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Research report

A ketogenic diet decreases sevoflurane-induced burst suppression in rats

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ABSTRACT

Background: The brain requires a continuous fuel supply to support cognition and can get energy from glucose and ketones. Dysregulated brain metabolism is thought to contribute to perioperative neurocognitive disorders and anesthesia-induced burst suppression. Therefore, we investigated the relationship between brain metabolites and neurophysiology during the behavioral states of sleep and anesthesia under a standard diet (SD) or a ketogenic diet (KD).

Methods: We measured prefrontal cortex glucose, lactate, and electroencephalogram in Fischer344 rats during spontaneous sleep/wake followed by 3 % sevoflurane anesthesia. Nine rats were fed a KD and 8 rats a SD. To assess the role of adenosine receptor-mediated ketone activity on burst suppression, 5 additional rats on the KD received an intraperitoneal injection of vehicle or the adenosine A1 receptor antagonist, DPCPX, before 3 % sevoflurane.

Results: Sevoflurane induced larger fluctuations in glucose ($p < 0.001$) and lactate ($p = 0.015$) concentrations compared to sleep as measured by the standard deviation (glucose 0.085 mM and lactate 0.16 mM in sleep/wake and 0.25 mM and 0.41 mM during sevoflurane respectively). Changes in glucose and lactate were closely tied to electrophysiological oscillations. Animals on the KD had reduced burst suppression ratio (mean 10 % in KD vs 30 % in SD) ($p = 0.007$) as well as increased time to loss of movement (mean 14 min in KD vs 8 min in SD) ($p = 0.003$) compared to SD. DPCPX in KD rats showed a trend to increased burst suppression, reduced the time to start of burst suppression (45 min in KD+vehicle to 37 min KD+DPCPX) ($p = 0.007$), and increased duration of burst suppression (49 min in KD+vehicle to 90 min in KD+DPCPX) ($p = 0.046$) compared to KD+vehicle.

Conclusions: It is thought that anesthesia-induced burst suppression reflects an underlying deficiency in brain energy. Accordingly, we found that upregulating ketones, which increase available brain ATP levels, delayed anesthetic induction and decreased burst suppression consistent with the idea that the underlying metabolic state of the brain influences an anesthetic's effect on the brain. These findings suggest that metabolic interventions could be useful therapeutic targets to modulate brain activity during sleep and anesthesia. Future studies will examine whether ketones can reduce the cognitive symptoms associated with postoperative delirium.

1. Introduction

Changes in brain metabolism, including mitochondrial dysfunction and insulin resistance, play a significant role in cognitive decline, poor sleep quality, perioperative neurocognitive disorders, and dementia (Camandola and Mattson, 2017). A continuous supply of energy is critical to support brain cognition and even brief periods of low energy substrate are detrimental to brain function (Turner, 2021). Brain energy metabolism is dependent on both neurons and astrocytes (Magistretti and Allaman, 2018). The astrocyte-neuron lactate shuttle theory suggests that astrocytic lactate is released into the extracellular space where neurons use it for energy. Brain glucose and lactate levels vary with behavioral state and lactate has been shown to be a good biomarker for sleep/wake states in rodents (Naylor et al., 2012). Anesthetic drugs not

Abbreviations: KD, ketogenic diet; SD, standard diet; EEG, electroencephalogram.

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only disrupt neuronal activity but also inhibit mitochondrial function (Niezgoda and Morgan, 2013). Anesthesia-induced burst suppression is characterized by patterns of high voltage activity (bursts) alternating with no activity (suppressions) in the electroencephalogram (EEG). Burst suppression is highly correlated with postoperative delirium (Fritz et al., 2016, 2018; Soehle et al., 2015) and is thought to result from deficits in brain energy (Ching et al., 2012; Shanker et al., 2021). However, studies that have actively adjusted the anesthesia level to decrease burst suppression have not been shown to reduce postoperative delirium (Shortal et al., 2019; Wildes et al., 2019). This may be due to burst suppression being a readout of a vulnerable brain vs the direct cause of delirium. Yet the connection between metabolism and delirium remains as patients with metabolic syndrome are at an increased risk for developing postoperative delirium and cognitive dysfunction (Feinkohl et al., 2023).

In addition to glucose and lactate, the brain can use ketones as fuel. Ketones are produced naturally from the breakdown of fatty acids and serve as a major fuel source for the brain during times of fasting, exercise, and high-fat, low-carbohydrate diets. The ketogenic diet (KD) has been used to treat epilepsy since the 1920s (Rho and Boison, 2022). Ketones prevent seizures, in part, through increased adenosine triphosphate (ATP) production and ATPs degradation to adenosine. Adenosine is an important neuromodulator in the brain and acts through primarily inhibitory adenosine A1 or excitatory A2 receptors. Ketones have been shown to improve seizures through adenosine A1 but not A2 (Brunner et al., 2021; Kovacs et al., 2024) receptors activating K_{ATP} channels to hyperpolarize cells (Kawamura et al., 2016), therefore we focused on adenosine A1 receptors. Ketones improve mitochondrial efficiency and increase ATP production by decreasing the nicotinamide adenine dinucleotide (NAD)+ / NAD+hydrogen (NADH) ratio while simultaneously increasing electrons passed from ubiquinol (QH2) to cytochrome c. This effectively increases the redox span (the difference in redox potentials of cytochrome c and ubiquinone/QH_2). Ketones can also feed electrons through production of succinate to Complex II, within the electron transport chain all while decreasing reactive oxygen species production (Norwitz et al., 2019). These mechanisms allow ketones to generate more ATP per carbon than glucose. The ketone bodies acetoacetate and β-hydroxybutyrate not only provide energy to the brain, but also have potent signaling and anti-inflammatory effects (Newman and Verdin, 2014). Inflammation is linked to sleep disturbance, dementia, postoperative delirium, and Alzheimer's disease.

Ketones have also been shown to play a role in regulating arousal state. Central injection of acetoacetate increases slow wave activity during subsequent NREM sleep in mice suggesting a role for ketones in the regulation of sleep homeostasis (Chikahisa et al., 2014). Interestingly, the KD and exogenous ketones have been shown to delay the onset of isoflurane-induced immobility in mice and rats (Ari et al., 2018), but no one has looked at the effect of ketones on deeper states of anesthesia. In addition, few studies have included simultaneous EEG recordings with high-resolution metabolite measurements across behavioural states. The prefrontal cortex mediates important cognitive domains such as attention, executive function, and working memory (Shao et al., 2020) and shows robust EEG changes across sleep and anesthesia. Therefore, we investigated the relationship between the metabolites lactate and glucose in the prefrontal cortex with high temporal resolution across the behavioral states of sleep/wake and sevoflurane anesthesia during two different dietary-induced metabolic states. We hypothesized that increasing ketones would improve brain resilience to anesthesia, demonstrated by reduced burst suppression, in part, due to the additional energy source.

2. Materials and methods

2.1. Animal care and use

Twenty-two, 6–8 month-old Fisher344 rats weighing 280–350 g (Charles River Laboratories, Wilmington, MA) were used in the study. All rats were kept on a 12:12 h (7 am:7 pm) light-dark cycle in a temperature and humidity controlled AAALAC-accredited facility and were housed in pairs until undergoing surgical procedures. Eight rats ate a standard diet (SD) (5P75 - Prolab® IsoPro® RMH 3000 diet (Caloric profile: 26.13 % protein, 14.38 % fat, 59.50 % carbohydrates) ad libitum. Fourteen rats ate a KD (F3666 Ketogenic Diet paste (Caloric profile: 4.70 % protein, 93.37 % fat, 1.8 % carbohydrate) Bio-Serv, Flemington, NJ)) 12 g/day replaced every 48 hours. Glucose and ketone levels were measured weekly using an electronic blood glucose and ketone monitoring system for the first 7 weeks in KD animals and 1 time at 1 month for the SD animals (Supplemental Figure 1 A) (Precision Xtra, Abbott Diabetes Care, Abingdon, UK). Nutritional ketosis over 1 mmol/L was achieved after 2 weeks on the diet. The KD was maintained for a minimum of 65 days. Body weight did not differ between groups (females SD 166.7 ± 31.7 g vs KD 150.3 ± 5 g: males SD 330.9 ± 27.2 g vs KD 351.3 ± 33.5 g *t*-test $p > 0.05$). Eleven male and 6 female rats were used for the biosensor experiments and an additional 5 male rats were used for the adenosine antagonist studies. No differences were observed in the range of glucose (0.4–3 mM) and lactate (0.2–4 mM) between the male and female rats during the biosensor recordings, so the data were analyzed for both sexes combined and the follow-up adenosine receptor antagonist study was performed in just male animals. All procedures involving animals were approved by the MGH institutional animal care and use committee (Protocol #: 2019N000143 approved Aug 4, 2019) and followed ARRIVE guidelines 2.0 published by NC3Rs in 2020.

