

AXON REFLEXES IN COLD-EXPOSED FINGERS

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INTRODUCTION

Prolonged immersion of fingers in cold water induces Cold-Induced Vasodilatation (CIVD). Although evidence is available that Arterio-Venous Anastomoses (AVAs) play an important role, the mechanism underlying CIVD remains unsolved. The main hypotheses are a paralysis of the AVAs due to an impaired neuromuscular transmission (1) and the occurrence of an axon reflex (2). In brief, the axon reflex theory states that peripheral cold pain fibers are triggered by the local cold. The resulting action potential releases vasodilator substances in all collateral-of the neuron. The result is vasodilatation in the cold-exposed body parts.

An experiment was set up to investigate the involvement of axon reflexes in CIVD. This was achieved using electrically evoked axon reflexes during cold-water immersion of a hand in 3 different thermal states of the body: hypothermia, hyperthermia and at thermoneutrality.

MATERIALS AND METHODS

Eight male volunteers were recruited. The subjects were 32 ± 7 years old, weighed 83 ± 13 kg and had a stature of 183 ± 5 cm. The protocol was approved by the Human Ethics Committee of the Defence and Civil Institute of Environmental Medicine.

The subjects underwent 3 measurement sessions (at least 48 h apart) in addition to a familiarization run. During the experiments, the subjects were seated on an office chair. In every session the left hand was immersed for 40 min in a water bath controlled at 35°C (warm hand) and the right hand was immersed in a water bath controlled at 5°C (cold hand). The 3 measurement sessions were performed in balanced order.

Thermoneutral conditions (N). The subjects were dressed in shorts and t-shirt and sat quietly in a 25°C , 60% relative humidity (RH) climatic chamber for 60 min prior to the immersion of the hands.

Hypothermic conditions (C). The subjects, wearing swimming gear, were cooled in a 15°C cold water bath for a maximum time of about 3 h until the esophageal temperature reached 35.5°C . Thereafter, they were transferred to a cold (10°C , 60% RH) climatic chamber, where the subjects immersed their hands in the water baths.

Hyperthermic conditions (W). The subjects, wearing shorts only, were warmed in a 48°C water perfused suit. When the esophageal temperature reached 38.0°C , the hands were immersed in the water, and the temperature of

the circulating water in the **suit** was adjusted such that the esophageal temperature was maintained at **38.0°C**. The subjects were sitting in a **30°C, 60% RH** climatic chamber.

In **all** sessions, the temperature of the ventral side of the distal phalanx of each finger (**T_f**) was continuously monitored with 40 gauge thermocouples fixed to the **skin** with surgical tape. The hunting reaction was quantified by the **minimal (T_{f-min})** and maximal finger skin temperature (**T_{f-max}**) during the first CIVD phase, time from immersion to **T_{f-min}** (onset time) and mean finger temperature from the 5th to 40th min of immersion (**T_f**). The **hands** were covered by thin surgical gloves. The fingers of both hands were immersed to the metacarpophalangeal joints in the water baths. Both hands were about at the level of the heart during the immersions.

Thermistor probes continuously **measured** esophageal temperature (**T_{es}**). Mean **skin** temperature (**T_{sk}**) of the body was determined using the weighed average of **12** thermistors on the **skin**.

The **axon** reflexes were evoked **15** and **30** min after **hand** immersion by electrical stimulation of the ventral part of the distal phalanx of the middle finger with a train of **16** pulses of **1** ms at **2** Hz (**3**). The current through the fingertip was determined individually in the familiarization **run** based on the pain rating and ranged from **15** to **30** mA. The maximum voltage was **set** at **300** V. Ag-Ag-Cl surface electrodes were placed on the ventral part of the distal phalanx of the middle finger. The reference electrode was placed at the dorsal side of the second phalanx of the same finger.

Perfusion of the finger **skin** was determined by laser Doppler flowmetry (**Perimed** 4000) on the middle fingers just beside the stimulation electrode and the little fingers of both hands. The finger skin perfusion reaction to the electrical stimulation was quantified by the baseline finger **skin** perfusion for a period of **1** min prim to stimulation (**F_{base}**), the maximal finger skin perfusion observed during a 10s period after stimulation (**F_{max}**) and the duration of the **axon** reflex.

