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Translational Physiology and SND Recordings in Humans and Rats: A Glimpse of the Recent Past with an Eye on the Future

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Abstract

The sympathetic nervous system (SNS) plays an important role in cardiovascular function, and based on the critical mechanistic relationship between altered sympathetic neural mechanisms and cardiovascular disease, it is important that the autonomic research community identify deficiencies in the translational exchange of information and strive for a more thorough understanding of the translational significance of findings from studies involving sympathetic nerve discharge (SND) regulation in human and animal subjects. The present review assesses the state of the literature regarding studies that have used direct recordings of SND during the past three decades in humans and rats, focusing on; 1) identifying the number of studies reporting SND recordings in humans and rats, 2) briefly describing the translational exchange of SND regulation information from these studies, 3) contrasting the number of studies completed in anesthetized and conscious rats, and 4) assessing the prevalence of long-term SND recording studies in conscious rats. The majority of SND recordings in rats have been completed using anesthetized preparations, although a substantial number of studies have been completed in conscious rats. However, few studies have completed long-term (>5 days) SND recordings in freely-behaving rats, and even fewer studies have used experimental preparations that combine long-term nerve recordings with the capacity for completing central neural microinjections, or have been completed in animal models of cardiovascular disease. The wide-spread implementation of long-term SND recordings in rodent models of cardiovascular disease would be expected to enhance the translational exchange of clinically-relevant information between animals and humans.

Keywords

sympathetic nerve discharge; conscious; anesthetized; humans; rats

INTRODUCTION

The sympathetic nervous system (SNS) plays a vital role in cardiovascular function and physiological regulation. As stated in a recent review by Wallin and Charkoudian (Wallin and Charkoudian, 2007), “It is literally impossible to consider systemic control of the cardiovascular system without integrating the roles and prominence of sympathetic neural mechanisms into any proposed scheme.” As reviewed by Barman and Kenney (Barman and Kenney, 2007), sympathetic nerves innervating the heart, blood vessels, and visceral organs

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are tonically active, and the background level of sympathetic nerve activity is characterized by the presence of synchronized bursts in both humans and animals. By altering important characteristics of sympathetic nerve discharge (SND), including the level of activity, the bursting pattern, and the formulation of nonuniform SND responses, central nervous system sympathetic circuits regulate target organ responses.

SNS dysregulation has been implicated in numerous pathophysiological states. Paroxysmal sympathetic hyperactivity is a clinical syndrome that affects a subgroup of patients that have survived traumatic brain injury (Baguley, 2008; Perkes et al, 2010; Perkes et al, 2011). Altered regulation of SND is considered a hallmark of heart failure (HF) (Cohn, 1990; DiBona and Sawin, 1994; Ferguson et al, 1990; Mark, 1995; Middlekauff et al, 1994). Muscle SND is increased in human HF patients (Ferguson et al, 1992; Leimbach et al, 1986) and renal SND has been reported to be higher in rats with HF when compared to sham controls (DiBona and Sawin, 1994). Human HF patients have an attenuated and/or absent low frequency component in efferent muscle SND (van de Borne et al, 1997). The results of experiments using biochemical, neurochemical and electrophysiological approaches support an important role for sympathetic dysregulation in the pathophysiology of hypertension (Grassi, 2004). Activation of the SNS is a common feature of obesity in humans and in animal models of obesity (Rahmouni et al, 2005). SNS dysregulation is associated with the individual components of the metabolic syndrome, including; visceral obesity, insulinemia, essential hypertension, and type II diabetes (Egan, 2003; Fagius, 2003; Hausberg et al, 2004; McCarty, 2004). The metabolic syndrome is considered to be a state of sympathetic nerve hyperactivity, especially in the presence of high blood pressure (Hugget et al, 2004). The prevalence of cardiovascular disease increases markedly with advancing age, as more than 70% of adult male and female Americans between the ages of 60–79 suffer from CV-related diseases (Rosamond et al, 2008). In a recent review titled, *Sympathetic Neural Mechanisms in Human Cardiovascular Health and Disease*, Charkoudian and Rabbitts (Charkoudian and Rabbitts, 2009) conclude that the current state of the literature “points to an important link between altered sympathetic neural mechanisms and the fundamental processes of cardiovascular disease.”