2.2. Surgical implantation of eeg and electromyogram (EMG) electrodes

Anesthesia was induced with 3 % isoflurane in 100 % oxygen and maintained at 1.5 %. Rats were secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA). A heating pad maintained the animal's body temperature at 37°C throughout the surgery. A micro drill was used to make bilateral craniotomies over the prefrontal cortex for the guide cannulas (BASi cannulas, Bioanalytical Systems, West Lafayette, IN) at + 3 mm anterior and + and – 2 mm lateral relative to bregma. The guide cannulas were lowered 1.75 mm below the skull at an angle of 18.9° (from 90° entering laterally proceeding medial) to position the probes in the prelimbic cortex. EEG electrodes (0.005-inch stainless steel; A-M Systems, Sequim, WA) were placed over the prefrontal cortex and parietal cortex as well as 5 anchor screws inserted (1.59 mm diameter, 3.2 mm long, Stoelting Co. Wood Dale, IL). Two EMG electrodes (0.002-inch seven stranded stainless steel; A-M Systems, Sequim, WA) were implanted into the nuchal muscle. Guide cannulas, EEG leads, anchor screws, and headstage were fixed using dental cement (Teets Dental Cement, A-M Systems, Sequim, WA). Surgeries lasted 2–3 hours. For post-operative care, rats were given ketoprofen (4 mg/kg) and 10 mL of normal saline every 24 hours as needed until fully recovered. Rats were given at least 7 days to recover before experiments and were housed individually for the rest of the study. A baseline sleep recording was performed to acclimate animals to the recording chamber and EEG cable.

2.3. Biosensor experiments

Implantable enzyme-based biosensors (Pinnacle Technology LLC, Lawrence, KS) were used to measure glucose and lactate changes in the rat prefrontal cortex. Pinnacle biosensors monitor real-time (1 sec resolution) changes in the concentration of the analyte of interest using a specific enzymatic reaction. Lactate oxidase for lactate and glucose oxidase for glucose generate hydrogen peroxide which is detected by oxidation at a platinum iridium electrode. Changes in current are recorded that are proportional to the level of analyte present. A passive membrane excludes electroactive interferants in the brain. On the day of the experiment (between 9 am and 11 am), biosensors were calibrated using 4 serial additions of glucose and lactate, 0.5 mM and 0.4 mM,

respectively, to 10x phosphate buffered saline (PBS) solution preheated to 37°C to ensure physiological conditions, both before insertion and immediately following extraction of the biosensor. Biosensors were inserted into guide cannulas of freely behaving rats and biosensor signals were equilibrated to the brain for approximately 1 hour. Both EEG/EMG and biosensor data were collected simultaneously with Pinnacle hardware and the same Sirenia acquisition software ensuring proper alignment of the two types of data with identical timestamps. EEG and EMG were used to score sleep/wake states and correlate them with changes in brain metabolism. Two hours of undisturbed sleep/wake activity was recorded between 10 am and 2 pm, followed by 3 % sevoflurane (which is used clinically more than isoflurane) in 100 % oxygen as is standard in rodents at 1.5 liters/minute for 1 hour 45 minutes, after which sevoflurane was stopped, and oxygen was maintained until sevoflurane cleared from the chamber and rats recovered consciousness. Three percent sevoflurane (1 MAC is 2.5 %) was chosen to be relevant for surgical depth of anesthesia and induced reliable burst suppression without creating a floor or ceiling effect on burst suppression. During the anesthesia portion of the experiment, a heating pad under the cage was used to maintain body temperature. Breathing rate was monitored visually. The sealed anesthesia chamber made it difficult to directly measure other physiological variables or righting reflex. The depth of anesthesia was assessed through analysis of the EEG and movement from the EMG. Induction was scored visually and defined by high theta (5–9 Hz) and beta (13–30 Hz) power in the EEG and low muscle tone in the EMG. Deep anesthesia was scored visually and defined by high delta (0.5–4 Hz) power in the EEG interspersed with burst suppression and low muscle tone in the EMG. Emergence was scored visually and defined by the return of theta and beta power in the EEG and the return of muscle tone in the EMG. EEG (filtered 0.1–500 Hz) and EMG (filtered 10–500 Hz) signals were acquired at a sampling rate of 500 Hz and were analyzed offline for Burst Suppression Ratio (BSR) in MATLAB and sleep state. Sleep was scored manually in 10 sec epochs using standard rodent sleep scoring criteria in Spike2 software (Cambridge Electronic Design) and then the results were exported to MATLAB and further analyzed in MATLAB. Briefly, wakefulness was defined by low amplitude high frequency EEG activity and high EMG activity. NREM sleep was defined by high delta (0.5–4 Hz) power in the EEG and low muscle tone in the EMG. REM sleep was defined by high theta (5–9 Hz) power in the EEG and no muscle tone in the EMG. Manual sleep scoring allowed for visual inspection of any artifacts that occurred during the sleep/wake recording and any artifact usually occurred during wakefulness when the animal was moving. Artifacts during anesthesia were rare since the animal was immobile.

2.4. Adenosine A1 receptor antagonist burst suppression experiments

On the day of the experiment, a solution of the adenosine A1 receptor antagonist, 1,3-dipropyl, 8-cyclopentylxanthine (DPCPX) was dissolved in 10 % DMSO in PBS (vehicle). Ten percent DMSO injected intraperitoneal (IP) has been shown not to alter sleep and wakefulness (Cavas et al., 2005) or affect time to immobility from isoflurane in rats (Kovacs et al., 2020). DPCPX at 0.2 mg/kg was administered via IP injection immediately prior to the EEG recording based on previous studies (Kovacs et al., 2020). The rat was anesthetized with 3 % sevoflurane (approximately 1.1 MAC) (Kashimoto et al., 1997) in 100 % oxygen at 3 liters per minute until the chamber reached 3 % and then 1.5 liters per minute for ~2 hours. A heating pad was used to maintain body temperature during anesthesia. The rat was allowed to recover in the recording chamber until it was ambulatory. Half of the animals were exposed to DPCPX first, and the other half to the vehicle first. At least a week was given between experiments to ensure any effect of DPCPX or sevoflurane had washed out.

2.5. Histology

Rats were anesthetized with 3 % isoflurane and transcardially perfused with 1x PBS followed by 10 % formalin for brain tissue fixation. Brains were extracted, and 50 μm sections were cut using a vibratome and mounted on slides with DAPI mounting medium. Slides were imaged using a fluorescent microscope (Zeiss Axio Imager.M2) and placement of the biosensor probes were confirmed with the Paxinos and Watson rat brain atlas as summarized in Supplementary Figure 2.

2.6. Data analysis

All statistical analyses, as described below and in the results, were performed using MATLAB from MathWorks®.

