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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 three 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.

Keywords

Advanced Age; Circadian Rhythm; *Cannabis*; Cognition; Chronopharmacology; Chronobiotic; Endocannabinoid; Hormesis

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

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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, since the deterioration of mental functions can greatly influence a person's quality of life. Though 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. Though sleep requirements change throughout the lifespan, sleep quality and consistency are known to markedly deteriorate with age (Bushey et al., 2010). This is relevant to cognitive decline since 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). Since proteostatic dysfunction is common in many pathologies of aging, disturbed sleep may play a causal role in age-related cognitive disorders. Although it remains 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 Figure 1 (Aschoff, 1965; Pittendrigh, 1960). Though 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; Nakamura et al., 2016; Pittendrigh and Daan, 1974). Additionally, 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). Though 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 $\sim 2.0^{\circ}\text{C}$, which declines to $0.5\text{--}1.0^{\circ}\text{C}$ 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 $\sim 50\%$ (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* underlies 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 Figure 2. When exposed to a normal 24-hour light cycle, neurons of the SCN rhythmically express these clock genes that 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, shiftwork, 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). Since 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, since neuronal activity in the SCN determines central clock rhythms, and peripheral cellular clocks are entrained by thermic signals, pharmacological interventions which 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 (Roosendaal et al., 1987; Tsukahara et al., 2005). In vivo electrophysiological recordings of the SCN show reduced amplitude and "noisy" signals as animals age, suggesting that neuronal function is compromised (Nakamura et al., 2011). Additionally, increases in reactive astrocytes have been observed in the SCN of aged rodents (Roosendaal 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., 2015; Farajnia et al., 2012). 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 lifespan across species is caloric intake, and evidence in flies suggests that this effect on lifespan 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, since 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, while CB2 is primarily located in peripheral immune cells (Herkenham et al., 1991; Herkenham et al., 1990; Howlett, 1995). The term *cannabinoid* refers to any compound which binds to these receptors, while 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-arachidonylethanolamine (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), while 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 post-mortem analyses showing reductions in CB1 radiolabeling in some studies, while 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 wildtype mice (Bilkei-Gorzo et al., 2005). Curiously, young CB1-deficient mice outperform wildtype 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 K_i for CB1 and CB2 is over 100 fold lower than that of THC on these receptors (Bow and Rimoldi, 2016). Though 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). Though 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 these effects can be partially blocked by co-administration 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 due to inconsistent compositions of phytocannabinoids, doses, and routes of administration (ROAs) (Boggs et al., 2018; Grotenhermen, 2003; McGilveray, 2005; McLaughlin, 2018). Additionally, 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 1mg/kg to 30mg/kg, however, current recreational and clinical amounts for humans are closer to 0.15mg/kg orally (Ahmed et al., 2014; Deiana et al., 2012; Killestein et al., 2002; Martin-Santos et al., 2012). While 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 0.002mg/kg (Fishbein et al., 2012; Sarne et al., 2018). Recent attempts have been made to more adequately model the ROAs 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 (3mg/kg in rodents, 0.15mg/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 which 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). Though 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 1.0mg/kg (Katsidoni et al., 2013). Based on this study, the authors concluded that an acute intraperitoneal injection of 0.1mg/kg THC induced reward-seeking behavior while 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 (3mg/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; Calabrese, 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, since 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 Figure 3A (Sarne et al., 2011; Sofia, 1972; Taylor and Fennessy, 1977). Additionally, exogenous cannabinoids alter anxiety-related behaviors in dose-dependent, bi-directional 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 and colleagues demonstrates that exceptionally small amounts of THC (0.002mg/kg) are sufficient to influence neurobiology. These studies reported that a single dose of 0.002mg/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 which supports the hormetic stimulatory response (Sarne et al., 2011). While 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 (0.002mg/kg) cause impairments in young animals, and the studies by Bilkei Gorzo et al. (3mg/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. (0.0005mg/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 (0.0005mg/kg) (Amal 2010). Since we are unaware of a study which

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. Though 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 two distinct properties have intriguing implications for the potential use of cannabinoids as therapeutics. Namely, that it may be possible to attain opposing physiological effects 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 Figure 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.

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Highlights

- Altered circadian rhythms are concomitant with numerous age-related disease states.
- The endocannabinoid system is a relatively novel target in aging research.
- Cannabinoids are capable of modifying both central and peripheral circadian clocks.
- Cannabinoids reportedly stimulate at low doses, suggesting they exhibit hormesis.
- Modulation of the endocannabinoid system may have therapeutic value in aging.

