THE WISDOM OF THE BODY REVISITED: THE ADRENOMEDULLARY RESPONSE TO MILD CORE HYPOTHERMIA IN HUMANS

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Objective. In the 1920s, Walter B. Cannon first described the adrenomedullary response to cold, using an ingenious *in vivo* bioassay based on a denervated heart preparation. Studies in humans about antecubital venous plasma concentrations of norepinephrine, the sympathetic neurotransmitter, and of epinephrine, the main adrenomedullary hormone, have suggested sympathetic nervous system activation without adrenomedullary activation. The present study used arterial levels of these catecholamines, to determine whether adrenomedullary stimulation occurs in response to decreased body temperature.

Methods. Eleven healthy volunteers underwent central intravenous infusion of warm (37°C) physiological saline, followed by infusion of the same volume of cold (4°C) saline. Brachial arterial and antecubital venous plasma concentrations of norepinephrine and epinephrine were measured by liquid chromatoraphy with electrochemical detection.

Results. Antecubital venous concentrations of norepinephrine increased markedly during cold saline infusion, with smaller and statistically borderline increases in concentrations of epinephrine. In contrast, concurrently obtained arterial concentrations of both norepinephrine and epinephrine increased significantly.

Conclusions. The results confirm Cannon's original inference that cold evokes adrenomedullary activation. Prior studies about antecubital venous levels of catecholamines did not take into account the local hemodynamic effects of cold, which would increase extraction of circulating catecholamines and underestimate the arterial epinephrine response.

Key words: Catecholamines – Hypothermia – Adrenomedullary response – Man

Walter B. Cannon, extending Claude Bernard's concept of the internal environment, introduced the term, "homeostasis," to describe the product of the "coordinated physiological processes which maintain most of the steady states in the organism" (CANNON 1929a, 1929b, 1939). Cannon suggested that rapid activation of homeostatic systems–especially of what he called the "sympathico-adrenal system"–preserves the internal environment, by producing compensatory and anticipatory adjustments that enhance the likelihood of survival.

These compensatory adjustments would include neuroendocrine responses to altered environmental temperature, sensed by the organism based on input to the brain from sensors of skin temperature and also on input within the brain from sensors of blood temperature.

Cannon used an ingenious experimental preparation to detect release into the bloodstream of a hormone from the adrenal medulla–which he called "adrenin." In this preparation, the heart was denervated surgically, and heart rate responses to various

stressors were measured in animals with or without bilateral adrenalectomies. When animals with intact adrenal glands were exposed to a cold room, the heart rate increased, but when animals with bilateral adrenalectomies were exposed to the cold, the heart rate did not increase (CANNON et al. 1927). From these results Cannon deduced that cold exposure stimulates release of "adrenin."

Much more recent studies have assessed sympathico-adrenal responses to cold, by assaying antecubital venous plasma levels of the catecholamines, norepinephrine and epinephrine. In mammals, norepinephrine is the chemical messenger of the sympathetic nerves, and epinephrine is the main adrenomedullary hormone. Many studies have shown that exposure of humans to cold–whether by external cooling, exposure to a stream of cold air, immersion of a hand in ice-cold water (the "cold pressor test"), or intravenous infusion of cold saline–elicits large increases in norepinephrine concentrations, with little or no increase in epinephrine concentrations in antecubital venous plasma (FRANK et al. 1997, 1999; GRAHAM et al. 1991; MCLEAN et al. 1992; LEBLANC et al. 1992; BLANDINI et al. 1995; JEZOVA et al. 1995; MARINO et al. 1998; PETTIT et al. 1999; KOZYREVA et al. 1999; JACOB et al. 2000; LEHOT et al. 1992; FRANK et al. 1995). These findings would seem to conflict with Cannon's inference about adrenomedullary stimulation in response to cold.

In interpreting antecubital venous plasma levels of catecholamines, one must keep in mind the possible effects of local hemodynamic changes in the forearm on the extraction of catecholamines from the arterial plasma (GROSSMAN et al. 1991). Cold-induced vasoconstriction would be expected to increase the extraction fraction of arterial catecholamines. This could lead to underestimation of arterial plasma epinephrine responses. In the present study, arterial and antecubital venous concentrations of norepinephrine and epinephrine were measured during mild core hypothermia in healthy humans, to address whether cold elicits adrenomedullary activation.

Subjects and Methods

Subjects. The subjects were 11 healthy men (mean age 29 ± 2 (SEM) years) who gave written, informed consent to participate in the protocol, which was approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke. All subjects had normal medical histories and physical examinations and were not taking any medications at the time of study.