Based on the critical relationships between SNS regulation and cardiovascular physiology and SNS dysfunction and cardiovascular pathophysiology, it is imperative that the biomedical research community strive for a thorough understanding of the translational significance of findings from studies involving SND regulation in human and animal subjects, as well as identifying deficiencies in the translational exchange of information. Translational research as defined by the American Physiological Society and stated in an editorial authored by Dr. John Hall in the *American Journal of Physiology Cell Physiology* is “the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory.” This statement defines translational research as a bidirectional process, an approach that synergizes and potentiates the finding of new information and the opening of novel investigative frontiers. The completion of studies involving animal models and human subjects has defined the research activities regarding SND regulation for the past three decades.

The present review assesses the state of the literature regarding studies that have used direct recordings of sympathetic nerve discharge (SND), with particular emphasis directed towards; 1) identifying the number of studies reporting SND recordings in human and rat subjects, 2) briefly describing the translational exchange of information regarding SND regulation emanating from human and rat studies, 3) contrasting the number of studies completed in anesthetized and conscious rats, and 4) assessing the prevalence of long-term SND recording studies in conscious rats. Long-term SND recordings in freely-behaving rats

provide an experimental paradigm that minimizes or obviates issues with anesthesia, pain, inflammation and other acute confounding issues. Although the physiology of sympathetic nervous system regulation and function involves many steps, the literature review was confined to studies that used direct recordings of sympathetic nerve activity because peripheral recordings provide a measure of central neural-generated sympathetic nerve outflow. In addition, the current literature review in animal preparations was confined to studies in which SND recordings were completed in rats because the majority of experimental models used for studying cardiovascular disease employ experimental rats. However, it is important to note that long-term SND recordings in conscious rabbits have provided, in many ways, a critical technical and methodological foundation for the development of long-term, conscious nerve recordings in rats, and have made significant contributions to understanding SND regulation in mammals (Barrett et al, 2003; Guild et al, 2005; Head et al, 2004; Ramchandra et al, 2006).

The current topical review is divided into three sections. The first section highlights the extraordinary productivity of autonomic neurophysiologists during the past three decades as demonstrated by the impressive number of studies that have been completed using direct recordings of sympathetic nerve activity in human and rat subjects, and the important translational exchange of information between human and rat studies. The fundamental premise that SNS regulation in rat subjects is a parallel model for studying alterations in SND regulation in human subjects provides the conceptual framework for highlighting in the second section the limited number of studies that have completed chronic SND recordings in rats. Specifically, few studies have completed long-term SND recordings in freely-behaving rats, and even fewer studies have used experimental preparations that combine long-term, conscious nerve recordings with the capacity for completing CNS microinjections, or have completed long-term SND recordings in rat models of cardiovascular disease. Considerations that may enhance the more wide-spread implementation of sustained nerve recordings and central microinjections in freely-behaving rats are discussed in the third section as a potential means for enhancing the translational significance of sympathetic neurophysiological studies.

