7 Effects of Cannabinoid Agonists and Antagonists on Sleep in Laboratory Animals

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Abstract

The cannabinoids are a family of chemical compounds that can be either synthesized or naturally derived. These compounds have been shown to modulate a wide variety of biological processes. In this chapter, the studies detailing the effects of cannabinoids on sleep in laboratory animals are reviewed. Both exogenous and endogenous cannabinoids generally appear to decrease wakefulness and alter rapid eye movement (REM) and non-REM sleep in animal models. In addition, cannabinoids potentiate the effects of sedative-hypnotic drugs. However, the individual contributions of each cannabinoid on sleep processes is more nuanced and may depend on the site of action in the central nervous system. Many studies investigating the mechanism of cannabinoid effects on sleep suggest that the effects of cannabinoids on sleep are mediated via cannabinoid receptors; however, some evidence suggests that some sleep effects may be elicited via non-cannabinoid receptor-dependent mechanisms. More research is necessary to fully elucidate the role of each compound in modulating sleep processes.

Keywords

Laboratory animals · In vivo · Cannabinoids · Cannabinoid receptors · Sleep

7.1 Introduction

The term "cannabinoids" refers to endogenously-produced, plant-derived, or synthetically-produced oxygen-containing C21 aromatic hydrocarbon compounds. The stereotypical and most widely known cannabinoid is Δ9-tetrahydrocannabinol (Δ9-THC), which is the major psychoactive constituent in the plant *Cannbis sativa* (also referred as cannabis, marijuana, etc.). Due to the high lipid solubility and low water solubility of cannabinoids, it was long believed that the pharmacological actions of cannabinoids were due to the disruption of phospholipids in the cell membrane (Pertwee 2005) Though there were hints that cannabinoids might bind to a receptor (Edery et al. 1971), it was not until the early 1990s that that two cannabinoid receptors were cloned, CB_1 (Matsuda et al. 1990) and CB_2 (Munro et al. 1993). Though other putative cannabinoid receptors have been described (Laprairie et al. 2017), the pharmacological

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actions of cannabinoids occur primarily at the CB_1 and CB_2 receptors, which are inhibitory G protein-coupled receptors (Howlett 2002).

Cannabinoids can be divided into two groups. The endogenous cannabinoids, referred to as endocannabinoids, comprise a class of lipophilic compounds based on the general structure of modified arachidonic acid (AA) derivatives (e.g. anandamide, 2-arachidonoylglycerol, etc.) that are naturally produced by cells, while exogenous cannabinoids represent the plant-derived or synthetically-produced compounds that can be either ingested, injected, or inhaled (Childers 2006; Martin et al. 2018). Both endogenous and exogenous cannabinoids bind to either CB_1, CB_2 or both CB_1/CB_2 receptors located on many tissues with varying degrees of affinity (Pertwee 2005). Moreover, both endogenous and exogenous cannabinoids can allosterically modulate other receptors, channels, and enzymes (Pertwee 2005; Hourani and Alexander 2018).

The effects of cannabinoids in health and disease are widely known (Lu and Anderson 2017). Here, we review the effects of cannabinoids on sleep in laboratory animals (Table 7.1).

7.2 Before the Discovery of Cannabinoid Receptors

7.2.1 Exogenous Cannabinoids

The very first studies of sleep and cannabinoids in laboratory animals involved the "classical" exogenous cannabinoids (e.g. Δ9-THC, Δ8-THC, cannabidiol, cannabinol, etc). This group consists of cannabinoids that are either cannabis-derived compounds (phytocannabinoids) or their synthetic analogues (Pertwee 2005). At a minimum, it was known that these classic cannabinoids caused a sedative, depressive, or cataleptic state in various laboratory animals, including nonhuman primates, dogs, cats, rats, mice, rabbits, and gerbils, though specific and detailed changes in sleep were not studied (Sassenrath and Chapman 1975; Grunfeld and Edery 1969; Edery et al. 1971; Scheckel et al. 1968; Carlini et al. 1970; Lipparini et al. 1969; Mechoulam and Gaoni 1967). After these preliminary experiments, researchers further examined the effects of cannabinoids on sleep.

