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Invited review

Cannabinoids as hippocampal network administrators

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ABSTRACT

Extensive pioneering studies performed in the hippocampus have greatly contributed to our knowledge of an endogenous cannabinoid system comprised of the molecular machinery necessary to process endocannabinoid lipid messengers and their associated cannabinoid receptors. Moreover, a foundation of knowledge regarding the function of hippocampal circuits, and its role in supporting synaptic plasticity has facilitated our understanding of the roles cannabinoids play in the diverse behaviors in which the hippocampus participates, in both normal and pathological states. In this review, we present an historical overview of research pertaining to the hippocampal cannabinoid system to provide context in which to understand the participation of the hippocampus in cognition, behavior, and epilepsy. We also examine potential roles for the hippocampal formation in mediating dysfunctional behavior, and assert that these phenomena reflect disordered physiological activity within the hippocampus and its interactions with other brain regions after exposure to synthetic cannabinoids, and the phytocannabinoids found in marijuana, such as Δ^9-THC and cannabidiol. In this regard, we examine contemporary hypotheses concerning the hippocampal endocannabinoid system's participation in psychotic disorders, schizophrenia, and epilepsy, and examine cannabinoid-sensitive cellular mechanisms contributing to coherent network oscillations as potential contributors to these disorders.

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Contents

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Abbreviations

CB_1R	Cannabinoid CB_1 receptor
Endocannabinoid	endogenous cannabinoid
CCK	Cholecystokinin
Δ^9-THC	Δ^9-tetrahydrocannabinol
AEA	Arachidonoylethanolamide
2-AG	2-arachodonoylglycerol
DSI	Depolarization-induced suppression of inhibition
DSE	Depolarization-induced suppression of excitation
mGluRI	group I metabotropic glutamate receptors
LTD	Long-term depression
PV	Parvalbumin
DA	Dopamine
VTA	Ventral tegmental area
NMDA	*N*-methyl-D-aspartate
MAM	methylazoxymethanol acetate
CBD	Cannabidiol
NRG-1	Neuroregulin-1
TRPV-1	Transient receptor potential cation channel, subfamily V, member 1

1. Introduction

Since the cloning of the first cannabinoid receptor (Matsuda et al., 1990), and initial studies localizing this CB_1 receptor (CB_1R) in the brain nearly 3 decades ago (Devane et al., 1988; Herkenham et al., 1990), our understanding of brain cannabinoid systems has expanded at a rapid pace. Moreover, the subsequent isolation of endogenous ligands for cannabinoid receptors (endocannabinoids), and characterization of the molecular processes necessary for their synthesis, release and metabolism (Lu and Mackie, 2016), provides insight into the potential roles these lipid molecules play in regulating brain function. Much of our fundamental understanding of cannabinoid receptor control of neuronal activity has been built upon a foundation of initial studies performed in the hippocampus. This results from the rich expression of CB_1Rs and molecular machinery necessary to process endocannabinoid molecules in the hippocampal formation, as well as the thorough understanding of cellular circuitry of this brain structure and its control by neuromodulators and synaptic plasticity. An understanding of the effects of endogenous and exogenous cannabinoids on hippocampal function also yields insight into their regulation of the diverse behavioral roles in which the hippocampus participates, in both normal and pathological states. It is our goal here to provide an overview of the hippocampal cannabinoid system and to provide context for understanding its participation in regulating cognition, and behavior, that are dependent upon this system. In addition, we will review contemporary studies in which the hippocampal endocannabinoid system either participates in, or is disrupted by pathological states, and relate this to the recreational use of cannabinoid drugs.