METHODS

The literature review involved completing National Library of Medicine PubMed searches using the primary search terms of sympathetic nervous system, sympathetic nerve activity, sympathetic nerve discharge, rat, muscle sympathetic nerve activity, skin sympathetic nerve activity, and human. Studies in humans and rats were initially screened to determine if direct recordings of SND had been completed. The focus on studies involving direct SND recordings excluded experimental studies involving neurotransmitters (e.g.; norepinephrine, epinephrine), neurotransmitter synthesis and release, adrenergic receptors, central and peripheral sympathetic neural anatomy, developmental sympathetic anatomy and physiology, etc. Experimental studies in rats were then reviewed to determine if nerve recordings were completed in conscious or anesthetized preparations; the conscious preparations were subsequently analyzed to determine if they were completed in rats that were restrained or freely-moving, and to determine the length of time that conscious nerve recordings were maintained in freely-moving rats. In many studies the time at which conscious nerve recording experiments were completed after implantation of the recording electrodes was explicitly stated (e.g., 4 hr, 24 hr), whereas in other studies a range of times was reported, such as, all experiments were completed in conscious rats 1–7 days after implantation of recording electrodes. Finally, in several studies (Hirakawa and Hayashida, 2006; Huang et al, 2006; Miki et al, 2003; Miki et al, 2003; Miki et al, 2004; Yoshimoto et al, 2004; Yoshimoto et al, 2010) it was reported that experiments were initiated not less than a specified number of days (typically 3 or 4 days) of recovery after implantation of the

recording microelectrodes, without indicating the absolute length of time that conscious nerve recordings were maintained. Because in these studies there was no indication that the conscious nerve recordings were sustained for an extended period of time beyond the stated number of recovery days, these studies were included in the data analysis as having maintained conscious nerve recordings for up to 5 days. Finally, data from studies reporting SND in freely-behaving rats were further screened to determine if nerve recordings were completed in models of cardiovascular disease (e.g., heart failure, hypertension, etc.) or in rats that had been prepared for central neural microinjections. Studies reporting SND recordings in decerebrate or brainstem-spinal cord preparations were not included in the current literature review. In total over 4,800 studies were screened and reviewed, and based on the criteria listed above, data from a little more than half of the screened studies were included in the current review.

TRANSLATIONAL PHYSIOLOGY AND SND RECORDINGS

During the past three decades autonomic neurophysiologists have been highly productive as demonstrated by the substantial number of publications involving the direct recording of SND in both humans and rats (Figure 1). As shown schematically in Figure 2, the translational exchange of findings from these studies, depicted by the dual parentheses, has substantially shaped the contemporary understanding of SND regulation directed to multiple targets under basal conditions, in response to periods of acute and chronic stress, and during states of health and illness, as well as enhancing the understanding of multiple indices of peripheral SND, including the total level of activity and frequency-domain characteristics. Importantly, microneurographic recordings of muscle and skin SND have provided substantial insight into the regulation of SND in a variety of pathophysiological conditions that affect human patients, including but not limited to heart failure, hypertension, obesity and sleep apnea (Charkoudian and Rabbitts, 2009).

It is well recognized that numerous inherent constraints limit the design and execution of experiments involving human subjects, therefore the completion of experiments in rat subjects has provided additional understanding regarding central mechanisms regulating the sympathetic nervous system (Figure 2, depicted by the single parenthesis). Studies in experimental rats have shaped the contemporary understanding of central mechanisms regulating basal SND and the role of central neural circuits in mediating changes in SND responses to acute stress. For example, it is well-established that central sympathetic neural circuits in experimental rats are capable of producing heterogeneous SND response profiles to numerous interventions, including directionally opposite changes in the level of activity in sympathetic nerves innervating different targets and selectivity in the frequency-domain characteristics of discharge bursts in different sympathetic nerves (Kenney, 1994; Kenney et al, 2002; Kenney et al, 1999; Morrison, 2001; Ramchandra et al, 2006; Weiss et al, 1996). Moreover, it is well-recognized that multiple levels of the neuraxis contribute to regulation of efferent SND and that various pathophysiological conditions can alter the central regulation of SND in experimental animals (Dampney, 1994; Dampney et al, 2003; Guyenet, 2006; Loewy, 1990; Strack et al, 1989; Sun, 1995). Without question, experimental research completed during the past thirty years has substantially enhanced the understanding of SND regulatory mechanisms.