2.6.1. Lactate Modeling

Amperometric biosensors measurement of absolute analyte concentrations may vary on a timescale of hours, making it difficult to compare temporally-distant lactate changes associated with fluctuating behavioral or oscillatory states. To accurately quantify these shorter time-scale changes in lactate, we used a simple dynamic model to estimate changes in lactate concentration that could be driven by observed behavioral and electrophysiological states. Scored wake, NREM, and REM states as well as induction and emergence phases of anesthesia were modeled as inputs to a linear response function. Behavioral state was scored visually, using EEG and EMG traces as well as the EEG multitaper spectrogram.

Lactate model details: Wake and REM epochs have been previously reported to coincide with an increase in lactate (Naylor et al., 2012), and were collapsed into a single control input array $u(t)$ for analysis of lactate during sleep / wake in MATLAB. Similarly, the induction and emergence phases of anesthesia were visually scored based on the presence of alpha, beta, and theta power (Guidera et al., 2017). Sleep/wake and anesthesia-associated lactate changes were modeled separately to allow for the comparison of the baseline difference in lactate associated with NREM and deep anesthesia respectively. The overall lactate concentration was modeled as the sum of a slowly-varying lactate baseline, modeled as a second-order polynomial, and the increases in lactate due to changes in behavioral/electrophysiological state, modeled as the control input $u(t)$ convolved with a gamma impulse response function:

$$h(t) \quad = \quad (t+1)^2 e^{-\alpha t}\beta$$

where h is the estimated lactate concentration, alpha is the time constant, and beta is the scaling coefficient. This gamma function was appropriate based on the form of the lactate and glucose time series, and more generally, and as a way of representing a multi-compartment linear system that could describe metabolic processes (Huppert et al., 2009; Taylor et al., 2018). We also note that this form of model is very similar to the "hemodynamic response functions" used in functional magnetic resonance imaging analyses. The gamma function beta parameter was estimated for each epoch $u_i(t)$ from the data to account for epoch-to-epoch variation in amplitude of the lactate signal. The lactate concentration h(t) associated with each epoch in u(t) was summed with the slowly varying baseline lactate term, which can be represented in matrix form:

$$y \quad = \quad X\beta \quad + \varepsilon$$

$$X \quad = \quad \left[1, \quad t/n, \quad (t/n)^2, \quad h_i(t) * u_i(t), \quad \ldots \quad h_l(t) * u_l(t)\right]$$

where y is the observed lactate concentration, n is the number of points in the lactate signal, X is the design matrix containing the baseline lactate concentration and gamma response function for each epoch $u_i(t)$, *and* ε is the error. In order for the scaling parameter beta to entirely capture the variation in lactate concentration with u(t), the same time

constant alpha was selected for all epochs $u_I(t)$, obtained using a grid search to minimize the squared error of the model fit.

EEG spectral analysis and Burst Suppression Ratio (BSR) calculations: Frequency analysis of EEG data was done using multitaper spectral estimation techniques with 10-second windows, time half-bandwidth product of 5 and 9 discrete prolate spheroidal sequences as tapers in MATLAB. The BSR was estimated by creating a binary array from the EEG data under anesthesia with a symmetrical threshold around zero for each recording. Isoelectric periods were defined as EEG signals that did not cross the threshold for a minimum of 0.5 seconds. BSR overtime was estimated by taking the binary array moving average with a window length of 20 minutes. Group BSR confidence intervals were estimated using the bootstrap resampling technique, where the BSR moving average was randomly sampled with replacement from the n BSR estimates, n times before taking the mean. This process was repeated 2000 times to create the bootstrapped distribution from which the upper and lower confidence intervals are the 95th and 5th percentiles, respectively. BSR from KD+vehicle and KD+DPCPX (measured in the same rat) were subtracted from one another to create a paired bootstrapped difference. For the bootstrapped difference, portions of the confidence intervals that do not contain zero are significantly different for alpha of 0.05.

3. Results

3.1. Prefrontal cortex glucose and lactate concentrations varied across NREM sleep, wakefulness, and sevoflurane anesthesia

We found increased lactate and decreased glucose during wakefulness, as well as reduced lactate and increased glucose during NREM sleep in both the SD and KD groups (Fig. 1). We had limited episodes of REM sleep due to the short recording time, but the observed trend was similar to that of wakefulness. We found that the absolute levels of glucose (2.0 mM and 2.0 mM) and lactate (2.3 mM and 2.4 mM) did not differ between the SD and KD respectively (Supplemental Figure 1B and C). Therefore, the remaining glucose and lactate analyses combined SD and KD.

Sevoflurane anesthesia produces distinct EEG oscillations in rats. The induction phase was characterized by increased alpha (10–15 Hz), beta (15–30 Hz), and theta (5–9 Hz) power. Glucose and lactate levels fluctuated upon initial oxygen and anesthesia delivery. During the induction phase, glucose levels decreased whereas lactate levels increased similar to wakefulness and may reflect paradoxical excitation (Figs. 2 and 3). As anesthesia deepened, higher frequency power decreased, and delta power increased (0.5–4 Hz). This transition to deep anesthesia was

