Exploring the relationships of gamma-hydroxybutyrate and sleep on metabolism, physiology, and behavior in humans

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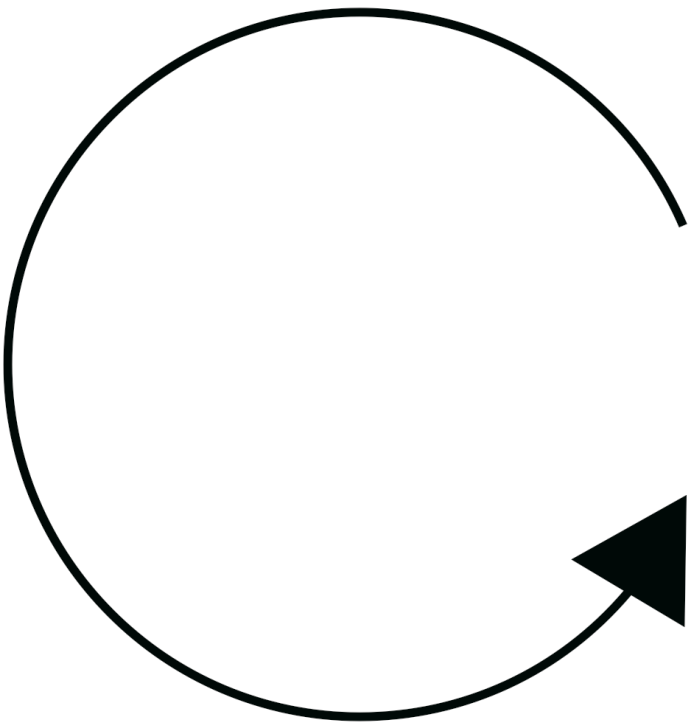
CHAPTER 11

Summary, Conclusions & Future Perspectives



Summary and conclusions

Part I - Neurobiological and Clinical Effects of Sodium Oxybate

GHB is an endogenous short-chain fatty acid synthesized locally within the CNS, mostly from its parent compound GABA. Approximately 1–2% of GABA converts to GHB, which is relatively rapidly converted into CO_2 and H_2O through the Krebs cycle. GHB for exogenous administration was first synthesized in the early 1960s and found to readily cross the blood-brain barrier into the CNS, where it displays distinct pharmacological effects. Evidence suggests a role for GHB as a neuromodulator/neurotransmitter, as GHB is synthesized in neurons heterogeneously distributed throughout the CNS, stored in vesicles, released via potassium-dependent depolarization into the synaptic cleft, and undergoes reuptake into the nerve terminal. Under endogenous conditions and concentrations, and depending on the cell group affected, GHB may increase or decrease neuronal activity by inhibiting the release of the primary co-localized neurotransmitter. For example, GHB may decrease neuronal activity when inhibiting the release of the excitatory neurotransmitter dopamine and increase neuronal activity when inhibiting the release of the inhibitory neurotransmitter GABA.

Sodium oxybate is the sodium salt of GHB used for its exogenous oral administration. The behavioral effects induced by SXB appear to be mediated by GHB acting as a neuromodulator/neurotransmitter at $GABA_B$ receptors. After exogenous administration, it is likely that GHB acts at GHB binding site(s) and $GABA_B$ receptors, although it appears that most of the behavioral effects are mediated through the $GABA_B$ receptor. On neurons, supraphysiological concentrations of GHB have a qualitatively different effect than endogenous GHB concentrations. These elevated levels, mostly acting through $GABA_B$ modulation on various neuron groups, decrease neuronal activity. On washout from supraphysiological concentrations, increased neuronal responsiveness has been observed. This activity may underlie the sleep modulation seen when GHB is administered before nighttime sleep onset and, conversely, the wakefulness stimulating effects observed during the day following nighttime administration.

