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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 1930's, 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.

Keywords

10-Hz rhythm; Cardiac-related activity; Respiratory-related activity; Spectral analysis

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, 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 clock son 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

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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.

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 re emerging 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 noninvasive 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 is 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 el 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.

Esler and colleagues have pioneered the use of radiotracer technology to assess norepinephrine spill over as an index of regional SNA since norepinephrine is the neurotransmitter released from sympathetic nerves (Esler et al., 1984). Regional norepinephrine spill over 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 spill over 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

Figures 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 the 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 (Figure 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 amongst 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. Figure 1B and 1C show 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 Figure 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 sympatho excitatory 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). Figure 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).

While these methods do indeed allow one to compare the level or total amount of SNA before and after different procedures, it does not provide any information about changes in the oscillatory character of SNA. For this one can use either time-domain (autocorrelation analysis) or frequency-domain (power density spectral analysis) methods. Autocorrelation analysis compares a signal with a replica of itself that is gradually shifted in time; it can detect periodicity that may be masked by random background activity (Bendat and Piersol, 1986; Brazier and Walter, 1973; Dutilleul, 1995; Jenkins and Watts, 1968). The periodicity is depicted in the resulting autocorrelogram in which the lags of maximum correlation correspond to the peaks and troughs of the original signal (Dutilleul, 1995; Jenkins and Watts, 1968). Although many algorithms can be applied to analyze a signal in its frequency domain, my laboratory has relied primarily on fast Fourier transform (FFT) which essentially converts a time-domain signal into its frequency components by matching the analog signal to sine waves over a range of frequencies (Bendat and Piersol, 1986; Brazier and Walter, 1973; Jenkins and Watts, 1968; Miller and Sigvardt, 1998). The autospectrum is the graphic depiction of the FFT and shows power (voltage squared) of the signal (y-axis) as a function of frequency (x-axis).

Advantages, disadvantages, and limitations of both time- and frequency-domain analyses have been discussed by others (Bendat and Piersol, 1986; Brazier and Walter, 1973; Dutilleul, 1995; Gootman and Sica, 1994; Jenkins and Watson, 1968; Miller and Sigvardt, 1998). Barman and Kenney (2007) and Gootman and Sica (1994) demonstrated why frequency-domain analysis is more suitable than time-domain analysis to quantify accurately a complex signal (i.e., one with multiple frequency components) such as SNA. They combined sine waves of various frequencies into a simulated mixed-frequency component signal. The precise rhythmicity within this complex signal was very difficult to detect by time-domain autocorrelation analysis, but was readily apparent when analyzed in the frequency domain. Figure 2 uses a comparable approach to further show that frequency domain analysis also accurately reflects the overall “amount of activity” within different frequency bands. The outputs of three sine wave generators with frequencies of 0.5, 3.0, and 10.0 Hz are displayed in the left panels. These frequencies were selected as they are typical of those occurring in SNA of urethane-anesthetized, conscious, or decerebrate-unanesthetized cats (Barman and Gebber, 2000, 2007; Barman et al., 1992; Green and Heffron, 1968; Ninomiya et al., 1990). The top trace on the right labeled “Mixed Signal” is the summation of the outputs of the three sine wave generators. The autospectrum of the “mixed signal” shows three very distinct peaks at 0.5, 3.0, and 10Hz; thus, spectral analysis faithfully reproduced the three original frequency components. This spectrum also faithfully reproduced the composite of the individual spectrum of the 0.5-Hz, 3-Hz, and 10-Hz sine waves. As will be shown later, in addition to assessing the pattern or character of SNA at a

given time, spectral analysis can be used to quantify changes in the “amount” as well as “character” of SNA over time or after a particular perturbation.

Time- and frequency-domain analyses are not only useful to identify the periodicity of a signal but also to assess the correlation between two signals (Bendat and Piersol, 1986; Brazier and Walter, 1973; Jenkins and Watts, 1968). A major advantage of coherence analysis in the frequency domain over its time-domain equivalent (cross correlogram) is that it defines the strength of linear correlation for each of the frequency components in the signals (Bendat and Piersol, 1986). A coherence value of 1.0 refers to a perfect correlation and a value of 0 means the two signals are completely unrelated. Examples of the use of coherence analysis to quantify the relationship between SNA and the arterial pulse or between the activities of two sympathetic nerves are seen in Figures 3 and 4.

