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Male prairie voles display cardiovascular dipping associated with an ultradian activity cycle

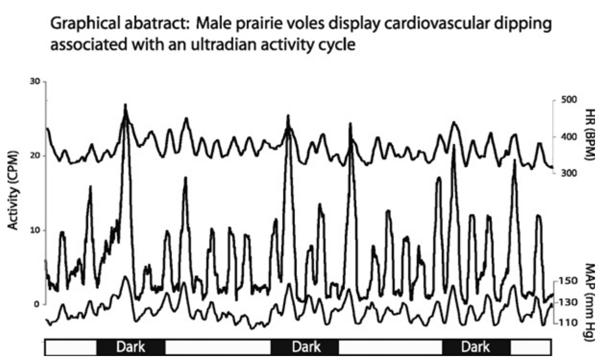
Robert Lewis, J. Thomas Curtis *

Department of Pharmacology and Physiology, Oklahoma State University Center for Health Sciences, 1111 W. 17th St., Tulsa, OK 74107, United States

HIGHLIGHTS

- A running average facilitates visualization of rhythmic patterns in a dataset.
- Male prairie voles display ultradian rhythms in MAP and HR as well as in activity.
- Activity and cardiovascular function retain the same temporal patterns across days.
- Prairie voles display ultradian dipping patterns in MAP and HR.
- The prairie vole may be a useful model in which to study blood pressure dipping.

GRAPHICAL ABSTRACT



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ABSTRACT

Mammals typically display alternating active and resting phases and, in most species, these rhythms follow a circadian pattern. The active and resting phases often are accompanied by corresponding physiological changes. In humans, blood pressure decreases during the resting phase of the activity cycle, and the magnitude of that "nocturnal dipping" has been used to stratify patients according to the risk for cardiovascular disease. However, in contrast to most mammals, prairie voles (*Microtus ochrogaster*) have periods of activity and rest that follow an ultradian rhythm with period lengths significantly < 24 h. While rhythmic changes in blood pressure across a circadian activity cycle have been well-documented, blood pressure patterns in species that display ultradian rhythms in activity are less well-studied. In the current study, we implanted pressure-sensitive radiotelemetry devices in male prairie voles and recorded activity, mean arterial pressure (MAP), and heart rate (HR) continuously for 3 days. Visualization of the ultradian rhythms was enhanced using a 1 h running average to filter the dataset. Positive correlations were found between activity and MAP and between activity and HR. During the inactive period of the ultradian cycle, blood pressure decreased by about 15%, which parallels the nocturnal dipping pattern seen in healthy humans. Further, the duration of inactivity did not affect any of the cardiovascular measures, so the differences in blood pressure values between the active and inactive periods are likely driven by ultradian oscillations in hormones and autonomic function. Finally, specific behavioral patterns also were examined. Both the instrumented animal and his non-instrumented cagemate appeared to show synchronized activity patterns, with both animals displaying sleep-like behavior for more than 90% of the inactive period. We propose that the prairie vole ultradian rhythm in blood pressure is an analogue for circadian blood pressure variability and can be used to study the long-term effects of commonly prescribed drugs on blood pressure dipping.

* Corresponding author.
E-mail addresses: robert.lewis11@okstate.edu (R. Lewis), tom.curtis@okstate.edu (J.T. Curtis).

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1. Introduction

Assessment of blood pressure throughout the day and night has facilitated the characterization of blood pressure rhythms in clinical and healthy populations [1,2]. Short-term and long-term rhythms have been identified; and among the most clinically relevant, is the circadian blood pressure rhythm. During sleep, blood pressure decreases 10–20% from the average waking value. The absence of this “nocturnal dipping” has emerged as a predictor of cardiovascular morbidity and mortality. Abnormal blood pressure rhythms, including attenuated dipping and non-dipping patterns, have been linked to higher risks of adverse cardiovascular events, such as ventricular hypertrophy and microalbuminuria [3,4]. Consequently, addressing circadian blood pressure variability, and not simply mean BP, may maximize the effectiveness of clinical interventions.

The mechanisms that regulate such blood pressure variations have been examined in human and animal models. Previous research has demonstrated that a variety of factors, including respiration, autonomic tone, and hormone levels, contribute to blood pressure dipping [1,2,4,5]. These physiological functions adapt to the metabolic demands associated with periods of activity and periods of rest. As a result, the blood pressure rhythm remains tightly linked to physical activity rhythms [6–8]. Diurnal mammals, for instance, will display a greater average blood pressure during the day, when the animal is most active, compared to during the night.

Understanding the strong connection between physical activity and cardiovascular function has been advanced by implantable telemetry in laboratory animals [6]. Importantly, these technologies have the ability to acquire blood pressure data during sleep [9,10], allowing for comparisons to be made between the active and resting periods. In addition to recording during sleep, the activity data from these devices can be used to identify the sleep/wake cycle. Recently, telemetry-derived activity measures were shown to correlate strongly with the sleep/wake cycle, which was estimated by recordings from electroencephalograms and electromyograms [11]. Accordingly, radiotelemetry could be used to track BP across the sleep/wake cycle.

