BIOCHEMICAL PHARMACOLOGY 75 (2008) 218–265

available at www.sciencedirect.com

ScienceDirect

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

Glutamatergic substrates of drug addiction and alcoholism☆

Justin T. Gass, M. Foster Olive *

Center for Drug and Alcohol Programs, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

ARTICLE INFO

Article history:
Received 3 May 2007
Accepted 26 June 2007

Keywords:
Drug addiction
Alcoholism
Glutamate
Synaptic plasticity
Pharmacotherapeutics
Relapse

ABSTRACT

The past two decades have witnessed a dramatic accumulation of evidence indicating that the excitatory amino acid glutamate plays an important role in drug addiction and alcoholism. The purpose of this review is to summarize findings on glutamatergic substrates of addiction, surveying data from both human and animal studies. The effects of various drugs of abuse on glutamatergic neurotransmission are discussed, as are the effects of pharmacological or genetic manipulation of various components of glutamate transmission on drug reinforcement, conditioned reward, extinction, and relapse-like behavior. In addition, glutamatergic agents that are currently in use or are undergoing testing in clinical trials for the treatment of addiction are discussed, including acamprosate, *N*-acetylcysteine, modafinil, topiramate, lamotrigine, gabapentin and memantine. All drugs of abuse appear to modulate glutamatergic transmission, albeit by different mechanisms, and this modulation of glutamate transmission is believed to result in long-lasting neuroplastic changes in the brain that may contribute to the perseveration of drug-seeking behavior and drug-associated memories. In general, attenuation of glutamatergic transmission reduces drug reward, reinforcement, and relapse-like behavior. On the other hand, potentiation of glutamatergic transmission appears to facilitate the extinction of drug-seeking behavior. However, attempts at identifying genetic polymorphisms in components of glutamate transmission in humans have yielded only a limited number of candidate genes that may serve as risk factors for the development of addiction. Nonetheless, manipulation of glutamatergic neurotransmission appears to be a promising avenue of research in developing improved therapeutic agents for the treatment of drug addiction and alcoholism.

☆ This work was supported by PHS grant AA013582 (MFO) and AA007474 (JTG) from the National Institute on Alcohol Abuse and Alcoholism, and a grant from the Alcoholic Beverage Medical Research Foundation (MFO).

* *Corresponding author at*: Center for Drug and Alcohol Programs, Department of Psychiatry and Behavioral Sciences, 67 President Street, PO Box 250861, Charleston, SC 29425, USA. Tel.: +1 843 792 1229; fax: +1 843 792 7353.
E-mail address: olive@musc.edu (M.F. Olive).

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); AC, adenylyl cyclase; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; Amyg, amygdaloid complex; ATP, adenosine triphosphate; BLA, basolateral amygdala; cAMP, cyclic adenosine monophosphate; CB, cannabinoid; CPP, conditioned place preference; CPu, caudate-putamen; DARPP-32, dopamine and cAMP-regulated phosphoprotein-32 kDa; EAAT, excitatory amino acid transporter; EPSC, excitatory postsynaptic current; ERK, extracellular signal-related kinase; FC, frontal cortex; GABA, gamma-aminobutyric acid; GPCR, G-protein coupled receptor; Hipp, hippocampus; ICSS, intracranial self-stimulation; iGluR, ionotropic glutamate receptor; IP_3, inositol triphosphate; IVSA, intravenous self-administration; KA, kainic acid; MAPK, mitogen-activated protein kinase; LTD, long-term depression; LTP, long-term potentiation; MDMA, methylenedioxymethamphetamine; mGluR, metabotropic glutamate receptor; MSN, medium spiny neuron; NAcc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; PKC, protein kinase C; PPT, pedunculopontine tegmentum; SNP, single nucleotide polymorphism; Thal, thalamus; THC, Δ9-tetrahydrocannabinol; VGCC, voltage-gated calcium channel; vGluT, vesicular glutamate transporter; VTA, ventral tegmental area; x_c, cystine-glutamate exchanger

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2007.06.039

1. Introduction

Drug addiction is defined by several diagnostic criteria set forth by the American Psychiatric Association [1]. These criteria include a loss of control over drug intake, repeated unsuccessful attempts at quitting or reducing drug use, continued drug use despite negative consequences, a reduction in engagement in social, occupational and recreational activities in lieu of drug-seeking or self-administration behavior, and the emergence of symptoms of tolerance or withdrawal. Historically, research into the neurobiological substrates that underlie the rewarding and reinforcing effects of drugs of abuse has focused on the mesolimbic dopamine reward circuitry, comprised primarily of dopaminergic neurons in the ventral tegmental area (VTA) that project rostrally to forebrain and limbic regions such as the nucleus accumbens (NAcc), amygdala (Amyg) and frontal cortex (FC) [2]. However, as can be seen in Fig. 1, there has been a dramatic increase in attention that has been given to the role of the excitatory amino acid glutamate in drug addiction and alcoholism over the past two decades. The purpose of this review is to summarize the effects of drugs of abuse on glutamatergic neurotransmission as well as key findings on the role of glutamate transmission in drug reinforcement, the rewarding effects of drugs of abuse, extinction of drug-seeking behavior, and relapse. Various glutamatergic medications that are either approved for clinical use or are being examined in clinical trials for the treatment of addictive disorders will also be discussed. Finally, a brief summary of findings on potential genetic linkages between individual components of glutamate neurotransmission and addiction is presented.

