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Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors

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ABSTRACT

The endogenous cannabinoid system is an important regulatory system involved in physiological homeostasis. Endocannabinoid signaling is known to modulate neural development, immune function, metabolism, synaptic plasticity and emotional state. Accumulating evidence also implicates brain endocannabinoid signaling in the etiology of drug addiction which is characterized by compulsive drug seeking, loss of control in limiting drug intake, emergence of a negative emotional state in the absence of drug use and a persistent vulnerability toward relapse to drug use during protracted abstinence. In this review we discuss the effects of drug intake on brain endocannabinoid signaling, evidence implicating the endocannabinoid system in the motivation for drug consumption, and drug-induced alterations in endocannabinoid function that may contribute to various aspects of addiction including dysregulated synaptic plasticity, increased stress responsivity, negative affective states, drug craving and relapse to drug taking. Current knowledge of genetic variants in endocannabinoid signaling associated with addiction is also discussed.

Contents

1. Introduction

The recreational use of psychoactive substances by humans has been documented for centuries, and it is well known that the repeated use of many abused drugs can lead to dependence and a progression toward addiction. Addiction is a persistent state characterized by compulsion to seek and take a drug, a loss of control in limiting drug intake even when serious negative consequences ensue and the emergence of a negative

Abbreviations: AEA, anandamide (*N*-arachidonoyl-ethanolamine); 2-AG, 2-arachidonoylglycerol; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CB1, cannabinoid receptor type 1; CeA, central nucleus of the amygdala; CNR1, cannabinoid receptor type 1 gene; CPA, conditioned place aversion; CPP, conditioned place preference; ECS, endogenous cannabinoid system; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAc, nucleus accumbens; nACh, nicotinic acetylcholine ion channel receptors; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PVN, paraventricular nucleus of the hypothalamus; sP, Sardinian alcohol-preferring rats; THC, Δ9-tetrahydrocannabinol; VTA, ventral tegmental area.

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emotional state (e.g. anxiety, depression, irritability) when access to the drug is prevented (Jaffe, 1990; O'Brien & McLellan, 1996; Hyman, 2005; O'Brien & Gardner, 2005; Hyman et al., 2006; Koob & Volkow, 2010). Addicts often have a persistent vulnerability to relapse to drug use after days or even years of abstinence, and this aspect of addiction presents the greatest difficulty in treating this psychiatric disease (O'Brien, 1997; Nestler, 2002; Shaham & Hope, 2005; O'Brien, 2008; Yahyavi-Firouz-Abadi & See, 2009).

An important goal of addiction research is to understand the neuropharmacological and neuroadaptive mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking that defines addiction. Investigations of the neural substrates mediating the positive reinforcing properties of various drugs have dominated the field of addiction research for several decades. This work has established an important role for increased mesolimbic dopamine signaling in the mediation of acute drug reward. Indeed, all drugs of abuse have been shown to increase extracellular dopamine levels in the nucleus accumbens (NAc) (Di Chiara et al., 2004) though this effect is relatively less pronounced for ethanol, nicotine and opioids as compared with psychostimulants. Further studies have demonstrated significant involvement of serotonin, glutamate, GABA, acetylcholine, and various neuroactive peptides in the positive reinforcing effects of various abused drugs (Bardo, 1998; Koob et al., 2004; Hyman et al., 2006; Ross & Peselow, 2009) and the relative importance of a large number of brain structures in addition to the mesolimbic system has been characterized (Bardo, 1998; McBride et al., 1999; Paulus, 2007).

In recent years there has been substantial effort to characterize the neural mechanisms underlying the shift from controlled to compulsive drug use and the associated transfer in motivational drive from positive to negative reinforcement that results from long-term drug exposure. The data suggest that the transition to drug dependence and addiction involves adaptations in many of the neurochemical systems implicated in the positive reinforcing effects of acute drug use, a dysregulation of synaptic plasticity and the development of maladaptive stress responses (Kalivas & O'Brien, 2008; Koob, 2008, 2009; Kalivas, 2009; Chen et al., 2010; Martin-Fardon et al., 2010; Wise & Morales, 2010).

A growing body of evidence points to an involvement of the endogenous cannabinoid system (ECS) in the acquisition and maintenance of drug taking behavior and in various physiological and behavioral processes associated with addiction. An assessment of this evidence is presented in the sections that follow, with a focus on the potential endocannabinoid (eCB) influence on drug reinforcement, drug-related synaptic plasticity, drug-seeking behavior (relapse), stress responsivity and affective state. We will first provide a brief overview of the ECS and a consideration of the behavioral effects produced by enhanced eCB signaling.