A review of the pharmacology and physiological actions of GHB and SXB is presented in the first part of Chapter 2. In the second part of the same chapter, I review the evidence supporting a modulatory effect of GHB and SXB on sleep and wakefulness, both in healthy and in clinical populations. In Chapter 3, I examine the safety and efficacy of SXB in individuals with PD and sleep disorders. In Chapter 4, I analyze the effect of nightly SXB administration on nocturnal sleep disruption in narcolepsy patients, a subject to which I return in Chapter 6. In Chapter 5, I review and compare the accessibility, purity, dosing, and misuse of illicit GHB and pharmaceutical SXB. In Chapter 7, I evaluate a possible association between narcolepsy, hypocretin neurons, the hormones ghrelin and leptin, and SXB.

GBH and SXB modulate sleep and wakefulness in healthy and in clinical populations

GHB has shown a dose-dependent effect in decreasing sleep onset latency, promoting delta activity and enhancing sleep maintenance. These effects have been reported in both healthy and clinical populations. A review of these effects is presented in the second part of Chapter 2.

In healthy subjects, GHB has been shown to decrease sleep onset latency, promote delta activity, and enhance SWS and sleep maintenance[14,46,184,239]. Similar effects have been described in clinical contexts. Evidence indicates that GHB/SXB may improve sleep in patients with insomnia[47,246]. Patients with fibromyalgia have also benefited from similar effects, with GHB/SXB being effective in decreasing not only sleep disruption, but also pain, fatigue and overall multidimensional function[37,38,228,229,250]. The beneficial effects of GHB/SXB in modulating sleep also extend to patients with neurodegenerative diseases. In the context of Alzheimer's disease, an association between NREM sleep impairment and disease pathogenesis has been revealed[267,268], with poor sleep correlating with the severity of cortical Aβ burden in Alzheimer's disease patients[272,273]. Given the effects of GHB in increasing NREM SWS[46], this establishes a therapeutic potential for GHB on Alzheimer's disease pathogenic processes.

In narcolepsy, the results of large, multicenter trials corroborate earlier work and demonstrate a consistent effect of SXB on SWS activity, yielding substantial, dose-related increases in SWS duration and delta power. Additionally, dose-related reductions in stage 1 sleep and number of awakenings are apparent in the larger studies, as well as modest increases in total sleep duration and reductions in REM sleep duration at a dose of 9 g. Multiple measures of daytime sleepiness demonstrated consistent short- and long-term improvement when SXB was administered in combination with stimulant therapy or as the only wake-promoting treatment. In addition, compared with modafinil, SXB as monotherapy appears to produce equal or greater improvement in daytime sleepiness in patients with narcolepsy with, or without, co-morbid cataplexy[174,290,292–295].

SXB can decrease excessive daytime sleepiness and fatigue in Parkinson's disease

Excessive daytime sleepiness and nocturnal sleep dysfunction associated with Parkinson's disease have been well documented. However, a correlation between them had not been confirmed, and no specific treatments for nocturnal sleep problems in the Parkinson's disease population had been explored. In chapter 3, the possibility of using SXB for EDS in subjects with Parkinson's disease was evaluated in a multicenter, open-label, polysomnographic study[1]. It was hypothesized that using SXB as a treatment for nocturnal sleep dysfunction could also have a therapeutic effect in Parkinson's disease-associated EDS.

Twenty-seven subjects with Parkinson's disease completed the study. The subjects started SXB therapy at a dose of 4.5 g per night, taken in 2 equal doses of 2.25 g, at bedtime and 2.5 to 4 hours later. After 2 weeks, the dose was increased to 6 g per night, and then increased weekly by 1.5 g to a maximum nightly dose of 9 g

(mean dose of 7.8 g SXB per night for 6 weeks). ESS scores were used as the primary efficacy point. The Fatigue Severity Scale, the Pittsburgh Sleep Quality Inventory, and PSG were assessed as secondary measures of daytime symptoms (FSS) and nocturnal symptoms (PSQI and PSG).

Overall, nightly administration of SXB increased SWS, decreased subjective nighttime and daytime sleep problems, and reduced daytime fatigue in individuals with Parkinson's disease. Improvements in the subjective ESS were similar to or better than those observed while using SXB as therapy for narcolepsy[297,299]. SXB was generally well tolerated.

These results indicate that nightly SXB administration can have beneficial effects on EDS and fatigue associated with Parkinson's disease. These findings also highlight the potential relevance of SXB as a therapeutic tool for Parkinson's disease-associated sleep dysfunctions.

