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Review

Aging circadian rhythms and cannabinoids

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ABSTRACT

Numerous aspects of mammalian physiology exhibit cyclic daily patterns known as circadian rhythms. However, studies in aged humans and animals indicate that these physiological rhythms are not consistent throughout the life span. The simultaneous development of disrupted circadian rhythms and age-related impairments suggests a shared mechanism, which may be amenable to therapeutic intervention. Recently, the endocannabinoid system has emerged as a complex signaling network, which regulates numerous aspects of circadian physiology relevant to the neurobiology of aging. Agonists of cannabinoid receptor-1 (CB1) have consistently been shown to decrease neuronal activity, core body temperature, locomotion, and cognitive function. Paradoxically, several lines of evidence now suggest that very low doses of cannabinoids are beneficial in advanced age. One potential explanation for this phenomenon is that these drugs exhibit hormesis—a biphasic dose-response wherein low doses produce the opposite effects of higher doses. Therefore, it is important to determine the dose-, age-, and time-dependent effects of these substances on the regulation of circadian rhythms and other processes dysregulated in aging. This review highlights 3 fields—biological aging, circadian rhythms, and endocannabinoid signaling—to critically assess the therapeutic potential of endocannabinoid modulation in aged individuals. If the hormetic properties of exogenous cannabinoids are confirmed, we conclude that precise administration of these compounds may bidirectionally entrain central and peripheral circadian clocks and benefit multiple aspects of aging physiology.

1. Biological aging

In humans, it is well accepted that the end of life is wrought with numerous concomitant disease states, which impose immense personal and social burden. As such, the study of core biological processes involved in aging has become an increasingly prominent topic. Interestingly, there is a clear dichotomy among individuals regarding measures of age-related performance (Rowe and Kahn, 2015). This phenotypic heterogeneity is particularly important when considering cognitive ability because the deterioration of mental functions can greatly influence a person's quality of life. Although many aspects of cognition decline with age, spatial orientation and speed of processing appear particularly susceptible to age-related dysfunction (Hedden and Gabrieli, 2004). Physiologically, the loss of neuronal synapses, chronic inflammation, oxidative stress, and impaired neurovascular coupling all contribute to declining cognitive performance with age (Ekdahl et al., 2009; Mariani et al., 2005; Morrison and Baxter, 2012). Fortunately, several studies indicate age-related cognitive impairment can be partially prevented or delayed using targeted pharmacological or hormonal interventions (Benedict et al., 2004; Cardinali et al., 2012; Lee and Silva, 2009; Li et al., 2011; Lichtenwalner et al., 2001).

One of the earliest reported symptoms of aging is disturbed sleep (Musiek et al., 2015; Rauchs et al., 2013). Sleep/wake cycles are one example of the biologic phenomenon known as circadian rhythms. Although sleep requirements change throughout the life span, sleep quality and consistency are known to markedly deteriorate with age (Bushey et al., 2010). This is relevant to cognitive decline because sleep is an integral factor in the consolidation of memory, and age-related sleep disruptions are often concomitant with cognitive impairment and/or neurodegenerative diseases (Dijk et al., 1999; Espiritu, 2008; Harand et al., 2012; Herculano-Houzel, 2013; Stickgold, 2012; Van Cauter et al., 2000). Despite the necessity of sleep for survival, defining the physiological *purpose* of sleep has been exceedingly difficult. However, relatively recent discovery of the glymphatic system and the sleep-dependent regulation of metabolite clearance from the brain indicates that sleep is vital to the maintenance of proteostasis in the central nervous system (Xie et al., 2013). Because proteostatic dysfunction is common in many pathologies of aging, disturbed sleep may play a causal role in age-related cognitive disorders. Although it remains

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unclear how age-dependent changes in the physiologic regulation of sleep are controlled, the maintenance of healthy sleep patterns in advanced age seems undeniably important to cognitive function.

2. Circadian rhythms and aging

Circadian rhythms are scale-invariant biological patterns that correlate to the cyclic relationship of the Sun and Earth (Pittendrigh, 1993; Refinetti, 2016). Extrinsic cues, such as light and environmental temperature, are known as *zeitgebers* (time-givers), which entrain organisms' behaviors to particular times of day and improve evolutionary fitness Fig. 1 (Aschoff, 1965; Pittendrigh, 1960). Although it has long been observed that animals behave in a manner inherently tied to the time of day, only recently have the molecular and physiological underpinnings of these processes been elucidated (Hardin et al., 1990; Konopka and Benzer, 1971; Liu et al., 1997). Importantly, changes in these *clock genes* are attributed to both the process of aging and the pathogenesis of age-related diseases (Kondratova and Kondratov, 2012; Kress et al., 2018; Musiek et al., 2015).

Seminal work in hamsters and mice revealed that when aged animals are housed in complete darkness, their *free-running* (intrinsic) circadian rhythms of locomotion are significantly different from younger animals (Nakamura et al., 2011, 2016; Pittendrigh and Daan, 1974). In addition, studies of molecular clocks indicate that both rhythm amplitude and regularity deteriorate with age (Yamazaki et al., 2002). More recent studies have confirmed these age-related changes in circadian rhythm amplitude and period are exacerbated in the absence of environmental cues (Nakamura et al., 2015). Although these findings suggest deteriorating rhythms can be masked or compensated by environmental cues, aberrant sleep/wake cycles have also been observed in several species of aged subjects under normal lighting conditions (Bushey et al., 2010; Espiritu, 2008; Saper et al., 2005a; Van Cauter et al., 2000).

In addition to impaired sleep, the amplitude of circadian locomotor activity and body temperature are known to decline in aging humans and rodents (Hu et al., 2013; Huang et al., 2002; Kramer et al., 2001). The circadian range of rectal temperature in mice is ~2.0 °C, which declines to 0.5 °C–1.0 °C in advanced age; a similar reduction in range has been reported in humans (Koster-van Hoffen et al., 1993; Satinoff, 1998; Weitzman et al., 1982). Daily locomotion also goes down in mice, with average daily running wheel counts declining by ~50% (Valentinuzzi et al., 1997). Furthermore, sleep-dependent production of the pleiotropic humoral factor growth hormone declines with age, and it is reported that these disruptions precede or are comorbid with cognitive dysfunction (Michael et al., 1980; Sonntag et al., 2013). A recent study suggests that age-related changes in the epigenetic regulation of the clock gene *Per1* underlie some aspects of cognitive decline (Kwapis et al., 2018). Whether circadian dysfunction is causal in age-related cognitive decline remains to be known, however the striking overlap of these observations warrants further investigation. Taken together, these observations suggest that both molecular and behavioral circadian rhythms might be responsive to and responsible for many aspects of biological aging.

Within the brain, the suprachiasmatic nuclei (SCN) of the mammalian hypothalamus are believed to be the primary neural sites of circadian integration (Saper, 2013). The SCN as a whole, through unknown mechanisms, integrates the oscillatory rhythm of each constituent neuron and collectively adopts a unified tone (Hastings et al., 2018; Liu et al., 1997; Welsh et al., 1995). Neuronal projections from the SCN transmit this coordinated rhythm to surrounding hypothalamic and brainstem structures responsible for basic physiological functions such as the sleep/wake cycle, locomotor activity, regulation of body temperature, and hormone production (Bass and Lazar, 2016; Hastings et al., 2003). At the molecular level, cellular circadian clocks consist of transcription-translation feedback loops which exhibit tightly coupled daily rhythms Fig. 2. When exposed to a normal 24-hour light cycle, neurons of the SCN rhythmically express these clock genes that

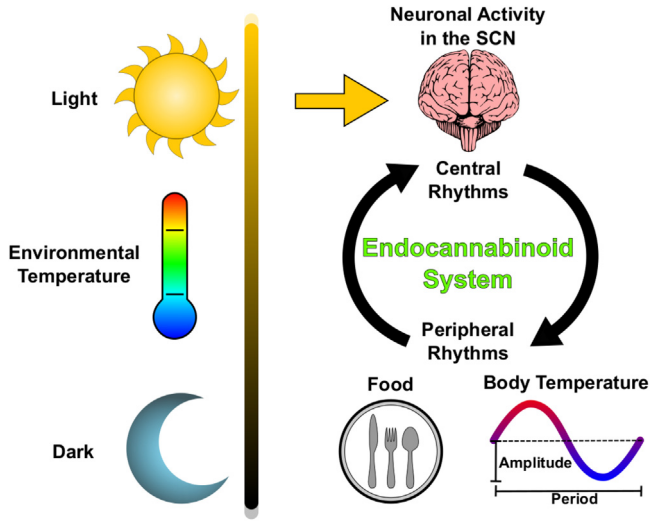

Fig. 1. Environmental inputs and physiological outputs of mammalian circadian rhythms. Routine daily exposure to light entrains the SCN to a 24-hour period via the retinohypothalamic tract. Neurons of the SCN rhythmically alter their rates of firing in response to changing environmental conditions and humoral signals. Outputs from SCN neurons drive central rhythms in hormone production, locomotor activity, feeding behavior, and body temperature. Peripherally, cellular rhythms are entrained by the daily oscillation of body temperature and food intake. Because endocannabinoid activity is known to regulate SCN neurons, body temperature, and food intake, evidence suggests that the endocannabinoid system is a key component of physiological circadian rhythms.

