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What can we learn about neural control of the cardiovascular system by studying rhythms in sympathetic nerve activity?

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ABSTRACT

Since the first recordings of sympathetic nerve activity in the 1930s, it was very clear that the activity was organized into bursts synchronized to the respiratory and cardiac cycles. Since the early studies, evidence has accumulated showing that sympathetic neural networks are quite complex and generate a variety of periodicities that range between ~0.04 and 10 Hz, depending on the physiological state, type of nerve being analyzed, age of the subject, and the species. Despite the ubiquity of sympathetic rhythms, many investigators have failed to consider this oscillatory characteristic of sympathetic nerve activity and instead rely on simply quantifying changes in the level of activity to make decisions about the role of the sympathetic nervous system in mediating certain behaviors. This review highlights work that shows the importance of including an assessment of the frequency characteristics of sympathetic nerve activity.

1. Introduction

Rhythms, with cycle times measured in terms of days, hours, seconds, or milliseconds, are essentially ubiquitous to biological processes. Rhythmicity offers several advantages over randomly occurring events (Pinsker and Ayers, 1983; Rapp, 1987). One, they permit stable temporal resolution of otherwise incompatible behaviors such as inspiration–expiration or flexion–extension. Two, periodic regulation promotes a temporal organization in the form of entrainment or synchronization. The concept of synchronization was first described in the 17th century when Huygens noted that the pendulum of clocks on different walls moved out of step with each other, but when the clocks were placed on the same wall, their pendulum began to move in synchrony (Minorsky, 1962). Three, rhythmic behavior allows one to predict repetitive events; for example, a circadian rhythm prepares an organism for physiological events that occur with a daily cycle. Four, a frequency-modulated (FM) signal is more resistant to distortion by noise compared to an amplitude-modulated signal. Consider the clarity of sound from an FM radio station compared to the static quality of the audio output of an AM radio station.

Like essentially all other physiological control systems, the autonomic nervous system and its target organs such as the cardiovascular system are characterized by the occurrence of rhythmic activity. Although most recognized for having cardiac-related and respiratory-related discharges, sympathetic neural networks are quite complex and generate a variety of periodicities that range between ~0.04 and 10 Hz or even higher, and even diurnal variations, depending on the physiological or pathophysiological conditions, type of nerve being analyzed, age of the subject, and the species (Barman and Gebber, 2000; Barman and Kenney, 2007; Chang et al., 1999; Charkoudian and Wallin, 2014; Hashimoto et al., 1999; Malpas, 1998, 2010; Narkiewicz et al., 2002).

Despite the nearly ubiquitous occurrence of rhythmic behavior, the actual purpose of some biological oscillations is not obvious. For example, why does sympathetic nerve activity (SNA) have a cardiac-related or 10-Hz rhythm if the organs controlled by sympathetic nerves such as the vasculature cannot respond at these rapid rates? What do very low (~0.04 Hz), low (~0.1 Hz), and high (~0.4 Hz) frequency oscillations in the variability of the heart beat and/or systolic pressure signify about the state of the cardiovascular system? What can one learn about neural control of the cardiovascular system by studying rhythms within the sympathetic nervous system?

Topics covered in this review include 1) methods used to record and quantify SNA, with special attention to its rhythmic pattern; 2) evidence that rhythms in SNA reflect the properties of central autonomic circuits rather than simply being imposed on these circuit, and 3) evidence implying that rhythmic activity leads to more effective activation of sympathetic neurons than randomly occurring activity, and 4) that rhythmicity is important for coordinating the discharges in sympathetic nerves supplying different cardiovascular target organs (e.g., heart and vasculature). Importantly, a major take home message is that one can misinterpret the effects of some manipulations on SNA by assessing only the "tonic" level of activity and ignoring its rhythmicity.

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2. Indirect and direct indices of SNA

Wallin and Charkoudian (2007) eloquently described the pivotal role played by the sympathetic nervous system in integrating physiological processes when they wrote: "*In an era when the importance of integrative systems physiology is reemerging into the spotlight of biomedical science, the sympathetic nervous system can be viewed as the ultimate integrator of systems physiology in control of cardiovascular function…Indeed, one of the most exciting aspects of measuring sympathetic neural activity is the ability of the investigators to see integrative physiology 'in action' every time they do an experiment*." Although these authors referred specifically to sympathetic control of the cardiovascular system, the comment is actually referable to sympathetic control in general. The sympathetic nervous system has long been recognized as being vital to the maintenance of homeostasis, allowing the organism to adapt to challenges imposed by internal and external forces (Benarroch, 1997; Cannon, 1914). Thus, to appreciate the very nature of survival we need to understand how to record and quantify the activity within this division of the autonomic nervous system.

Investigators have used a multitude of ways to assess a role of SNA at rest and during various perturbations (see reviews by Charkoudian and Wallin, 2014; Guild et al., 2010; Malpas, 2010). Many of these offer only an indirect assessment of SNA. For example, one can compare the fall in blood pressure following interruption of transmission in autonomic ganglia under different conditions. Surgical or drug-induced ganglionic blockade prevents an action of SNA on the vasculature (as well as all other autonomic target organs) so a fall in blood pressure accompanying ganglionic blockade is assumed to reflect the loss of SNA. On this basis, investigators have concluded that certain forms of hypertension (e.g., angiotensin II-induced and salt-induced hypertension) are due to elevated levels of SNA because blood pressure falls to a greater extent in the hypertensive model than in the normotensive control model (King et al., 2007; Yoshimoto et al., 2010).

