Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Roles for the endocannabinoid system in ethanol-motivated behavior

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ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 15 June 2015
Accepted 22 June 2015
Available online xxxx

Keywords:
Alcohol
Cannabinoid
CB_1
Endocannabinoid
Ethanol

ABSTRACT

Alcohol use disorder represents a significant human health problem that leads to substantial loss of human life and financial cost to society. Currently available treatment options do not adequately address this human health problem, and thus, additional therapies are desperately needed. The endocannabinoid system has been shown, using animal models, to modulate ethanol-motivated behavior, and it has also been demonstrated that chronic ethanol exposure can have potentially long-lasting effects on the endocannabinoid system. For example, chronic exposure to ethanol, in either cell culture or preclinical rodent models, causes an increase in endocannabinoid levels that results in down-regulation of the cannabinoid receptor 1 (CB_1) and uncoupling of this receptor from downstream G protein signaling pathways. Using positron emission tomography (PET), similar down-regulation of CB_1 has been noted in multiple regions of the brain in human alcoholic patients. In rodents, treatment with the CB_1 inverse agonist SR141716A (Rimonabant), or genetic deletion of CB_1 leads to a reduction in voluntary ethanol drinking, ethanol-stimulated dopamine release in the nucleus accumbens, operant self-administration of ethanol, sensitization to the locomotor effects of ethanol, and reinstatement/relapse of ethanol-motivated behavior. Although the clinical utility of Rimonabant or other antagonists/inverse agonists for CB_1 is limited due to negative neuropsychiatric side effects, negative allosteric modulators of CB_1 and inhibitors of endocannabinoid catabolism represent therapeutic targets worthy of additional examination.

1. Introduction

Alcohol dependence is a highly prevalent disorder, which affects an estimated eight million Americans and inflicts a tremendous cost (in excess of $223.5 billion annually) to society (Bouchery et al., 2011; Grant et al., 2004). Pharmaceutical treatments for alcohol dependence include the use of the opioid receptor antagonist naltrexone, and the broadly-acting drug, acamprosate. While naltrexone has been shown clinically to reduce alcohol intake and relapse (Foa et al., 2013; Kranzler et al., 2004; Latt et al., 2002), acamprosate appears to be more effective, compared to placebo, at increasing the percent of abstinent days (Mason et al., 2006). A recent meta-analysis of the efficacy of both naltrexone and acamprosate for alcohol treatment demonstrated that these effects, though significant, are modest. Only 12–19% of individuals treated with naltrexone and 7–13% treated with acamprosate had better outcomes compared to those treated with placebo (Bouchery et al., 2011; Grant et al., 2004; Kranzler and Van Kirk, 2001). These studies illustrate the limitations of currently available pharmacotherapies and emphasize the need to expand therapeutic options for treating alcohol dependence.

Here we review the most current evidence demonstrating that ethanol can modulate endocannabinoid system (ECS) signaling in preclinical rodent models. Our review complements and builds on other excellent reviews on the interactions between the ECS and alcohol

Abbreviations: (2-AG), 2-arachidonoyl-glycerol; (Δ^9-THC), delta-9-tetrahydrocannabinol; (AA), Alko Alcohol preferring; (ABHD), alpha/beta hydrolase domain-containing protein; (ADE), alcohol deprivation effect; (AEA), N-arachidonoylethanolamine; (CB_1), cannabinoid receptor 1; (CB_2), cannabinoid receptor 2; (CPP), conditioned place preference; (DAG), diacylglycerol; (DID), drinking in the dark; (DTs), delirium tremens; (ECS), endocannabinoid system; (EPSP), excitatory post-synaptic potential; (FAAH), fatty-acid amide hydrolase; (FR), fixed-ratio; (GIRK), G protein-coupled inward rectifying potassium channel; (GLAST), glutamate aspartate transporter; (GPR55), G protein-coupled receptor 55; (HIC), handling-induced convulsions; (KO), knock-out; (LORR), loss of righting reflex; (MAGL), monoacylglycerol lipase; (MAPK), mitogen-activated protein kinase; (msP), Marchigian Sardinian alcohol-preferring rat; (NAc), nucleus accumbens; (NADA), N-arachidonoyl dopamine; (NAPE), N-acylphosphatidylethanolamine; (NAT), N-acetyltransferase; (noladin ether), 2-arachidonoyl glyceryl ether; (NP), non alcohol preferring; (P), alcohol preferring; (PE), phosphatidylethanolamine; (PET), positron emission tomography; (PFC), pre-frontal cortex; (PLA_2), phospholipase-A_2; (PLC), phospholipase C; (PLD), phospholipase-D; (PR), progressive ratio; (PSR), Pavlovian spontaneous recovery; (SA), self-administration; (sNP), Sardinian alcohol non-preferring; (sP), Sardinian alcohol preferring; (SR1), SR141716A; (O-arachidonoyl ethanolamine), virodhamine; (VGCC), voltage-gated calcium channel; (VTA), ventral tegmental area.