In cats administered an oral form of a marijuana distillate daily for 180 days, a decrease in slow-wave sleep (SWS) and an increase in "drowsy-light" sleep occurred at the 20th day of drug administration. Moreover, these changes in sleep persisted 40 days after cessation of the drug. There were also changes in time spent awake and in rapid eye movement (REM) sleep on isolated days, but no significant and consistent changes were observed throughout the drug trial (Barratt and Adams 1973). Similar findings were found in squirrel monkeys, where orally administered Δ9-THC decreased SWS and increased drowsy sleep and awake time (Adams and Barratt 1975). Rabbits administered intravenous (IV) Δ9-THC had a decreased number of REM bouts on the first day that returned to normal on the third day post-IV injection (Fujimori and Himwich 1973). In a similar study, cats administered Δ8-THC IV or intraperitoneal (IP) had fewer but longer REM sleep bouts (Wallach and Gershon 1973). These early studies provided evidence that cannabinoids modulate sleeping patterns in laboratory animals.

Most of the later studies with cannabinoids have been completed in rat and mouse models. Many of these studies investigated the potentiation of barbiturate or sedative-hypnotic drug-induced sleeping time. The use of "sleeping time" produced by a subsequent IP injection of a barbiturate/sedative-hypnotic was a measure of central nervous system (CNS) activity produced by either: the stimulant or depressive effects on the CNS of the co-administered drug, the co-administered drug increasing or decreasing penetration of the barbiturate into the CNS, or the modulation of metabolism of the barbiturate derived from the co-administered drug (Stevenson and Turnbull 1974). Since the cannabinoid receptors were not yet known, it was thought that cannabinoids modulated sleeping time though modifying metabolism or penetration of the barbiturates. Various THC isomers and their derivatives/metabolites, either inhaled or injected IP, increased barbiturate-induced sleeping time (Stevenson and Turnbull 1974; Berger

Table 7.1 Summary of cannabinoids and their effect on sleep

	Wakefulness	Total sleep	NREM/SW sleep	REM sleep	Drug-induced sleeping time
Exogenous agonists					
Δ9-THC	NC	Increased/ NC	Decreased/NC	Decreased	Increased
Δ8-THC	–	Increased/ NC	Decreased/NC	Decreased	Increased
Marijuana distillate	–	–	Decreased	Decreased	Increased
CBN	–	Increased	–	Decreased	Increased/NC
CBD	Increased	–	Decreased	Decreased	Increased
Cannabichromene	–	–	NC	NC	Increased
Cannabigerol	–	Increased	–	NC	–
CP47,497	–	–	Decreased/ increased	NC	–
WIN55,212	Decreased	Increased	Increased	Decreased	–
ACEA	–	Increased	–	–	–
HU-210	–	Increased	–	–	–
HU-310	–	Increased	–	–	–
PhAR-DBH-Me	NC	–	NC	Decreased	–
Endocannabinoids					
2-AG					
Infused	NC	–	NC	Increased	–
Synthesis inhibited	Increased	–	Decreased	NC	–
Anandamide					
Infused	Decreased	–	Increased	Increased	Increased
Infused Precursor: AA	Increased	–	Decreased	NC	–
Reuptake inhibitor: VDM-11	Decreased	–	Increased	Increased	–
Reuptake inhibitor: OMDM-2	Decreased	–	Increased	Increased	–
Oleamide	Decreased	Increased	Increased	Increased/ decreased	Increased
FAAH inhibitors					
URB597	Increased	–	Decreased	–	–
AM3506	–	–	Increased	Decreased	–
AA-5-HT	Decreased	–	Increased	Increased	–
FAAH knockout	Decreased	–	Increased	–	–
CB receptor knockout	Increased	–	Decreased	Decreased	–
Antagonists/inverse agonists					
Compound 64	Increased	–	Decreased	Decreased	–
SR141716	Increased	–	Decreased	Decreased	–
AM251	Increased/ NC	NC/ Decreased	Increased/NC	Decreased	–
AM281	–	–	NC	–	–
ABD459	NC	NC	NC	Decreased	–
AM630	NC	NC	NC	NC	–