Testing procedure. The catheter was placed percutaneously into an antecubital vein. nother intravenous catheter was advanced into the axillary vein. A brachial arterial catheter was inserted percutaneously after local anesthesia of the overlying skin. A thermocouple device was placed in the auditory canal against tympanic membrane, for measurements of core temperature.

After a period of at least 20 minutes of supine rest, a baseline (BL) blood sample was obtained from the antecubital vein and brachial artery. Warm saline was then infused via the central intravenous catheter at a rate of 80 ml/min for 25 minutes. Upon completion of the warm saline infusion, blood samples were obtained from the antecubital venous and brachial arterial catheters (WARM NS). After a rest period of 30 minutes, a second set of baseline blood samples was obtained (BL-2), followed by infusion of cold saline via the central intravenous catheter at the same rate and duration as the warm saline. A final set of blood samples were obtained from the antecubital venous and brachial arterial catheters, upon completion of the cold saline infusion (COLD NS).

Catecholamine assays. Plasma concentrations of norepinephrine and epinephrine were assayed by liquid chromatography with electrochemical detection, after barch alumina extraction, as described previously by our group (HOLMES et al. 1994).

Data analysis and statistical evaluation. Data for antecubital venous and brachial arterial levels of norepinephrine and epinephrine in the BL, WARM NS, and COLD NS conditions were analyzed by repeated-measures analyses of variance.

Results

As expected, core temperature remained unchanged during warm saline infusion and decreased during cold saline infusion in all subjects, by a mean of 1.0 ± 0.1 °C.

Antecubital venous levels of norepinephrine were higher during cold saline infusion than during warm saline infusion ($P<0.0001$), whereas the mean epi-

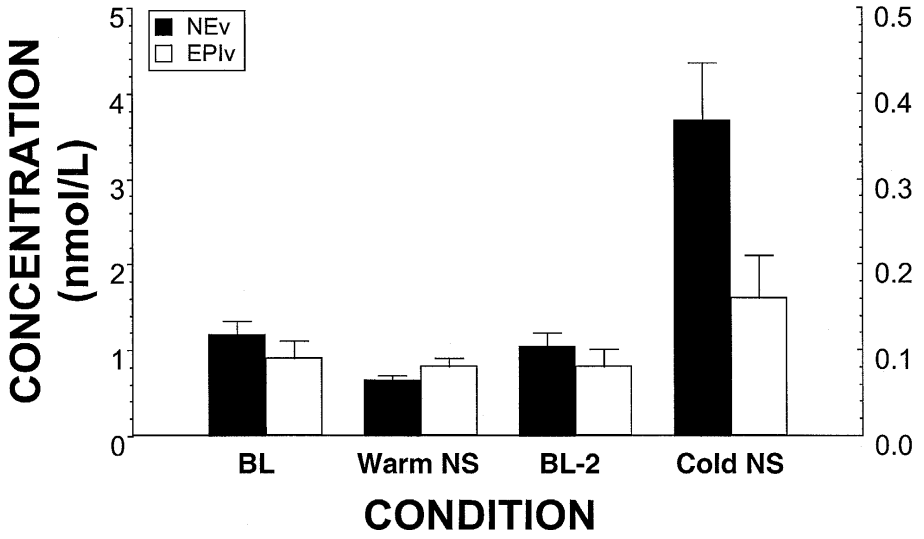

Figure 1 Antecubital venous mean (± SEM) concentrations of norepinephrine and epinephrine during central intravenous infusion of warm and then cold saline. Abbreviations: BL = baseline; Warm NS = warm normal saline; BL-2 = second baseline; Cold NS = cold normal saline.

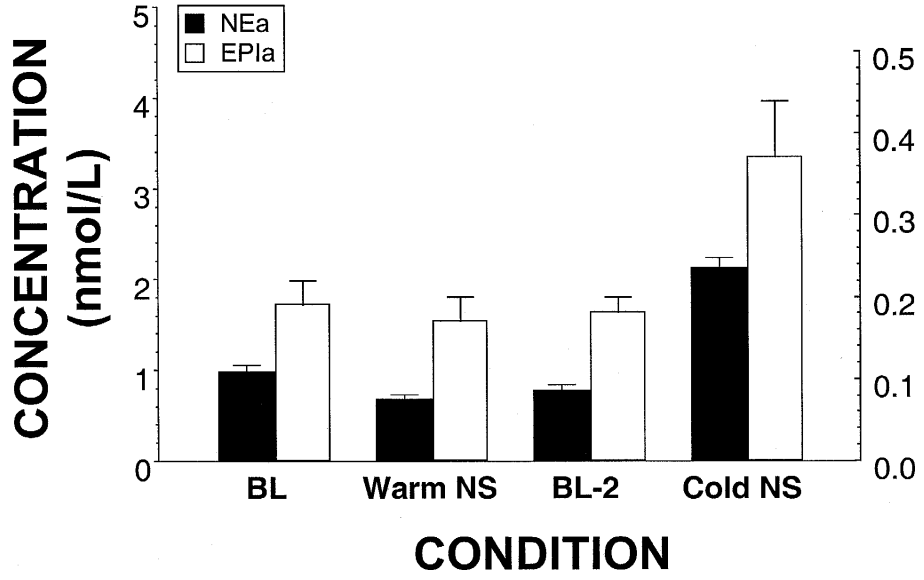

Figure 2 Arterial mean (± SEM) concentrations of norepinephrine and epinephrine during central intravenous infusion of warm and then cold saline. Same abbreviations as for Figure 1.