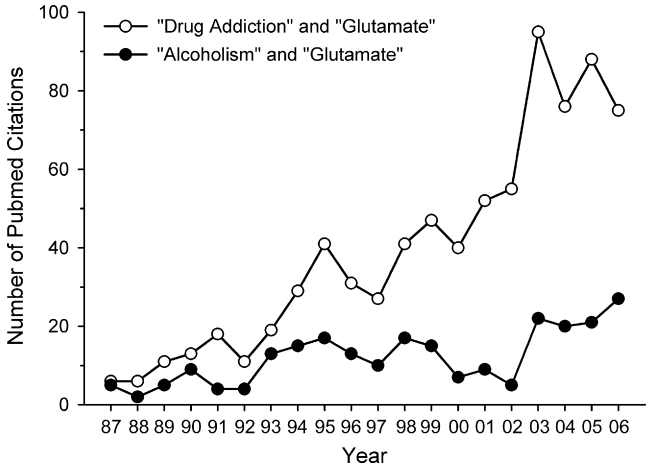

Fig. 1 – Graph showing the increasing number of publications on the topic of glutamate and addiction over the past 20 years. Two separate PubMed searches were performed in April 2007, one using "drug addiction" and "glutamate" as key words (open circles) and the other using "alcoholism" and "glutamate" as key words (filled circles). The resulting number of publications (including review articles and commentaries) are plotted by year for 1987–2006.

2. Animal models of drug addiction and alcoholism

One of the most widely used methods to study drug addiction in animals is the intravenous self-administration (IVSA) paradigm [3]. In this model, experimental animals are implanted with indwelling intravenous catheters (most often in the jugular vein in rodent studies) and are trained to perform an operant task (i.e., lever press or nose-poke) in order to receive an intravenous infusion of cocaine, amphetamine, nicotine, etc. In the case of alcohol (ethanol), execution of the operant task results in presentation of a small amount of an alcohol-containing solution in a receptacle where the animal can consume the solution orally (some studies measure alcohol consumption in the home cage by presentation of two or more bottles containing ethanol solutions). By definition, if the delivery or presentation of the drug solution increases this behavior (i.e., appropriate lever pressing or nose-poking), the drug or alcohol solution is considered to be a positive reinforcer. Environmental cues, such as presentation of stimulus lights or auditory tones, are often paired with drug delivery or alcohol presentation to promote stimulus-drug associations, which enhance drug-taking behavior and can be utilized in subsequent reinstatement tests (see below). The effects of experimental manipulations (i.e., administration of test compounds either systemically or intracerebrally) on drug or alcohol self-administration behavior can then be assessed. However, the effects of any such manipulation must be interpreted with caution. For example, while it is tempting to interpret an observed decrease in self-administration behavior as signifying a reduction in the desire to self-administer the drug (and thus having possible therapeutic applications), there are equally plausible alternative explanations for the observed reduction in drug self-administration. For example, the experimental manipulation might have caused an overall reduction motor output, or an increase in sensitivity to the drug, resulting in less drug required to produce the same subjective effects. Therefore, in this review, to avoid the pitfalls of these alternative explanations, we will refer to alterations in operant drug IVSA or ethanol consumption as changes in *reinforcement*.

The operant self-administration paradigm is also amenable to studying the phenomenon of relapse. The most widely used animal model of relapse is the reinstatement paradigm [3]. While this model by no means perfectly mirrors the phenomenon of relapse in humans, it is considered to be the best model developed thus far [4]. In the reinstatement paradigm, following the achievement of stable levels of drug self-administration, animals undergo extinction training procedures, where the behavior that previously resulted in the delivery of the drug solution (i.e., lever press or nose-poke) no longer produces any consequences. As a result of this imposed drug unavailability (i.e., "forced abstinence"), animals will gradually extinguish (i.e., reduce) the behavior that previously resulted in drug delivery. Once predesignated extinction criteria have been obtained (for example, presses on the "active" drug-delivering lever are reduced to less than 20% of those observed when the drug was available), it is possible to "reinstate" operant responding by presenting one of the three main types of stimuli that are known to evoke relapse in humans: exposure to