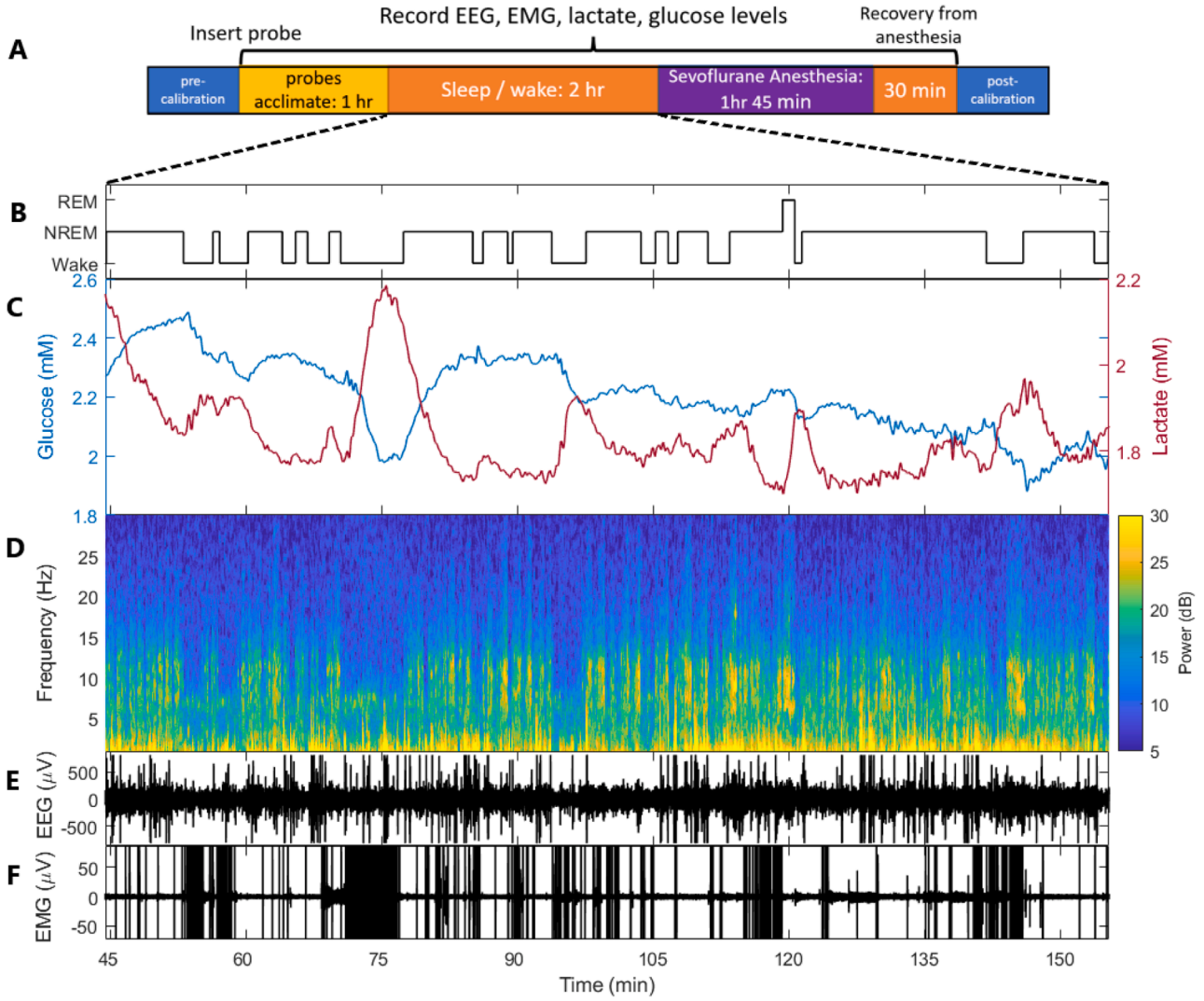


Fig. 1. Prefrontal cortex (PFC) glucose and lactate levels vary with the sleep wake cycle in rat (representative trace from an animal on the ketogenic diet (KD)). A) Experiment timeline on the day of the experiment. B) Hypnogram. C) Extracellular glucose (blue) and lactate (red) concentration in the PFC. D) Multitaper spectrogram of the PFC EEG. E) PFC EEG voltage trace. F) EMG voltage trace.

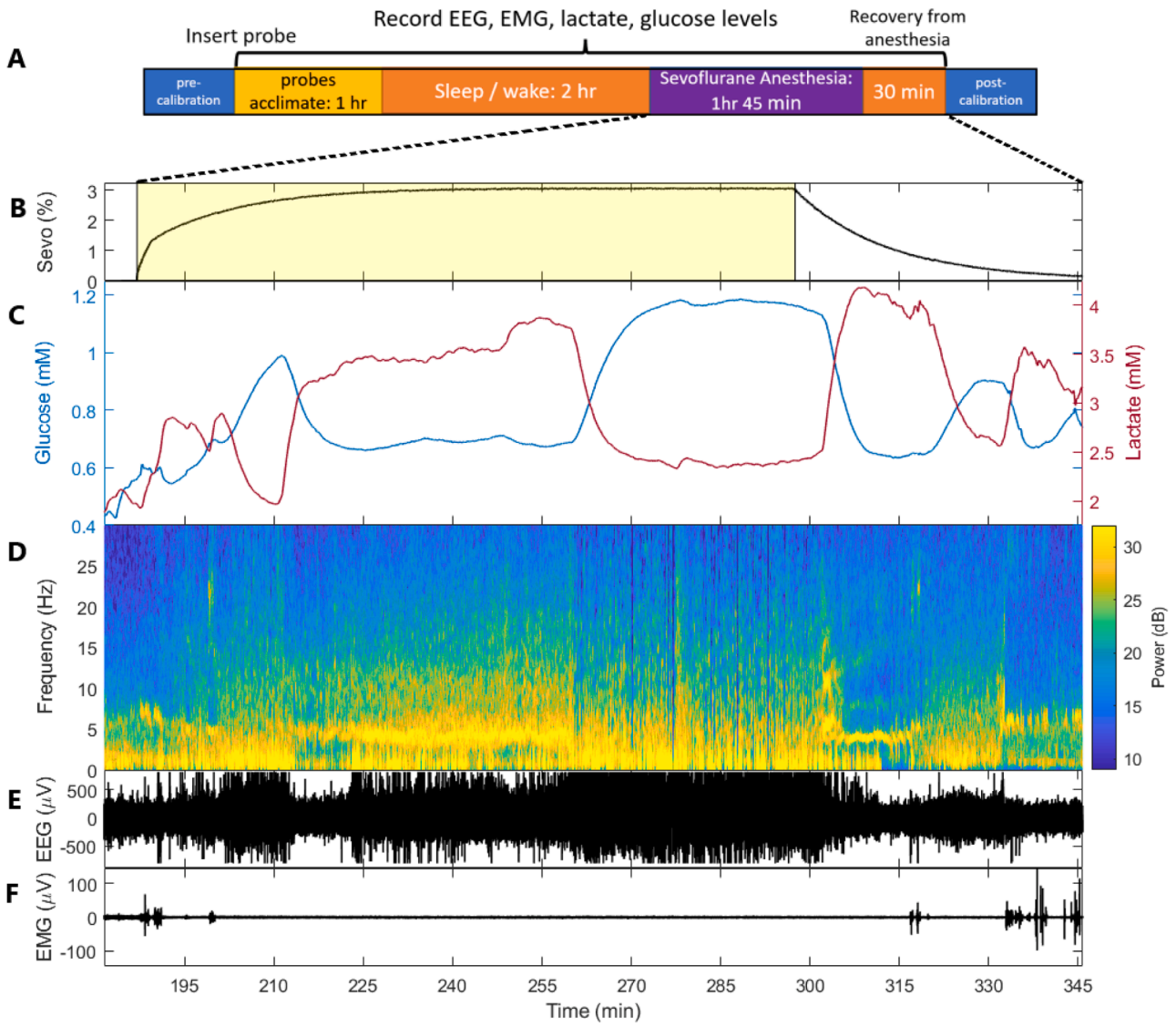


Fig. 2. Prefrontal cortex (PFC) glucose and lactate levels have a biphasic relationship with sevoflurane anesthesia (representative trace from a different animal on the ketogenic diet (KD)). Lactate increases during periods of high alpha and theta power associated with induction and emergence phases of anesthesia. Glucose increases during high delta power and burst suppression phases. A) Experimental timeline on the day of the experiment. B) Sevoflurane concentration in the chamber. C) Extracellular PFC glucose (blue) and lactate (red) concentration. D) Multitaper spectrogram of the PFC EEG. E) PFC EEG voltage trace. F) EMG voltage trace.

accompanied by a distinct switch to lower lactate and higher glucose, similar to NREM sleep but larger in amplitude. During the emergence phase of anesthesia, theta and alpha power increased and slow/delta power decreased while lactate increased and glucose decreased, similar to wakefulness (Fig. 2). Glucose and lactate's inverse relationship and pattern was similar during deep sevoflurane and NREM sleep with high glucose and low lactate. Emergence was similar to wakefulness with low glucose and high lactate. However, the absolute levels and dynamic range of glucose and lactate were greater during anesthesia compared to sleep/wake as measured by the standard deviation (glucose 0.085 mM and lactate 0.16 mM in sleep/wake and 0.25 mM and 0.41 mM during sevoflurane respectively) (paired *t*-test, Glucose: $p < 0.001$; Lactate: $p = 0.015$, Fig. 3 E&F).

Modeling the lactate signal across sleep/wake and anesthesia allowed us to compare the change in lactate concentration across time and between animals. Beta coefficients associated with increasing lactate during wake/REM were found to be statistically different from those during sevoflurane induction and emergence using the Kruskal-Wallis one-way analysis of variance ($p = 0.001$), and a multiple-comparison corrected post hoc test (wake/REM vs induction: $p = 0.003$, wake/REM vs emergence: $p = 0.007$, Fig. 3C). Modeled lactate concentration during NREM sleep (1.35 mM) was significantly lower than deep anesthesia (2.05 mM) using a two-sample *t*-test ($p < 0.001$, Fig. 3D).

3.2. The KD delays loss of movement and reduces sevoflurane-induced burst suppression

The KD animals had a lower burst suppression ratio (BSR) of 10 % averaged over the entire course of anesthesia exposure (approximately 120 min) compared to 30 % in SD animals ($p = 0.007$, Fig. 4D). KD animals had delayed induction time of 14 min (time to loss of movement) compared to 8 min in SD animals ($p = 0.0032$, Fig. 4E). There was no difference in recovery time associated with the KD (Fig. 4F). KD and SD BSR were statistically different between minutes 43.3 and 129.8 (where the bootstrapped confidence intervals of the estimated BSR over time were non-overlapping, alpha = 0.05) (Fig. 5A&B).