2. Cannabinoid control of intrinsic hippocampal circuitry

Initial studies demonstrating relatively high concentrations of cannabinoid binding sites in the hippocampal formation (Devane et al., 1988; Herkenham et al., 1990) also indicated that they are G-protein coupled receptors (Devane et al., 1988; Howlett et al., 1990), and hinted at their potential role in regulating the function of this brain structure. A functional role for what was later recognized as the CB_1R was established initially by the observation that activation of these receptors inhibited cyclic AMP accumulation in the hippocampus (Bidaut-Russell et al., 1990), whereas other studies showed that I_A potassium currents were increased in cultured hippocampal pyramidal neurons (Childers et al., 1993). Later studies in hippocampus soon established what has become one of the tenets of the cannabinoid system in the CNS; that it represents a critical mediator of axon terminal control by providing strong and ubiquitous inhibition of neurotransmitter release (Hoffman and Lupica, 2000; Katona et al., 1999; Misner and Sullivan, 1999; Shen et al., 1996; Shen and Thayer, 1999; Tsou et al., 1999). Additional work also established that cannabinoids inhibit both glutamate and GABA release in the hippocampus through the inhibition of voltage-dependent calcium channels (N and P/Q-type) present in axon terminals, via liberation of βγ G-protein subunits during CB_1R activation (Hoffman and Lupica, 2000; Sullivan, 1999; Twitchell et al., 1997). These studies were aided by the synthesis of the first cannabinoid receptor antagonist, known as SR141716A (rimonabant; Rinaldi-Carmona et al., 1994), that was later shown to also possess inverse agonist properties (Bouaboula et al., 1997; Landsman et al., 1997). Among the principles established by early cannabinoid research in the hippocampus was that CB_1Rs are expressed at very high levels on GABAergic neurons that co-localized the neuropeptide cholecystokinin (CCK), and at much lower, but functionally relevant levels on glutamate neurons (Katona et al., 1999; Kawamura et al., 2006; Tsou et al., 1999). It was also established that the primary psychoactive constituent found in the cannabis plant, Δ^9-tetrahydrocannabinol (Δ^9-THC), activated CB_1Rs at both glutamate and GABA axon terminals in the hippocampus, acting as a partial agonist at glutamate axon terminals, and a full agonist at GABAergic terminals (Laaris et al., 2010; Shen and Thayer, 1999). This distinction was ascribed to the presence of "spare" CB_1Rs on GABA axons, a pharmacological principle in which abundant expression of receptors can permit a full physiological response upon occupation of a relatively small proportion of the total receptor population (Hoyer and Boddeke, 1993; Laaris et al., 2010). Several recent studies have also established that the activation of CB_1Rs on mitochondria can regulate synaptic function (Benard et al., 2012; Hebert-Chatelain et al., 2016).

As the ability of Δ^9-THC to disrupt cognition, and in particular memory and learning, is well-established (Abel, 1970), and the role of the hippocampus in these phenomena well-understood (Drew and Miller, 1974; Essman, 1984; Hampson and Deadwyler, 1998; Miller and Branconnier, 1983), it was hypothesized that these effects of Δ^9-THC occurred through interaction with hippocampal circuitry (Drew et al., 1980; Hampson and Deadwyler, 1998; Howlett et al., 1990). Subsequently, several studies supported this assertion by demonstrating that injections of cannabinoid agonists directly into the hippocampus disrupted spatial memory (Lichtman et al., 1995) and that hippocampal-dependent function was perturbed by peripheral injections of these drugs (Heyser et al., 1993). These studies thereby firmly established that cannabinoids altered hippocampal neuronal function, resulting in impaired hippocampal-dependent information processing. As will be discussed further, these actions are now thought to reflect widespread impairment of hippocampal network activity by cannabinoids.

Whereas development of synthetic cannabinoid molecules such as CP-55,490 and WIN55,212-2, and the use of the phytocannabinoid Δ^9-THC contributed greatly to an understanding of cannabinoid receptors and their roles in regulating neuronal activity and behavior, it was not until the isolation of endocannabinoids, such as anandamide (arachidonoylethanolamide, AEA) and 2-arachodonoylglycerol (2-AG), in mammalian brain tissue (Devane et al., 1992; Stella et al., 1997) that the implications of a brain