer and Mann, 2010; Reilly et al., 2008), most current theories posit that acamprosate restores the imbalances between excitatory and inhibitory amino acid neurotransmission that result from chronic alcohol consumption (De Witte et al., 2005; Kiefer and Mann, 2010; Spanagel et al., 2005; Umhau et al., 2010).

2.1.2. Clinical efficacy

The first demonstration of the clinical efficacy of acamprosate in reducing the incidence of relapse in alcoholics was published in the mid-1980s (Lhuintre et al., 1985). Over the years, acamprosate has