SXB can reduce measures of sleep disruption and increase SWS in patients with narcolepsy.

PSG studies have repeatedly demonstrated pathological changes in the nocturnal sleep of patients with narcolepsy[525–527]. Therapeutic approaches for narcolepsy-associated nocturnal sleep disruption have provided limited benefit in improving daytime symptoms. Likewise, therapies for daytime symptoms of narcolepsy have provided little benefit for disrupted nocturnal sleep[528].

Multiple studies have reported improvements in subjective and objective measures of nocturnal sleep and daytime symptoms in patients with narcolepsy after nightly administration of SXB[172,291,294,295]. One such study demonstrated that 8 weeks of nightly SXB administration robustly increased stage 3 and 4 sleep and delta power, while the frequency of nocturnal awakenings significantly decreased[298], with these changes being associated with significant improvements in daytime narcolepsy symptoms[49,298].

Chapter 4 aims at further characterizing the efficacy of SXB for the treatment of EDS in patients with narcolepsy. A double-blind, placebo-controlled study was conducted in patients with narcolepsy undergoing stable therapy with modafinil (200–600 mg/day) for the treatment of EDS[2]. The effect of SXB was assessed both as monotherapy and in combination with modafinil. The intent-to-treat population consisted of 222 patients randomized to receive treatment with placebo (n=55), SXB (n=50), modafinil (n=63), or SXB + modafinil (n=54).

Patients receiving modafinil maintained their previous dosage. Patients receiving SXB started the trial at a dose of 6 g/night, administered in two equal doses (at bedtime and 2.5–4 h later) for the first 4 weeks; the dose of SXB was then increased to 9 g/night for an additional 4 weeks. Treatment efficacy was assessed using overnight PSG, ESS and Maintenance of Wakefulness Test scores, and daily diary recordings.

After 4 weeks of treatment, patients treated with SXB, either alone or in combination with modafinil, showed significant increases in stage 3 and 4 sleep. SXB/modafinil-treated patients also demonstrated significant increases in total NREM sleep and delta power, along with decreased stage 1 sleep and nocturnal awakenings. After an additional 4 weeks of treatment with SXB at the 9 g/night dose, these changes became even more robust and were statistically significant in both SXB groups. It remained unclear whether this increased robustness of effects was related to the dose (6 or 9 g/night), the duration of SXB treatment (4 or 8 weeks), or both.

MWT sleep latency was significantly increased in SXB/modafinil-treated patients, compared to baseline modafinil treatment, whereas patients receiving either modafinil or SXB alone showed no significant change in MWT sleep latency. SXB-treated patients and SXB/modafinil-treated patients also experienced significant improvements in ESS scores, as had been previously reported in detail[299].

The results from this trial, the first controlled study evaluating SXB as a single agent for the treatment of EDS in narcolepsy, suggested that, in addition to improving EDS, the nightly administration of SXB was associated with reduced nocturnal sleep disruption and improved sleep continuity, as indicated by the observed decreases in nighttime awakenings and increases in stage 3 and 4 sleep.

SXB has less risk of misuse and abuse than illicit GBH

Gamma-hydroxybutyrate sodium is the chemical name for SXB, but the acronym GHB also refers to the illicit formulations of the drug. Reports of abuse of illicit GHB as a “club drug” and “date-rape drug” have led to the scheduling of GHB as a controlled substance. The use of the chemical name ‘GHB’ to refer to both illicit GHB and to SXB has blurred the distinction between them and has clouded the notion that illicit GHB and SXB have different risks or liabilities of abuse.

In Chapter 5, I address this issue by means of a review that aims at summarizing the differences in accessibility, purity, dosing, and relative abuse liability of pharmaceutical SXB (Xyrem®) and illicit GHB, focusing on the availability and prevalence of non-medical use, and the risks and consequences of misuse and abuse[3].

This review draws information from three types of sources: data from the peer-reviewed scientific literature; data from national surveys of drug use, abuse, and law enforcement activity in the U.S., Europe, and Australia; and data from clinical trials and post-marketing surveillance from Jazz Pharmaceuticals on the rates of abuse, diversion, drug-facilitated sexual assault, and deaths associated with SXB.