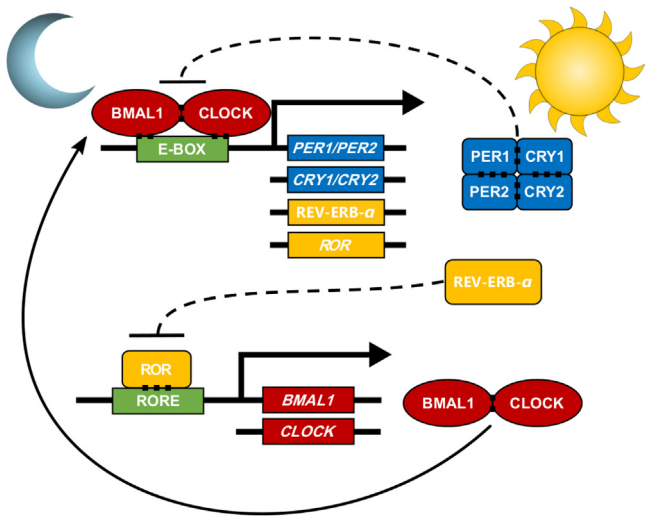

Fig. 2. Molecular components of cellular circadian rhythms. The core circadian molecular loop consists of 2 proteins, Brain and muscle arnt-like 1 (BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK), which interact to form a transcriptional activator complex that stimulates transcription of the Period and Cryptochrome genes (*PER1, PER2, CRY1,* and *CRY2*). The Per and Cry proteins accumulate in the cytoplasm throughout the day and ultimately bind to the BMAL1:CLOCK complex. Sufficient binding of the PER:CRY complex to the BMAL1:CLOCK complex prohibits transcription of *PER* and *CRY* mRNA. As protein levels of PER and CRY diminish, the BMAL1:CLOCK complex is allowed to stimulate transcription once more.

oscillate with periods of roughly 24 hours (Bass and Lazar, 2016; Menaker et al., 1978). Light, temperature, food, and pharmaceuticals can all act as zeitgebers, which modulate endogenous clock gene activity by extending or shortening the period of oscillation (Longo and Panda, 2016; Saper et al., 2005b). Such drugs, known as *chronobiotics,* influence circadian physiology by either directly impinging on core clock molecules or altering entrainment systems. Therapeutically, chronobiotics are used to shift or amplify endogenous circadian rhythms and reduce dissonance with environmental conditions (Redfern et al., 1994). Though circadian dysregulation is reported with chronic or uncontrolled use of exogenous substances such as caffeine, cannabis, and stimulant medications (Burke et al., 2015; Hasler et al., 2012; Stein et al., 2012; Whitehurst et al., 2015). Promising ongoing research suggests that chronobiotics may be beneficial in cases of jet-lag, shift-work, and potentially aging, (Arendt and Skene, 2005; Potter et al., 2016).

The SCN is often considered the primary regulator of mammalian circadian rhythms, although cell-autonomous molecular feedback loops have been observed in nearly all tissues throughout the body (Schibler et al., 2015; Yamazaki et al., 2000). In peripheral tissues, the period of each cell's rhythm is very near to 24 hours, although their exact rates are determined by body temperature, humoral factors, and nutritional state (Hattar et al., 2003; Longo and Panda, 2016; Pittendrigh, 1960; Pittendrigh and Minis, 1964; Rosenwasser and Turek, 2015; Welsh et al., 1995). Critically, in contrast to the clock gene rhythms of peripheral tissues, neurons of the SCN appear resistant to entrainment by body temperature (Buhr et al., 2010; Mohawk et al., 2012). Because the SCN is directly responsible for the rhythm of body temperature, this presents a potential mechanism through which the SCN can regulate clocks in peripheral tissues (Partch et al., 2014; Schibler et al., 2015). Core body temperature—a vital physiological output which exhibits circadian rhythmicity—has consistently been shown to decline with age and older subjects exhibit impaired thermogenesis (Balmagiya and Rozovski, 1983; Harper et al., 2005; Van Someren, 2007). If the circadian rhythms of peripheral tissues are functionally entrained by body temperature, then age-related impairments of thermoregulatory capacity could explain why the rhythms of some peripheral tissues are unable to be properly maintained. Furthermore, because neuronal activity in the SCN determines central clock rhythms, and peripheral cellular clocks are entrained by thermic signals, pharmacological interventions that influence both neuronal activity and body temperature are of particular interest.

Declining circadian function with age is not associated with changes in overall SCN volume; however, several studies report altered physiological properties in this brain region (Roozendaal et al., 1987; Tsukahara et al., 2005). In vivo electrophysiological recordings of the SCN show reduced amplitude and "noisy" signals as animal's age, suggesting that neuronal function is compromised (Nakamura et al., 2011). In addition, increases in reactive astrocytes have been observed in the SCN of aged rodents (Roozendaal et al., 1987; Tsukahara et al., 2005). This is further emphasized by the concomitant age-related reduction in neural excitability within one downstream region of the hypothalamus innervated by the SCN, the subparaventricular zone. Mechanistically, reductions in several forms of potassium conductance have been shown to contribute to age-related alterations in SCN neural activity (Farajnia et al., 2012, 2015). More work is needed to understand the molecular mechanisms that precipitate these functional changes in the SCN and to determine their specific role age-related circadian dysfunction.

Even if targeting the SCN is not currently feasible, several studies demonstrate pharmacological manipulation of the peripheral clock network is possible (Balsalobre et al., 1998; Yamazaki et al., 2000). One of the most profound regulators of life span across species is caloric intake, and evidence in flies suggests that this effect on life span is mediated via peripheral circadian clock gene expression (Katewa et al., 2016). Pharmacologically, dexamethasone was shown to alter clock gene expression in the liver, kidney, and heart via hormonal glucocorticoid signaling (Balsalobre et al., 2000). Peripheral circadian rhythms have also been modulated by drug-induced increases in cAMP levels (Yamazaki et al., 2000). These findings show that although some aged tissues are arrhythmic, they can still be pharmacologically induced to oscillate. Such reports are promising because they suggest the machinery governing clock gene expression in the periphery remains intact even when the system is desynchronized. Targeting cAMP receptors is particularly exciting as G-protein coupled receptors (GPCRs) are often regulators of cAMP. GPCRs are commonly successful drug targets, and over 35% of currently approved drugs act on these receptors (Sriram and Insel, 2018). Collectively, this implies that a large number of proteins may be amenable to therapeutically regulating circadian signaling. Future studies aimed at restoring circadian function within the SCN or preventing peripheral dysregulation may simultaneously benefit multiple pathologies of aging.

3. The endocannabinoid system in advanced age

One potential target for the pharmacological manipulation of circadian rhythms in advanced age is the endocannabinoid system (Howlett et al., 2002). Discovery of the endocannabinoid system occurred when searching for the receptors responsible for the psychotropic effects of plants from the genus *Cannabis* (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993). Multiple cannabinoid receptors have been identified in mammals, including the canonical CB1 and CB2 as well as more-recently identified receptors like GPR55 and GPR18 (Console-Bram et al., 2014; Howlett et al., 2002; Irving et al., 2017; Jarai et al., 1999). These cannabinoid receptors are GPCRs, which exhibit distinct binding affinities for various endogenous and exogenous ligands (Console-Bram et al., 2014; Henstridge et al., 2010; Howlett et al., 2002). Radiographic localization of these receptors revealed profound expression of CB1 in the brain and central nervous tissue, whereas CB2 is primarily located in peripheral immune cells (Herkenham et al., 1990, 1991; Howlett, 1995). The term *cannabinoid* refers to any compound which binds to these receptors, whereas the term *endocannabinoid* specifically refers to endogenously produced ligands (Howlett et al., 2002). The endocannabinoid system consists of these receptors and their endogenous ligands, which include N-arachidonoylethanolamine (Anandamide) and 2-Arachidonoyl glycerol (2-AG) among others (Pertwee, 2014; Wilson and Nicoll, 2002). Numerous studies of the endocannabinoid system demonstrate that these ligands and receptors collectively regulate sleep, hunger, body temperature, and cognition—several of the circadian behaviors disrupted in advanced age (Abel, 1970; Barratt and Adams, 1973; Carlini et al., 1970; Cone et al., 1988).

As with many other physiological processes, the endocannabinoid system varies markedly with age (Bilkei-Gorzo, 2012). There have been conflicting reports regarding age-related changes of CB1 in the brain. Some reports in rodents suggest that CB1 mRNA expression is reduced in advanced age (Canas et al., 2009; Romero et al., 1998), whereas others indicate there is no change or even region-specific increases in CB1 (Berrendero et al., 1998; Liu et al., 2003; Mailleux and Vanderhaeghen, 1992; Wang et al., 2003). These discrepancies are also observed in humans, with postmortem analyses showing reductions in CB1 radiolabeling in some studies, whereas newer PET scans of living individuals showing sex-specific increases in CB1 reactivity within aged females (Mato and Pazos, 2004; Van Laere et al., 2008; Westlake et al., 1994). Despite the various reported changes in expression, studies have shown a

reduction in CB1-stimulated GTPγS functional activity in rodents and humans (Mato and Pazos, 2004; Romero et al., 1998; Wang et al., 2003). In addition to potential changes in receptor expression and function, reductions in the endocannabinoid ligand 2-AG have been observed in advanced age (Piyanova et al., 2015). Considering the importance of this brain region to learning, memory, and pathologies of aging, it is likely that the changing endocannabinoid system impacts cognitive behaviors. In support of this idea, studies using CB1-deficient mice show that reducing these signals leads to the development of unique age-related behavioral disturbances earlier than wild-type mice (Bilkei-Gorzo et al., 2005). Curiously, young CB1-deficient mice outperform wild-type controls in social and object recognition tasks as well as operant learning paradigms, suggesting that the effects of the endocannabinoid system are influenced by the developmental age of the animals (Albayram et al., 2012; Bilkei-Gorzo et al., 2005; Reibaud et al., 1999). Although the exact mechanisms of these fluctuations are still under investigation, it appears that the preservation of endocannabinoid system function is vital to the aging brain.

