Neuroscience and Biobehavioral Reviews 77 (2017) 14–31

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

Metabotropic and ionotropic glutamate receptors as potential targets for the treatment of alcohol use disorder

Sunil Goodwani[a,b], Hannah Saternos[a], Fawaz Alasmari[a], Youssef Sari[a,*]

[a] University of Toledo, College of Pharmacy and Pharmaceutical Sciences, Department of Pharmacology and Experimental Therapeutics, Toledo, OH 43614, USA

[b] The Neurodegeneration Consortium, Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston, TX, 77054, USA

ARTICLE INFO

Article history:
Received 31 October 2016
Received in revised form 13 February 2017
Accepted 22 February 2017
Available online 24 February 2017

Keywords:
mGluR1/5
mGluR2/3
mGluR7
NMDA
AMPA
Glutamate
Alcohol

ABSTRACT

Emerging evidence indicates that dysfunctional glutamate neurotransmission is critical in the initiation and development of alcohol and drug dependence. Alcohol consumption induced downregulation of glutamate transporter 1 (GLT-1) as reported in previous studies from our laboratory. Glutamate is the major excitatory neurotransmitter in the brain, which acts via interactions with several glutamate receptors. Alcohol consumption interferes with the glutamatergic signal transmission by altering the functions of these receptors. Among the glutamate receptors involved in alcohol-drinking behavior are the metabotropic receptors such as mGluR1/5, mGluR2/3, and mGluR7, as well as the ionotropic receptors, NMDA and AMPA. Preclinical studies using agonists and antagonists implicate these glutamatergic receptors in the development of alcohol use disorder (AUD). Therefore, the purpose of this review is to discuss the neurocircuitry involving glutamate transmission in animals exposed to alcohol and further outline the role of metabotropic and ionotropic receptors in the regulation of alcohol-drinking behavior. This review provides ample information about the potential therapeutic role of glutamatergic receptors for the treatment of AUD.

Contents

Abbreviations: AC, adenylyl cyclase; ADE, alcohol deprivation effect; AMG, amygdala; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **AUD**, **Alcohol Use Disorder**; BLA, basolateral amygdala; CNS, central nervous dystem; CPP, conditioned place preference; DAG, diacylglycerol; EAAT, excitatory amino acid transporter; GABA, γ-aminobutyric acid; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; GPCR, G-protein coupled receptor; HPC, hippocampus; iGluR, ionotropic glutamate receptor; IP3, inositol (1,4,5)-triphosphate; KA, kainic acid receptor; MC, motor cortex; mGluR, metabotropic glutamate receptor; MT, motor thalamus; NAc, nucleus accumbens; NARP, neural activity dependent pentraxin; NMDA, N-Methyl -D-aspartic acid; PFC, prefrontal cortex; PKC, phosphokinase C; PLC, phospholipase C; SNr, substantia niagra; VGLUT, vesicular glutamate transporter; VP, ventral pallidum; VS, ventral striatum; VTA, Ventral Tegmental Area; xCT, Cystine/Glutamate Exchange Transporter.

* Corresponding author at: University of Toledo, College of Pharmacy and Pharmaceutical Sciences, Department of Pharmacology and Experimental Therapeutics, Health Science Campus, 3000 Arlington Avenue, Toledo, OH 43614. USA.
E-mail address: youssef.sari@utoledo.edu (Y. Sari).

http://dx.doi.org/10.1016/j.neubiorev.2017.02.024
0149-7634/

1. Introduction

Alcoholism is a progressive and chronic relapsing disorder, consequently leading to detrimental health outcomes. The positive reinforcing effect, known as the rewarding effect, associated with initial alcohol consumption is suggested to be the driving force promoting chronic alcohol consumption, subsequently leading to the development of alcohol use disorder (AUD) [For review see ref. (Gilpin and Koob, 2008)]. This effect is associated with changes in brain neurochemistry, specifically alterations of the neurotransmitters that are sensitive to the acute effects of alcohol (Weiss and Porrino, 2002).