4. Multiple rhythms in SNA

The data in Figure 3 are from a spontaneously breathing, urethane-anesthetized cat and they illustrate several important features of SNA. One, the prominent cardiac-related and respiratory-related periodicities in SNA are evident in the raw recordings in Figure 3A; the traces show arterial pressure (AP), intra tracheal pressure (ITP, a monitor of respiration), and inferior cardiac SNA but it is quantified by spectral analysis (solid gray trace in the middle panel of Figure 3C). Two, the pattern of SNA is changed markedly after disrupting the input from baroreceptor afferents onto central autonomic circuits (Figure 3B and black line trace in the middle panel of Figure 3C). Although SNA remained synchronized into bursts, there were no longer any distinct peaks in the autospectrum of SNA. In this example, the irregular periodicity in SNA primarily occurred at frequencies of < 6 Hz. The loss of a cardiac-related rhythm is evident by the lack of coherence between the AP and SNA (compare solid gray and black line traces in the top panel of Figure 3C). Three, the synchronous bursts of SNA do not look like simple sine waves; rather the duration and interval between bursts are quite variable, especially after baroreceptor denervation. Indeed, central sympathetic circuits are dynamic and can generate different burst patterns depending on the physiological state of the animal, the type of nerve being studied, as well as 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).

The cardiac-related rhythm results from baroreceptor-induced entrainment of a brainstem sympathetic network that generates irregular 2- to 6-Hz oscillations in cats (Gebber, 1976; Orer et al, 1999; Taylor and Gebber, 1975) and 0.4 to 0.7 Hz oscillations in humans (Barman et al., 2003; Fagius et al., 1985). The respiratory-related rhythm reflects the influences of both brainstem respiratory neurons and lung inflation afferents on the central sympathetic network (Bainton et al, 1985; Barman and Gebber, 1976, Cohen et al., 1980; Phillips et al., 2005; Zhong et al., 1997).

In addition to the cardiac- and respiratory-related rhythms in SNA, a 10-Hz rhythm has been best characterized in cats and is most apt to occur under conditions of reduced baroreceptor activity in un anesthetized-decerebrate, urethane-anesthetized, or conscious animals (Barman and Gebber, 2000; Barman et al., 1992; Cohen and Gootman, 1970, Ninomiya et

al., 1990). Figure 4 shows the simultaneous recordings from two branches of the same stellate ganglion, the inferior cardiac and vertebral nerves (i.e., sympathetic control of the heart and vasculature of the forelimb, respectively) in a urethane-anesthetized cat. This recording shows that the three most common rhythms in SNA (respiratory-related, cardiac-related, and 10-Hz rhythms) can co-exist under some circumstances. By changing the level of blood pressure in a partially baroreceptor innervated cat (aortic depressor nerve cut; carotid sinus nerve intact), it is possible to shift the balance between the cardiac-related and 10-Hz bursts in SNA (Barman and Gebber, 1997; Barman et al., 1994). At relatively high levels of mean arterial pressure (150 mmHg), the cardiac-related rhythm dominates; when mean arterial pressure is ~100 mmHg, the 10-Hz rhythm dominates. At intermediate levels of mean arterial pressure, there is a variable mixture of the two rhythms. The co-existence of the two rhythms proved to be of value when identifying brainstem neurons responsible for controlling the pattern of SNA (see below).