The effects of compounds listed above on wakefulness, total sleep, NREM/slow-wave (SW) sleep, REM sleep, and on drug-induced sleeping time. These compounds either increased, decreased, or had no change (NC)
Δ8-THC Δ8-tetrahydrocannabinol, *Δ9-THC* Δ9-tetrahydrocannabinol, *2-AG* 2-arachidonoylglycerol, *AA* arachidonic acid, *AA-5-HT* N-arachidonoyl-serotonin, *ACEA* arachidonyl-2-chloroethylamide, *CB* cannabinoid, *CBD* Cannabidiol, *CBN* cannabinol, *FAAH* fatty acid amide hydrolase

and Krantz 1972; Bhattacharyya et al. 1980; Bose et al. 1963; Lazaratou et al. 1980; Hatoum et al. 1981; Kaneto and Nagaoka 1981; Katsunori et al. 1993; Martin et al. 1975; Oishi et al. 1988; Sofia and Knobloch 1973, 1974; Sofia 1977; Rating et al. 1972; Segelman et al. 1974; Siemens et al. 1974; Stone et al. 1976; Paton and Pertwee 1972; Watanabe et al. 1980, 1982, 1987, 1990; Kubena and Barry 1970; Giusti et al. 1980; Chiarotti et al. 1980; Yoshimura et al. 1978; Siemens and Kalant 1974; Sofia and Barry 1983; Fujimoto 1972; Narimatsu et al. 1983, 1984, 1985). Similarly, Δ9-THC also increased alcohol-induced sleeping time (Friedman and Gershon 1974). Dogs trained to inhale marijuana smoke also showed an increase in barbiturate-induced sleeping time (Sullivan and Willard 1978). Cannabidiol (CBD) and its derivatives and/or metabolites have been shown in multiple studies to increase barbiturate sleeping time, in part, by modifying liver metabolism of the barbiturate (Stone et al. 1976; Bornheim et al. 1981; Borys et al. 1979; Carlini et al. 1975; Karler et al. 1979; Leite et al. 1982; Yamamoto et al. 1988, 1991). Another cannabinoid, cannabichromene, also increased barbiturate sleeping time (Hatoum et al. 1981). For cannabinol (CBN), there was either no increase or slight increase in barbiturate sleeping time (Fernandes et al. 1974a; Chesher et al. 1974). In combination studies, CBD with Δ9-THC increased barbiturate sleeping time compared to Δ9-THC alone, while CBN with Δ9-THC decreased the sleeping time (Fernandes et al. 1974a, b; Chesher et al. 1974; Krantz et al. 1971; Takahashi and Karniol 1975; Karniol and Carlini 1973). Though the original hypothesis of cannabinoids increasing barbiturate-/sedative-hypnotic-induced sleeping time by decreasing metabolism of the barbiturates/sedative-hypnotics was incorrect, it is now known that the increased sleeping time is due to the increased depressant effect of barbiturates and cannabinoids via their respective receptors (Szabo and Schlicker 2005; Jembrek and Vlainic 2015).

More detailed studies on the effect of cannabinoids on sleep have been completed. Δ9-THC, CBN and cannabigerol injected IP increased total sleep and REM sleep onset in rats; however, Δ9-THC and CBN only decreased time spent in REM (Colasanti et al. 1984a, b). In another study that used single IP injection of Δ9-THC, Δ8-THC, or marjuana distillate, all three compounds reduced SWS and REM sleep, and no REM sleep rebound was observed 5 days post injection. That same study also investigated chronic use (i.e. 20 days) of Δ9-THC, Δ8-THC, or marijuana distillate, and found that REM sleep returned to normal on the fourth day, thus the rodents developing tolerance to the cannabinoids (Moreton and Davis 1973). Δ9-THC injected IP was also associated with EEG changes during SWS and REM sleep (Buonamici et al. 1982). Another cannabinoid, cannabichromene, had no effect (Colasanti et al. 1984a). CBD, after single doses, decreased sleep-wave sleep latency at 20 mg/kg, while at 40 mg/kg, increased SWS time. Following chronic injections of CBD, tolerance developed (Monti 1977). These earlier studies, once again, showed that cannabinoids modulate sleep.