Given the extensive activity of endocannabinoids throughout the central nervous system, there appears to be a substantial link between the endocannabinoid system and those physiological processes subject to age-related dysfunction. Additional evidence suggests that the endocannabinoid system plays a key role in circadian physiology. Several circadian behaviors are intricately linked to endocannabinoid signaling, namely: thermoregulation, nociception, locomotion, and food intake (Abel, 1970; Barratt and Adams, 1973; Carlini et al., 1970; Cone et al., 1988). Centrally, neurons of the SCN express CB1 and have been shown to alter their firing rates in the presence of synthetic cannabinoid agonists and antagonists (Acuna-Goycolea et al., 2010; Sanford et al., 2008). A recent primate study also revealed a circadian rhythm of cannabinoid receptor transcription in both the central nervous system and peripheral tissues (Mure et al., 2018). Moreover, cannabinoids are powerful regulators of body temperature, which has been shown to entrain peripheral as previously mentioned. Taken together, these findings demonstrate a connection between the behavioral impairments observed in advanced age, disrupted circadian rhythms, and alterations in the endocannabinoid system.

4. Cannabinoid behavioral pharmacology

Although the endocannabinoid system is regulated by endogenous molecules like 2-AG and anandamide, exogenous cannabinoids such as those found in *Cannabis* are also known to modulate this system. Rigorous pharmacological study of *Cannabis* (also known as Marijuana, Marihuana) has a long and complex history (Farnsworth, 1969). Historical records of *Cannabis* use have been documented for millennia, but the structures and potential functions of the chemicals synthesized within *Cannabis* are still being elucidated (Gaoni and Mechoulam, 1964; Matsuda et al., 1990; Munro et al., 1993; Russo, 2014). Two of the most studied *phytocannabinoids* (plant-derived cannabinoids) are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), although growing bodies of literature exist for cannabigerol (CBG), cannabivarin (CBV), and many others (Pertwee, 2014). THC is considered to be the primary psychoactive compound in *Cannabis* and is an agonist of both CB1 and CB2 (Gaoni and Mechoulam, 1964). The mechanism by which CBD exerts its physiological effects is unknown and widely disputed, as the Ki for CB1 and CB2 is over 100 fold lower than that of THC on these receptors (Bow and Rimoldi, 2016). Although most of the focus is on phytocannabinoids like THC, it is important to also note that *Cannabis* produces a wide variety of monoterpenoids and sesquiterpenoids, which may also act directly on cannabinoid receptors (Bahi et al., 2014; Russo, 2011). Extensive reviews of *Cannabis*, phytocannabinoids (Pertwee, 2014), cannabinoid receptors (Howlett et al., 2002), and endocannabinoid pharmacology (Howlett and Abood, 2017) have previously been published.

Human empirical and anecdotal evidence demonstrates that exogenous cannabinoids profoundly impact cognition and physiology (Farnsworth, 1969; Russo, 2014; Zuardi, 2006; Zuardi et al., 2012). However, studies of phytocannabinoids are somewhat difficult to interpret, given the extreme diversity of compounds present in raw plant matter or extracts. As such, knowledge of each cannabinoid's specific pharmacological profile is crucial to consider any potential therapeutic applications for these substances. Receptor-subtype–specific compounds have been vital to delineating the shared and specific effects of CB1 and CB2 on physiological functions (Pertwee, 2006; Soethoudt et al., 2017). Many synthetic cannabinoids have been identified using the Tetrad Assay—a battery of behavioral tasks for assessing CB1 function in rodents (Howlett et al., 2002; Metna-Laurent et al., 2017). These tests measure locomotion, catalepsy, thermoregulation, and analgesia as endpoints of CB1 receptor activity (Metna-Laurent et al., 2017). Although the Tetrad Assay has proven useful as a drug screening mechanism, its relatively limited scope does not permit full characterization of an animal's behavioral status, especially when one considers the behaviors altered in advanced age. In addition to nociception, locomotion, and thermoregulation, CB1 activity has been shown to regulate learning and memory, sleep/wake activity, food intake, anxiety, attention, and cardiovascular function (Babson et al., 2017; Hlozek et al., 2017; Javadi-Paydar et al., 2017; Jensen et al., 2015; Long, L. E. et al., 2010; Maldonado et al., 2016; Rohleder et al., 2016; Tai et al., 2015).

In both animals and humans, memory impairment following acute or chronic administration of CB1 agonists has been repeatedly reported (Essman, 1984; Heyser et al., 1993; Lichtman et al., 1995; Nakamura et al., 1991; Taffe, 2012). However, alternative studies indicate that these memory-impairing effects are dose and age dependent (Amal et al., 2010; Bilkei-Gorzo et al., 2017; Bolla et al., 2002; Fishbein et al., 2012; Stark and Dews, 1980; Suliman et al., 2017). Recent evidence in rodents suggest that some of these effects can be partially blocked by coadministration with CBD, a finding which may explain why anecdotes of whole-plant *Cannabis* use often disagree with the receptor-specific effects seen in animal studies (Morgan et al., 2010; Mori et al., 2017). The diverse behavioral phenotypes elicited from modulation of the endocannabinoid system emphasize the importance of understanding this integral physiological system.

Despite the large volume of studies conducted on exogenously administered cannabinoids, synthesis of this data is difficult because of inconsistent compositions of phytocannabinoids, doses, and routes of administration (Boggs et al., 2018; Grotenhermen, 2003; McGilveray, 2005; McLaughlin, 2018). In addition, there is a significant disparity between preclinical dosing regimens and those currently accepted for human consumption. Regarding THC, many rodent experiments use intraperitoneal doses ranging from 1 mg/kg to 30 mg/kg; however, current recreational and clinical amounts for humans are closer to 0.15 mg/kg orally (Ahmed et al., 2014; Deiana et al., 2012; Killestein et al., 2002; Martin-Santos et al., 2012). Although the pharmacokinetic profiles vary markedly between rodents and humans (Reagan-Shaw et al., 2008), several studies now show that injections of THC can alter animal behavior and molecular signaling at doses as low as 0.002 mg/kg (Fishbein et al., 2012; Sarne et al., 2018). Recent attempts have been made to more adequately model the routes of administrations used by humans (Grella et al., 2014; Hlozek et al., 2017; Javadi-Paydar et al., 2017; Nguyen et al., 2016; Swortwood et al., 2017; Vandrey et al.,

2017). The results of these studies indicate that cannabinoids administered orally have a delayed onset and longer duration of action than when they are inhaled (Hart et al., 2002; Hlozek et al., 2017; Vandrey et al., 2017). These route of administration-dependent effects are to be expected; however, preliminary evidence suggests that chronic *Cannabis* use may also alter the gut microbiome (Panee et al., 2017). Given that recreational and medicinal cannabinoids are often administered orally, future studies of microbiome-mediated cannabinoid metabolism are of particular importance. Taken together, it is imperative that these discrepancies in dosing and route of administration are carefully considered and discussed in future studies.

5. Hormesis and cannabinoid chronopharmacology

There is little debate regarding the deleterious effects of cannabinoids in high doses; however, the reported effects of more modest amounts are somewhat conflicting. High doses of THC ($\geq$3 mg/kg in rodents, $\geq$0.15 mg/kg in humans) are consistently reported to disrupt cognitive function in rodents and produce psychoactive effects in humans (Abel, 1971, 1975; Bolla et al., 2002; Essman, 1984; Filbey et al., 2014; Heyser et al., 1993). Despite the consistent inhibitory or soporific effects of cannabinoids at higher doses, studies that have examined lower amounts often report stimulatory effects at the lowest doses tested (Crawley et al., 1993; Grisham and Ferraro, 1972; Katsidoni et al., 2013; Long, Leonora E et al., 2010; Rey et al., 2012; Sulcova et al., 1998; Suliman et al., 2017; Taylor and Fennessy, 1977). Although exogenous cannabinoids are known to induce hypothermia and hypolocomotion, several investigations have reported increased body temperature and locomotion following treatment at low doses (Sofia, 1972; Taylor and Fennessy, 1977; Tselnicker et al., 2007). A similar biphasic effect of THC on intracranial self-stimulation was reported in rats treated with 0.1 or 1.0 mg/kg (Katsidoni et al., 2013). Based on this study, the authors concluded that an acute intraperitoneal injection of 0.1 mg/kg THC induced reward-seeking behavior, whereas the higher dose elicited anhedonia. Mechanistically, the effects of higher doses appear to be mediated in-part by CB1 signaling in GABAergic neurons (Rey et al., 2012). A growing body of literature now suggests that low doses ($\leq$3 mg/kg) of THC and other synthetic cannabinoids may prevent certain aspects of age-related cognitive decline in rodents (Bilkei-Gorzo et al., 2017; Marchalant et al., 2008; Sarne et al., 2018; Suliman et al., 2017).