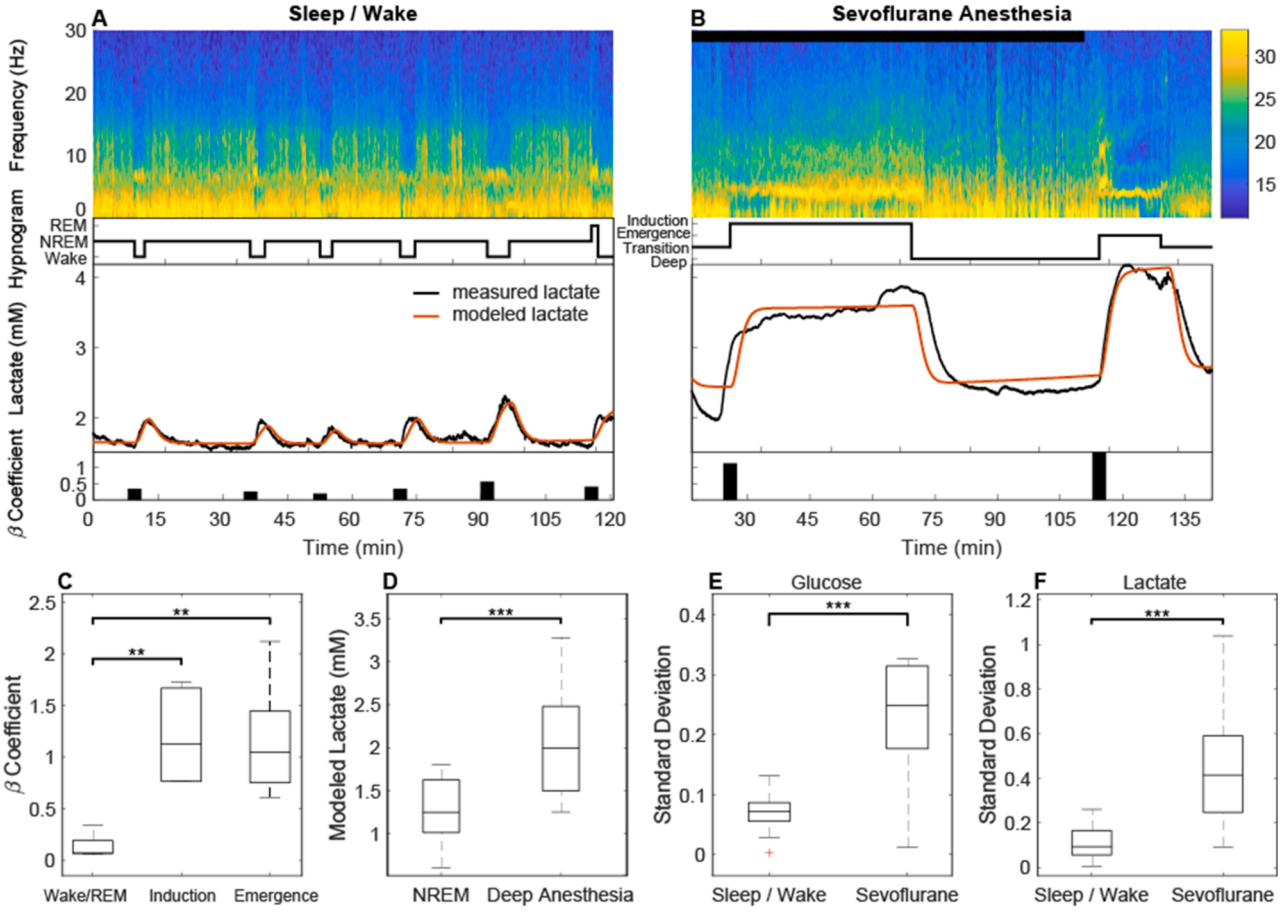


Fig. 3. Extracellular lactate levels vary across behavioral state and are higher during sevoflurane anesthesia compared to sleep and wakefulness. A) Spectrogram of the EEG, hypnogram of the scored state, example lactate model fit for sleep/wake where the black line indicates the lactate concentration measured from the biosensor and the orange line indicates the modeled lactate concentration. Beta coefficients from the lactate model show the magnitude of the lactate increase from NREM to wake/REM sleep. B) Example lactate model fit for corresponding sevoflurane condition. C) Beta coefficients associated with lactate changes during Wake/REM, induction, and emergence compared to NREM/deep anesthesia lactate levels were statistically different using the Kruskal-Wallis one way analysis of variance ($p = 0.001$). A multiple-comparison corrected post hoc test found lactate to be lower during Wake/REM compared to induction and emergence. (Wake/REM vs induction: $p = 0.003$, Wake/REM vs emergence: $p = 0.007$). D) Lactate model concentrations for NREM sleep and deep anesthesia are significantly different ($p < 0.001$). The dynamic range in mM of glucose (E) and lactate (F) is greater during sevoflurane than sleep/wake (Glucose, paired *t*-test: $p = 0.0002$; Lactate, paired *t*-test: $p = 0.015$). Box plots show the median plus the lower quartile Q1 and upper quartile Q3 where the whiskers are the (non-outlier) minimum and maximum values.

3.3. The adenosine A1 receptor antagonist, DPCPX, reverses the KD-induced reduction in burst suppression

One mechanism by which the KD exerts its anti-epileptic effects is through adenosine A1 receptors (Masino et al., 2011). To determine if the KD reduces burst suppression through adenosine A1 receptors, we gave IP administration of the adenosine A1 receptor antagonist, DPCPX immediately before 3 % sevoflurane. The BSR for KD+vehicle and KD+DPCPX were statistically different during minutes 8–35 and 65.4–112.8, in total 45.6 % of the two hours of sevoflurane exposure (Fig. 5C&D). The difference in electrophysiological states between the DPCPX and KD control groups is evident in the average spectrogram, where the KD control group exhibits strong theta and alpha oscillations from 80 minutes onwards, while the DPCPX group remains in burst suppression during this time (Fig. 6A&B). The BSR averaged over the entire sevoflurane exposure was not significantly different (Fig. 6C). DPCPX significantly reduced the time to the start of burst suppression compared to control (45 min in KD+vehicle to 37 min KD+DPCPX) ($p = 0.007$, Fig. 6D). The KD+vehicle control group stopped burst suppression before sevoflurane ended and in four of five rats this was counteracted by the DPCPX. Overall, this change in the end of burst suppression timing was not significant (Fig. 6E). The duration of burst suppression, as measured by the length of time from the first isoelectric period to the last, was greater in the DPCPX group (49 min in KD+vehicle to 90 min in KD+DPCPX) ($p = 0.046$ Fig. 6F).

4. Discussion

Changes in brain metabolic function are highly relevant for sleep, perioperative neurocognitive disorders, and Alzheimer's disease (Mattson and Arumugam, 2018; Yin et al., 2016). In this study, we aimed to better understand behavioral state-dependent changes in brain metabolism and determine the effect of a KD intervention on sleep and anesthesia. We measured prefrontal cortex glucose and lactate levels across sleep, wakefulness, and sevoflurane anesthesia with simultaneous EEG activity in animals eating a SD or KD. Our data provide useful insights into the bi-directional relationship between glucose and lactate across sleep/wake or anesthetic states and show that a KD modulates the depth of sevoflurane-induced anesthesia in rats, indicated by reduced burst suppression. Administration of the adenosine A1 receptor antagonist, DPCDX, abolished the KD effects on burst suppression suggesting that KD effects are mediated, in part, through adenosine A1 receptors similar to a mechanism by which KD decreases seizures (Masino et al., 2011).

