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Sympathetic neural adaptations to exercise training in humans

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ABSTRACT

Physiological adaptations to exercise training are well recognized and contribute importantly to health and fitness. Cardiovascular diseases, such as hypertension and heart failure, are often associated with elevated activity of the sympathetic nervous system. This review aims to provide comprehensive overview on the role of exercise training on muscle sympathetic nerve activity (MSNA) regulation in humans, with a focus on recent advances in at-risk populations. Collectively, these studies converge to demonstrate that aerobic exercise training reduces resting MSNA in populations at heightened cardiovascular risk, but do not appear to alter resting MSNA in healthy adults. We provide directions for future research which might address gaps in our knowledge regarding sympathoneural adaptations to exercise training.

1. Introduction

Physical activity is associated with beneficial effects on cardiovascular health. This association is evident by the direct links between a sedentary lifestyle and the risk of cardiovascular and other disease states. Cardiovascular diseases, such as hypertension and heart failure, are often associated with elevated activity of the sympathetic nervous system (Cohn et al., 1984; Esler et al., 2003). Conversely, exercise training is associated with reduced resting blood pressure, improved cardiac function, increased maximal skeletal muscle blood flow, and more effective redistribution of blood flow during exercise (Pescatello et al., 2004; Rowell, 1993; Tipton, 1991). It is generally believed that reductions in sympathetic outflow represent a major adaptation of exercise training, and a mechanism which contributes to blood pressure decreases at rest. Evidence also indicates that exercise training reduces central sympathetic outflow in both healthy and cardiovascular diseased animals (Mueller, 2007; Zucker et al., 2004). Collectively, these data suggest that physical activity may decrease, and physical inactivity may increase, the incidence of cardiovascular disease via alterations in the sympathetic nervous system. Moreover, the role of exercise training on neural cardiovascular reactivity to both physical and mental stress is important because sympathoexcitation to stressors is believed to contribute to the development and progression of cardiovascular diseases (Rozanski et al., 1999).

In 1998, Ray and Hume (1998) reviewed the role of exercise training on muscle sympathetic nerve activity (MSNA) in humans. While this review (Ray and Hume, 1998) included data from both cross-sectional and longitudinal studies, only five longitudinal manuscripts had been published at the time (Grassi et al., 1994; Sheldahl et al., 1994; Sinoway et al., 1996; Somers et al., 1992; Svedenhag et al., 1984). Moreover, all five studies were performed in healthy adults (Grassi et al., 1994; Sheldahl et al., 1994; Sinoway et al., 1996; Somers et al., 1992; Svedenhag et al., 1984), four studies lacked a sedentary control group (Sheldahl et al., 1994; Sinoway et al., 1996; Somers et al., 1992; Svedenhag et al., 1984), four studies included only male participants (Sheldahl et al., 1994; Sinoway et al., 1996; Somers et al., 1992; Svedenhag et al., 1984), and training durations were relatively modest (range, 4–12 wk). Since the review by Ray and Hume (1998), an additional 21 longitudinal studies have been published on the influence of exercise training on MSNA in humans, and this will be the focus of the current review. These additional studies have included 1) randomized control experimental approaches, 2) populations at-risk for adverse cardiovascular events (i.e., heart failure, metabolic syndrome, hypertension, etc), 3) both aerobic and resistance training, and 4) training durations of up to 6 months. This review aims to provide comprehensive overview on the role of exercise training on MSNA regulation in humans, with a focus on recent advances in at-risk populations.

2. Microneurography

Microneurography is presently the only method available for direct recordings of postganglionic sympathetic traffic in humans. Briefly, this technique involves insertion of a tungsten microelectrode into accessible nerves in the upper (i.e., radial, medial, ulnar nerves) or lower

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(i.e., peroneal, tibial nerves) limbs (Vallbo et al., 2004). Sympathetic nerve activity to both the skin and muscle can be recorded, and this review will focus on sympathetic outflow to skeletal muscle.

The most common analysis and quantification method is the use of an integrated signal of multiple nerve fibers to report sympathetic nerve activity as burst frequency (bursts/min), burst incidence (bursts/100 heart beats), and total MSNA (mean burst amplitude or area × number of bursts). An alternative to the multi-fiber approach is the quantification of single fiber sympathetic nerve activity (Macefield et al., 1994). This approach is technically more difficult than the multi-fiber approach, but can provide a more selective measurement of sympathetic neural outflow.

Although microneurography provides a gold standard assessment of sympathetic nerve activity, it has several limitations. First, the technique is invasive and restricted to a controlled laboratory environment. Second, the limb from which sympathetic traffic is being recorded needs to remain relaxed and immobile. Some sympathoexcitatory maneuvers used in concert with microneurography can lead to dislodgement of the microelectrode and/or slight shifts within the neurogram, which can result in complete or partial loss of analysis. Third, this technique cannot be applied to internal organs such as the heart, kidneys, and liver. However, certain studies that have simultaneously measured norepinephrine spillover and MSNA have revealed that MSNA is generally a good marker of sympathetic responses to several internal organs (Macefield et al., 1994; Wallin et al., 1992; Wallin et al., 1996). Finally, microneuography is technically difficult and obtaining/maintaining quality recordings can be challenging at times for even the most experienced microneurographers.

