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Aerobic Training Improves *in vivo* Cholinergic Responsiveness but not Sensitivity of Eccrine Sweat Glands

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TO THE EDITOR

Aerobic training improves thermal tolerance (Armstrong and Pandolf, 1988), which is postulated to result in part from improved evaporative cooling (Shibasaki *et al.*, 2006; Taylor, 1986). Previous observations indicate that aerobic training either lowers the internal temperature at which sweating begins (sweating threshold) or increases the slopes of the internal temperature-sweat rate (Roberts *et al.*, 1977) or exercise intensity-sweat rate relations (Yanagimoto *et al.*, 2002). In contrast, deconditioning or detraining, associated with bedrest, increases the sweating threshold and decreases the slope of internal temperature-sweat rate relation (Lee *et al.*, 2002). Importantly these deconditioning related responses can be prevented by exercising during bedrest (Shibasaki *et al.*, 2003). These studies, although informative, do not provide mechanistic insight into whether altered sweating responses to aerobic training are mediated by a central sympathetic component or at the level of the eccrine gland.

Application of cholinergic agonists directly in the dermal space without repeated injections or electric current can isolate peripheral sweating responses (Crandall *et al.*, 2003; Morgan *et al.*, 2006; Schlereth *et al.*, 2006). Cross-sectional studies (comparing aerobic trained vs. untrained) using electrical current drug delivery (iontophoresis) have observed increased sweating capacity and number of activated sweat glands with aerobic training (Buono and Sjoholm, 1988; Buono *et al.*, 1992). However, these studies provided minimal insight into whether these adaptatory responses were mediated by changes in receptor responsiveness and sensitivity, or where simply a function of subject population selected. Accordingly, we

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CONFLICT OF INTEREST

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tested the hypothesis that 8-weeks of aerobic training increases *in vivo* cholinergic sensitivity and responsiveness of eccrine sweat glands, without altering the number of exogenous acetylcholine-activated glands.

Eleven sedentary, young (age=26±1), healthy, non-obese (BMI<30kg/m^2), normotensive (<140/90mmHg), non-smokers participated in this institutional (PSUCOM) approved longitudinal training study that adhered to Declaration of Helsinki guidelines. Each subject provided written informed consent and received a medical history and physical exam before participating in the study. Two intradermal microdialysis membranes were placed ~3cm apart in dorsal forearm skin in a similar location pre- and post-training which unlike previous studies allows for continuous monitoring of sweat glands at a prescribed agonist concentration (Morgan *et al.*, 2006). This technique involved placing a small (200-μm outer diameter, 10-mm length) semipermeable membrane (20-kDa-cutoff) intradermally at a depthof approximately 0.3–1.0mm below the epidermis (Kellogg *et al.*, 1999). Eight doses of acetylcholine (10^{-7} to 1M ACh) in a lactated Ringer's vehicle were administered for 5 min at 2μl/min via a microdialysis infusion pump. Sweat rate was measured via capacitance hygrometry and the number of activated sweat glands was quantified using a starch-iodine technique during infusion of 1M ACh. Cholinergic dose-response relations were determined by logistic regression modeling. Endurance training consisted of running or cycling 4 times/ week for 8 weeks. Subjects wore a heart rate monitor during all exercise sessions to ensure maintenance of target heart rates. Training began with exercising for 20 min at a work rate sufficient to achieve 80% of maximum heart rate. Exercise times increased to 60 min as training progressed, and high-intensity interval exercises were added twice/week during the second week to further stimulate training adaptations.

Peak oxygen uptake increased from 32.9 to 40.7ml•kg^{-1}•min^{-1} or 19±2% ($P<0.05$) and resting heart rate decreased 9±2bpm ($P<0.05$) indicative of a training effect. The number of cholinergic-activated glands was unchanged by training (pre-training=40±6 and post-training=39±7 glands per 0.5cm^2). This indicates that a similar number of glands were recruited both pre- and post-training and that this type and duration of training does not increase the number of exogenous cholinergic-activated glands. Dose-response relations were established with goodness of fit (R^2) relations of 0.67±0.02 for pre-training and 0.72±0.02 for post-training, indicating that the logistic regression modeling adequately modeled the data (Figure 1). Training did not affect the ED_{50}, but increased the maximal responses of the dose-response relation (Figure 2).