Another important feature about SNA seen in Figure 4 is that even though the cardiac and vertebral nerves arise from the same sympathetic ganglion, the discharge patterns are not identical. As discussed by Morrison (2001), differences in the activity patterns in sympathetic outflow have implications with regard to non-uniform influences of central and peripheral inputs to these nerves. For example, whereas sympathetic nerves controlling visceral organs are powerfully inhibited during activation of the baroreceptor reflex; sympathetic nerves controlling the vasculature of the skin, epinephrine release from the adrenal gland, and brown adipose tissue are only modestly affected by this stimulus. Also, visceral sympathetic activity is increased and cutaneous vasoconstrictor activity is decreased by peripheral noxious stimuli. Even the “hallmark” cardiac-related rhythm is not seen in all sympathetic nerves. For example, this rhythm is absent in the activity recorded from cutaneous vasoconstrictor fibers, sudomotor fibers, epinephrine-regulating adrenal preganglionic neurons, and nerves supplying the brown adipose tissue (Janig et al., 1983; Johnson and Gilbey, 1994; Mace field and Wallin, 1996; Morrison, 1999; Morrison and Cao, 2000).

SNA also has oscillations occurring at frequencies (~0.04 – 0.4 Hz) below the respiratory rate in conscious human and animal subjects (Ando et al., 1997; Brown et al., 1994; Jannssen et al., 1997; Stauss and Kregel, 1996). The bursting activity in the sympathetic nerve supplying thermoregulatory organs including the vasculature of the rat tail has been called a T-rhythm; it has a burst frequency of 0.4–1.2 Hz (Johnson and Gilbey, 1996; Smith and Gilbey, 2000).

5. Central control of rhythmicity in SNA

Many levels of the central nervous system (from the forebrain to the spinal cord) have been shown to contain neurons that can influence the rhythmicity in SNA of various animal models (see reviews by Barman, 2012; Barman and Gebber, 2000 and Malpas, 1998). Most work has been focused on the role of different regions of the brainstem in regulating the pattern of SNA. Barman and Gebber and their colleagues have used several approaches in anaesthetized cats to identify central neurons that generate and/or transmit rhythmic activity to the spinal intermediolateral cell column that contains the cell bodies of preganglionic

neurons. These include 1) applying correlation analyses (spike-triggered averaging and coherence analysis) to the simultaneously recorded activity of individual brainstem neurons and sympathetic nerves, 2) microinjecting agonists or antagonists of putative central neurotransmitters, including glutamate, GABA, serotonin, catecholamines, into different medullary and pontine regions to characterize changes in SNA rhythmicity, and 3) using the technique of antidromic activation to determine interconnections of medullary neurons and projections of brainstem neurons to the IML (Barman and Gebber, 1992, 1993, 1997, 1998, 2007; Barman et al., 1994, 1997, 1999, 2002, 2005; Orer et al., 1999, 2008).

It is beyond the scope of this review to provide the details of these studies, but the wiring diagram shown in Figure 5 summarizes some of the findings related to the organization of central pathways involved in regulating the cardiac-related and 10-Hz rhythms in SNA. Five brainstem regions were explored to identify the distribution of neurons with activity correlated to only the cardiac-related rhythm in SNA, only the 10-Hz rhythm in SNA, and to both the cardiac-related and 10-Hz rhythms in SNA. As described above, the level of blood pressure can be adjusted to change the expression of the cardiac-related and 10-Hz rhythms in SNA (Barman and Gebber, 1993, 1997, 1998; Barman et al., 1999). This afforded the opportunity to determine whether an individual neuron has activity correlated to one or both of these common rhythms in SNA. As shown in Figure 5, two regions contained a rather uniform population of neurons with activity correlated to SNA. Specifically, the medullarylateral tegmental field (LTF) only contained neurons with activity correlated to the cardiac-related rhythm in SNA and the CVLM contained neurons with activity correlated to only the 10-Hz rhythm in SNA. In contrast, the rostral ventrolateral medulla (RVLM), caudal medullary raphe nuclei (CMR), caudal ventrolateral pons (CVLP), and rostral dorsolateral pons (RDLP) each contained a mixture of all three types of neurons (Barman and Gebber, 2000). Antidromic mapping experiments revealed that within the RVLM, CMR, and CVLP only those neurons with activity correlated to both the cardiac-related and 10-Hz rhythms in SNA projected to the spinal IML.