7.3 After the Discovery of Cannabinoid Receptors

7.3.1 Exogenous Cannabinoid Agonists

After the cloning of the cannabinoid receptors in the early 1990s, investigations of cannabinoid agonists and antagonists centered around the role of these receptors in the CNS in the various stages of sleep. In addition, the specificity of these receptors in central sleep-wake centers have also been examined.

In congruence with earlier studies, systemic administration of CBD modulates sleep, as high doses of CBD injected IP increases the percentage of sleep time but increases the latency to REM (Chagas et al. 2013). CBD and some halogenated derivatives of this molecule potentiated the effects of barbiturates on sleep time in mice when injected IV (Usami et al. 1999). However, CBD generally appears to increase wakefulness when injected centrally. In rats, intracerebroventricular (ICV) injection of CBD increased

wakefulness and decreased REM compared to sham or vehicle-injected groups (Murillo-Rodríguez et al. 2006). CBD also increased wakefulness and decreased SWS and REM when injected into the lateral hypothalamus (Murillo-Rodríguez et al. 2008a, 2011) or dorsal raphe (Murillo-Rodríguez et al. 2008a) of rats. These findings are supported by sleep quality studies that demonstrate that injection of CBD into the lateral hypothalamus or dorsal raphe nuclei increased alpha power, yet decreased delta and theta power (Murillo-Rodríguez et al. 2008a). In addition, CBD dose-dependently prevented sleep rebound in sleep-deprived rats (Murillo-Rodríguez et al. 2011).

CBD may increase wakefulness by increasing the activation of wake centers in the hypothalamus or dorsal raphe, as CBD administered ICV increased c-Fos expression in these regions (Murillo-Rodríguez et al. 2006, 2008a). CBD may also work, at least in part, to enhance monoamine transmission, as CBD administration increased extracellular levels of norepinephrine, epinephrine, dopamine, and serotonin in the nucleus accumbens (Murillo-Rodríguez et al. 2006, 2011). CBD injected into the lateral hypothalamus also increased adenosine levels in the nucleus accumbens a few hours post-injection (Mijangos-Moreno et al. 2014). Thus, site of CBD administration must be taken into consideration when interpreting the findings of these studies.

CBD may also work indirectly to reverse stress-induced alterations in sleep by modulating anxiety rather than influencing sleep. Rats repeatedly exposed to an open field increases anxiety-like behavior and decreases REM sleep; injection of CBD into the central amygdala decreases open field anxiety-like behavior and decreased stress-induced REM suppression (Hsiao et al. 2012).

No recent studies have focused on the specific, direct effects of CBN on sleep architecture, although CBN and some halogenated derivatives of CBN potentiated the effects of barbiturates on sleep time (Yoshida et al. 1995).

Δ9-THC appears to modulate REM sleep, as IP injection decreased REM (Calik and Carley 2017; Carley et al. 2002). However, this effect does not appear to be mediated by either CB_1 or CB_2 receptors, as the effects of Δ9-THC on REM sleep was not blocked by either AM251 or AM630, CB_1 and CB_2 receptor antagonists, respectively (Calik and Carley 2017). Δ9-THC may also play a more general role in sedation, as Δ9-THC and some halogenated derivatives of Δ9-THC potentiated the effects of barbiturates on sleep time (Usami et al. 1998).