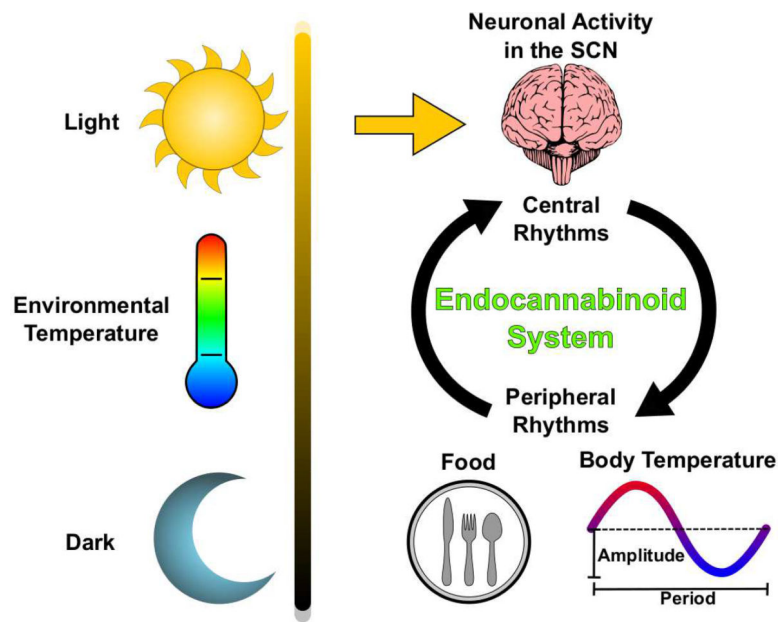


Figure 1. Environmental inputs and physiological outputs of mammalian circadian rhythms. Routine daily exposure to light entrains the SCN to a 24-hour period via the retinohypothalamic tract. Neurons of the SCN rhythmically alter their rates of firing in response to changing environmental conditions 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. Since 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.

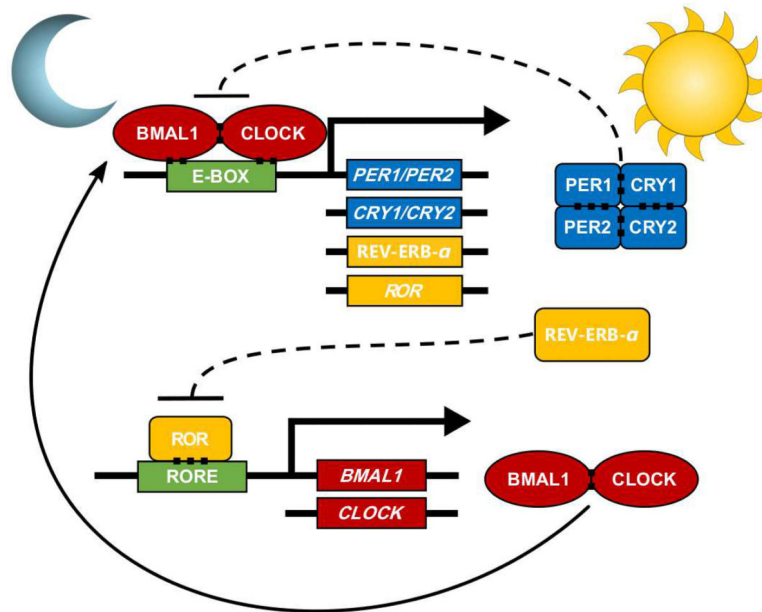


Figure 2: Molecular components of cellular circadian rhythms.

The core circadian molecular loop consists of two 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.

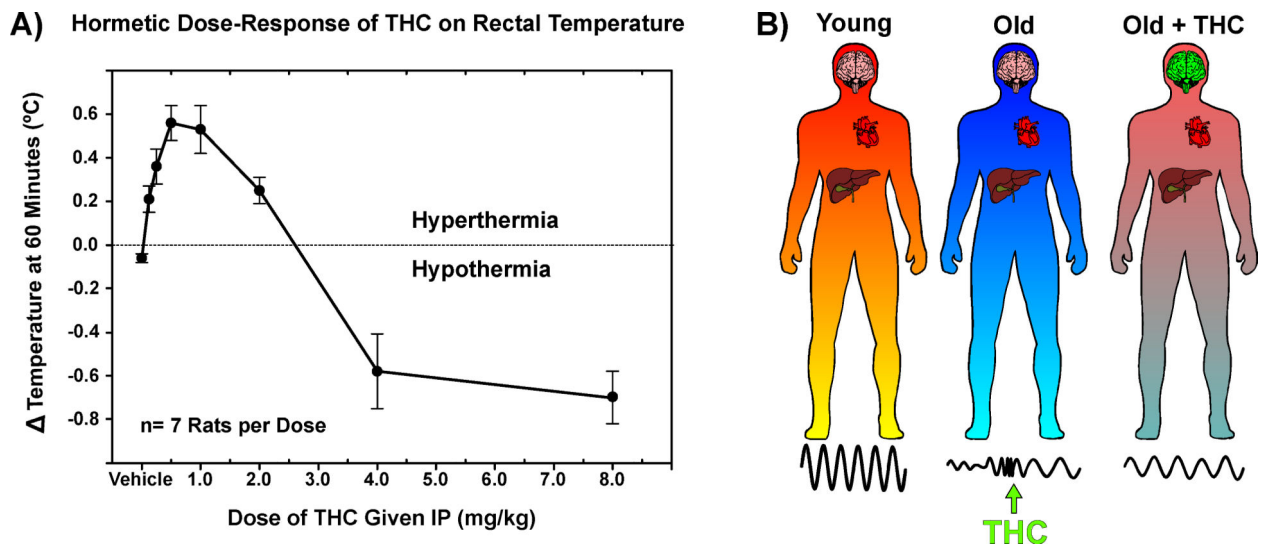


Figure 3: Hormesis and the chronobiotic potential of THC in aged subjects.

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.