Within the context of exogenously administered cannabinoids and cognition, the hormetic dose-response of this compound may rectify these disparate reports (Calabrese and Rubio-Casillas, 2018). *Hormesis* describes a biphasic dose-response where low amounts of a substance produce opposite effects of higher doses (Calabrese and Baldwin, 2002). Great efforts have been made in recent years to catalog and characterize reports of dose-response experiments, which cannot be explained by traditional, linear models (Calabrese, 2013). Continued work in this field now suggests that one explanation for this biphasic response is through *preconditioning* (Calabrese, 2016, 2018; Sarne et al., 2011). This is in line with work previously presented by Sarne et al., which indicates that exposure to low doses of exogenous cannabinoids blunt the negative impacts of subsequent insults (Sarne, 2018; Sarne et al., 2011). These findings have intriguing implications for the study of aging because preconditioning biological systems during critical developmental windows may bolster resilience to age-related dysfunction (Calabrese and Mattson, 2017; Gidday, 2015).

Interestingly, the hormetic dose-response of THC on body temperature has been reported for many years Fig. 3A (Sarne et al., 2011; Sofia, 1972; Taylor and Fennessy, 1977). In addition, exogenous cannabinoids alter anxiety-related behaviors in dose-dependent, bidirectional manner, although the nature of this relationship is poorly understood (Jenniches et al., 2016; Witkin et al., 2005; Wotjak, 2005; Zlebnik and Cheer, 2016). Early observations regarding the time and temperature dependence of THC's effects may also shed light on these seemingly incongruent findings. A classic study by Ernest Abel revealed that the time of day in which THC is administered drastically affects the physiological response, a phenomenon now referred to as *chronopharmacology* (Abel, 1973). Similarly, an elegant study by Pertwee and Tavendale in 1977 revealed that the ambient temperature markedly altered rates of oxygen consumption and body temperature changes induced by THC administration (Pertwee and Tavendale, 1979). Furthermore, sex-specific responses to cannabinoids may present a confounding factor when interpreting these results, as previous reports have indicated that doses of THC that impaired cognition in males actually improved measures in females (Craft et al., 2013; Makela et al., 2006).

Given the current evidence, it is difficult to discern whether the cognitive-enhancing effects of low-dose cannabinoids are due to "true" hormesis, age-dependent changes in endocannabinoid function, or both. The work by Sarne et al. demonstrates that exceptionally small amounts of THC (0.002 mg/kg) are sufficient to influence neurobiology. These studies reported that a single dose of 0.002 mg/kg, IP produced neuroprotection in young male mice and lasting cognitive enhancement in old females (Fishbein et al., 2012; Sarne et al., 2018; Senn et al., 2008; Tselnicker et al., 2007). Critically, pilot studies at this dose were reported to increase body temperature and stimulate locomotion—a finding that supports the hormetic stimulatory response (Sarne et al., 2011). Although the evidence presented by Suliman also supports that the effects of cannabinoids are age dependent, the data from this study indicate that there is a "window" in which cannabinoids may improve function (Suliman et al., 2017). Although there are not enough doses in these studies to clearly demonstrate hormesis, we feel that this evidence is supportive nonetheless.

The range of doses studied by Sarne et al. indicate that doses which improve cognitive performance in old animals (0.002 mg/kg) cause impairments in young animals, and the studies by Bilkei Gorzo et al. (3 mg/kg THC) in old animals also support this. These findings, and others, indicate a clear effect of aging on response to exogenous cannabinoid administration. The possibility remains, however, that the lowest dose of THC reported by Sarne et al. (0.0005 mg/kg THC, IP) in young animals may still lie above the stimulatory hormetic range for this age group. This hypothesis is supported by their biochemical studies, which report the highest activation of P-ERK in the cerebella of young animals at this dose (0.0005 mg/kg) (Amal, 2010).

To date, we are unaware of a modern study specifically designed to determine if cannabinoids exhibit hormesis, and whether this hormetic dose-range is altered with age. Even if preliminary evidence suggests there is cannabinoid hormesis in young animals, it remains to be seen if this same hormetic curve persists with age or if the stimulatory range might change. Although there are several potential mechanistic explanations for these age-dependent effects, recent studies support a desensitization of endocannabinoid machinery with age. Ultimately, additional studies testing multiple doses in young and old animals are required to directly compare the hormetic range of exogenous cannabinoids.

Despite the importance of these pharmacological considerations across different compounds and systems, hormesis and chronopharmacology remain understudied components of many biomedical studies, particularly those in aged animals (Dallmann et al., 2014). These 2 distinct properties have intriguing implications for the potential use of cannabinoids as therapeutics. Namely, that it may be possible to attain opposing physiological effects

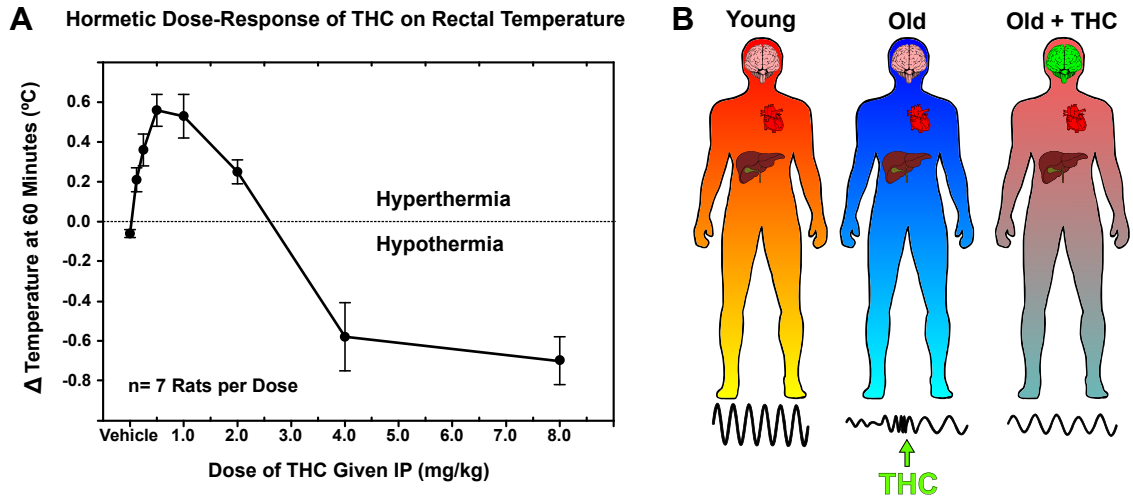

Fig. 3. Hormesis and the chronobiotic potential of THC in aged subjects. (A) Hormetic dose-response of THC on rectal temperature in rats. Data redrawn from: Sofia, R.D., 1972. A paradoxical effect for 1-tetrahydrocannabinol on rectal temperature in rats. Research communications in chemical pathology and pharmacology, 4(2), pp.281–288. (B) Declining amplitude and increasing lability of central and peripheral rhythms with age may be amenable to therapeutics, which simultaneously alter neuronal activity in the SCN and body temperature. Using the chronopharmacological properties and hormetic dose-response of THC, low-dose exposure may help to rescue dysfunctional clocks in aging systems.

based solely on the dose and time-of-administration. To this end, application of these pharmacological properties to a highly dynamic and heterogenous condition such as age-dependent circadian dysfunction may provide a wide range of therapeutic potential Fig. 3B.

6. Conclusions

Taken together, the findings discussed here suggest that altered circadian rhythms are a potential biomarker of aging, and restoration or preservation of these rhythms in aged individuals might benefit certain age-related pathologies. The endocannabinoid system is a promising target in the treatment of age-related disease, given the diverse physiological processes it regulates. Centrally, modulation of SCN activity by cannabinoids supports their classification as a chronobiotics, and careful, therapeutic application use of these compounds may serve to restore abnormal behavioral rhythms in aged subjects. Moreover, the biphasic effects of cannabinoids on body temperature may allow for the “tuning” of peripheral molecular clocks. Many additional experiments are necessary to fully characterize the hormetic dose-response of exogenous cannabinoids such as THC and examine their potential efficacy in the amelioration of age-related circadian dysfunction. As societal opinions of "aging as a disease" and "cannabinoids as medicine" shift, further inquiry of these previously intractable topics may prove greatly beneficial to human health.

Disclosure

The authors have no actual or potential conflicts of interest.