The overall results of these studies support the following notions about this organization: 1) the cardiac-related and 10-Hz rhythms in SNA are an emergent properties of a distributed network oscillator comprised of functionally heterogeneous neurons, none of which appear to have pacemaker properties in vivo and 2) the cardiac-related and 10-Hz rhythms are likely generated by different groups of neurons but they use the same set of bulbo spinal neurons to relay this information to spinal preganglionic neurons in the IML.

In addition to the brainstem, neurons in more rostral (forebrain) and very caudal (spinal cord) levels of the neuraxis contribute to rhythmicity. For example, blockade of GABA receptors in the hypothalamic paraventricular nucleus brings out the appearance of low-frequency bursts that are synchronized to neither the respiratory nor cardiac cycle in anesthetized rats (Kenney et al., 2001, 2003). Using an in situ rat spinal cord preparation, Marina et al. (2006) showed that an intrathecal application of serotonin induces the T-rhythm (0.4–1.2 Hz) in the sympathetic innervation to tail circulation. And, using a chronic spinal cord transected cat model, Ardell et al. (1982) showed that a spinal segmental network is also capable of an irregular low frequency (<6-Hz) oscillation in SNA.

6. Functions of rhythms in SNA

Although only a small percent of the total power in an autospectrum of SNA is at frequencies less than 0.4 Hz, these low frequency oscillations are the only ones that are able to directly induce a corresponding rhythm in the smooth muscle of the vasculature (Johnson and Gilbey, 1996; Leonard et al., 2000; Malpas, 1998). Malpas (1998) suggested that these low frequency bursts in SNA and blood flow lead to improved organ perfusion.

Vascular smooth muscle acts as a low-pass filter with a cut-off frequency well below that of the cardiac-related or 10-Hz rhythm in SNA, implying that oscillations at these frequencies would not be transmitted to the cardiovascular system. Interestingly, a sudden spontaneous switch from a cardiac-related to a 10-Hz rhythm in SNA was accompanied by a large rise in blood pressure (Barman and Gebber, 2000). Likewise, blood pressure is significantly reduced by manipulations that disrupt the 10-Hz rhythm such as the chemical inactivation of brainstem neurons (Barman et al. 1994, 1997, 2005; Zhong et al., 1993). Barman and Gebber (2000) suggested that synchrony within the brainstem circuits that generate the 10-Hz rhythm may activate more preganglionic and postganglionic neurons, thus leading to an increase in blood pressure.

As described above, Figure 4 provides an example in which the activity of both the cardiac and vertebral nerves (CAN, VNA) contained a mixture of the three most common rhythms in SNA (respiratory-related, cardiac-related, and 10-Hz). The autospectra of CNA and VNA (Fig. 4B, top and middle) shows that considerable a periodic activity co-existed with the rhythmic activity. A periodic activity is evidenced by the large portion of the power density spectra that was not concentrated within one of the three peaks. Interestingly, the coherence function (Fig. 4B, bottom) shows that the rhythmic components of CNA and VNA were much more strongly correlated than the a periodic activity. This high coherence between the rhythmic activities in two sympathetic nerves is not limited to nerves that share a common ganglion. High coherence values relating rhythmic activity is seen when pairing a postganglionic sympathetic nerve arising from the upper thoracic level with one arising from the lower thoracic or lumbar level; and the activity of nerves on the left and right sides of the body are also strongly coherent (Gebber et al., 1994, 1995; Zhong et al., 1993). The fact that rhythmic activity is more highly correlated than a periodic activity is consistent with the hypothesis that rhythms help synchronize or coordinate the activity within different components of the sympathetic nervous system.

The sympathetic nervous system can respond to acute and chronic stressors by changing the absolute level of SNA and/or the frequency of SNA bursting. In response to either a progressive increase (from 38°C to 41°C) or decrease (from 38°C to 30°C) in internal body temperature, the cardiac-related rhythm in SNA is converted to irregular, low-frequency oscillations in anesthetized rats (Kenney et al. 1998, 1999). Since arterial blood pressure increased during this procedure, the loss of cardiac-related periodicity in SNA does not appear to be due to reduced baroreceptor nerve activity. Acute heat stress or mild hypothermia also enhanced the respiratory-related rhythm in SNA. However, when body temperature fell below 30°C, this respiratory-related rhythm was disrupted. Thus, changing

either the level of SNA or its burst pattern may be an important strategy used to maintain homeostasis.