Ample evidence suggests the involvement of the mesocorticolimbic dopaminergic system in the development of drug dependence. In addition, enhanced dopaminergic transmission in the nucleus accumbens (NAc) plays a key role in the initiation of addictive behavior. It is important to note that the reward pathways involve multiple brain regions, including the ventral tegmental area (VTA) and NAc (Russo and Nestler, 2013). Alcohol acts as a positive reinforcer in the mesocorticolimbic reward system by inducing the release of dopamine in the VTA, which stimulates the reinforcing effect of alcohol (Imperato and Di Chiara, 1986). For instance, studies have reported that acute administration of alcohol induced rewarding effects due to an increase in dopaminergic neurotransmission in the VTA and NAc [For review see ref. (Spanagel and Weiss, 1999)]. However, an increase in the number of spontaneously active dopaminergic neurons was found in the posterior VTA after chronic alcohol consumption (Morzorati et al., 2010). Importantly, the primary dopaminergic projections within this system originate in the VTA and innervate several areas, including the NAc and the prefrontal cortex (PFC). However, the circuitry is complex and involves innervation through dopaminergic, glutamatergic and GABAergic projections. Moreover, enhanced responses of postsynaptic glutamate receptors are responsible for the increase in dopaminergic firing (Fitzgerald et al., 2012). This later study suggests that glutamatergic innervation in the VTA plays a crucial role in glutamate-stimulated dopamine release. The dysfunctional connectivity and alteration in glutamatergic transmission are associated with chronic alcohol seeking, relapse, craving, tolerance and withdrawal (Alasmari et al., 2015a; Bäckström and Hyytiä, 2004; Dahchour et al., 1998; Krupitsky et al., 2007a; Nagy, 2008; Rossetti et al., 1999), which provide evidence of the involvement of glutamate transmission in the NAc and VTA in alcohol-seeking behavior. The apparent role of glutamate in the development of AUD suggests the glutamatergic system as a potential therapeutic target to block the reinforcing effects of alcohol as well as to attenuate chronic and reinstatement of alcohol-seeking behavior (Alasmari et al., 2016; Bäckström and Hyytiä, 2004; Besheer et al., 2010; Qrunfleh et al., 2013).

2. Neurocircuitry involving glutamate transmission in AUD

Dependence on drugs of abuse involve a number of brain regions, including the NAc, located in the ventral striatum (Sobolevsky et al.), VTA, basal lateral amygdala (BLA), PFC, hippocampus (HPC), dorsal medial thalamus (DMT), ventral palladium (VP), substantial nigra (SNr), motor thalamus (MT), and motor cortex (MC) (Koob and Volkow, 2010) (Fig. 1). Each of these regions has glutamatergic projections and neurons containing glutamate receptors, providing an anatomical basis for glutamatergic transmission in addiction (Gass and Olive, 2008).

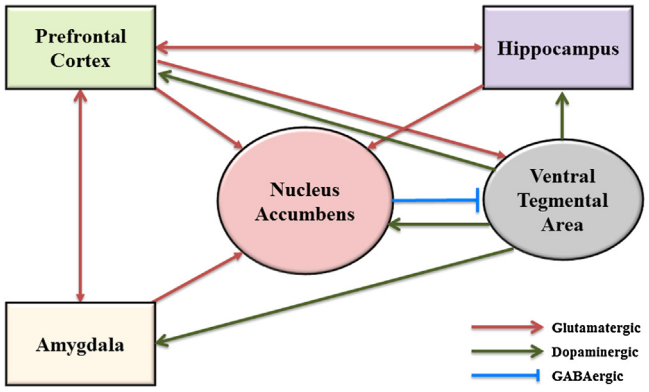

Fig. 1. Neurocircuitry involved in AUD. The brain reward circuitry is comprised of five major brain regions – nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala (AMG), hippocampus (HPC) and ventral tegmental area (VTA) – which are interconnected by the glutamatergic and dopaminergic excitatory pathways as well as the inhibitory GABAergic pathway. (A) Glutamatergic System – NAc receives glutamatergic inputs from PFC, AMG and HPC, while all three latter regions are interconnected by reciprocating glutamatergic projections. (B) Dopaminergic System – VTA relays dopaminergic projections to NAc, PFC, AMG and HPC. (C) GABAergic System – NAc sends GABAergic inputs to VTA.

Glutamatergic projections from the PFC to the NAc have been implicated in the initiation and learning of addictive behaviors (Moussawi and Kalivas, 2010), which are subsequently regulated by dopaminergic projections from the VTA (Deng et al., 2009). These glutamatergic pathways, between the PFC and NAc, are also thought to play a key role in addictive behaviors and are important for reinstituting drug seeking behavior (Kalivas and Volkow, 2005). Glutamatergic projections from the AMG and HPC to the PFC and NAc establish and provide previously learned information associated with experience, further influencing complex behavioral responses (Kalivas and Volkow, 2005). Interestingly, it is also found that the glutamatergic system plays a critical role in alcohol-associated dependence, including chronic alcohol seeking and relapse (Alasmari et al., 2015a; Bäckström and Hyytiä, 2004; Dahchour et al., 1998; Krupitsky et al., 2007a; Nagy, 2008; Rossetti et al., 1999).

The NAc is a key player in the mesolimbic dopaminergic system, which receives dopaminergic inputs through afferent connections from the VTA [For review see ref. (Alasmari et al., 2015b; Pistillo et al., 2015)]. It is important to note that the NAc shell receives dopaminergic projections from the VTA and is responsible for motivation and reward; however, the NAc core is innervated mainly by glutamatergic projections from the HPC and AMG and is responsible for sensory motor integration, goal-directed behavior, and emotional cues (Guo et al., 2009; Suto et al., 2010). Despite the complexity of the brain regions and signaling pathways, chronic alcohol exposure is characterized by a reduced function of the reward neurocircuitry and an increased glutamatergic system function (Vengeliene et al., 2008).