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References

Abel, E.L., 1970. Marijuana and memory. Nature 227, 1151–1152.
Abel, E.L., 1971. Marihuana and memory: acquisition or retrieval? Science 173, 1038–1040.
Abel, E.L., 1973. Chronopharmacology of delta9-tetrahydrocannabinol hypothermia in mice. Experientia 29, 1528–1529.
Abel, E.L., 1975. Marihuana, learning, and memory. Int. Rev. Neurobiol. 18, 329–356.
Acuna-Goycolea, C., Obrietan, K., van den Pol, A.N., 2010. Cannabinoids excite circadian clock neurons. J. Neurosci. 30, 10061–10066.
Ahmed, A.I., van den Elsen, G.A., Colbers, A., van der Marck, M.A., Burger, D.M., Feuth, T.B., Rikkert, M.G., Kramers, C., 2014. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: a randomized controlled trial. Eur. Neuropsychopharmacol. 24, 1475–1482.
Albayram, O., Bilkei-Gorzo, A., Zimmer, A., 2012. Loss of CB1 receptors leads to differential age-related changes in reward-driven learning and memory. Front. Aging Neurosci. 4, 34.
Amal, H., Fridman-Rozevich, L., Senn, R., Strelnikov, A., Gafni, M., Keren, O., Sarne, Y., 2010. Long-term consequences of a single treatment of mice with an ultra-low dose of Delta9-tetrahydrocannabinol (THC). Behav. Brain Res. 206, 245–253.
Arendt, J., Skene, D.J., 2005. Melatonin as a chronobiotic. Sleep Med. Rev. 9, 25–39.
Aschoff, J., 1965. Circadian rhythms in man. Science 148, 1427–1432.
Babson, K.A., Sottile, J., Morabito, D., 2017. Cannabis, cannabinoids, and sleep: a review of the literature. Curr. Psychiatry Rep. 19, 23.
Bahi, A., Al Mansouri, S., Al Memari, E., Al Ameri, M., Nurulain, S.M., Ojha, S., 2014. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. Physiol. Behav. 135, 119–124.
Balmagiya, T., Rozovski, S.J., 1983. Age-related changes in thermoregulation in male albino rats. Exp. Gerontol. 18, 199–210.
Balsalobre, A., Brown, S.A., Marcacci, L., Tronche, F., Kellendonk, C., Reichardt, H.M., Schütz, G., Schibler, U., 2000. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. Science 289, 2344–2347.
Balsalobre, A., Damiola, F., Schibler, U., 1998. A serum shock induces circadian gene expression in mammalian tissue culture cells. Cell 93, 929–937.
Barratt, E.S., Adams, P.M., 1973. Chronic marijuana usage and sleep-wakefulness cycles in cats. Biol. Psychiatry 6, 207–214.
Bass, J., Lazar, M.A., 2016. Circadian time signatures of fitness and disease. Science 354, 994–999.
Benedict, C., Hallschmid, M., Hatke, A., Schultes, B., Fehm, H.L., Born, J., Kern, W., 2004. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 29, 1326–1334.
Berrendero, F., Romero, J., Garcıa-Gil, L., Suarez, I., De la Cruz, P., Ramos, J., Fernandez-Ruiz, J., 1998. Changes in cannabinoid receptor binding and mRNA levels in several brain regions of aged rats. Biochim. Biophys. Acta 1407, 205–214.
Bilkei-Gorzo, A., 2012. The endocannabinoid system in normal and pathological brain ageing. Philos. Trans. R Soc. Lond. B Biol. Sci. 367, 3326–3341.
Bilkei-Gorzo, A., Albayram, O., Draffehn, A., Michel, K., Piyanova, A., Oppenheimer, H., Dvir-Ginzberg, M., Racz, I., Ulas, T., Imbeault, S., Bab, I.,

Schultze, J.L., Zimmer, A., 2017. A chronic low dose of Delta(9)-tetrahydrocannabinol (THC) restores cognitive function in old mice. Nat. Med. 23, 782–787.
Bilkei-Gorzo, A., Racz, I., Valverde, O., Otto, M., Michel, K., Sastre, M., Zimmer, A., 2005. Early age-related cognitive impairment in mice lacking cannabinoid CB1 receptors. Proc. Natl. Acad. Sci. U. S. A. 102, 15670–15675.
Boggs, D.L., Nguyen, J.D., Morgenson, D., Taffe, M.A., Ranganathan, M., 2018. Clinical and preclinical evidence for functional interactions of cannabidiol and delta(9)-tetrahydrocannabinol. Neuropsychopharmacol : official Publ. Am. Coll. Neuropsychopharmacol. 43, 142–154.
Bolla, K.I., Brown, K., Eldreth, D., Tate, K., Cadet, J.L., 2002. Dose-related neurocognitive effects of marijuana use. Neurology 59, 1337–1343.
Bow, E.W., Rimoldi, J.M., 2016. The structure–function relationships of classical cannabinoids: CB1/CB2 modulation. Perspect. Med. Chem. 8, 17–39.
Buhr, E.D., Yoo, S.H., Takahashi, J.S., 2010. Temperature as a universal resetting cue for mammalian circadian oscillators. Science 330, 379–385.
Burke, T.M., Markwald, R.R., McHill, A.W., Chinoy, E.D., Snider, J.A., Bessman, S.C., Jung, C.M., O'neill, J.S., Wright, K.P., 2015. Effects of caffeine on the human circadian clock in vivo and in vitro. Sci. Transl. Med. 7, 305ra146.
Bushey, D., Hughes, K.A., Tononi, G., Cirelli, C., 2010. Sleep, aging, and lifespan in Drosophila. BMC Neurosci. 11, 56.
Calabrese, E.J., 2013. Hormetic mechanisms. Crit. Rev. Toxicol. 43, 580–606.
Calabrese, E.J., 2016. Preconditioning is hormesis part I: documentation, dose-response features and mechanistic foundations. Pharmacol. Res. 110, 242–264.
Calabrese, E.J., 2018. Hormesis: path and progression to significance. Int. J. Mol. Sci. 19, 2871.
Calabrese, E.J., Baldwin, L.A., 2002. Defining hormesis. Hum. Exp. Toxicol. 21, 91–97.
Calabrese, E.J., Mattson, M.P., 2017. How does hormesis impact biology, toxicology, and medicine? NPJ Aging Mech. Dis. 3, 13.
Calabrese, E.J., Rubio-Casillas, A., 2018. Biphasic effects of THC in memory and cognition. Eur. J. Clin. Invest. 48, e12920.
Canas, P.M., Duarte, J.M., Rodrigues, R.J., Köfalvi, A., Cunha, R.A., 2009. Modification upon aging of the density of presynaptic modulation systems in the hippocampus. Neurobiol. Aging 30, 1877–1884.
Cardinali, D.P., Vigo, D.E., Olivar, N., Vidal, M.F., Furio, A.M., Brusco, L.I., 2012. Therapeutic application of melatonin in mild cognitive impairment. Am. J. Neurodegener. Dis. 1, 280–291.
Carlini, E.A., Hamaoui, A., Bieniek, D., Korte, F., 1970. Effects of (–) delta-9-trans-tetrahydrocannabinol and a synthetic derivative on maze performance of rats. Pharmacology 4, 359–368.
Cone, E.J., Johnson, R.E., Paul, B.D., Mell, L.D., Mitchell, J., 1988. Marijuana-laced brownies: behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J. Anal. Toxicol. 12, 169–175.
Console-Bram, L., Brailoiu, E., Brailoiu, G.C., Sharir, H., Abood, M.E., 2014. Activation of GPR18 by cannabinoid compounds: a tale of biased agonism. Br. J. Pharmacol. 171, 3908–3917.
Craft, R.M., Marusich, J.A., Wiley, J.L., 2013. Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? Life Sci. 92, 476–481.
Crawley, J.N., Corwin, R.L., Robinson, J.K., Felder, C.C., Devane, W.A., Axelrod, J., 1993. Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents. Pharmacol. Biochem. Behav. 46, 967–972.
Dallmann, R., Brown, S.A., Gachon, F., 2014. Chronopharmacology: new insights and therapeutic implications. Annu. Rev. Pharmacol. Toxicol. 54, 339–361.