Data presented in this review supports the conclusion that there are substantial differences in the availability, purity, and dosing of illicit GHB compared to pharmaceutical SXB, and that the risks associated with illicit GHB are greater than those associated with pharmaceutical SXB. This review shows that the prevalence of illicit GHB use, abuse, intoxication and overdose has declined in the U.S. since it

became illegal, and that the abuse and misuse of pharmaceutical SXB has been rare since its introduction to the market.

SXB can improve sleep fragmentation associated with narcolepsy

In Chapter 6, I extend the studies from Chapter 4 by further analyzing the effects of nightly SXB administration on nocturnal sleep in narcolepsy patients. Chapter 6 describes the first large randomized, double-blind, placebo-controlled, parallel group trial examining the impact of SXB on sleep architecture and narcolepsy symptoms[4]. The data presented in this chapter focus on the changes in nocturnal PSG parameters, providing additional information on the effects of SXB on nocturnal sleep.

The trial was conducted with 228 adult patients with narcolepsy/cataplexy in the U.S., Canada, and Europe. Patients received either 4.5, 6, or 9 g/night of SXB or placebo, administered in 2 equally divided doses each night for 8 weeks. Following randomization, patients were started on placebo in single-blind fashion and recorded baseline cataplexy occurrences over a 14-day period. After the baseline analysis, patients started receiving SXB or placebo, and were titrated to their final dose during the first 4 weeks of treatment. Patients were then maintained at their assigned dose for the remaining 4 weeks of the study, before returning for the final efficacy and safety assessments. PSG and MWT were performed, and changes in narcolepsy symptoms and adverse events were recorded in daily diaries.

Results showed that sleep latency was not significantly altered at any dose or treatment time. Total sleep time was significantly increased at the 8th week of treatment with the 9 g/night dose. The number of nocturnal awakenings significantly decreased at 4 weeks with all doses and remained so with the 6 and 9 g/night doses at 8 weeks. Wake after sleep onset significantly decreased in the 9 g/night group at 8 weeks. There was a significant association between dose and increased total sleep time, decreased number of awakenings, and decreased wake after sleep onset at 8 weeks.

The duration of stage 1 sleep was significantly decreased with all SXB doses at 4 weeks and remained so with the 6 and 9 g/night doses at 8 weeks; a significant dose association for the decrease in stage 1 sleep was found. The duration of stage 2 sleep was unaltered. The duration of stage 3 and 4 sleep was significantly increased with the 6 g/night and 9 g/night groups at 4 weeks and with all SXB doses at 8 weeks, being significantly dose-dependent at both 4 weeks and 8 weeks. Median delta power was significantly increased with all SXB doses at both 4 and 8 weeks, but a significant dose relationship was not observed. The duration of REM sleep was significantly decreased with the 9 g/night dose at 4 and 8 weeks.

Other measures of efficacy, reported elsewhere, indicated that the nightly administration of 4.5, 6, and 9 g/night doses of SXB significantly decreased cataplexy attacks, and significantly improved subjective and objective measures of EDS and quality of life[49,298,529].

These results indicated that SXB induces dose-related improvements in measures of sleep continuity and that SXB may improve the sleep fragmentation that is commonly associated with narcolepsy. The continued improvements from week 4 to week 8 also suggest a possible time-dependent effect.

SXB's influence on BMI is unlikely to involve changes in in the secretion of ghrelin or leptin

Ghrelin and leptin, two hormones with important roles in regulating energy homeostasis[201,375,376,381], can be directly sensed by hypocretin neurons, and their interaction with the hypocretin system has been shown to be involved in ingestive behavior[202].

Because hypocretin influences sympathetic nervous system activity, which in turn can affect the expression of both leptin and ghrelin, hypocretin deficiency may lead to altered levels of these hormones, potentially affecting ingestive behavior and energy metabolism.