Spectral analysis of heart rate and blood pressure variability is a non-invasive approach to assess the level of autonomic activity. As recently reviewed by Reyes del Paso et al. (2013), this has been widely used to evaluate the integrity of the autonomic nervous system, both vagal-mediated control of heart rate and sympathetic-mediated control of cardiovascular function, in either healthy subjects or in those with some known pathology such as heart failure. Although there is general agreement that changes in the high frequency component of heart rate variability are a good index of vagal nerve activity, there is less agreement that changes in the low frequency component of heart rate and systolic blood pressure variability are reliable indices of changes in SNA. For example, Reyes del Paso et al. (2013) point out that many physiological and psychological manipulations that are known to increase SNA do not increase (and, in fact, sometimes decrease) low frequency power in heart rate or systolic blood pressure variability.

Eslerand colleagues have pioneered the use of radiotracer technology to assess norepinephrine spillover as an index of regional SNA since norepinephrine is the neurotransmitter released from sympathetic nerves (Esler et al., 1984). Regional norepinephrine spillover is now regarded as a gold-standard for quantifying changes in SNA, especially in human subjects. This approach relies on an intravenous infusion of small amounts of tritiated norepinephrine followed by regional venous blood sampling. The norepinephrine spillover is quantified as the arteriovenous norepinephrine difference across an organ (after correction for the extraction of arterial norepinephrine) multiplied by the organ plasma flow. One of the major limitations of this approach is that it can only assess the level of SNA at a single point in time, so is not useful for evaluating short term changes in SNA.

The most direct assessment of SNA is to actually record the activity from a sympathetic nerve bundle. Adrian and colleagues were the first to publish a recording of SNA in anesthetized cats and rabbits (Adrian et al., 1932). They noted bursts of activity in cervical and abdominal sympathetic fibers that were synchronized to the phases of the cardiac cycle (cardiac-related activity), and the amplitude of these bursts waxed and waned on the time scale of the respiratory cycle (respiratory-related activity). About 36 years later, Karl-Erik Hagbarth introduced the use of microneurography to record muscle SNA (MSNA) in humans by inserting a needle into his own ulnar nerve (see Vallbo et al., 2004). He too noted the cyclic nature of bursts of MSNA on the time scale of the cardiac and respiratory cycles. Over time, many investigators have recorded from sympathetic nerves projecting to a variety of target organs, including the heart, kidney, mesentery, skeletal muscle vasculature, and skin. With a few exceptions (see below), the appearance of respiratory- and cardiac-related rhythmic activity is now considered the hallmark of SNA in many mammalian species. Recent advancements in telemetric technologies have allowed for chronic recordings of SNA in conscious animals with an aim toward learning whether changes in SNA precede or occur subsequent to development of a cardiovascular disease (see Wehrwein and Barman, 2014).

3. Quantifying the level and pattern of SNA

Figs. 1 and 2 show some of the common strategies used to quantify SNA in animal and human subjects. There are several recent reviews that discuss some of major methods used to quantify SNA in experimental models and explain some of the pros and cons of the various techniques (Charkoudian and Wallin, 2014; Guild et al., 2010; Malpas, 2010). These reviews can be consulted for specific details about recording techniques (filters, amplifiers, integration) as well as approaches to analyzing the recordings.

Most investigators that use microneurography in human subjects quantify MSNA by reporting burst frequency (either the number of bursts per 100 heart beats or bursts per minute) and/or the average amplitude and area of individual bursts (Fig. 1A); an estimate of "total activity" is made by determining the number of bursts times the average burst area during a recording period (Charkoudian and Wallin, 2014). There are large differences in resting levels of MSNA among individuals, varying from a few to ~100 bursts per 100 heart beats (Charkoudian and Wallin, 2014; Wallin and Charkoudian, 2007). Nonetheless, within an individual, the pattern of MSNA is reproducible over extended time periods (e.g., months, even years), conceivably making it possible to study changes in resting MSNA associated with a disease onset or progression or after therapeutic interventions. MSNA burst frequency increases with age and during exposure to high altitudes; and burst incidence is higher in individuals with various cardiovascular pathologies such as chronic renal failure, congestive heart failure, diabetes, hypertension, metabolic syndrome, obesity, and obstructive sleep apnea (Charkoudian and Wallin, 2014; Wallin and Charkoudian, 2007).

When recording from sympathetic nerves, especially in anesthetized animals, some form of "cumulative integration" is often used to quantify the "total amount" of SNA. In essence this method sums the amplitude (voltage) values in a signal over time. Fig. 1B and C shows two variations of this technique. In the first example, the integrator resets after reaching a certain time interval; one can then quantify changes in the average amplitude of the integrated signal in response to some intervention. In the example illustrated in Fig. 1B, the intravenous administration of sodium cyanide (NaCN) was used as a potent stimulus of the chemoreceptor reflex which drives both sympathetic and respiratory activity (Daly, 1997). The sympathoexcitatory nature of this stimulus is indicated by the higher amplitude of the integrated epochs immediately after the stimulus compared to baseline values (Orer et al., 2004). Fig. 1C shows results another type of summation in which the integrator is reset after reaching a particular summated voltage level. With this approach, one can quantify the average duration of integrated epoch or the slope of the integrated signal. In this example, the amount of SNA markedly decreased as sequential injections of a GABA-A receptor antagonist (upward tick marks in the trace below SNA) were made into the caudal ventrolateral medulla (CVLM) of a urethane-anesthetized cat (Barman and Gebber, 2007).

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