Deiana, S., Watanabe, A., Yamasaki, Y., Amada, N., Arthur, M., Fleming, S., Woodcock, H., Dorward, P., Pigliacampo, B., Close, S., 2012. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive–compulsive behaviour. Psychopharmacology 219, 859–873.
Devane, W.A., Dysarz 3rd, F.A., Johnson, M.R., Melvin, L.S., Howlett, A.C., 1988. Determination and characterization of a cannabinoid receptor in rat brain. Mol. Pharmacol. 34, 605–613.
Dijk, D.J., Duffy, J.F., Riel, E., Shanahan, T.L., Czeisler, C.A., 1999. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J. Physiol. 516 (Pt 2), 611–627.
Ekdahl, C., Kokaia, Z., Lindvall, O., 2009. Brain inflammation and adult neurogenesis: the dual role of microglia. Neuroscience 158, 1021–1029.
Espiritu, J.R., 2008. Aging-related sleep changes. Clin. Geriatr. Med. 24, 1–14.
Essman, E.J., 1984. Marijuana intoxication in rats: interruption of recent memory and effect on brain concentration of delta 9-tetrahydrocannabinol. Psychol. Rep. 55, 563–567.
Farajnia, S., Meijer, J.H., Michel, S., 2015. Age-related changes in large-conductance calcium-activated potassium channels in mammalian circadian clock neurons. Neurobiol. Aging 36, 2176–2183.
Farajnia, S., Michel, S., Deboer, T., vanderLeest, H.T., Houben, T., Rohling, J.H., Ramkisoensing, A., Yasenkov, R., Meijer, J.H., 2012. Evidence for neuronal desynchrony in the aged suprachiasmatic nucleus clock. J. Neurosci. 32, 5891–5899.
Farnsworth, N.R., 1969. Pharmacognosy and chemistry of "cannabis sativa. J. Am. Pharm. Assoc. 9, 410–414 passim.
Filbey, F.M., Aslan, S., Calhoun, V.D., Spence, J.S., Damaraju, E., Caprihan, A., Segall, J., 2014. Long-term effects of marijuana use on the brain. Proc. Natl. Acad. Sci. 111, 16913–16918.
Fishbein, M., Gov, S., Assaf, F., Gafni, M., Keren, O., Sarne, Y., 2012. Long-term behavioral and biochemical effects of an ultra-low dose of Delta9-tetrahydrocannabinol (THC): neuroprotection and ERK signaling. Exp. Brain Res. 221, 437–448.
Gaoni, Y., Mechoulam, R., 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86, 1646–1647.
Gidday, J.M., 2015. Extending injury-and disease-resistant CNS phenotypes by repetitive epigenetic conditioning. Front Neurol. 6, 42.
Grella, C.E., Rodriguez, L., Kim, T., 2014. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in Los Angeles. J. Psychoactive Drugs 46, 263–272.
Grisham, M.G., Ferraro, D.P., 1972. Biphasic effects of 9 -tetrahydrocannabinol on variable interval schedule performance in rats. Psychopharmacologia 27, 163–169.
Grotenhermen, F., 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin. Pharmacokinet. 42, 327–360.
Harand, C., Bertran, F., Doidy, F., Guenole, F., Desgranges, B., Eustache, F., Rauchs, G., 2012. How aging affects sleep-dependent memory consolidation? Front. Neurol. 3, 8.
Hardin, P.E., Hall, J.C., Rosbash, M., 1990. Feedback of the Drosophila period gene product on circadian cycling of its messenger RNA levels. Nature 343, 536–540.
Harper, D.G., Volicer, L., Stopa, E.G., McKee, A.C., Nitta, M., Satlin, A., 2005. Disturbance of endogenous circadian rhythm in aging and Alzheimer disease. Am. J. Geriatr. Psychiatry 13, 359–368.
Hart, C.L., Ward, A.S., Haney, M., Comer, S.D., Foltin, R.W., Fischman, M.W., 2002. Comparison of smoked marijuana and oral Delta(9)-tetrahydrocannabinol in humans. Psychopharmacology (Berl) 164, 407–415.
Hasler, B.P., Smith, L.J., Cousins, J.C., Bootzin, R.R., 2012. Circadian rhythms, sleep, and substance abuse. Sleep Med. Rev. 16, 67–81.
Hastings, M.H., Maywood, E.S., Brancaccio, M., 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat. Rev. Neurosci. 1.
Hastings, M.H., Reddy, A.B., Maywood, E.S., 2003. A clockwork web: circadian timing in brain and periphery, in health and disease. Nat. Rev. Neurosci. 4, 649–661.
Hattar, S., Lucas, R.J., Mrosovsky, N., Thompson, S., Douglas, R.H., Hankins, M.W., Lem, J., Biel, M., Hofmann, F., Foster, R.G., Yau, K.W., 2003. Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. Nature 424, 76–81.
Hedden, T., Gabrieli, J.D., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5, 87.
Henstridge, C.M., Balenga, N.A., Schröder, R., Kargl, J.K., Platzer, W., Martini, L., Arthur, S., Penman, J., Whistler, J.L., Kostenis, E., 2010. GPR55 ligands promote receptor coupling to multiple signalling pathways. Br. J. Pharmacol. 160, 604–614.
Herculano-Houzel, S., 2013. Neuroscience. Sleep it out. Science 342, 316–317.
Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1991. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J. Neurosci. 11, 563–583.
Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1990. Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci. U. S. A. 87, 1932–1936.
Heyser, C.J., Hampson, R.E., Deadwyler, S.A., 1993. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. J. Pharmacol. Exp. Ther. 264, 294–307.
Hlozek, T., Uttl, L., Kaderabek, L., Balikova, M., Lhotkova, E., Horsley, R.R., Novakova, P., Sichova, K., Stefkova, K., Tyls, F., Kuchar, M., Palenicek, T., 2017. Pharmacokinetic and behavioural profile of THC, CBD, and THC+CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion in vivo of CBD to THC. Eur. Neuropsychopharmacol. : J. Eur. Coll. Neuropsychopharmacol. 27, 1223–1237.
Howlett, A.C., 1995. Pharmacology of cannabinoid receptors. Annu. Rev. Pharmacol. Toxicol. 35, 607–634.
Howlett, A.C., Abood, M.E., 2017. CB1 and CB2 receptor pharmacology. Adv. Pharmacol. 80, 169–206.
Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G., 2002. International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. 54, 161–202.
Hu, K., Harper, D.G., Shea, S.A., Stopa, E.G., Scheer, F.A., 2013. Noninvasive fractal biomarker of clock neurotransmitter disturbance in humans with dementia. Sci. Rep. 3, 2229.
Huang, Y.-L., Liu, R.-Y., Wang, Q.-S., Van Someren, E.J., Xu, H., Zhou, J.-N., 2002. Age-associated difference in circadian sleep–wake and rest–activity rhythms. Physiol. Behav. 76, 597–603.
Irving, A., Abdulrazzaq, G., Chan, S.L.F., Penman, J., Harvey, J., Alexander, S.P.H., 2017. Cannabinoid receptor-related orphan G protein-coupled receptors. Adv. Pharmacol. 80, 223–247.
Jarai, Z., Wagner, J.A., Varga, K., Lake, K.D., Compton, D.R., Martin, B.R., Zimmer, A.M., Bonner, T.I., Buckley, N.E., Mezey, E., Razdan, R.K., Zimmer, A., Kunos, G., 1999. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc. Natl. Acad. Sci. U. S. A. 96, 14136–14141.
Javadi-Paydar, M., Nguyen, J.D., Grant, Y., Vandewater, S.A., Cole, M., Taffe, M.A., 2017. Effects of Δ9-THC and Cannabidiol Vapor Inhalation in Male and Female Rats. Psychopharmacology (Berl) 235, 2541–2557.