3. Exercise training — experimental approach

Exercise training programs used to examine MSNA adaptations have taken diverse approaches, which makes interpretation of the literature more challenging. Training paradigms are often designed in conjunction with the question being asked by the investigators. If the study is addressing how training alters the regulation of muscle reflexes on MSNA reactivity, small muscle groups, such as the forearm, can be used. In contrast, if generalized reductions of resting MSNA are being sought, the use of whole-body, large muscle mass exercise, such as running and cycling, are generally used. However, the complexity only begins there. Studies have used various training intensities, frequencies, and durations, and all three factors can have dramatic effects on physiological adaptations. Specific attention to the duration of the exercise training may be particularly important. The human training studies highlighted in this review are relatively short in duration, and this is particularly true in studies of healthy subjects where resting MSNA adaptations to exercise training are largely lacking. Studies in clinical populations have tended to use longer training durations, resulting in consistent and pronounced reductions in MSNA. Although most studies have used aerobic endurance training, there are some studies using resistive exercise training. These studies are important because maintenance of muscle mass is important for health and healthy aging. We will repeatedly come back to issues of experimental approach throughout this review.

4. Aerobic training and resting MSNA

4.1. Young healthy adults

Five longitudinal studies have been conducted examining resting MSNA responses to aerobic exercise training in young, healthy adults with a mean study age of ≤25 years (Cooke et al., 2002; Grassi et al., 1994; Ray, 1999; Ray and Carter, 2010; Svedenhag et al., 1984). Four of the five studies report no change in resting MSNA (Cooke et al., 2002; Ray, 1999; Ray and Carter, 2010; Svedenhag et al., 1984). In contrast, Grassi et al. (1994) reported a significant reduction of resting MSNA in 9 young adults when compared to 4 nonrandomized controls.

An additional four studies in middle age and older healthy adults (range, 35–70 years) also reveal no change of resting MSNA with aerobic exercise training (Laterza et al., 2007; Roveda et al., 2003; Sheldahl et al., 1994; Ueno et al., 2009). However, these four studies lacked a randomized, age-matched, sedentary control groups because most were serving an extra "trained healthy control" treatment arm for a study in at-risk populations. Nevertheless, when considered with the data from young, healthy adults (several of which also lack randomized control groups), 8 of 9 publications report no change in resting MSNA with aerobic exercise training in young, middle-age, and older healthy adults.

4.2. Heart failure

In 2003, Roveda et al. (2003) published the first randomized control trial examining the influence of supervised aerobic exercise training on resting MSNA in heart failure (HF) patients. The authors (Roveda et al., 2003) report that 4 months of aerobic training resulted in nearly a 50% reduction of resting MSNA (~46 to ~24 bursts/min). These dramatic reductions of resting MSNA were not observed in the sedentary HF controls (~44 to ~43 bursts/min) or exercise training healthy controls (~27 to ~26 bursts/min). Since the findings of Roveda et al. (2003), an additional four studies have been conducted in heart failure patients, and all four report significant reductions of resting MSNA with the same 4 month aerobic exercise training regimen. Reductions of resting MSNA persist when HF patients are on carvedilol (Fraga et al., 2007) or have sleep apnea (Ueno et al., 2009). Moreover, reductions of resting MSNA with aerobic training are similar in men and women HF patients (Antunes-Correa et al., 2010), as well as middle age and older HF patients (Antunes-Correa et al., 2012).

Franco et al. (2006) noted that the sympathoinhibitory responses to 4 months of supervised aerobic training in HF patients were no longer statistically different after a 4 month follow-up with a home-based aerobic training regimen (total study duration of 8 months). The authors suggested this may be due, in part, to a drift back toward baseline peak VO_2 (Franco et al., 2006). However, we find this explanation unlikely given that peak VO_2 was not statistically different between baseline, supervised training, and home-based training. Regardless of the underlying mechanism, the study by Franco et al. (2006) calls into question the long-term stability of the sympathoinhibition associated with aerobic training for the general public, where consistent and supervised aerobic training is cost prohibitive.

4.3. Myocardial infarction

Mimura et al. (2005) conducted the first randomized control trial examining the influence of supervised aerobic exercise training on resting MSNA in myocardial infarction (MI) patients. All trained and untrained subjects began the study within 2 weeks of their first clinically diagnosed MI. Four weeks of unsupervised, at-home aerobic training significantly reduced resting MSNA.

Martinez et al. (2011) examined the influence of partially supervised aerobic training on resting MSNA in MI patients. As opposed to the prior MI study that examined a relatively short training period (Mimura et al., 2005), this study examined MI patients at several time points and included 6 consecutive months of aerobic training. MI patients were tested: 1) 2–5 days post-MI, 2) one month post-MI after physician monitored rehabilitation with no formal aerobic training, 3) two months after aerobic training, and 4) six months of aerobic training. Untrained, randomized MI controls were advised to follow a home-based activity program that included mild walking, but no regular, moderate exercise. Aerobic training elicited an over 50% reduction of resting MSNA after 6 months of training when compared to 2–5 days post-MI (Martinez et al., 2011). It is interesting to note that the reduction of