nephrine level only tended to differ between the two conditions (P=0.05, Figure 1).

Arterial levels of norepinephrine were also higher during cold saline infusion than during warm saline infusion (P<0.0001), but to a lesser extent than were the antecubital venous levels (Figure 2). The mean arterial epinephrine level was also higher during cold saline infusion than during warm saline in-

fusion (P=0.0003), with the proportionate increase smaller than for norepinephrine.

Discussion

The present results demonstrate that during mild core hypothermia in healthy humans, arterial plasma concentrations of both norepinephrine and epinephrine increase. The finding of a significant increase in arterial plasma epinephrine concentrations in this setting supports the inference drawn by Cannon more than 75 years ago, based on the denervated heart preparation.

We wish to propose an explanation as to why other studies of plasma catecholamine responses to cold in humans have reported little if any increases in plasma epinephrine concentrations. Cold elicits substantial cutaneous vasoconstriction, from local release of norepinephrine. All other things being the same, the extraction fraction of arterial catecholamines in the arm varies inversely with the blood flow (Grossman et al. 1991; Goldstein et al. 1987). Decreased forearm blood flow during cold exposure or core hypothermia would increase the extraction fraction of epinephrine delivered to the forearm tissues by the arterial inflow. The increased extraction of the arterial epinephrine could offset the increased arterial plasma concentration of epinephrine, resulting in antecubital venous concentrations underestimating the arterial concentrations.

The same explanation may apply to norepinephrine concentrations, as follows. As for the antecubital venous plasma epinephrine concentration, the antecubital venous plasma norepinephrine concentration would underestimate that in the arterial inflow. In the case of norepinephrine, however, there would be a large increase in the release of norepinephrine from sympathetic nerves in the forearm and hand, as a result of cold-induced activation of local sympathetic nerves. Thus, the use of antecubital venous concentrations would not only underestimate the arterial epinephrine but also overestimate the arterial norepinephrine response to cold.

To decrease core temperature even slightly by infusing cold saline requires a high rate of i.v. infusion. This would be expected to dilute catecholamines in the plasma and thereby understimate increments from baseline pre-infusion values for catecholamine concentrations. The dilution might account for decreased arterial plasma norepinephrine concentrations during warm saline infusion. In the present study, however, the key comparisons were between the warm and cold saline conditions, and the total volume administered was the same for the infusions at the two temperatures. Blood volume expansion would also not explain the differences between arterial and plasma concentrations of catecholamines.

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FIRST ANNOUNCEMENT AND CALL FOR ABSTRACTS

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"LIPIDS AND INSULIN RESISTANCE: THE ROLE OF FATTY ACID METABOLISM AND FUEL PARTITIONING"

August 29 - September 2, 2001 Smolenice Castle, Slovak Republic
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You are invited to participate in the 4th International Smolenice Castle Symposium on "Lipids and Insulin resistance". This outstanding series of symposia was started 12 years ago to allow world leaders and younger scientists in the "lipid arm" of insulin action cascade to meet every 4 years in particularly convivial circumstances, with an emphasis to share the most recent findings, to facilitate discussions and collaborations between those established in the field and the newcomers, and to produce books of proceedings containing close to everything in the state-of-the-art in the given area and time period.

The objective of this 4th Symposium is to pay a special attention to the recently emerging new and exciting data on the role of the fatty acid metabolism in regulation of fuel partitioning, and consequently of insulin action. The presentations will approach the topic from many perspectives including molecular, genetic, animal and clinical. Potential ideas for treatment of the syndrome with special emphasis in aspects of lipid turnover and new techniques useful in monitoring of the syndrome will be presented.

The scientific program will be arranged similarly as during the last three (1988', 1992', 1996') symposia organized at the medieval Smolenice Castle in Slovakia. Thus, it will include one invited State-of-the-Art, Plenary and 29 regular Invited Lectures to be given by renown researchers and/or clinicians from more than 10 countries of 3 continents.

There will also be Oral Presentations selected from submitted abstracts and comprehensive Poster Sessions. A special attention is being paid to attract young and internationally established experts for oral presentations.

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