Jenniches, I., Ternes, S., Albayram, O., Otte, D.M., Bach, K., Bindila, L., Michel, K., Lutz, B., Bilkei-Gorzo, A., Zimmer, A., 2016. Anxiety, stress, and fear response in mice with reduced endocannabinoid levels. Biol. Psychiatry 79, 858–868.
Jensen, B., Chen, J., Furnish, T., Wallace, M., 2015. Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr. Pain Headache Rep. 19, 50.
Katewa, S.D., Akagi, K., Bose, N., Rakshit, K., Camarella, T., Zheng, X., Hall, D., Davis, S., Nelson, C.S., Brem, R.B., 2016. Peripheral circadian clocks mediate dietary restriction-dependent changes in lifespan and fat metabolism in Drosophila. Cell Metab. 23, 143–154.
Katsidoni, V., Kastellakis, A., Panagis, G., 2013. Biphasic effects of Δ9-tetrahydrocannabinol on brain stimulation reward and motor activity. Int. J. Neuropsychopharmacol. 16, 2273–2284.
Killestein, J., Hoogervorst, E.L., Reif, M., Kalkers, N.F., Van Loenen, A.C., Staats, P.G., Gorter, R.W., Uitdehaag, B.M., Polman, C.H., 2002. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology 58, 1404–1407.
Kondratova, A.A., Kondratov, R.V., 2012. The circadian clock and pathology of the ageing brain. Nat. Rev. Neurosci. 13, 325–335.
Konopka, R.J., Benzer, S., 1971. Clock mutants of Drosophila melanogaster. Proc. Natl. Acad. Sci. U. S. A. 68, 2112–2116.
Koster-van Hoffen, G., Mirmiran, M., Bos, N., Witting, W., Delagrange, P., Guardiola-Lemaitre, B., 1993. Effects of a novel melatonin analog on circadian rhythms of body temperature and activity in young, middle-aged, and old rats. Neurobiol. Aging 14, 565–569.
Kramer, A., Yang, F.C., Snodgrass, P., Li, X., Scammell, T.E., Davis, F.C., Weitz, C.J., 2001. Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. Science 294, 2511–2515.
Kress, G.J., Liao, F., Dimitry, J., Cedeno, M.R., FitzGerald, G.A., Holtzman, D.M., Musiek, E.S., 2018. Regulation of amyloid-β dynamics and pathology by the circadian clock. J. Exp. Med. 215, 1059–1068.
Kwapis, J.L., Alaghband, Y., Kramár, E.A., López, A.J., Ciernia, A.V., White, A.O., Shu, G., Rhee, D., Michael, C.M., Montellier, E., 2018. Epigenetic regulation of the circadian gene Per1 contributes to age-related changes in hippocampal memory. Nat. Commun. 9, 3323.
Lee, Y.S., Silva, A.J., 2009. The molecular and cellular biology of enhanced cognition. Nat. Rev. Neurosci. 10, 126–140.
Li, R.C., Guo, S.Z., Raccurt, M., Moudilou, E., Morel, G., Brittian, K.R., Gozal, D., 2011. Exogenous growth hormone attenuates cognitive deficits induced by intermittent hypoxia in rats. Neuroscience 196, 237–250.
Lichtenwalner, R.J., Forbes, M.E., Bennett, S.A., Lynch, C.D., Sonntag, W.E., Riddle, D.R., 2001. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 107, 603–613.
Lichtman, A.H., Dimen, K.R., Martin, B.R., 1995. Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats. Psychopharmacology (Berl) 119, 282–290.
Liu, C., Weaver, D.R., Strogatz, S.H., Reppert, S.M., 1997. Cellular construction of a circadian clock: period determination in the suprachiasmatic nuclei. Cell 91, 855–860.
Liu, P., Bilkey, D.K., Darlington, C.L., Smith, P.F., 2003. Cannabinoid CB1 receptor protein expression in the rat hippocampus and entorhinal, perirhinal, postrhinal and temporal cortices: regional variations and age-related changes. Brain Res. 979, 235–239.
Long, L.E., Chesworth, R., Huang, X.-F., McGregor, I.S., Arnold, J.C., Karl, T., 2010. A behavioural comparison of acute and chronic Δ9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. Int. J. Neuropsychopharmacol. 13, 861–876.
Longo, V.D., Panda, S., 2016. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 23, 1048–1059.
Mailleux, P., Vanderhaeghen, J.J., 1992. Age-related loss of cannabinoid receptor binding sites and mRNA in the rat striatum. Neurosci. Lett. 147, 179–181.
Makela, P., Wakeley, J., Gijsman, H., Robson, P.J., Bhagwagar, Z., Rogers, R.D., 2006. Low doses of Δ-9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in young, healthy adults. Neuropsychopharmacology 31, 462.
Maldonado, R., Banos, J.E., Cabanero, D., 2016. The endocannabinoid system and neuropathic pain. Pain 157 (Suppl 1), S23–S32.
Marchalant, Y., Cerbai, F., Brothers, H.M., Wenk, G.L., 2008. Cannabinoid receptor stimulation is anti-inflammatory and improves memory in old rats. Neurobiol. Aging 29, 1894–1901.
Mariani, E., Polidori, M., Cherubini, A., Mecocci, P., 2005. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. J. Chromatogr. B Analyt. Technol Biomed Life Sci 827, 65–75.
Martin-Santos, R., Crippa, J.A., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., Allen, P., Seal, M., Langohr, K., Farre, M., Zuardi, A.W., McGuire, P.K., 2012. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr. Pharm. Des. 18, 4966–4979.
Mato, S., Pazos, A., 2004. Influence of age, postmortem delay and freezing storage period on cannabinoid receptor density and functionality in human brain. Neuropharmacology 46, 716–726.
Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.C., Bonner, T.I., 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346, 561–564.
McGilveray, I.J., 2005. Pharmacokinetics of cannabinoids. Pain Res. Manag. 10 (Suppl A), 15A–22A.
McLaughlin, R.J., 2018. Toward a translationally relevant preclinical model of cannabis use. Neuropsychopharmacology 43, 213.
Menaker, M., Takahashi, J.S., Eskin, A., 1978. The physiology of circadian pacemakers. Annu. Rev. Physiol. 40, 501–526.
Metna-Laurent, M., Mondesir, M., Grel, A., Vallee, M., Piazza, P.V., 2017. Cannabinoid-induced Tetrad in mice. Curr. Protoc. Neurosci. 80.
Michael, S.D., Kaplan, S.B., Macmillan, B.T., 1980. Peripheral plasma concentrations of LH, FSH, prolactin and GH from birth to puberty in male and female mice. J. Reprod. Fertil. 59, 217–222.
Mohawk, J.A., Green, C.B., Takahashi, J.S., 2012. Central and peripheral circadian clocks in mammals. Annu. Rev. Neurosci. 35, 445–462.
Morgan, C.J., Schafer, G., Freeman, T.P., Curran, H.V., 2010. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. Br. J. Psychiatry 197, 285–290.
Mori, M.A., Meyer, E., Soares, L.M., Milani, H., Guimaraes, F.S., de Oliveira, R.M., 2017. Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia. Prog. Neuropsychopharmacol. Biol. Psychiatry 75, 94–105.
Morrison, J.H., Baxter, M.G., 2012. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat. Rev. Neurosci. 13, 240.
Munro, S., Thomas, K.L., Abu-Shaar, M., 1993. Molecular characterization of a peripheral receptor for cannabinoids. Nature 365, 61–65.
Mure, L.S., Le, H.D., Benegiamo, G., Chang, M.W., Rios, L., Jillani, N., Ngotho, M., Kariuki, T., Dkhissi-Benyahya, O., Cooper, H.M., 2018. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. Science 359, eaao0318.
Musiek, E.S., Xiong, D.D., Holtzman, D.M., 2015. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. Exp. Mol. Med. 47, e148.
Nakamura, E.M., da Silva, E.A., Concilio, G.V., Wilkinson, D.A., Masur, J., 1991. Reversible effects of acute and long-term administration of delta-9-tetrahydrocannabinol (THC) on memory in the rat. Drug Alcohol Depend. 28, 167–175.
Nakamura, T.J., Nakamura, W., Tokuda, I.T., Ishikawa, T., Kudo, T., Colwell, C.S., Block, G.D., 2015. Age-related changes in the circadian system unmasked by constant conditions(1,2,3). eNeuro 2.
Nakamura, T.J., Nakamura, W., Yamazaki, S., Kudo, T., Cutler, T., Colwell, C.S., Block, G.D., 2011. Age-related decline in circadian output. J. Neurosci. 31, 10201–10205.
Nakamura, T.J., Takasu, N.N., Nakamura, W., 2016. The suprachiasmatic nucleus: age-related decline in biological rhythms. J. Physiol. Sci. 66, 367–374.
Nguyen, J.D., Aarde, S.M., Vandewater, S.A., Grant, Y., Stouffer, D.G., Parsons, L.H., Cole, M., Taffe, M.A., 2016. Inhaled delivery of Delta(9)-tetrahydrocannabinol (THC) to rats by e-cigarette vapor technology. Neuropharmacology 109, 112–120.
Panee, J., Gerschenson, M., Chang, L., 2017. Associations between microbiota, mitochondrial function, and cognition in chronic marijuana users. J. Neuroimmune Pharmacol. 1–10.
Partch, C.L., Green, C.B., Takahashi, J.S., 2014. Molecular architecture of the mammalian circadian clock. Trends Cell Biol. 24, 90–99.
Pertwee, R., 2006. The pharmacology of cannabinoid receptors and their ligands: an overview. Int. J. Obes. 30, S13–S18.
Pertwee, R.G., 2014. Handbook of Cannabis. Oxford University Press, USA.
Pertwee, R.G., Tavendale, R., 1979. Effects of δ 9-tetrahydrocannabinol, 2.4-dinitrophenol and pentolinium tartrate on behavioural thermoregulation in mice. Br. J. Pharmacol. 66, 39–50.
Pittendrigh, C.S., 1960. Circadian rhythms and the circadian organization of living systems. Cold Spring Harb. Symp. Quant. Biol. 25, 159–184.
Pittendrigh, C.S., 1993. Temporal organization: reflections of a Darwinian clock-watcher. Annu. Rev. Physiol. 55, 16–54.
Pittendrigh, C.S., Daan, S., 1974. Circadian oscillations in rodents: a systematic increase of their frequency with age. Science 186, 548–550.
Pittendrigh, C.S., Minis, D.H., 1964. The entrainment of circadian oscillations by light and their role as photoperiodic clocks. Am. Nat. 98, 261–294.
Piyanova, A., Lomazzo, E., Bindila, L., Lerner, R., Albayram, O., Ruhl, T., Lutz, B., Zimmer, A., Bilkei-Gorzo, A., 2015. Age-related changes in the endocannabinoid system in the mouse hippocampus. Mech. Ageing Dev. 150, 55–64.
Potter, G.D., Skene, D.J., Arendt, J., Cade, J.E., Grant, P.J., Hardie, L.J., 2016. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. Endocr. Rev. 37, 584–608.
Rauchs, G., Carrier, J., Peigneux, P., 2013. Sleep and cognition in the elderly. Front. Neurol. 4, 71.
Reagan-Shaw, S., Nihal, M., Ahmad, N., 2008. Dose translation from animal to human studies revisited. FASEB J. 22, 659–661.
Redfern, P., Minors, D., Waterhouse, J., 1994. Circadian rhythms, jet lag, and chronobiotics: an overview. Chronobiol. Int. 11, 253–265.
Refinetti, R., 2016. Circadian Physiology. CRC press, Boca Raton, FL.
Reibaud, M., Obinu, M.C., Ledent, C., Parmentier, M., Bohme, G.A., Imperato, A., 1999. Enhancement of memory in cannabinoid CB1 receptor knock-out mice. Eur. J. Pharmacol. 379, R1–R2.
Rey, A.A., Purrio, M., Viveros, M.-P., Lutz, B., 2012. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA B receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology 37, 2624.
Rohleder, C., Muller, J.K., Lange, B., Leweke, F.M., 2016. Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. Front Pharmacol. 7, 422.