2. The endogenous cannabinoid system

In the early 1990s two arachidonic acid derivatives were identified as endogenous cannabinoid receptor ligands. The first eCB to be discovered was anandamide (*N*-arachidonoyl-ethanolamine; AEA) (Devane et al., 1992) and within two years a second endogenous lipid, 2-arachidonoyl-glycerol (2-AG), was shown to function as signaling molecule at CB_1 and CB_2 receptors (Mechoulam et al., 1995; Sugiura et al., 1995). Other endogenous molecules have been identified that exert cannabinoid-like effects including 2-arachidonoyl-glycerol ether (noladin ether) (Hanus et al., 2001), *N*-arachidonoyl-dopamine (NADA) (Bisogno et al., 2000; Huang et al., 2002), virodhamine (Porter et al., 2002), *N*-homo-γ-linolenoylethanolamine (HEA) and *N*-docosatetraenoylethanolamine (DEA) (Hanus et al., 1993; Pertwee et al., 1994). However, the presence of many of these lipids in intact tissue has been a matter of debate and their pharmacological activity and metabolism have not yet been thoroughly characterized. Endocannabinoid congeners including palmitoylethanolamide (PEA) (Re et al., 2007), and oleoylethanolamide (OEA) (Rodriguez de Fonseca et al., 2001) have also been identified, though these moieties do not interact with cannabinoid receptors. Accordingly, AEA and 2-AG are still considered the primary endogenous mediators of cannabinoid signaling.

Unlike classical neurotransmitters, eCBs are not stored in intracellular compartments but are synthesized on an "as needed" basis by cleavage from membrane lipid precursors and immediate extrusion from neurons through distinct calcium-dependent mechanisms (see Fig. 1). AEA derives from the phospholipid precursor *N*-arachidonoyl-phosphatidylethanolamine (NAPE) (Cadas et al., 1996; Piomelli, 2003). The precise pathways through which NAPE is converted to AEA remains controversial, and at least four routes have been proposed including a direct transacylation-phosphodiesterase pathway catalyzed by a *N*-acyl-phosphatidylethanolamine-selective phosphodiesterase (NAPE-PLD) (Okamoto et al., 2004; Di Marzo & Petrosino, 2007; Liu et al., 2008) whose activity is regulated by depolarization and/or activation of ionotropic (Stella & Piomelli, 2001; Piomelli, 2003) or metabotropic receptors (Giuffrida et al., 1999; Varma et al., 2001; Kim et al., 2002). Although this has been considered to be a major route for AEA production, NAPE-PLD knockout mice were found to have unaltered AEA levels in brain (Leung et al., 2006) clearly pointing to the presence of additional metabolic pathways for AEA formation. At least two pathways distinct from NAPE-PLD have been proposed. One pathway involves the double-*O*-deacylation of NAPEs by α,β-hydrolase (ABHD4) to form glycerophospho-*N*-acylethanolamines (GP-NAEs), followed by conversion of these intermediates to NAEs by glycerophosphodiesterase-1 (GDE1) (Simon & Cravatt, 2006; Simon & Cravatt, 2008). Another pathway utilizes a phospholipase C (PLC) to produce phopho-*N*-arachidonoylethanolamine (pAEA) from NAPE, followed by conversion of pAEA into AEA by phosphatases such as PTPN22 and SHIP1 (Liu et al., 2006, 2008). 2-AG derives primarily from the hydrolytic metabolism of 1,2-diacylglycerol (DAG) mediated by two sn-1-selective DAG lipases, DAGL-α and DAGL-β (Stella et al., 1997; Bisogno et al., 2003; Piomelli, 2003) though alternate biosynthetic routes have been described (Sugiura et al., 1995).

Inactivation of eCB signaling is mediated by cellular reuptake into both neurons and glial cells (Beltramo et al., 1997; Hillard & Jarrahian, 2000) and subsequent intracellular hydrolysis. Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) have been identified as enzymes primarily responsible for the degradation of AEA and 2-AG, respectively. FAAH can also hydrolyze 2-AG (Goparaju et al., 1998) and other fatty acid primary amides, N-acyltaurines and N-acyl amino acids. The cloning, structural and kinetic properties, distribution in the body and crystal structure of FAAH have been described (McKinney & Cravatt, 2005; Ahn et al., 2008). FAAH is abundantly expressed in the CNS and FAAH-positive neurons are found in proximity to CB_1 receptor-containing terminals, supporting a role for this enzyme in eCB inactivation (McKinney & Cravatt, 2005). 2-AG hydrolysis is performed by multiple enzymes, though the primary mechanism of clearance appears to be mediated by MAGL (Dinh et al., 2002; Blankman et al., 2007). MAGL cloning, structural and catalytic properties have recently been reviewed (Saario & Laitinen, 2007). In addition to MAGL, the enzymes ABHD6 and ABHD12 appear to play an important role in 2-AG metabolism (Blankman et al., 2007; Marrs et al., 2010).

Two major types of cannabinoid receptors have been characterized and cloned: CB_1 and CB_2. CB_1 receptors are highly expressed in brain and are also found in peripheral tissues (Howlett et al., 1990; Herkenham et al., 1990, 1991a, 1991b; Batkai et al., 2001). CB_2 receptors are mainly located in immune cells (Munro et al., 1993), although there is evidence for CB_2 receptor expression on neurons, glia and endothelial cells in brain (Van Sickle et al., 2005; Onaivi et al., 2006; Ashton & Glass, 2007; Brusco et al., 2008a, 2008b; Jhaveri et al.,