In narcolepsy patients, altered ingestive behavior and obesity are commonly observed and have been associated with hypocretin deficiency[530–532]. Since the hypocretin system has a key role in the regulation of sleep and wakefulness, with hypocretin deficiency also being associated with narcolepsy, it is possible that hypocretin deficiency may dysregulate feeding behavior and energy homeostasis. Therefore, in Chapter 7, I examine the link between narcolepsy, hypocretin neurons, the hormones ghrelin and leptin, and SXB, aiming at evaluating whether human hypocretin deficiency or SXB can alter the levels of these hormones, which could help explain the altered ingestive behavior and increased BMI seen in narcolepsy patients[5]. We investigated whether total blood ghrelin or leptin levels are altered in hypocretin-deficient narcoleptic patients compared to controls, and whether total ghrelin or leptin levels are influenced by SXB.

Eight medication-free, male hypocretin-deficient narcolepsy with cataplexy patients and 8 healthy male controls, matched for age, BMI, and body fat percentage were included in this study. Plasma total ghrelin and leptin levels were assessed at baseline and after 5 consecutive nights of SXB treatment at a total dose of 6 g/night, administered in two equal doses of 3 g, 4 hours apart. PSG recordings were also performed.

Both in controls and in narcolepsy patients, administration of SXB resulted in a significant decrease in stages 1/2 NREM and REM sleep over 24 hours, while at night, awakenings were significantly reduced and the percentage of SWS increased more than 2-fold. During the day, time spent in stages 1/2 NREM and REM sleep was reduced, and a trend towards longer periods of wakefulness was observed. No differences in ghrelin or leptin levels nor any effects of SXB on the plasma levels of either hormone were found.

Even though a small number of patients was included in this study, the small intergroup differences indicate that the increased BMI of narcolepsy patients is

unlikely to be mediated by hypocretin deficiency-mediated changes in total ghrelin or leptin levels, and that SXB's influence on body weight is unlikely to involve changes in the secretion of the hormones.

Part II: Sleep, Eating, and Metabolism

An overview of the epidemiological evidence linking sleep and obesity is presented in Chapter 8. In addition, I discuss how sleep affects metabolic, endocrine, immune, and circadian processes, how brain-processing circuits and functions are affected by sleep loss, and how this altered brain function can influence eating behavior. Chapter 9 discusses how manipulation of a single night of sleep may influence food preferences in humans. Chapter 10 examines how a short, outdoor excursion under Paleolithic-like eating, living, and sleeping conditions improves physiological and metabolic parameters in the body.

Epidemiology shows a correlation between sleep loss and obesity

The first part of Chapter 8 addresses the question of whether there is an epidemiological relationship between sleep loss and obesity. In 2012, 70 million U.S. adults reported getting less than six hours of sleep at night[533]. Sleep is a major public health concern, and insufficient sleep is related to motor vehicle crashes, industrial accidents, and medical errors[534]. Epidemiology studies show that there is a relationship between sleep duration and body weight, and show that sleep disruption impacts metabolism, immune function, and circadian rhythms. Because obesity rates are rising worldwide in adults and children[305,535], it will be important to understand how sleep duration and quality affect human health.

Objective measures of sleep reveal that total sleep time has not decreased over the last 50 years

The second part of Chapter 8 addresses the question of whether actual sleep time as decreased in the last 50 years. A literature review found that sleep duration increased in some countries (Bulgaria, Poland, Canada, France, Britain, Korea, and the Netherlands), decreased in others (Japan, Russia, Finland, Germany, Belgium, and Austria), and was inconsistent in the U.S. and Sweden[536], and later reports have shown that the number of individuals sleeping 6 hours or less has increased[537,538]. However, these studies cannot differentiate between people reporting that they sleep less versus people actually sleeping less. Objective measures of sleep duration can only be observed in a sleep laboratory under controlled conditions using sleep-recording techniques like PSG and actigraphy. Researchers first made use of this type of data in a meta-analysis of 65 studies over 40 years to determine that sleep duration decreases with age[539]. Similarly, other researchers have used this type of data to determine that sleep duration has not decreased over the past 50 years[540].

Sleep manipulation can drive food preferences in humans

Many laboratory studies and epidemiologic research have shown a connection between reduced sleep and increased weight. However, laboratory studies have used fairly extreme models of sleep in order to observe substantial changes in

metabolic parameters. Chapter 9 discusses how lowered alertness by a moderate change in sleep restriction might drive an individual's food preferences and total calorie consumption.