CP47,497, a potent cannabinoid CB_1 receptor agonist, had a circadian-dependent effect on sleep in mice. Activation of CB_1 receptors with CP47,497 induced more non-rapid eye movement (NREM) sleep and increased NREM bout duration during the dark phase but reduced NREM sleep and decreased NREM bout duration during the light phase. These effects were abolished by CB_1 antagonism with AM281 (Pava et al. 2016). WIN55,212, another potent cannabinoid CB_1 receptor agonist, increased total sleep time, increased NREM sleep, and reduced wakefulness and REM sleep in mice. WIN55,212 also decreased latency to NREM sleep and increased NREM sleep bout duration, while having the opposite effects on REM sleep latency and duration. WIN 55,212 caused a global suppression of normalized spectral power (Goonawardena et al. 2015). Other cannabinoid agonists, arachidonyl-2-chloroethylamide (ACEA), HU-210 (R(−)-7-hydroxy-delta-6-tetrahydrocannabinol-dimethylheptyl), and HU-310 (2-O-arachidonoylglycerylether) increased sleep duration in mice, which was partially mediated by CB_1 receptors (Schuster et al. 2002).

Some newer cannabinoid receptor-targeting drugs also appear to modulate sleep. IP injection of PhAR-DBH-Me ((R,Z)-18-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-18-oxooctadec-9-en-7-yl phenylacetate PhAR-DBH-Me), a putative CB_1 receptor agonist, increased REM sleep in rats. This effect was blocked by AM251, indicating that CB_1 may be mediating

the effects of PhAR-DBH-Me on REM sleep (López et al. 2010).

7.3.2 Endogenous Cannabinoid Agonists

The endogenous cannabinoids, or endocannabinoids, were discovered shortly after the cloning of the cannabinoid receptors (Mechoulam et al. 2014). Since then, numerous studies have investigated the involvement of endocannabinoids on sleep.

Injection of 2-arachidonoylglycerol (2-AG) into the lateral hypothalamus increased REM, but had no effect on waking or SWS. The effects of 2-AG appear to be mediated by CB_1 receptors, as increased REM sleep induced by 2-AG is blocked by AM251 (Pérez-Morales et al. 2013). Diacylglycerol lipase (DAGL) is an enzyme involved with the synthesis of 2-AG. Inhibition of DAGL by a compound injected into the lateral hypothalamus decreased SWS duration, increased wakefulness, and increased latency to REM (Pérez-Morales et al. 2014a). These findings support the role of 2-AG in serving as a sleep-enhancing molecule. 2-AG has also been shown to be present in the laterodorsal tegmentum, a brainstem area involved with arousal and sleep (Soni et al. 2017). Direct injection of 2-AG into the lateral hypothalamus increased c-fos expression in melanin-concentrating neurons of the hypothalamus, an area that increases firing during REM (Pérez-Morales et al. 2013).

Infusions of 2-AG have also been shown to reverse the effects of early life separation on sleep states. Early life maternal separation increased wakefulness, and decreased NREM and REM sleep in adulthood in male rats. 2-AG injection into the lateral hypothalamus of rats subjected to maternal separation decreased wakefulness, and increased NREM and REM. These effects are likely mediated by CB_1 receptors, as the effects of 2-AG in maternally separated rats are blocked by administration of AM251 (Pérez-Morales et al. 2014b). It is unknown, in this early life stress paradigm, whether 2-AG enhances sleep directly or indirectly by altering anxiety-inducing processes, as has been proposed for CBD (Hsiao et al. 2012).

Anandamide (N-arachidonoylethanolamide) is an endocannabinoid that enhances the effects of sleep. Anandamide is present in the laterodorsal tegmentum, a brainstem area involved with arousal and sleep (Soni et al. 2017). Anandamide administered to the cerebral ventricles in male rats decrease waking, increases SWS, and increases REM (Murillo-Rodríguez et al. 1998, 2001). Systemic injection of anandamide also decreases waking and increases SWS (Murillo-Rodriguez et al. 2003) and prolonged pentobarbital-induced sleep time (Watanabe et al. 1999). Some of the effects of anandamide on sleep stages appear to be mediated by CB_1 receptors, as the effects on waking, SWS, and REM are blocked by administration of the CB_1 receptor antagonist SR141716 (Murillo-Rodríguez et al. 2001, 2003).