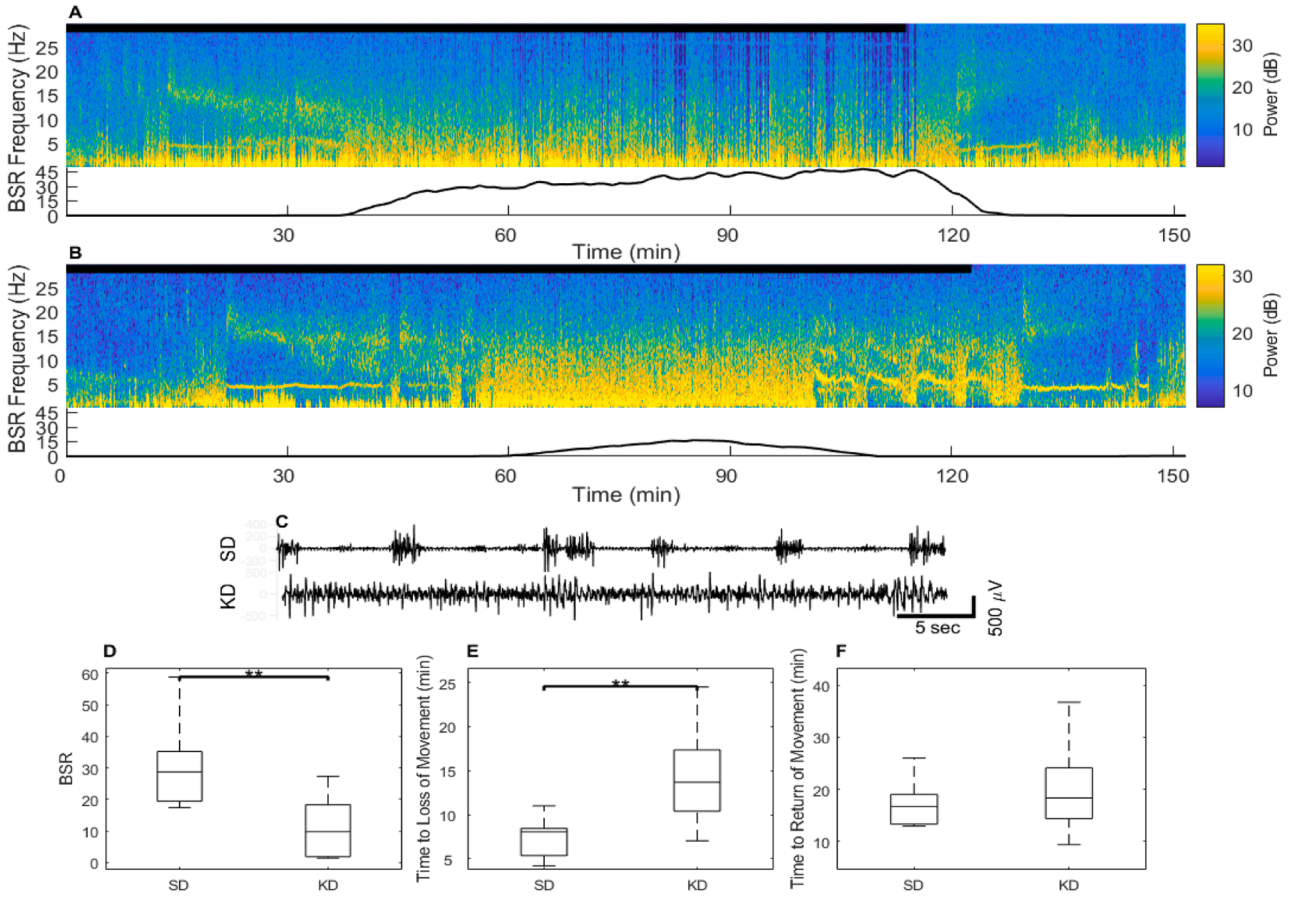


Fig. 4. Rats on the ketogenic diet (KD) have less burst suppression than rats on the standard diet (SD) at the same level of sevoflurane anesthesia. Example multitaper spectrograms of the EEG are shown for a rat on the SD (A) or KD (B) under 3 % sevoflurane anesthesia (indicated by black bars) and the burst suppression ratio (BSR) overtime is shown below each spectrogram. C) Raw EEG voltage traces from the above example recordings at 50 minutes showing the differences in burst suppression between the two groups. D) Animals on the KD had a lower group mean BSR compared to animals on the SD (two sample *t*-test, $p = 0.007$). E) Animals on the KD took longer to lose movement from sevoflurane than animals on the SD as measured by EMG activity (two sample *t*-test, $p = 0.003$). F) There was no significant difference in time to return of movement measured from the end of sevoflurane. Box plots show the median plus the lower quartile Q1 and upper quartile Q3 where the whiskers are the minimum and maximum. ($n = 8$, SD; $n = 9$, KD).

Previous studies show that glucose, lactate, and glutamate levels vary across vigilant states (Dash et al., 2012; Naylor et al., 2012; Wisor et al., 2013). Consistent with previous findings, glucose levels decreased during wakefulness and increased during NREM sleep (Figs. 1C and 3E), suggesting a shift away from glucose utilization during NREM sleep. Also, lactate levels were high during wakefulness and declined during NREM sleep (Figs. 1 and 3), possibly due to glymphatic system clearance or higher utilization of lactate during NREM sleep (Lundgaard et al., 2017). The present study did not include sleep deprivation, so we did not observe the previously found dissociation between glucose levels and prolonged wakefulness. As shown previously (Naylor et al., 2012), lactate was a robust biomarker of sleep/wake states (Figs. 2 and 3).

4.1. *Both glucose and lactate levels were higher overall during sevoflurane anesthesia than sleep*

We measured prefrontal cortex glucose and lactate during sleep, wakefulness, and sevoflurane anesthesia in the same animal for a direct comparison of absolute levels between states. Interestingly, both glucose and lactate levels increased significantly during sevoflurane compared to sleep/wake consistent with previous studies (Fig. 3). Within this higher range, the inverse relationship between glucose and lactate remained and the pattern of high glucose and low lactate during NREM sleep was also seen during deeply sedated periods and the pattern of low glucose and high lactate during wakefulness was seen during emergence (Figs. 2 and 3). Prefrontal cortex lactate initially increased with sevoflurane during induction and light anesthesia. This is consistent with previous microdialysis studies that found volatile anesthetics caused a 300 % increase in lactate from baseline in mouse hippocampus and striatum with isoflurane, sevoflurane, or halothane (Horn and Klein, 2010) and magnetic resonance spectroscopy studies of these halogenated ethers in mice found an increase in lactate from 1.0 to 6.2 mM or a 520 % increase (Boretius et al., 2013). In slight contrast to previous studies, we found that when deep anesthesia (defined by higher delta power and intermittent burst suppression) occurred, lactate decreased and glucose increased, similar to NREM sleep, thought the absolute levels were still higher than during sleep or wakefulness. Our study combined the high temporal resolution of the EEG and enzymatic biosensors to be able to differentiate this biphasic pattern in lactate and glucose at a finer temporal level than previous studies.