Romero, J., Berrendero, F., Manzanares, J., Pérez, A., Corchero, J., Fuentes, J.A., Fernández-Ruiz, J.J., Ramos, J.A., 1998. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to Δ9-tetrahydrocannabinol. Synapse 30, 298–308.
Roozendaal, B., van Gool, W.A., Swaab, D.F., Hoogendijk, J.E., Mirmiran, M., 1987. Changes in vasopressin cells of the rat suprachiasmatic nucleus with aging. Brain Res. 409, 259–264.
Rosenwasser, A.M., Turek, F.W., 2015. Neurobiology of circadian rhythm regulation. Sleep Med. Clin. 10, 403–412.
Rowe, J.W., Kahn, R.L., 2015. Successful aging 2.0: conceptual expansions for the 21st century. J. Gerontol. B Psychol. Sci. Soc. Sci. 70, 593–596.
Russo, E.B., 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br. J. Pharmacol. 163, 1344–1364.
Russo, E.B., 2014. The Pharmacological History of Cannabis. Handbook of Cannabis. Oxford University Press, Oxford, pp. 23–43.
Sanford, A.E., Castillo, E., Gannon, R.L., 2008. Cannabinoids and hamster circadian activity rhythms. Brain Res. 1222, 141–148.
Saper, C.B., 2013. The central circadian timing system. Curr. Opin. Neurobiol. 23, 747–751.
Saper, C.B., Cano, G., Scammell, T.E., 2005a. Homeostatic, circadian, and emotional regulation of sleep. J. Comp. Neurol. 493, 92–98.
Saper, C.B., Scammell, T.E., Lu, J., 2005b. Hypothalamic regulation of sleep and circadian rhythms. Nature 437, 1257–1263.
Sarne, Y., 2018. THC for age-related cognitive decline? Aging 10, 3628–3629.
Sarne, Y., Asaf, F., Fishbein, M., Gafni, M., Keren, O., 2011. The dual neuroprotective–neurotoxic profile of cannabinoid drugs. Br. J. Pharmacol. 163, 1391–1401.
Sarne, Y., Toledano, R., Rachmany, L., Sasson, E., Doron, R., 2018. Reversal of age-related cognitive impairments in mice by an extremely low dose of tetrahydrocannabinol. Neurobiol. Aging 61, 177–186.
Satinoff, E., 1998. Patterns of circadian body temperature rhythms in aged rats. Clin. Exp. Pharmacol. Physiol. 25, 135–140.
Schibler, U., Gotic, I., Saini, C., Gos, P., Curie, T., Emmenegger, Y., Sinturel, F., Gosselin, P., Gerber, A., Fleury-Olela, F., 2015. Clock-talk: Interactions between Central and Peripheral Circadian Oscillators in Mammals. Cold Spring Harb. Symp. Quant. Biol. 80, 223–232.
Senn, R., Keren, O., Hefetz, A., Sarne, Y., 2008. Long-term cognitive deficits induced by a single, extremely low dose of tetrahydrocannabinol (THC): behavioral, pharmacological and biochemical studies in mice. Pharmacol. Biochem. Behav. 88, 230–237.
Soethoudt, M., Grether, U., Fingerle, J., Grim, T.W., Fezza, F., de Petrocellis, L., Ullmer, C., Rothenhausler, B., Perret, C., van Gils, N., Finlay, D., MacDonald, C., Chicca, A., Gens, M.D., Stuart, J., de Vries, H., Mastrangelo, N., Xia, L., Alachouzos, G., Baggelaar, M.P., Martella, A., Mock, E.D., Deng, H., Heitman, L.H., Connor, M., Di Marzo, V., Gertsch, J., Lichtman, A.H., Maccarrone, M., Pacher, P., Glass, M., van der Stelt, M., 2017. Cannabinoid CB2 receptor ligand profiling reveals biased signalling and off-target activity. Nat. Commun. 8, 13958.
Sofia, R.D., 1972. A paradoxical effect for 1 -tetrahydrocannabinol on rectal temperature in rats. Res. Commun. Chem. Pathol. Pharmacol. 4, 281–288.
Sonntag, W.E., Deak, F., Ashpole, N., Toth, P., Csiszar, A., Freeman, W., Ungvari, Z., 2013. Insulin-like growth factor-1 in CNS and cerebrovascular aging. Front. Aging Neurosci. 5, 27.
Sriram, K., Insel, P.A., 2018. G protein-coupled receptors as targets for approved drugs: how many targets and how many drugs? Mol. Pharmacol. 93, 251–258.
Stark, P., Dews, P.B., 1980. Cannabinoids. I. Behavioral effects. J. Pharmacol. Exp. Ther. 214, 124–130.
Stein, M.A., Weiss, M., Hlavaty, L., 2012. ADHD treatments, sleep, and sleep problems: complex associations. Neurotherapeutics 9, 509–517.
Stickgold, R., 2012. To sleep: perchance to learn. Nat. Neurosci. 15, 1322–1323.
Sulcova, E., Mechoulam, R., Fride, E., 1998. Biphasic effects of anandamide. Pharmacol. Biochem. Behav. 59, 347–352.
Suliman, N.A., Taib, C.N.M., Moklas, M.A.M., Basir, R., 2017. Delta-9-Tetrahydrocannabinol ((9)-THC) induce neurogenesis and improve cognitive performances of male sprague dawley rats. Neurotox. Res. 33, 402–411.
Swortwood, M.J., Newmeyer, M.N., Andersson, M., Abulseoud, O.A., Scheidweiler, K.B., Huestis, M.A., 2017. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. Drug Test. Anal. 9, 905–915.
Taffe, M.A., 2012. Delta(9)Tetrahydrocannabinol impairs visuo-spatial associative learning and spatial working memory in rhesus macaques. J. Psychopharmacol. 26, 1299–1306.
Tai, S., Hyatt, W.S., Gu, C., Franks, L.N., Vasiljevik, T., Brents, L.K., Prather, P.L., Fantegrossi, W.E., 2015. Repeated administration of phytocannabinoid Delta(9)-THC or synthetic cannabinoids JWH-018 and JWH-073 induces tolerance to hypothermia but not locomotor suppression in mice, and reduces CB1 receptor expression and function in a brain region-specific manner. Pharmacol. Res. 102, 22–32.
Taylor, D.A., Fennessy, M.R., 1977. Biphasic nature of the effects of delta9-tetrahydrocannabinol on body temperature and brain amines of the rat. Eur. J. Pharmacol. 46, 93–99.
Tselnicker, I., Keren, O., Hefetz, A., Pick, C.G., Sarne, Y., 2007. A single low dose of tetrahydrocannabinol induces long-term cognitive deficits. Neurosci. Lett. 411, 108–111.
Tsukahara, S., Tanaka, S., Ishida, K., Hoshi, N., Kitagawa, H., 2005. Age-related change and its sex differences in histoarchitecture of the hypothalamic suprachiasmatic nucleus of F344/N rats. Exp. Gerontol. 40, 147–155.
Valentinuzzi, V.S., Scarbrough, K., Takahashi, J.S., Turek, F.W., 1997. Effects of aging on the circadian rhythm of wheel-running activity in C57BL/6 mice. Am. J. Physiol. 273 (6 Pt 2), R1957–R1964.
Van Cauter, E., Leproult, R., Plat, L., 2000. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 284, 861–868.
Van Laere, K., Goffin, K., Casteels, C., Dupont, P., Mortelmans, L., de Hoon, J., Bormans, G., 2008. Gender-dependent increases with healthy aging of the human cerebral cannabinoid-type 1 receptor binding using [18F] MK-9470 PET. Neuroimage 39, 1533–1541.
Van Someren, E.J., 2007. Thermoregulation and aging. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R99–R102.
Vandrey, R., Herrmann, E.S., Mitchell, J.M., Bigelow, G.E., Flegel, R., LoDico, C., Cone, E.J., 2017. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. J. Anal. Toxicol. 41, 83–99.
Wang, L., Liu, J., Harvey-White, J., Zimmer, A., Kunos, G., 2003. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. Proc. Natl. Acad. Sci. 100, 1393–1398.
Weitzman, E.D., Moline, M.L., Czeisler, C.A., Zimmerman, J.C., 1982. Chronobiology of aging: temperature, sleep-wake rhythms and entrainment. Neurobiol. Aging 3, 299–309.
Welsh, D.K., Logothetis, D.E., Meister, M., Reppert, S.M., 1995. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron 14, 697–706.
Westlake, T., Howlett, A., Bonner, T., Matsuda, L., Herkenham, M., 1994. Cannabinoid receptor binding and messenger RNA expression in human brain: an in vitro receptor autoradiography and in situ hybridization histochemistry study of normal aged and Alzheimer's brains. Neuroscience 63, 637–652.
Whitehurst, L.N., Fogler, K., Hall, K., Hartmann, M., Dyche, J., 2015. The effects of chronic marijuana use on circadian entrainment. Chronobiology Int. 32, 561–567.
Wilson, R.I., Nicoll, R.A., 2002. Endocannabinoid signaling in the brain. Science 296, 678–682.
Witkin, J.M., Tzavara, E.T., Nomikos, G.G., 2005. A role for cannabinoid CB1 receptors in mood and anxiety disorders. Behav. Pharmacol. 16, 315–331.
Wotjak, C.T., 2005. Role of endogenous cannabinoids in cognition and emotionality. Mini Rev. Med. Chem. 5, 659–670.
Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., Takano, T., Deane, R., Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. Science 342, 373–377.
Yamazaki, S., Numano, R., Abe, M., Hida, A., Takahashi, R.-i., Ueda, M., Block, G.D., Sakaki, Y., Menaker, M., Tei, H., 2000. Resetting central and peripheral circadian oscillators in transgenic rats. Science 288, 682–685.
Yamazaki, S., Straume, M., Tei, H., Sakaki, Y., Menaker, M., Block, G.D., 2002. Effects of aging on central and peripheral mammalian clocks. Proc. Natl. Acad. Sci. U. S. A. 99, 10801–10806.
Zlebnik, N.E., Cheer, J.F., 2016. Beyond the CB1 receptor: is cannabidiol the answer for disorders of motivation? Annu. Rev. Neurosci. 39, 1–17.
Zuardi, A.W., 2006. History of cannabis as a medicine: a review. Braz J Psychiatry 28, 153–157.
Zuardi, A.W., Crippa, J.A., Hallak, J.E., Bhattacharyya, S., Atakan, Z., Martin-Santos, R., McGuire, P.K., Guimaraes, F.S., 2012. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Curr. Pharm. Des. 18, 5131–5140.