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http://dx.doi.org/10.1016/j.pnpbp.2015.06.011
0278-5846/

(Pava and Woodward, 2012). Preclinical rodent models have been used to show that genetic and pharmacological inhibition of ECS signaling can profoundly reduce voluntary ethanol consumption, reward for ethanol, as well as reinstatement and relapse of ethanol-motivated behaviors. Understanding the precise mechanisms through which alcohol influences the ECS and vice versa has the potential to positively impact treatment of alcohol use disorder. Recent preclinical work has investigated the therapeutic potential of drugs that manipulate endocannabinoid levels directly (Ramesh et al., 2013), or act as allosteric modulators of the cannabinoid receptor 1 (CB_1) (Gamage et al., 2014; Jing et al., 2014). Both approaches are capable of providing therapeutic benefits through modulation of the ECS while avoiding possible side effects associated with direct CB_1 inverse agonism or antagonism.

2. Endocannabinoid signaling system

The ECS consists of three main components: the endogenous ligands (endocannabinoids), the cannabinoid receptors, and the enzymes that are responsible for synthesis and catabolism of endocannabinoids. Two cannabinoid receptors have been cloned and characterized (Matsuda et al., 1990; Munro et al., 1993). CB_1 is predominately presynaptic (Katona et al., 1999) and is expressed widely throughout the nervous system (Devane et al., 1988; Herkenham et al., 1990, 1991; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1990; Tsou et al., 1998). CB_1 is responsible for mediating the psychoactive effects of delta-9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive cannabinoid in the cannabis plant (Ledent et al., 1999; Monory et al., 2007). Within the nervous system, CB_1 is involved in modulation of a diverse range of physiological functions including pain (Ledent et al., 1999; Lichtman and Martin, 1997), synaptic plasticity related to learning and memory (Kreitzer and Regehr, 2001b; Marsicano et al., 2002; Wilson et al., 2001), reward signaling (Hungund et al., 2003; Riegel and Lupica, 2004), and mood (Hill and Gorzalka, 2005; Martin et al., 2002). CB_1 is also present in peripheral "non-neuronal" tissues including liver, adipose tissue, and pancreas, where it has a prominent role in metabolism (Cota et al., 2003; Osei-Hyiaman et al., 2005; Ravinet Trillou et al., 2004). The other cannabinoid receptor, CB_2, was first cloned from a human promelocytic leukemia cell line (HL60) and is most abundant in immune cells (Munro et al., 1993), although low neuronal CB_2 expression has been reported in the brain (Van Sickle et al., 2005). CB_1 is a G protein-coupled receptor that is typically coupled to $G\alpha_{i/o}$ proteins. Agonist activation has been shown to lead to stimulation of MAPK (Bouaboula et al., 1995) and G protein-coupled inward rectifying potassium channels (GIRKs) (Mackie et al., 1995) as well as inhibition of adenylyl cyclase (Howlett, 1985; Howlett and Fleming, 1984; Howlett et al., 1986) and voltage-gated calcium channels (VGCCs) (Mackie and Hille, 1992; Mackie et al., 1993).

Endocannabinoid production is post-synaptic and occurs in response to increased levels of intracellular calcium and/or excitatory post-synaptic potential (EPSP)-induced depolarization of the plasma membrane (Maejima et al., 2001, 2005). Endocannabinoids diffuse in a retrograde manner across the synapse where they act at presynaptic CB_1 receptors to suppress neurotransmission (Kreitzer and Regehr, 2001a; Maejima et al., 2001; Wilson et al., 2001). Two main endocannabinoids have been identified, N-arachidonoylethanolamine (AEA; anandamide) (Devane et al., 1992) and 2-arachidonoyl-glycerol (2-AG) (Stella et al., 1997; Sugiura et al., 1995). However, three other putative endocannabinoid ligands, N-arachidonoyl dopamine (NADA) (Huang et al., 2002), O-arachidonoyl ethanolamine (virodhamine) (Porter et al., 2002), and 2-arachidonoyl glyceryl ether (nolandin ether) (Hanus et al., 2001) have also been identified.