Fifty healthy, young participants completed two 3-hour study sessions. The first session was a baseline evaluation after an unmodified night of sleep. On the night prior to the second session, the amount of time in bed was manipulated to be 60-130% of an individual's sleep time. Changes in time in bed were linearly associated with changes in scores on the Stanford Sleepiness Scale, so that individuals who had less time in bed were less subjectively alert during the second session. During the middle of each session, participants were allowed to eat from eight different food items with varying degrees of healthfulness, caloric density and distribution, and number of calories.

There was a linear relationship between a change in subjective alertness and a change in total calories consumed and total calories consumed relative to body weight. In addition, there was a positive correlation between subjective alertness and the number of calories consumed from "bad" food choices (i.e., gummy bears, cinnamon-sugar walnuts, toffee peanuts, and sweetened trail mix), but no correlation with the number of calories consumed from "good" food choices (i.e., apple rings, apricots, almonds, and fig bars). There was also a negative association between subjective alertness and the food quality rated by the participants, such that when participants rated themselves less alert, they ate foods that they rated less healthy.

The study showed that manipulation of next-day alertness via the manipulation of sleep for a single night can have a detrimental impact on eating behaviors. Increased subjective feelings of sleepiness correlated with an increase in total calories consumed and with an increase in calories categorized as "bad" by the investigators and "less healthy" by the participants. This study suggests that when a person feels less alert, the hedonic processing for tempting foods may be increased. Previous studies have shown using fMRI that a night of sleep deprivation amplifies regions of the brain responsible for food decisions, and that these changes are associated with a greater desire for caloric density[524]. In addition, simulation of shift work under experimental conditions increases the likelihood of participants eating high-fat breakfast items compared to that of the control condition[541]. This agrees with a study showing that participants consumed a greater percentage of calories from fat compared to carbohydrates the day after a night of total sleep deprivation compared to a day following baseline sleep[542].

Alternatively, sleep loss might relax personal inhibitions against unhealthy foods. Sleep deprivation alters effort discounting, a principle that suggests that the value attached to a reward is inversely related to the amount of effort required to obtain it[543]. Perhaps participants with impaired alertness in our study ate unhealthy foods they might have otherwise avoided because they were less likely to make an effort as a result of their sleep deprivation. Sleep loss may also have shifted the focus of participants to foods that subjectively taste better, which correlates with less

healthy foods, from a focus on eating healthier foods. This type of bias has been reported in the context of economic preferences for monetary gambling where sleep deprivation favors the pursuit of large rewards, and reduces minimization of loss[544]. In our study, monetary gains would correspond to the pleasure of eating unhealthy foods, and losses would correspond to the detrimental effects of eating less healthy foods. Thus, sleep-deprived participants may have eaten more of the unhealthier food options because they were more pleasurable and discounted the negative effects of those unhealthy foods.

Importantly, our study examined moderate impairments in sleep loss rather than total sleep deprivation. Insufficient sleep is a major health problem and related to an increase in chronic diseases, such as diabetes, depression, obesity, cancer, increased mortality, and reduced quality of life[534]. In addition, it has been shown that several consecutive days of chronic sleep restriction below 7 hours results in significant cognitive impairments that accumulate to levels comparable to that after a night of total sleep deprivation[445]. Thus, our study is relevant to food preferences and sleep impairments in modern society and consistent with epidemiological studies that show a relationship between sleep loss and weight gain[338,545,546].

A short outdoor excursion under Paleolithic living conditions improves metabolic function and increases weight loss

For more than 2.5 million years, humans have relied on foraging and gathering to supply food. Abundant, regular physical activity under natural lighting and temperature conditions to forage and hunt for food, and large meals in the evening, were the norm. The evolutionarily recent shift to readily available and calorically dense foods has contributed to a wave of 'Western diseases,' such as diabetes and obesity. Permanent food availability, increased meal frequency, and high glycemic foods have resulted in alternating peaks in blood sugar and elevated basal insulin levels[547,548], which leads to visceral obesity, glucose intolerance, persistent elevated insulin, and low-grade inflammation[549–551]. As a result, the incidence of type 2 diabetes has been rising worldwide for decades[552]. Furthermore, obesity is caused a chronic imbalance between energy intake and energy expenditure and results in persistent low-grade inflammation throughout the body, such as elevated tumor-necrosis factor alpha (TNF-α), interleukin-1-beta (IL-1β), and macrophage counts in visceral adipose tissue[553,554]. TNF-α in cooperation with IL-1β enhances insulin resistance[555], and experimentally induced hyperglycemia increases TNF-α and other pro-inflammatory cytokines, such as IL-6 and C-reactive protein[556–558]. While pancreatic insulin secreted from elevated glucose levels suppresses inflammation[559–561], this anti-inflammatory effect is reduced in a state of chronic insulin resistance.