Anandamide may be working to modulating sleep by specifically targeting various regions involved in sleep. Intra-hippocampal injection of anandamide in rats increases REM but does not alter wake time or SWS. This effect was blocked by AM251. The sleep-inducing effect may be somewhat specific to the hippocampus, as the effects of anandamide on sleep was not observed when anandamide was injected into the cortex (Rueda-Orozco et al. 2010). Other regions may also be mediating the effects of anandamide. Anandamide injected into the entopeduncular nucleus increases NREM and REM (Méndez-Díaz et al. 2013). The effects of anandamide may partially mediated by the pedunculopontine tegmental nucleus, but not the hypothalamic medial preoptic area (Murillo-Rodríguez et al. 2001).

Altering the processes of endogenous anandamide regulation supports the role of anandamide in modulating sleep, although the results are less straightforward. AA, a precursor for anandamide, administered ICV, increases waking and decreases SWS with no change in REM sleep (Murillo-Rodríguez et al. 1998). VDM-11, an inhibitor of facilitated membrane transport of anandamide, decreases wake time, and increases SWS and REM time. However, the effects of VDM-11 on the length of these parameters were

not completely blocked by SR141716, indicating that processes involved with enhancing sleep quantity may not be entirely mediated by CB_1 receptors. On the other hand, CB_1 receptors may be more involved with regulating sleep quality. VDM-11, presumably by increasing anandamide content, increased delta and theta power. When VDM-11 was combined with SR141716, delta and theta power was partially decreased relative to VDM-11 alone (Murillo-Rodríguez et al. 2008b). Additionally, VDM-11 enhanced c-Fos expression in the anterior hypothalamic area, paraventricular thalamic nucleus, and pedunculopontine tegmental nucleus, all brain areas involved in sleep regulation, and reduced the extracellular levels of dopamine collected from nucleus accumbens (Murillo-Rodríguez et al. 2008b, 2012). OMDM-2, another anandamide reuptake inhibitor, also decreased wakefulness and increased NREM and REM sleep, and was also associated with reduced extracellular dopamine levels (Murillo-Rodríguez et al. 2012).

There are several proposed mechanisms for the effects of anandamide on modulating sleep. The effects of anandamide may involve the activity of phospholipase C (Murillo-Rodríguez et al. 2001). Anandamide administration was associated with an accumulation of adenosine in the lateral preoptic area, which may inhibit cholinergic wake-active neurons (Murillo-Rodriguez et al. 2003).

Oleamide (cis-9,10-octadecenamide, also known as cerebrodiene) was first isolated and identified in the cerebrospinal fluid (CSF) of sleep-deprived cats (Lerner et al. 1994). Sleep deprivation did not increase oleamide in plasma, suggesting that deprivation-induced increases in oleamide are specific to the CNS (Basile et al. 1999). Fatty acid amide hydrolase (FAAH), the enzyme associated with the catabolism of oleamide and anandamide, was identified in rat choroid plexus, which may regulate oleamide content in the CSF (Egertová et al. 2000).

Oleamide appears to have a hypnotic effect when administered exogenously and can also dose-dependently potentiate barbiturate-induced sleeping time and decrease sleep latency induced by a subthreshold dose of barbiturate (Yang et al. 1999). When oleamide was administered either centrally or systemically, sleep in rodents increased (Cravatt et al. 1995). Administration of oleamide decreased sleep latency, an effect that was blocked by the antagonism of CB_1 receptors with SR141716 (Mendelson and Basile 1999). Oleamide administered IP decreased wake time and sleep latency, increased NREM and total sleep, and decreased REM in rodents (Laposky et al. 2001; Yang et al. 2003; Huitrón-Reséndiz et al. 2001). However, the effects of oleamide appear to be dependent on the dose, as low doses decreased wake and increased REM, and high doses increased NREM and REM (Carley et al. 2002). Thus, more work is needed to clarify this potential biphasic effect of oleamide on sleep regulation.

Maternal separation (MS) in the early life period increases waking, decreases NREM and REM sleep during adulthood in male rats. Oleamide restored the parameters of MS rats to the same levels observed in non-separated siblings (NMS), but did not alter sleep parameters in NMS rats. The effects of oleamide were not blocked by AM251 in MS rats (Reyes Prieto et al. 2012), indicating a CB_1-receptor independent mechanism.

