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Autonomic Neuroscience: Basic and Clinical 123 (2005) 76 – 81

AUTONOMIC NEUROSCIENCE: Basic & Clinical

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Somatotopic arrangement of sudomotor axon reflex sweating in humans

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Received 3 May 2005; received in revised form 11 July 2005; accepted 4 August 2005

Abstract

Background: Impaired sweating may be one of the first symptoms in neuropathies, and therefore the evaluation of sweating might facilitate their early detection. Sudomotor axon reflexes can be quantified by two different methods: quantitative sudomotor axon reflex testing (QSART) measures the amount of local sweating, whereas staining with the iodine starch reaction assesses the extension of the sudomotor axon reflex area. The aim of our study was to compare both tests at three different sites on the leg: foot, lower leg and thigh.
Methods: QSART and iodine starch staining after iontophoretic stimulation with acetylcholine were performed on 15 male volunteers (mean age: 25; range 24–27 years) on the left resp. the right leg during a single session.
Results: QSART response, measured as area under the curve (AUC), was maximal at the lower leg (911 AUC), smaller at the dorsum of the foot (585 AUC) and even smaller at the thigh (480 AUC). The difference between lower leg and thigh was significant ($p<0.02$). The sudomotor axon reflex area was also biggest on the lower leg (39 cm^2) followed by the foot dorsum (28 cm^2), and then the thigh (16 cm^2). The differences between lower leg and thigh as well as between lower leg and foot were significant ($p<0.01$, resp. $p<0.04$). The size of the sudomotor axon reflex areas and QSART responses were correlated ($p<0.01$).
Conclusions: QSART and sudomotor axon reflex areas had similar somatotopic arrangements in human skin. The bigger the axon reflex area was the stronger the QSART response was. This indicates that the size of the innervation territories of sudomotor fibres covaries with the amount of local sweat production. The latter is a surrogate for increased sweat gland density or capacity in skin areas of dense sudomotor innervation.

Keywords: QSART; Sweating; Sudomotor axon reflex; Iodine starch staining; Somototopy; Human

1. Introduction

Thermoregulation is an important mechanism for human homeostasis. Humans and apes have the characteristic ability of evaporative heat loss by eccrine sweat production (Sato, 1997). Sweating is regulated by the sympathetic nervous system. These sudomotor nerves can be stimulated locally by electrical current (Wilkins et al., 1938; Lang et al., 1993) or cholinergic agents (Sato, 1997). The cholinergic local sweat response consists of two components: the first is the direct activation of sweat glands via muscarinic receptors (Low et al., 1992) and the second is the axon reflex sweating in the vicinity of the stimulation site, which is initiated by stimulation of nicotinic receptors on sudomotor axons and impulse distribution by peripheral nerve arborisations (Low and Kennedy, 2002).

Since axon reflex sweating depends on the integrity of peripheral sudomotor axons, it is widely used for the evaluation of sudomotor function in peripheral nerve diseases like polyneuropathies. Quantitative sudomotor axon reflex testing (QSART) is commonly used for that purpose (Low et al., 1983; Baser et al., 1991; Kihara et al., 1993; Stewart et al., 1994; Shimada et al., 2001). QSART combines the induction of axon reflex sweating by transcutaneous iontophoresis of cholinergic agents with capacitance hygrometry for the quantification of sweat output from a constant area within the sudomotor axon reflex (Lang et al., 1993).

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doi:10.1016/j.autneu.2005.08.004