These findings provide important insight into the adaptatory mechanism(s) of eccrine sweat glands to longitudinal aerobic training in humans. First, we did not observe a leftward shift in the ED_{50} of the cholinergic dose-response curve, strongly suggesting that exercise training does not alter eccrine sweat gland *in vivo* cholinergic sensitivity as previously suggested (Buono *et al.*, 1992; Roberts *et al.*, 1977). However, these reports suggesting an increase in cholinergic sensitivity used an iontophoresis drug delivery system to engage muscarinic receptors with pilocarpine or observed an increase in the slope of internal temperature-sweat rate relation. Pilocarpine iontophoresis, although beneficial for determining gross changes in sweating such as occur with cystic fibrosis (Quinton, 2007), has certain limitations (Hjortskov *et al.*, 1995). These limitations include possible direct damage to the sweat gland that could result in erythemia and release of inflammatory mediators, and a poor ability to precisely adjust drug doses. Previous reports of increased slope of the internal temperature-sweat rate relation are also methodologically limited (Cheuvront *et al.*, 2009) and likely gauge the sensitivity of the homeostatic gain rather than the sweat gland *per se*.

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Second, the observed increases in *in vivo* cholinergic responsiveness in the eccrine sweat gland after aerobic training suggests that adaptations are due to changes in peripheral glandular function rather than via a central sympathetic component. Previously, isolated sweat glands from trained or acclimated individuals were reported to possess larger secretory coils that were more responsive to direct application of methylcholine (Sato and Sato, 1983). This finding of normal but enlarged ultrastructure is also observed in focal hyperhidrosis patients (Bovell *et al.*, 2001). As adaptations to aerobic exercise training appear to also include larger, more responsive eccrine glands, the possibility exists that exercise training could provide a model for studying alterations in sweat gland structure and function associated with hyperhidrosis. Another dermatological application includes reduced sweating responses, such as occurs in skin graft patients, where sweat gland adaptations may be used to increase their sweating responses (Davis *et al.*, 2009; Wingo *et al.*, 2008). Combined with Crandall et al.'s (Crandall *et al.*, 2003) cholinergic dose-response data, our findings allow the formation of a sweating adaptation model where bedrest attenuates, exercise during bedrest rescues, and exercise training accentuates *in vivo* cholinergic responsiveness.

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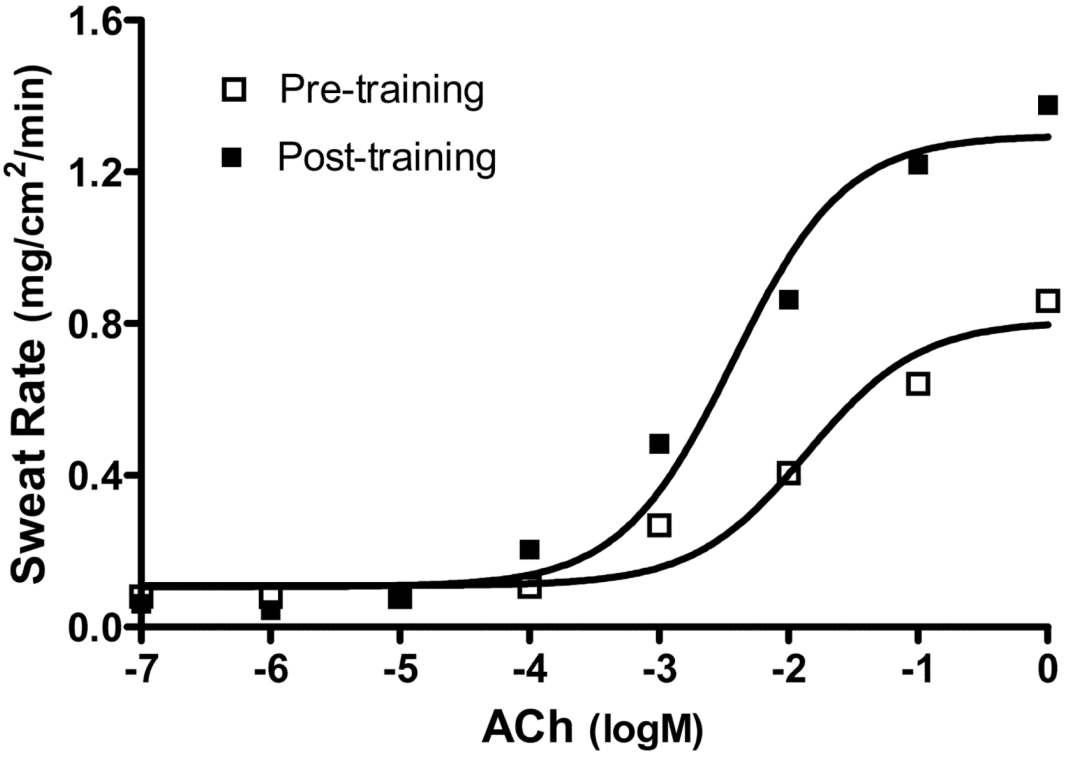