Early in our evolutionary history, caloric intake was counterbalanced by its seasonal availability, physical efforts, and knowledge of the surrounding environment[562,563]. Exercise before eating lowers postprandial inflammation and produces non-inflammatory molecules, such as lactoferrin, immunoglobulin A (IgA), and lysozyme[564]. These molecules are absent or reduced in overweight

individuals[565] and they have increased postprandial inflammation, which leads to the development of cardiovascular disease, obesity, insulin resistance, and chronic low-grade inflammation[565–567]. Animal experiments have revealed that caloric restriction and intermittent fasting can suppress weight-gain-related illness and extend lifespan. In mice, caloric restriction increases lifespan by 30–40% by reducing levels of CRP and TNF-α[568–570]. Human studies have also begun to reveal the beneficial effects of caloric restriction[571].

In Chapter 10, I describe a study that examines participants on an outdoor nature trip for 4 days under Paleolithic-like living conditions. Individuals lived outdoors without tents and were required to hike throughout the day to simulate the activity level of gathering food. A small snack was provided after noon to mimic the delayed time to gather food, and a meal without modern, processed foods was provided at dinner time. This relatively moderate lifestyle change over a period of 4 days resulted in dramatic improvements in physiological and metabolic parameters. Body weight, body fat, BMI, and visceral fat area all decreased as expected because of reduced caloric intake and increased exercise. Fasting glucose, insulin and HOMA also decreased significantly and CRP, the main indicator of low-grade inflammation, increased. Previously, it has been shown that trips into the forest stimulates human immune function and improves cardiovascular parameters[572–574], perhaps as anticipatory protection from bacteria, viruses, insects, or other predators. Natural living in our study may have had similar effects.

This study shows that a short intervention under Paleolithic living conditions can dramatically improve physiological and metabolic parameters, which may aid in the prevention of obesity and type 2 diabetes. The individual factors responsible for these improvements are difficult to parse without further studies that isolate caloric restriction, outdoor activity, and intermittent fasting, but likely a combination of all three were partially responsible for the beneficial effects.

Future perspectives

In Chapter 3, we evaluated the possibility of using SXB for EDS in subjects with Parkinson's disease. Our results provided an indication that nightly SXB administration can have beneficial effects on EDS and fatigue associated with Parkinson's disease. These putative therapeutic effects of SXB are worth pursuing in controlled trials using objective measures of daytime sleepiness. Confirming these results could establish SXB as an important therapeutic tool for Parkinson's disease, with the capacity to improve patients' quality of life.

In Chapter 4, we studied the efficacy of SXB for the treatment of EDS in patients with narcolepsy. The results from this first controlled study evaluating SXB as a single agent for the treatment of EDS in narcolepsy suggested that, in addition to improving EDS, the nightly administration of SXB was associated with reduced nocturnal sleep disruption and improved sleep continuity, as indicated by the decreases in nighttime awakenings and increases in stage 3 and 4 sleep. This study was extended in Chapter 6 by further analyzing the effects of nightly SXB administration on nocturnal sleep in narcolepsy patients. The results indicated that SXB induces dose-related improvements in measures of sleep continuity and that SXB may improve the sleep fragmentation that is commonly associated with narcolepsy.

Although a dose-dependent effect was observed, it remained unclear whether the changes in sleep architecture of narcolepsy patients induced by SXB are related only to the dose or also to the duration of SXB treatment. The continued improvements from week 4 to week 8 suggest a possible time-dependent effect that warrants further clarification.