BY THE NUMBERS: SND RECORDINGS IN ANESTHETIZED AND CONSCIOUS RATS

Over the past three decades SND recordings have been completed in both anesthetized and conscious rats, with the majority of studies using anesthetized preparations (Figure 3; anesthetized), although a substantial number of studies involving SND recordings have been

completed in conscious rats (Figure 3; restrained + freely-behaving). The majority of studies involving SND recordings in conscious rats have been completed under experimental conditions described by investigators as freely-behaving or unrestrained, and, for the most part, SND recordings in these studies have been sustained for a few hours to five days (Figure 3; bar graph, conscious freely-behaving, short-duration up to 5 days), see inset for more detail highlighting the temporal distribution of short-term SND recordings in conscious, freely-behaving rats. Although an impressive group of studies have completed chronic SND recordings for longer than 5 days, spearheaded by the laboratories of Dr. Hiroshi Kannan, Dr. John Osborn, and Dr. Kenju Miki (Kannan et al, 1990; Kannan et al, 1991; Kannan et al, 1994; Kannan et al, 1996; Kannan et al, 1998; Kato et al, 1999; Kato et al, 2009; Miki et al, 2002; Saita et al, 1998a; Saita et al, 1998b; Yoshimoto et al, 2010), and highlighted by a recent study by Yoshimoto et al. (Yoshimoto 2010) who reported maintaining chronic SND recordings for up to 28 days, in a relative sense few studies have been completed in freely-behaving rats with chronic, long-term SND recordings (Figure 3, >5 days, blue highlighted area, left column). Moreover, few if any studies have completed long-term SND recordings in rats that also include the capacity for central nervous system microinjections (Figure 3, blue highlighted area, middle column), or have implemented these techniques in rat models of cardiovascular disease (Figure 3, blue highlighted area, right column). These are critical omissions as the translational exchange of information would be expected to be enhanced by completing long-term recording studies in rat models of cardiovascular disease and in conjunction with central neural microinjections.

CONSIDERATIONS FOR OVERCOMING THE CRITICAL BARRIERS

The completion of chronic, long-term SND recording and central neural microinjection studies in freely-behaving rats would be expected to facilitate understanding critical links between altered sympathetic neural regulatory mechanisms and the fundamental processes of cardiovascular disease. Several factors must be considered to make these experimental steps successful. First, the development of accessible long-term SND recording and CNS microinjection techniques in conscious rats will require the collective expertise of investigators that have substantial experience in peripheral and central autonomies. Importantly, the autonomic research community has a wealth of investigators with SND recording and central neural experience and is well-positioned to provide information to an area of research that is clinically relevant yet is characterized by a profound lack of data. Second, the slow onset for the wide-spread implementation of long-term SND recordings in conscious rats may be a function of intrinsic technical and experimental issues, including but not limited to concerns regarding the ability to maintain robust, stable nerve recordings secondary to changes in the nerve-electrode interface, difficulties in parsing changes in afferent vs. efferent discharges in intact peripheral sympathetic nerves, and concerns regarding the viability of activity in lesioned sympathetic nerves in experiments in which recordings of efferent SND are desired. However, and as stated previously, long-term SND recordings have been maintained in conscious rats (Kannan et al, 1990; Kannan et al, 1991; Kannan et al, 1994; Kannan et al, 1996; Kannan et al, 1998; Kato et al, 1999; Kato et al, 2009; Miki et al, 2002; Saita et al, 1998a; Saita et al, 1998b; Yoshimoto et al, 2010), supporting the experimental viability of these recording procedures. Moreover and as recently reviewed by Burke et al. (Burke et al, 2011), chronic SND recordings in rats can now be completed using an implanted wireless telemetric system. The introduction of this technology for studies in rats is a significant advancement for extending the recording life of chronic nerve preparations which in turn would be expected to open new frontiers for use in rodent models of cardiovascular disease (e.g., heart failure, hypertension, obesity, etc.) and in autonomic behavioral neuroscience. Third, developmental funding and dedicated research time are essential elements for success in the pursuit of long-term recording and microinjection techniques. Although the funding portfolio of the American Heart