Another possibility to assess small fiber function would be to analyze the spatial extension of axon reflexes. The areas of axon reflexes are determined by the number of axons, which are activated e.g. by ACh iontophoresis, and the peripheral arborisations of these axons (i.e. innervation territories) (Schmidt et al., 2002). In dying-back polyneuropathies (e.g. diabetic neuropathy) rarefication of nerve arborisations might be the first stage of nerve damage. Then axon reflex areas shrink from the periphery since their innervation territories do not overlap and fiber loss becomes apparent. In the vicinity of the stimulation site in the center of the axon reflex area the overlap of different innervation territories still compensates for beginning fiber loss and skin reaction might stay unaltered (Kramer et al., 2004). Accordingly, in previous studies we have been able to show that the measurement of the vasodilator axon reflex sizes is much more sensitive to detect early C-fiber loss in polyneuropathies than the impairment of vasodilation within the area of axon reflexes (Benarroch and Low, 1991; Bickel et al., 2002; Kramer et al., 2004). To assess vasodilator axon reflexes usually a laser-Doppler imaging device is necessary. For sudomotor axon reflexes there is the possibility to visualize the extension of the sudomotor flare by indicator methods, e.g. by iodine starch staining (Minor, 1927; Riedl et al., 1998; Schlereth et al., 2005). Iodine starch staining is often used to visualize focal hyperhidrosis (Naumann et al., 1998; Simonetta et al., 2003; Kreyden and Scheidegger, 2004), but is less frequently used for the determination of axon reflex sweating (Sato et al., 1988), although there might be some advantages of this method as indicated above. Moreover, measurement of the sudomotor axon reflex area has never been compared to QSART in its ability to detect peripheral neuropathies.

The aim of the present study was therefore to provide the basis for future studies on this field. We compared the measurement of the extension of sudomotor axon reflex areas to a standard method of sweat quantification—the QSART. Three different body sites were tested—feet, lower legs and thighs—in order to explore characteristics of the somatotopy of sweating. Our results should thereby increase our knowledge about peripheral mechanisms of sweating and sweating dysfunction.

2. Methods

We investigated 15 healthy men (mean age: 25; range 24–27 years). The restriction to male subjects was done since sweating is sex-dependent (Namer et al., 2004). Written informed consent was obtained from all subjects according to the Declaration of Helsinki. The study was approved by the local Ethics committee.

Stimulation sites were the middle of the dorsum of the foot, the lateral part of the lower leg 10 cm distal of the tibial tuberosity and 5 cm lateral of the anterior margin of the tibia and the thigh half way from the knee to the hip.

Sudomotor stimulation was done by iontophoresis of 10% acetylcholine (ACh) diluted in deionized water. For this purpose a cotton swab soaked with acetylcholine solution was laid between the skin and the iontophoresis electrode. This silver anode had a diameter of 5 mm. The corresponding cathode consisted of a silver plate of about 10 cm^2 under which a cellulose pad soaked with saline was positioned. For stimulation a constant current of 1 mA was applied for 5 min by a constant current stimulator (World Precision, WPI A 360). This current was well tolerated by all subjects. Stimulation conditions were kept constant for all experiments.

For determination of the sudomotor axon reflex size we used iodine starch staining (Minor, 1927). An alcoholic iodine solution and starch powder were applied to the skin. These substances turn violet when they get wet. To prevent evaporation the skin was covered with an acetate sheet, which was fixed with tape. In the center of the acetate sheet a hole was left for the iontophoresis electrode, which was insulated by double adhesive tape (Riedl et al., 1998). Digital photos were taken and the area of axon reflex sweating was analysed planimetrically using pixel-based software (Nischik and Forster, 1997). For calibration purposes an L-shaped card with an area of 10 cm^2 was attached on the plastic film. Flare sizes were evaluated 10 min after the end of ACh iontophoresis.

QSART measurements were done on the opposite leg in the same session. Stimulation mode and side were balanced across all subjects. A cylindrical sweat capsule of 1.25 cm radius covering an area of 5 cm^2 was attached to the skin. In the middle of this sweat capsule was a separate chamber for insertion of the iontophoresis electrode. Dry nitrogen gas was passed through the sweat chamber at a constant flow (270 ml/min). The relative humidity was measured by capacitance hygrometers (Hygroscope DV 2, Rotronic AG, Basel, Switzerland). The recordings began 2 min before stimulation (baseline) and were continued until 15 min after the end of the stimulation. Since the sweating reaction leads to a broad sweat curve, the area under this curve for 15 min was calculated (Birklein et al., 1997). Results are given as relative units (area under the curve, AUC). In addition the latencies until onset and peak of sweat responses were recorded.

2.1. Statistical analysis

All values are given as median and interquartile ranges (25th and 75th quartile). Since normal distribution could not be assumed in all data sets, non-parametric statistics were used. Paired comparisons were analyzed by Wilcoxon's matched-pairs signed-rank test, which was corrected for multiple comparisons. Correlations between different variables were determined by the Spearman correlation coef-