Endocannabinoids are synthesized on demand from plasma membrane phospholipids (Piomelli, 2003). The production of AEA from phosphatidylethanolamine (PE) can occur via multiple synthetic pathways. However, one synthetic pathway that is particularly relevant to the effect of ethanol on the ECS involves phospholipase A2 (PLA_2) conversion of N-arachidonoyl phosphatidylethanolamine (NAPE) to Lyso-NAPE, which is then cleaved, by lyso-phospholipase D, to AEA (Sun et al., 2004). The majority of 2-AG is produced via a two-step process involving sequential action of phospholipase C (PLC) to produce diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP_2), followed by the action of sn-1-diacylglycerol lipase alpha and beta (DAGL α/β) to convert DAG to 2-AG (Bisogno et al., 2003). Signaling by these modulatory lipids is terminated by their breakdown. Hydrolysis of AEA is catalyzed by fatty-acid amide hydrolase (FAAH) (Cravatt et al., 1996) while 2-AG is hydrolyzed by either monoacylglycerol lipase (MAGL; 85% of 2-AG breakdown) (Dinh et al., 2002) or the alpha/beta hydrolase domain (ABHD)-containing proteins ABHD6 and ABHD12 (Blankman et al., 2007; Marrs et al., 2010).

3. Voluntary ethanol drinking

Using the two bottle choice assay, CB_1 knock-out (KO) mice have been shown to exhibit decreased voluntary drinking of ethanol. Consumption of 10% ethanol was decreased in CB_1 KO mice given six or eight hours of limited access to ethanol per day (Poncelet et al., 2003; Thanos et al., 2005). Under continuous access conditions, ethanol consumption was decreased for multiple ethanol concentrations in both male and female CB_1 KO mice compared to wild-type controls (Hungund et al., 2003; Naassila et al., 2004; Vinod et al., 2008b). However, the inhibitory effect of CB_1 deletion on ethanol intake was more profound in female mice, which generally show higher overall basal ethanol consumption compared to their male counterparts (Hungund et al., 2003). Additionally, age-related decreases in ethanol drinking were shown to be absent in CB_1 KO mice, suggesting that the decrease in ethanol consumption that occurs during aging is mediated by endocannabinoid signaling (Wang et al., 2003).

Voluntary ethanol intake is attenuated in rodents following treatment with CB_1 inverse agonists, including SR141716A (Rimonabant). Treatment with SR141716A decreased ethanol drinking and sensitization to the locomotor effects of ethanol (Marinho et al., 2015) in ethanol-preferring C57Bl6 mice as well as in non-preferring DBA/2J mice (Arnone et al., 1997; Vinod et al., 2008b). In Sardinian ethanol-preferring rats selected for high ethanol consumption (sP), systemic SR141716A treatment decreased voluntary consumption of 10% ethanol under limited and continuous access conditions (Colombo et al., 1998; Serra et al., 2001). Likewise, treatment with the CB_1 inverse agonists AM251 and SR147778 reduced ethanol consumption in both Fawn Hooded (Femenia et al., 2010) and Wistar (Lallemand and De Witte, 2006) rats chronically exposed to ethanol vapor. These results demonstrate that disruption of CB_1 signaling in mice and rats causes a robust and highly reproducible reduction in voluntary ethanol consumption.

The effect of CB_1 agonists on voluntary drinking of ethanol has been examined but is generally less understood than the effect of CB_1 deletion or pharmacological blockade on consumption of ethanol. Systemic administration of a CB_1 full agonist (WIN 55,212-2), enhanced ethanol consumption in C57Bl6 mice subjected to the drinking in the dark (DID) model of binge-like ethanol drinking (Linsenbardt and Boehm, 2009). Systemic injection of WIN 55,212-2 or CP 55,940, another full agonist of CB_1, has been shown to elicit a dose-dependent increase in voluntary ethanol drinking in sP rats given continuous access to 10% ethanol (Colombo et al., 2002). The stimulatory effects of systemic WIN 55,212-2 and CP 55,940 on voluntary ethanol drinking were blocked by pretreatment with SR141716A, providing evidence that these effects are CB_1-mediated (Colombo et al., 2002).

The effect of altering endocannabinoid levels on voluntary ethanol drinking has been examined using both FAAH KO mice and mice treated with the FAAH inhibitor, URB597. Mice lacking FAAH, which causes catabolism of the endocannabinoid AEA, exhibit increased voluntary consumption and preference for ethanol across a wide range of concentrations (Basavarajappa et al., 2006; Blednov et al., 2007; Vinod et al.,

Please cite this article as: Henderson-Redmond, A.N., et al., Roles for the endocannabinoid system in ethanol-motivated behavior, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.06.011