4.2. *The KD decreases sevoflurane-induced burst suppression*

The 2 prominent theories of burst suppression focus on hypometabolism (Ching et al., 2012) and hyperexcitability (Mader et al., 2014; Shanker et al., 2021). The hypometabolism theory suggests that burst suppression reflects decreased neural metabolism and ATP deficit (Ching et al., 2012). The hyperexcitability theory suggests that burst suppression is the result of cortical hyperexcitability arising from an imbalance of excitation and inhibition (Mader et al., 2014; Shanker

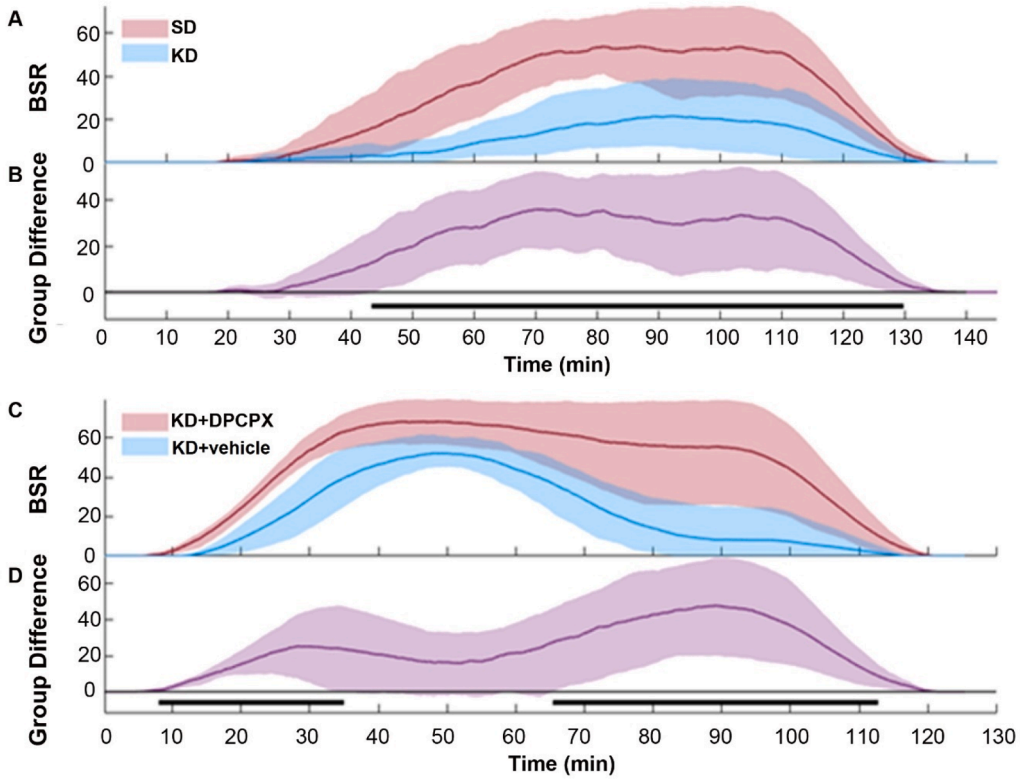


Fig. 5. Rats on the ketogenic diet (KD) have significantly reduced burst suppression compared to rats on the standard diet (SD) and DPCPX reverses the KDs reduced burst suppression. A) SD and KD burst suppression ratio bootstrapped 95 % confidence intervals. B) SD and KD bootstrapped difference, black bar along the bottom indicates time period where BSR is significantly different at alpha = 0.05. SD and KD BSR significantly different from minute 43.4–129.8. C) Adenosine A1 antagonist DPCPX counteracts the reduction in BSR due to the KD. D) Bootstrapped paired difference with 95 % confidence intervals. Of note, A/B experiments had a slower rise in sevoflurane whereas C/D experiments had a faster rise in sevoflurane based on the flow rate of oxygen delivering sevoflurane. KD (n = 9) and KD+DPCPX (n = 5) BSR significantly different from minute 8–35, and from 65.4 to 112.8.

et al., 2021). Our data adds support to both theories. First, the KD increased the time to loss of movement and decreased burst suppression levels (Fig. 4), suggesting ketones increase anesthetic resistance. Ketone bodies such as β-hydroxybutyrate increase mitochondrial ATP production by modulating the redox potential across electron carriers of the respiratory chain and reducing the NAD^+/NADH ratio (Norwitz et al., 2019). Our findings may be due, in part, to KD increasing ATP levels so the brain does not run out of energy as quickly resulting in less burst suppression which supports the hypometabolism theory. Volatile anesthetics also inhibit mitochondrial complex 1 (Cohen, 1973) and β-hydroxybutyrate can bypass complex 1 by feeding electrons to complex 2 through succinate production thereby replenishing oxidative fuel (Tieu et al., 2003). In addition, it has been shown that patients with mitochondrial defects at complex 1, have a greater sensitivity to volatile anesthetics like sevoflurane suggesting that complex 1 is the main target for volatile anesthetics to cause ATP deficits (Morgan et al., 2002). Some anesthetics like thiopental, propofol, and etomidate disrupt astrocytic glycolysis (Hadjihambi et al., 2020). These mechanisms may explain, in part, how KD provides additional energy and protects the brain during anesthesia.

Increased anesthetic resistance in the presence of ketones is consistent with previous studies using isoflurane where both the KD and exogenous ketones delayed the onset of isoflurane anesthesia (Ari et al., 2018; Kovacs et al., 2020). The time to return of movement did not correlate with the KD, which is consistent with the idea that emergence time is thought to be primarily a function of drug clearance (Shortal et al., 2019). Even though the time to return of movement was not significantly shortened, many animals in the KD group showed EEG signatures of lighter anesthesia before the sevoflurane anesthesia was turned off. In contrast, a recent study found an increase in recovery time from isoflurane anesthesia with a ketone ester/ MCT supplement in a rat model of epilepsy. They speculate that ketones increase adenosine, which is somnogenic and that the mild acidosis with ketosis may change the respiratory rate (Kovacs et al., 2023). These factors may contribute to their finding of delayed emergence, but more studies are needed.

The KD works through multiple pathways which may contribute to its effectiveness for multiple neurological conditions. These include increasing available fuel/ATP, decreasing oxidative stress, decreasing inflammation, direct signaling through HCARs, epigenetic regulation through HDAC inhibition, microbiome changes, altering neurotransmitters such as glutamate and GABA balance, and improving mitochondrial function (Rho and Boison, 2022). Here, we explore 1 pathway known to be involved in the KDs ability to reduce seizures, the adenosine A1 receptor (Masino and Rho, 2012; Poff et al., 2019). Ketones increase both intracellular and extracellular ATP, resulting in increased breakdown to adenosine (Kawamura et al., 2010). Adenosine binds to adenosine A1 receptors, which activate K_{ATP} channels, resulting in decreased neuronal firing (Masino et al., 2011) (Fig. 6G). K_{ATP} channels are important integrators of the metabolic status of the cell and cellular excitability (Martinez-Francois et al., 2018). Ketones may also modulate neuronal firing and seizures through direct activation of these K_{ATP} channels (Chegodaev et al., 2022; Kim et al., 2015; Yellen, 2008). Antagonist studies tell us about the role of endogenous ligands, in this case adenosine. Our study found that an adenosine A1 receptor antagonist blocked the KD's reduced burst suppression (Figs. 4, 5 and 6), suggesting that ketones primarily decrease burst suppression through adenosine A1 receptors versus direct activation of K_{ATP} channels. The adenosine A1 receptor antagonist data along with previous studies of epilepsy suggest that ketones stabilize neural excitability, in part, through K_{ATP} channels (Masino et al., 2011), supporting the