Additionally, it would be valuable to understand if the observed impact of SXB on sleep EEG activity represents pharmacologically-induced alterations in true sleep-related activity, effects representing anesthetic-like changes, or epiphenomenal EEG activity unrelated to either sleep or anesthesia.

In Chapter 7, we examined the link between narcolepsy, hypocretin neurons, the hormones ghrelin and leptin, and SXB, aiming at evaluating whether human hypocretin deficiency or SXB can alter the levels of these hormones, which could help explain the altered ingestive behavior and increased BMI observed in narcolepsy patients. Given that no differences in ghrelin or leptin levels nor any effects of SXB on the plasma levels of either hormone were found, it is unlikely that changes in total plasma ghrelin or leptin concentrations underlie the increased BMI and altered ingestive behavior in narcolepsy, as well as the effects of SXB administration on BMI.

The small number of patients included in this study calls for further future investigations to confirm these findings and to further evaluate whether or not the sleep-wake instability intrinsic to hypocretin-deficiency drives the altered energy balance associated with narcolepsy.

In Chapter 8, we detailed the epidemiological evidence for the impact of sleep on human health. Future epidemiological studies will need to continue to monitor the rising rates of obesity, and how reduced sleep and impaired sleep quality affect this growing problem. Importantly, sleep is also related to depression, immune function, cancer, circadian rhythms, and other physiological processes. Because sleep is so interconnected to other processes, and loss of sleep has both human health and economic consequences, understanding how to improve and increase sleep will be central to happy workers and healthy economies.

In Chapter 9, we showed that moderate manipulation of alertness via a sleep intervention for a single night can have a detrimental impact on eating behaviors including increased total caloric intake and increased caloric intake from unhealthy foods. However, we did not objectively record sleep with polysomnography or actigraphy, nor was manipulation of sleep controlled in a sleep laboratory. Furthermore, instead of relying on self-reported sleep as the main predictor in our analysis, we used the consequence of sleep loss—subjective daytime sleepiness. Future studies could measure and manipulate sleep loss in a more controlled fashion in a sleep laboratory to determine if objective measures of sleep and impairment correspond to our findings. In addition, because sleep curtailment was relatively mild, this probably reduced the statistical power of our correlation analysis compared to that of studies of severely impaired sleep or total sleep deprivation. Nevertheless, we could detect significant and meaningful correlations between small changes in alertness, typical of sleep disruptions in modern society, and changes in food preferences.

Another caveat of our study is that we could not distinguish between changes in alertness and disruptions in an individual's circadian rhythm. Participants were asked to delay their bedtime, which may have caused a small shift in circadian phase. Future studies could examine melatonin levels in participants to understand the relationship between a participant's circadian rhythms, reduced alertness, and changes in food preferences. In addition, we only analyzed data from 50 participants and 40 of the participants were women. To understand if there are differences between men and women, or to examine other demographic differences, such as ethnicity and age, future studies would need to include a larger sample size.

In Chapter 10, we showed that a 4-day Paleolithic lifestyle change improved many bioelectric and biochemical parameters in study participants, including body weight, body fat, BMI, visceral fat area, fasting glucose, fasting insulin, and HOMA. C-reactive protein, which is a major indicator of low-grade inflammation, increased by an average of approximately 170%. However, we did not distinguish among the effects of caloric restriction, increased exercise, and outdoor living. Future studies could isolate these individual variables to determine which has the most impact on a participant's health. Moreover, an increased number of participants as well as control subjects that do not undergo the intervention would improve the statistical robustness of these preliminary findings.

Another caveat is that the duration of the intervention lasted for only 4 days. It's unclear if the participants' metabolic parameters would return to where they were before the intervention as they re-adapt to modern society. Another possibility is that extended periods of living under Paleolithic-like conditions may cause unintended or unforeseen harm. For example, increased exposure to parasites, bacteria, etc., or other increased environmental stresses could be detrimental to an individual's wellbeing. Future studies could extend the trial intervention to longer periods of time or repeat the intervention at some periodic interval to assess if occasional, short-term natural trips have a longer-term, beneficial impact on health. In any case, this study provides an entry point to examine how simple lifestyle interventions can have dramatic improvements on an individual's health.

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