Further support for endogenous cannabinoid regulation of sleep comes from studies manipulating the enzymatic regulation of endocannabinoids. The FAAH inhibitor, URB597, when injected ICV in male rats, dose-dependently increased wake time, decreased SWS, but had no effect on REM. URB597 also increased c-Fos in the hypothalamus and dorsal raphe. URB597 increased dopamine content and decreased L-DOPA in the nucleus accumbens (Murillo-Rodríguez et al. 2007, 2016). URB597 blocked sleep rebound in sleep-deprived rats (Murillo-Rodríguez et al. 2016). However, systemic administration of URB597 had no effect on sleep (Pava et al. 2016). When a longer lasting FAAH inhibitor, AM3506, was used, NREM sleep increased and REM sleep decreased (Pava et al. 2016). N-arachidonoyl-serotonin (AA-5-HT), another inhibitor of FAAH, dose-dependently decreased waking, increased SWS, and increased REM during the dark phase. These

effects were associated with decreased alpha EEG power spectra, and increased delta and theta power spectra. Administration of AA-5-HT increased adenosine, but decreased dopamine, norepinephrine, epinephrine, and serotonin in the nucleus accumbens. AA-5-HT blocked the effects of CBD and modafinil, a putative dopamine transporter inhibitor, on sleep parameters, EEG power spectra, and extracellular levels of other sleep-modulating neurotransmitters during the lights-on period. CBD and modafinil prevented sleep rebound induced by sleep deprivation, but AA-5-HT blocked these effects (Murillo-Rodríguez et al. 2017). In studies using mice knocked out for FAAH enzyme, FAAH(−/−) mice had decreased brief awakenings, decreased wake time, and increased duration of SWS bouts during the light period compared to wild-type littermates. FAAH(−/−) mice also had decreased EEG power density during wake and REM, while EEG power density was increased during SWS. There was no genotype-specific effects observed in recovery from sleep deprivation (Huitron-Resendiz et al. 2004).

7.4 Antagonists/Inverse Agonists of Cannabinoid Receptors

Numerous antagonists have been investigated to clarify the role of cannabinoid receptors in sleep-associated processes. Compound 64, a potent and selective CB_1 receptor inverse agonist, decreased REM and NREM sleep in rats while increasing wakefulness (Jacobson et al. 2011). SR141716A, a CB_1 receptor antagonist/inverse agonist, increased wakefulness at the expense of SWS and REM sleep, delayed the occurrence of REM sleep, and decreased EEG spectral power during SWS, in part, by increasing adenosine (Murillo-Rodriguez et al. 2003; Jacobson et al. 2011; Santucci et al. 1996). However, other studies using SR141716A showed no effect on sleep parameters (Mendelson and Basile 1999; Navarro et al. 2003). In another study, SR141716 blocked sleep rebound after sleep deprivation by increasing dopamine, norepinephrine, epinephrine, serotonin, and adenosine levels in the brain (Murillo-Rodríguez et al. 2016). AM281, another CB_1 antagonist/inverse agonist, caused fragmented NREM sleep, depending on the time of day AM281 was administered. AM281 also produced broadband changes in EEG power spectral features, and did not reduce NREM sleep rebound caused by sleep deprivation (Pava et al. 2016). A more frequently studied CB_1 receptor antagonist/inverse agonist is AM251, with conflicting reports on its effects on sleep. In regards to total sleep time, AM251 has been shown in two reports to have no change on total sleep time (Calik and Carley 2017; Schuster et al. 2002), while one report showed a decrease in sleep time (Goonawardena et al. 2015). Consistently, AM251 has been shown to decrease REM sleep, while increasing wakefulness (Calik and Carley 2017; Goonawardena et al. 2015; Pérez-Morales et al. 2013; Méndez-Díaz et al. 2013; Reyes Prieto et al. 2012; Herrera-Solís et al. 2010). However, one studied showed no change in wakefulness with AM251 (Calik and Carley 2017). Another study also showed a decrease in REM sleep, but it did not reach statistical significance (López et al. 2010). AM251 has inconsistently been shown modulate NREM sleep, with some studies showing AM251 increasing NREM sleep (Méndez-Díaz et al. 2013; Reyes Prieto et al. 2012; López et al. 2010), while others showing no effect on NREM sleep (Calik and Carley 2017; Goonawardena et al. 2015; Pérez-Morales et al. 2013; Herrera-Solís et al. 2010). AM251 also has been shown to decrease latency to NREM sleep, while increasing latency to REM sleep, and modifying EEG spectral power (Goonawardena et al. 2015). These conflicting results with AM251 could be due to differences between rodent models or dosage of AM251, since AM251 is known to allosterically modulate non-cannabinoid receptors (Baur et al. 2012). ABD459, a neutral antagonist of the CB_1 receptor, only decreased REM sleep, and had no effect on total sleep time or NREM sleep (Goonawardena et al. 2015). AM630, a CB_2 receptor antagonist, had no effect on sleep parameters (Calik and Carley 2017).