Association includes an Innovative Research Grant that is intended “to support highly innovative, high-risk, high-reward research that could ultimately lead to critical discoveries or major advancements that will accelerate the field of cardiovascular and stroke research”, it must be recognized that in most instances funding for the development and refinement of methodological approaches is limited. In addition, although many investigative teams will routinely refine an experimental technique to assist in the completion of experiments directed towards addressing a specific research aim, most principal investigators are reticent, rightfully so, to dedicate substantial amounts of research resources and time to an undertaking as formidable as developing and refining recording and microinjection techniques in conscious animals. Despite these substantial caveats, there is no question that if an aggressive shift towards long-term sympathetic nerve recording and central neural microinjection techniques is to occur then developmental funding and dedicated research time will need to be an integral part of the paradigm shift. Fourth, an important experimental approach for investigating mechanisms regulating central sympathetic neural circuits focuses on the functionality of specific neurotransmitters and neuromodulators in selected nuclei. In fact, much of the contemporary understanding of central regulation of SND in young, anesthetized mammals has been determined using microinjection techniques to investigate regulatory components of sympathetic neural networks. To establish the experimental foundation for understanding mechanisms mediating the long-term (weeks to months) central regulation of SND, it is imperative that procedures for the completion of central neural microinjections and chronic SND recordings be simultaneously developed and implemented.

CONCLUSION

Direct recordings of SND in human and animal subjects completed during the past three decades have substantially shaped the contemporary understanding of mechanisms contributing to the regulation and dysregulation of the SNS. The majority of SND recordings in rats have been completed in anesthetized preparations, and for the most part, sympathetic recordings in conscious rats have typically been maintained for a few hours to approximately five days, with a rather limited number of studies reporting data from long-term SND recordings in freely-behaving rats. In addition, so few studies have used central neural microinjection techniques in conjunction with SND recordings in freely-behaving rats that it is difficult to develop an evidence-based framework regarding mechanisms mediating central regulation of SND in conscious rats.

The completion of chronic, long-term SND recording and central neural microinjection studies in freely-behaving rats would provide an important experimental step towards understanding the critical link between altered sympathetic neural regulatory mechanisms and the fundamental processes of cardiovascular disease, thereby enhancing the translational exchange of clinically-relevant information between animal models and human patients. Importantly, these contributions can only be realized if the autonomic research community demonstrates a focused shift towards the development and refinement of chronic, long-term recording and microinjection techniques in conscious animals, an effort that must match or exceed the intensity that defined the progression of studies in conscious humans and anesthetized animals during the past three decades.

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Figure 1.

Bar graphs summarizing the number of published studies that have reported directly-recorded sympathetic nerve discharge (SND) in human (left) and rat (right) subjects during the previous three decades (1981–2010).

Figure 2. Schematic diagrams summarizing the contribution of published studies to understanding sympathetic nerve discharge (SND) regulation in human (left) and rat (right) subjects. The translational exchange of information between human and rat studies is depicted in the lower section of the figure, whereas the upper section highlights the contribution from studies in rats towards understanding central mechanisms regulating SND.

Figure 3.

Bar graphs summarizing the number of published studies reporting directly-recorded sympathetic nerve discharge (SND) in rat subjects from 1981–2010 in six experimental conditions: anesthetized, conscious (total number; restrained + freely-behaving preparations), conscious freely-behaving (short-duration recordings, from several hours up to 5 days, see figure inset), conscious freely-behaving (long-duration recordings, > 5 days), conscious freely-behaving, long-duration recordings (>5 days) accompanied by central nervous system (CNS) microinjections, and conscious freely-behaving, long-duration recordings (>5 days) completed in rat models of cardiovascular (CV) disease.