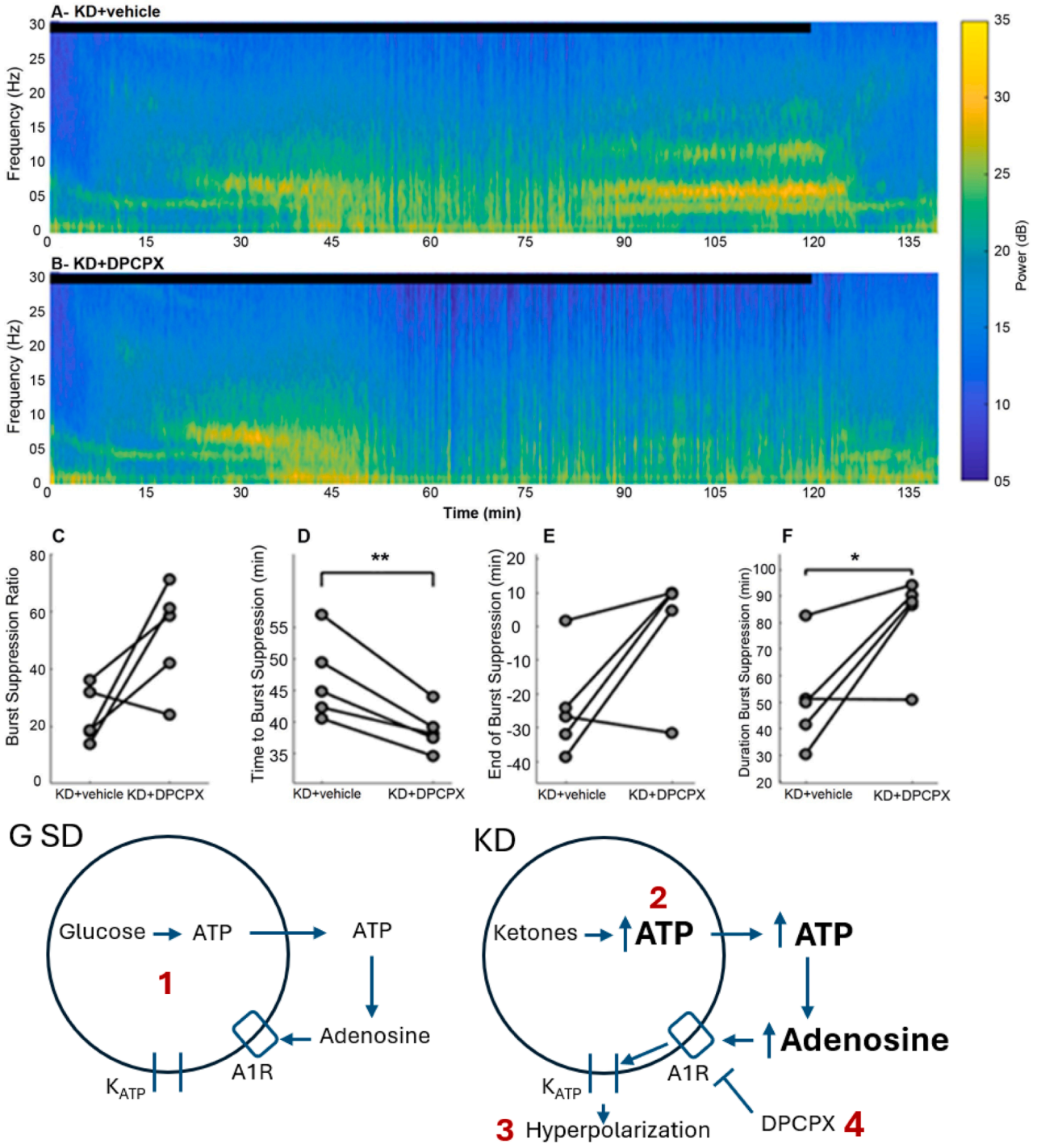


Fig. 6. The adenosine A1 receptor antagonist, DPCPX reverses the ketogenic diet-induced reduction in burst suppression. A,B) The average multitaper spectrogram during 3 % sevoflurane (indicated by the black bar) for animals on the ketogenic diet (A) and the same animals on the ketogenic diet given 0.2 mg/kg DPCPX in an intraperitoneal injection just before the start of sevoflurane anesthesia (B). C) The total mean burst suppression ratio was not significant between KD+vehicle and KD+DPCPX (pairwise comparison). D) DPCPX reverses the delay in burst suppression associated with the KD, $p = 0.007$. E) The time to the end of burst suppression as measured relative to the end of sevoflurane was not significant (where 0 min is the end of sevoflurane administration). Negative values indicate animals that stopped showing burst suppression before sevoflurane ended. F) DPCPX increased the duration of burst suppression compared to the ketogenic diet alone (paired *t*-test, $p = 0.046$, $n = 9$, KD+vehicle; $n = 5$ KD+DPCPX). G) 1) Under standard diet (SD) conditions, glucose primarily provides ATP resulting in a baseline level of extracellular ATP and adenosine. 2) Support for the hypometabolism theory of burst suppression: the ketogenic diet (KD) increases ATP so that the brain does not run out of energy as quickly resulting in less burst suppression. 3) Support for the hyperexcitability theory of burst suppression: KD increases intra and extracellular ATP which increases extracellular adenosine which binds to adenosine A1Rs which activates K_{ATP} channels and stabilizes the hyperexcitability of burst suppression. 4) DPCPX blocks adenosine A1Rs and reverses the KD-induced decrease in burst suppression back to a level more similar to the SD condition where baseline levels of adenosine are present.

hyperexcitability theory of burst suppression. While 45.6 % of the time, the burst suppression ratio was significantly different between KD+vehicle and KD+DPCPX, when the data was collapsed over the 2 hours of sevoflurane exposure, the average burst suppression rate did not differ (Fig. 6C). This may be due to one animal that did not respond to the ketogenic diet as measured by average burst suppression ratio (Fig. 6C), timing of when burst suppression ended (Fig. 6E), or total duration of burst suppression (Fig. 6F) highlighting individual animal variability in response to the ketogenic diet. Studies using DPCPX to investigate KD-induced time to immobility with isoflurane found that DPCPX given to animals on the SD had no effect on time to immobility (Kovacs et al., 2020). We speculate that since adenosine is also present in the SD condition, only at a lower level, that DPCPX in SD animals would either have no effect or increase burst suppression further since the level of burst suppression observed in the SD condition had not reached a maximum of 100 % or isoelectric EEG. Future studies will explore a more nuanced role of adenosine in regulating burst suppression. Though systemic administration of adenosine receptor agonists can cause negative cardiovascular effects and sedation.

4.3. Limitations

In order to compare the glucose and lactate dynamics in the same animal across sleep and anesthesia, given the limited biosensor recording time, the present study did not record sleep for long enough to determine if the KD alters sleep quality or sleep architecture. Future studies will record sleep for longer periods with the KD. We did not include sleep deprivation in the present study to dissociate the levels of glucose with prolonged wakefulness, as has already been done (Naylor et al., 2012). Previous studies have observed different lactate dynamics for injectable versus volatile anesthetics (Horn and Klein, 2010). Future studies with both EEG and the temporal resolution of biosensors are needed to determine if IV anesthetics like propofol also have more complex lactate temporal/EEG oscillatory dynamics like sevoflurane did in the present study. Future studies will perform behavior tests to determine if the KD-induced decrease in burst suppression has consequences for postoperative cognitive function. While it's known that KDs increase brain ATP levels, it would be interesting to see if there are state dependent and brain region dependent changes in ATP from the diet. Since brain glucose and lactate levels did not differ between dietary groups, further studies measuring other intermediary metabolites in the brain will help to identify which pathways are altered from the KD that influence burst suppression. We use the burst suppression ratio and movement to infer anesthetic depth in the present study as EEG burst suppression is a well characterized phenomena of deep anesthesia (Joyce et al., 2024; Wang et al., 2021). Future studies could use the righting reflex or other cognitive assays to increase the ways to investigate anesthetic depth. We based our concentration of DPCPX on previous literature, for a fuller pharmacological understanding of the interaction of adenosine receptors and ketones, a dose response curve could be helpful. Future studies could also investigate the relationship between ketones and other adenosine receptors like the adenosine A2 receptor in anesthesia. There are many tools to increase ketones now including fasting, ketone salts, ketone esters, and medium chain triglycerides which could be used to study the role of ketones in anesthesia-induced burst suppression. Future studies could add additional metabolic parameters to help elucidate the mechanistic effect of ketones on the brain.

5. Conclusions

Adequate energetic support is necessary for many neurological functions including cognition after sleep and anesthesia. Brain lactate and glucose levels were tightly correlated with EEG oscillatory patterns seen during sleep and anesthesia. The KD, which increases available brain ATP levels, delayed anesthetic induction and decreased the depth of anesthesia (indicated by decreased burst suppression) consistent with the idea that the underlying metabolic state of the brain influences an anesthetic's effect on the brain. These findings suggest that metabolic interventions could be useful therapeutic targets to modulate brain activity during sleep and anesthesia. Future studies will examine whether ketones can reduce the cognitive symptoms associated with postoperative delirium.

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Declaration of Competing Interest

None

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2025.111274.

Data availability

Data will be made available on request.

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