7.5 Allosteric Modulation

Cannabinoids are known to allosterically modulate non-cannabinoid receptors (Pertwee 2005). In mice with a targeted mutation at the GABA-A receptor, oleamide administration failed to increase NREM sleep at the expense of wakefulness as seen in the wild-type mice. It is interesting to note that the mutant and wild type mice had no difference in baseline physiological sleep parameters (Laposky et al. 2001). Indeed, work in vitro on GABA-A receptors shows that oleamide is a non-selective modulator of inhibitory ionotropic receptors (Coyne et al. 2002; Lees and Dougalis 2004).

Similarly, oleamide-induced increases in NREM sleep was prevented by serotonin reuptake inhibitors and by activation of serotonin 1A (5-HT_{1A}) receptors. Blockade of the 5-HT_{1A} receptor by WAY100635, a selective antagonist, rescued the oleamide-induced sleep changes (Yang et al. 2003), indicating that serotonergic modulation is involved with cannabinoid effects on sleep. Oleamide may enhance the function of 5-HT_2 receptors (Cheer et al. 1999) and/or GABA receptors (Coyne et al. 2002). In GABA-Aβ3 knockout mice, the effects of oleamide on sleep parameters are not observed at low doses. Only high doses of oleamide administered to these knockout animals were associated with decreased REM and increased sleep latency (Mendelson and Basile 1999).

7.6 Effect of Cannabinoid Receptors on Sleep

Endocannabinoid signaling is important for sleep architecture. A strategy to investigate endocannbinoids' effect of sleep was to knockout the CB_1 receptor. Genetic deletion of CB_1 receptor in mice exhibited increased wakefulness as a result of reduced NREM and REM sleep with no change in NREM delta power (Silvani et al. 2014). These results can be attributed to endocannabinoids modulating up-/down-state transitions in pyramidal neurons (Pava et al. 2014). These studies using targeted genetic manipulations demonstrate the importance of endocannabinoids in modulating sleep.

7.7 Conclusion

Decades of research has shown that cannabinoids, both exogenous and endogenous, modulate sleep in laboratory animals (Table 7.1). Cannabinoids have been shown to potentiate sleeping time induced by other drugs. More directly, introducing exogenous cannabinoid agonists into laboratory animals generally decreased wakefulness, increased NREM sleep, and decreased REM sleep, though in a minority of studies there were conflicting results. Similar results were obtained if endogenous cannabinoids were increased, with the exception that both NREM and REM sleep were increased. These effects of exogenous and endogenous were partially mediated by cannabinoid receptors, though some evidence points to cannabinoids allosterically modulating other receptor systems to affect sleep. Moreover, cannabinoid antagonists, or if cannabinoid receptors were removed, generally increased wakefulness. Though some work has teased out mechanisms with which cannabinoids modulate the sleep systems in the CNS, more work needs to be conducted to clarify the sleep-inducing effects of cannabinoids.

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