RESULTS

The body temperatures were significantly different **between** hyperthermia (**T_{es}: 38.0 ± 0.1°C; T_{sk}: 37.9 ± 0.7°C**), thermoneutrality (**T_{es}: 36.8 ± 0.2°C; T_{sk}: 31.8 ± 0.7°C**) and hypothermia (**T_{es}: 36.1 ± 0.8°C; T_{sk}: 21.2 ± 1.9°C**).

Table 1. Hunting parameters¹ for the coldwater immersed hand

	Hypothermia (C)	Thermoneutrality (N)	Hyperthermia (W)
T_{f-min} (°C)	5.4 ± 0.2	69 f 1.4	139 ± 32
T_{f-max} (°C)	83 f 1.7	11.0 f 3.2	20.9 ± 2.1
T_f (°C)	6.8 ± 1.2	8.1 f 1.7	16.5 ± 2.3
Onset time (min)	13.0 ± 3.8	7.2 ± 2.2	

¹Values averaged over all subjects and shown as means ± SD. Differences between C, N, and W are significant for all parameters (**P < 0.05**)

Table 1 shows the hunting parameters as measured in the cold hand for each experimental condition averaged over the subjects. T_{fi} , T_{fi-min} and T_{fi-max} are higher for the N than for the C condition. In the W condition, the finger skin temperature continuously stayed at a high level. Therefore, the onset time could not be determined in the W condition. In the C condition, the onset time was significantly prolonged as compared with the N condition.

In the warm hand, axon reflexes were clearly visible from the significant increase in skin perfusion after the electrical stimulation. No increase in skin perfusion was seen in the cold hand. Table 2 shows the results averaged over both stimulations (minutes 15 and 30) and all subjects.

Table 2. Skin perfusion in the middle finger tip of the cold and warm hand, measured before and after electrical stimulation.

Hand	Hypothermia (C)		Thermoneutrality (N)		Hyperthermia (W)	
	F_{base}	F_{max}	F_{base}	F_{max}	F_{base}	F_{max}
Cold	19 ± 16	18 ± 15	59 ± 45	55 ± 43	131 ± 54	122 ± 56
Warm	57 ± 32	109 ± 69	136 ± 48	276 ± 81	231 ± 75	276 ± 59

¹Values shown are means, in perfusion units ±SD. Differences between C, N and W are significant for all parameters ($P < 0.05$), except between N and W for the warm hand F_{max} is higher than F_{base} for C and N of the warm hand.

The mean duration of the axon reflex was shortest during condition C (68 ± 79 s), followed by conditions N (154 ± 95 s) and W (199 ± 152 s). Pain was more pronounced in the warm hand.

DISCUSSION

In the cold hand, a normal CIVD pattern was found, which was dependent on the thermal status of the body. In that same hand, no increase in skin perfusion was found after electrical stimulation. If an axon reflex is the origin of CIVD, as hypothesized, it is remarkable that electrical stimulation did not cause an increase in skin perfusion. The afferent impulses from the cold fibers in the skin, which are supposed to trigger the axon reflex, may have an increased neurogenic drive as compared with the afferent impulses from the local electrical stimulation. Increasing the electrical stimulation parameters further, however, is unethical, because on average, the subjects already qualified the pain as "painful" after stimulation. Moreover, the same stimulation parameters were strong enough to cause unambiguous axon reflexes in the warm hand.

Homyak et al. (3) found a reduced (electrically evoked) axon reflex when the body core was cold. In our study, the axon reflex in the warm hand was shorter when the body core was colder. In hyperthermia the axon reflex was reduced in magnitude.

Some differences exist between an electrically evoked axon reflex and the axon reflex held responsible for **CND**. Electrically evoked axon reflexes are associated with a sharp pain, which is different from the "numb" pain, which is experienced during local cold exposure of the fingers. However, in both cases the nociceptive C fibers are involved, and the mechanism is identical. Therefore, our results are not in line with the hypothesis that an axon reflex is the origin of CIVD.

CONCLUSIONS

CIVD occurred in all experimental conditions in the cold band and was dependent on the thermal state of the body. Electrical stimulation of the middle finger led to an increase in skin perfusion of the warm hand and no change in the cold hand. This indicates that the axon reflex is not a likely explanation for CIVD.

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