Figure 1.
Representative dose-response relations of acetylcholine (ACh) to sweat rate from pre- to post-training in one subject.

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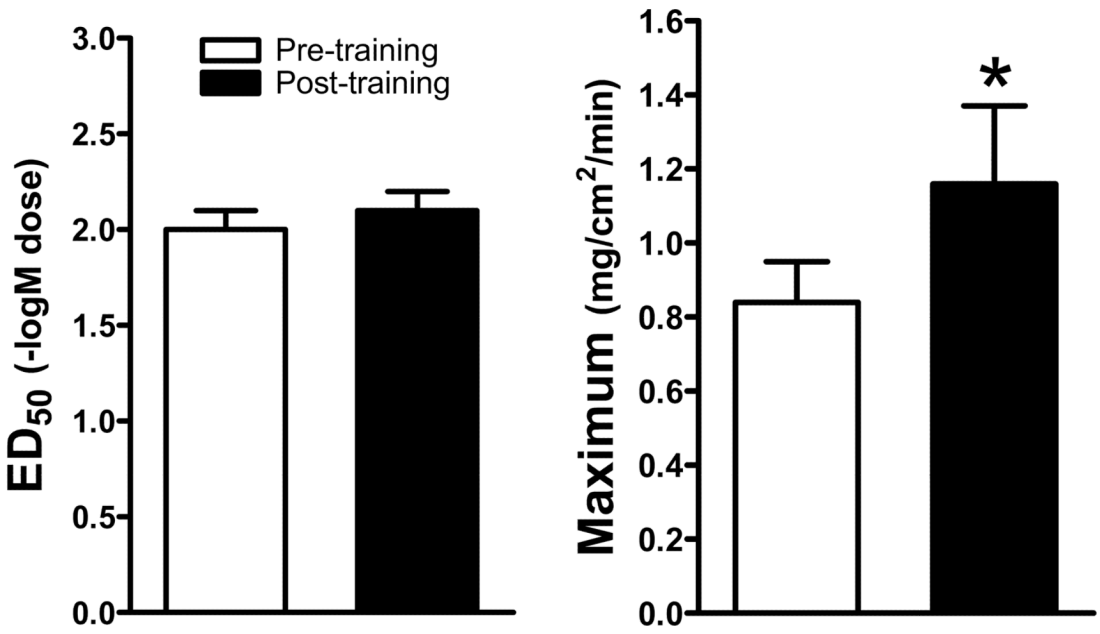

Figure 2.

Effect of aerobic training on *in vivo* cholinergic dose-response relations. ED_{50} is the effective dose causing 50% of the maximal response and is an indicator of sensitivity. Maximum is the maximal response of the cholinergic dose-response relation and is indicative of responsiveness. * denotes a significant difference from the previous time point ($P<0.05$).