7. Importance of assessing rhythmicity in SNA

At the outset of this review, the question was posed: What can one learn about neural control of autonomic regulation by studying rhythms within the sympathetic nervous system? Here I have shown that there are several prominent rhythmic components in SNA that are the signature of central (brainstem) generators that share a common pathway to the spinal cord. Rhythms in SNA can contribute to at least transient changes in blood pressure, allow for coordination of activity among different nerves, and contribute to the maintenance of homeostasis in response to acute physical stressors. But does evaluating rhythmicity really tell us anything more about neural control of the circulation than what we could learn by just studying changes in the amount of level of SNA? Data in Figures 6 and 7 say that indeed one can seriously misinterpret the effects of at least some manipulations by assessing only the “tonic” level of activity and ignoring its rhythmicity. Figure 6 shows the effects of bilateral microinjections of an antagonist of n-methyl-D-aspartate (NMDA) receptors in the LTF in an artificially ventilated (ITP as an index of respiration), urethane-anesthetized cat. Based simply on cumulative integration, the conclusion would be that NMDA receptors in the LTF do not affect SNA; that is, the average epoch duration was similar before and after microinjection of the NMDA receptor antagonist.

The spectral analysis shown in Figure 7 is for the same experiment as Figure 6. When comparing the shape of the autospectrum of SNA before (solid gray trace) with that after (black line trace) blockade of NMDA receptors in the LTF, it is quite obvious that the respiratory- and cardiac-related rhythmicity in SNA was abolished. Also note that the marked reduction in the coherence values relating the AP and SNA and ITP and SNA after NMDA receptor blockade in the LTF. The conclusion from this analysis is that NMDA receptors within the LTF play a critical role in mediating the influence of vagal lung inflation afferents and baroreceptor afferents on the entrainment of SNA to the respiratory and cardiac cycles. The data in Figure 1, C and D, also show the value in considering the frequency characteristics of SNA when evaluating the effects of blockade of GABA receptors in the CVLM of a urethane-anesthetized cat. Cumulative integration showed that this caused a reduction in the level of SNA but the spectral analysis showed that the 10-Hz component of SNA was selectively eliminated. These data were used to show that GABA receptors in the CVLM contribute to the formation of the 10-Hz rhythm in SNA (Barman and Gebber, 2007).

8. Perspectives for the future

The 21st century has brought renewed energy in assessing the role of the sympathetic nervous system in the genesis and/or maintenance of elevated level of arterial pressure in animal models of cardiovascular disease and in human subjects. As mentioned above, recent advancements in telemetric technologies now allow for chronic recordings of SNA in conscious animal to open the opportunity to look at the time course of changes in SNA as disorders such as hypertension develop (see Wehrwein and Barman, 2014) recently reviewed

several reports that have attempted to find a link between SNA and hypertension. They note that to date, few studies have been shown unequivocally that an increase in SNA underlies the development or maintenance of hypertension. A factor not considered in the most of these studies is the potential for a change in the pattern or rhythmicity of SNA to mediate an increase in blood pressure in these models of hypertension. It is hoped that in the future there is a greater consideration of looking at not only the level of SNA but also its frequency characteristics.

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- Brief review of methods to record and quantify sympathetic nerve activity
- Characterization and basis for of multiple rhythms in sympathetic nerve activity
- Functions of rhythms in sympathetic nerve activity
- Changes in rhythmicity versus level of sympathetic nerve activity during various perturbations

Figure 1.