Radiotelemetry in rat and mouse models of cardiovascular disease have been used to understand the mechanisms that contribute to disturbances in blood pressure dipping. [12–17]. Nevertheless, traditional rodent models are not without their limitations [18]. Rats and mice are nocturnal, and thus, show only one BP dipping event every 24 h. Examination of long-term effects of experimental manipulations on blood pressure dipping could be better assessed in a model organism with an accelerated activity cycle that is largely independent of the time of day.

In contrast to traditional laboratory rodents, many of the microtine rodents, including voles, do not show circadian rhythms in activity. Rather, these animals exhibit ultradian activity rhythms in which activity cycles occur throughout the day and night with period lengths of 1–4 h [19–21]. The period lengths of the ultradian rhythms in activity are resistant to changes in the environment [21]. Recently, radiotelemetry has been used to identify ultradian rhythms in core body temperature and heart rate in microtine rodents [22,23]. However, no one has examined blood pressure dipping in a species that shows ultradian rhythms in activity.

Here, we performed a detailed analysis of blood pressure across an ultradian activity cycle. In studies of biological rhythms, data often are collected at scheduled intervals [24] with the major advantage being that the amount of ‘noise’ in the dataset is reduced. However, accurate detection of the period length of a rhythm depends on the frequency with which data are acquired [25]. If the frequency or phase of an ultradian rhythm is variable or unknown, then a scheduled interval may not capture each peak for each animal [25]. In contrast, we acquired cardiovascular and activity data continuously and then filtered the dataset with a one-hour running average. While commonly used for financial forecasting in business [26–28], running averages are rarely used in physiology. Consistent with the effects on financial data, we predicted that the running average filter would facilitate the visualization of each animal's ultradian rhythms. Also, because of the link between activity and cardiovascular function in species that show circadian rhythms, we hypothesized that prairie voles would display ultradian rhythms in HR and BP and that those rhythms would correlate positively with activity. Lastly, we hypothesized that prairie voles would show an ultradian blood pressure dipping pattern that parallels blood pressure dipping in animals with circadian rhythms.

2. Methods

2.1. Animals

Subjects were adult male prairie voles from a captive breeding-colony at Oklahoma State University's Center for Health Sciences and were of the F3–F4 generation relative to the most recent outcrossing with wild stock. After weaning (20 ± 0.5 days of age), animals were housed as same-sex pairs in shoebox style cages (10 × 17 × 28 cm). Animals had ad libitum access to food (Purina rabbit chow supplemented with black oil sunflower seeds) and water. The colony is kept on a 14:10 light/dark cycle in a temperature-controlled room (about 21 °C) throughout the year. All subjects were sexually naïve adults (86.1 ± 9.5 days of age) with an average mass of 48.4 ± 3.0 g at the beginning of the experiment. All experimental procedures were approved by the Oklahoma State University Center for Health Sciences Institutional Animal Care and Use Committee.

2.2. Surgery

Radiotelemetry devices (PA-C10, Data Sciences International) were implanted in male prairie voles under isoflurane anesthesia. These devices are designed for use in mice, which typically are about ½ the size of voles. Thus, the weight of the device (1.4 g) is about 3% of the mass of the voles used in this study. Neither this small amount of added mass, nor the presence of the device per se appeared to impede the animals' performance in any way.

Body temperatures were maintained by placing the animals on a heating pad during the surgery. A small incision was made in the throat, and a sub-cutaneous pocket was created on each animal's dorsum, near the right scapula, into which the body of the telemetry device was placed. The left common carotid artery was exposed by blunt dissection, after which the artery was carefully isolated from the vagus nerve. The pressure-sensitive tip of the device was inserted into the left common carotid artery and advanced 14–14.5 mm relative to the carotid bifurcation to place the tip in the aortic arch. The carotid artery was selected as the implantation site because it is associated with a higher survival rate than is implantation of the abdominal aorta [29]. A subcutaneous injection of isotonic saline (0.5 mL) was given to animals that lost more than a minimal amount of blood. Each animal received perioral administration of 0.05–0.1 mL of meloxicam (1.5 mg/mL) on the day of surgery. All animals were within about 95% of their pre-surgery weights and were allowed six days to recover with data recording commencing on day 7 after surgery. This recovery period is consistent with recovery periods used in other studies [29,30]. Further, normal circadian rhythms return by day 6 post-surgery in CD-1 mice [31].

2.3. Overview of the experimental design

Surgical implantation of the telemetry devices was performed on day 0. Animals were returned to their home cages with their same-sex cagemates. Animals were given 6 days post-surgery to recover. For days 0–5, the subjects were separated from their cagemates using a wire mesh barrier, which permitted visual, auditory, and olfactory stimulation but prevented physical contact while the surgical wounds healed. On day 6 post-surgery, the wire mesh barrier was removed. On day 7, the subjects were moved into the testing room and then