Quantifying the level of sympathetic nerve activity (SNA). A: A short travel of muscle SNA (MSNA) in a human subject to show relationship of bursts to the heart beat from the electrocardiogram (ECG) as well as measurements of burst amplitude and burst area. B: Use of cumulative integration to quantify changes in SNA produced during chemoreceptor reflex activation in a urethane-anesthetized cat. Traces (top to bottom) are blood pressure (BP, mmHg), SNA, cumulative integration (reset every 50 ms). SNA was recorded monophasically from the central ends of the cut nerves on platinum bipolar electrodes with the preamplifier band pass set at 30–1,000 Hz. C: Use of cumulative integration to quantify changes in SNA sequential injections of a GABA-A receptor antagonist (upward tick marks in the trace below SNA) were made into the caudal ventrolateral medulla of a urethane-anesthetized cat. D: Spectral analysis of the same data shown in panel C before (solid gray trace) and after (black line trace) microinjection of the GABA-A receptor antagonist. SNA recording used a preamplifier band pass of 1–1,000 Hz. The autopectrum of SNA was based on 47 5-s windows with 50% overlap and a frequency resolution of 0.2 Hz per bin.

Figure 2.

Use of frequency-domain analysis to quantify the characteristics of a complex analog signal. The outputs of three sine wave generators are shown separately (0.5 Hz, 3.0 Hz, and 10 Hz) as well as when combined (Mixed Signal). Time scale, 1 s/division. The middle panel on the right shows the autospectrum of the “mixed signal,” and the bottom panel on the right shows the overlapping spectra of each of the individual sine wave signals. Spectra are based on 29 20-s windows with 50% overlap, and they have a frequency resolution of 0.05 Hz per bin.

Figure 3.

Spectral analysis is used to show changes in the respiratory-related and cardiac-related rhythms in SNA of a urethane-anesthetized cat. A, B: Recordings of AP and SNA (preamplifier band pass, 1–1,000 Hz) before and after bilateral section of the aortic depressor, carotid sinus, and vagal afferent fibers. C: Traces, top to bottom, show autospectra of AP and SNA and the coherence function relating AP and SNA. Spectra are based on 35 20-s windows with 50% overlap and a frequency resolution of 0.05 Hz per bin.

Figure 4.

Spectral analysis is used to show the coexistence of respiratory-related, cardiac-related, and 10-Hz rhythms in simultaneously recorded from two sympathetic nerves of a urethane-anesthetized cat. A: Moving averaged records of vertebral and cardiac nerve activity (VNA, CNA); time scale, 1 s/division; preamplifier band pass of 30 – 3K Hz, moving averager with a 50-ms time constant. B: Traces show (top to bottom) autospectra of VNA and CNA and coherence function relating their activity; spectra are based on 3520-s windows with 50% overlap and a frequency resolution of 0.05 Hz per bin.

Figure 5.

Wiring diagram showing interconnections of brainstem neurons with activity correlated to the cardiac-related and/or 10-Hz rhythms in SND. CMR, caudal medullary raphe; CVLM, caudal ventrolateral medulla; CVLP, caudal ventrolateral pons; IML, intermediolateral nucleus in the thoracolumbar spinal cord; LTF, lateral tegmental field; RDLP, rostral dorsolateral pons; RVLM, rostral ventrolateral medulla.

Figure 6. Effects of blockade of N-methyl-D-aspartate (NMDA) receptors in the medullarylateral tegmental field on SNA in a urethane-anesthetized cat. Traces, top to bottom, show arterial pressure (AP), intratracheal pressure (ITP), SNA (preamplifier band pass, 30– 1,000 Hz), and integrated SNA (cumulative integration) before (A) and after microinjection of the NMDA receptor antagonist (B).

Figure 7.

Effects of blockade of N-methyl-D-aspartate (NMDA) receptors in the medullarylateral tegmental field on frequency components of SNA. Data are from same animal as in Figure 6. Traces show autospectra of SNA and coherence functions relating arterial pressure (AP) and intratracheal pressure (ITP) to SNA before (solid gray trace) and after (solid black trace) microinjection of the NMDA receptor antagonist; spectra are based on 3220-s windows with 50% overlap and a frequency resolution of 0.05 Hz per bin. SNA used for spectral analysis

were based on moving averaged records; preamplifier band pass of 30 – 3K Hz; moving averager with a 50-ms time constant.

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