Thermoregulatory Nonshivering Thermogenesis in Men, with Special Reference to Lipid Metabolism

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Abstract The existence of thermoregulatory nonshivering thermogenesis, with special reference to lipid metabolism, was investigated in men. Acute cold exposure (10°C, 60 min) produced a marked increase in heat production, with concomitant elevation of plasma free fatty acid (FFA) level, modest increase of ketone body concentration and lowered respiratory quotient (R.Q.). The correlation of heat production to plasma FFA levels was significantly positive; that is, subjects with higher heat production showed higher plasma FFA levels. Moreover, correlation of either heat production or plasma FFA levels to R.Q. was significantly negative, respectively. On the other hand, exposure to cold after an administration of nicotinic acid, which has a suppressive effect on FFA mobilization from adipose tissue, resulted in less cold-elevated heat production, a significant fall of plasma FFA and ketone body concentrations, and no change in R.Q. Although no visible or only slight shivering was observed in control cold exposure study, greater shivering occurred in the nicotinic acid cold exposure study. These results appear to indicate that nonshivering thermogenesis as a source of heat production achieved by enhanced utilization of lipids is also present in men.

Enhanced nonshivering thermogenesis has been indicated as a characteristic index of cold adaptation in rats (SELLERS *et al.*, 1954; HART *et al.*, 1956). The decrease in shivering has been noted in cold-adapted men (IRVING, 1960). The evidence of regulatory nonshivering thermogenesis in men was first presented by DAVIS (1961). Men could be artificially (DAVIS, 1961) and seasonally (DAVIS and JOHNSTON, 1961) acclimated to cold by means of nonshivering thermogenesis. HURLEY *et al.* (1964) and GIRLING (1964) also confirmed the presence of nonshivering thermogenesis in men acclimated to cold climate. As to the mechanism

involved, JOY (1963) found that norepinephrine may be the primary mediator of nonshivering thermogenesis occurring with cold acclimation in men. ITOH (1974) and his coworkers suggested that the Ainu, aboriginal inhabitants in Hokkaido, the northernmost island of Japan, is equipped with adaptive mechanism characterized by norepinephrine-sensitive thermogenesis. These previous results apparently indicate that cold acclimation in men is also closely associated with enhanced nonshivering thermogenesis, which is mainly regulated by norepinephrine. On the contrary, GLICKMAN *et al.* (1967) have shown that the increase in heat production in the cold was directly proportional and almost entirely attributable to the activity of muscle in seasonally cold-acclimated men. KANG *et al.* (1970) also suggested that the development of nonshivering thermogenesis is not the main feature of cold acclimation in men, at least in Korean women divers. However, men living in Hokkaido were considered to be well adapted to cold, especially in winter. During the winter they exhibit higher levels of basal metabolism (OHNO and KUROSHIMA, 1973), plasma free fatty acids (FFA) and urinary excretion of nitrogen (KUROSHIMA *et al.*, 1973). Men born in Hokkaido also showed the greater cold adaptability than those born in Honshu the main island in the pressor response and the finger temperature response to local cooling (ITO, 1974), which have been used as one of the methods for the assessment of cold adaptability.

Therefore, it seems to be interesting to clarify whether or not any specific signs of cold acclimatization are observed in the subjects who are adapted to winter cold in Hokkaido, and whether nonshivering thermogenesis can be found in them. The present experiments were designed to verify the presence of nonshivering thermogenesis and furthermore to elucidate the mechanism of nonshivering thermogenesis in men.

SUBJECTS AND METHODS

Experiments were conducted to ten male medical students, aged 18–26 years, in Asahikawa in Hokkaido, Japan. Their physical characteristics are shown in Table 1. The thickness of double folds of skin and subcutaneous fat at 10 sites recommended by ALLEN *et al.* (1956) were measured with Harpenden skinfold caliper (British Indication Co., Ltd.). The experiments were conducted during the winter, January and February. Meteorological data in Asahikawa are tabulated

Table 1. The physical characteristics of the subjects.

Subjects	Age	Ht. (cm)	Wt. (kg)	Surface area (m ²)	Skinfold thickness(mm)
Male students (10)	22±1.0	170±1.8	63±2.2	1.72±0.037	9.9±1.52

Number in the parenthesis indicates the number of subjects. Each value represents the mean±standard error. Skinfold thickness was the average value of those measured at 10 sites.

Table 2. Mean outdoor temperature (°C).

Place	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sept.	Oct.	Nov.	Dec.
Asahikawa (1941-70)	-8.5	-7.7	-3.0	4.5	11.4	16.1	20.4	20.9	15.3	8.5	1.3	-4.9

in Table 2. The subjects had previously wintered in the area more than three times. Histories of the subjects did not reveal any remarkable thermal backgrounds, serious diseases nor any suggestion that the subjects lived differently from other individuals in the college. The activities of subjects were of a sedentary nature and none participated in activities that would increase physical fitness before and during the period of study.

Two series of tests were performed on the same subjects in each experiment. In the first (control study) experiment, the subjects wearing only T shirts and shorts were exposed to a standard cold exposure (temperature, 10°C; relative humidity, 60-70%; wind velocity, less than 0.5 m/sec) in a supine position on the bed. The second (nicotinic acid study) experiment was carried out 3-4 days later, the subjects were submitted to the same cold exposure as in the control study after an administration of an oral dose of 200 mg nicotinic acid just before the exposure to cold. The subjects reported to the laboratory at 8:00 a.m. in a postabsorptive state that lasted for about 12 hr and were made to rest under a blanket on a bed for 1 hr before the experiment. After 1 hr stabilization, the initial measurements of heat production, rectal and skin temperatures, pulse rate, and blood pressure were performed. The oxygen consumption was determined before and during cold exposure. On each occasion, the expired gas over a period of 10 min was collected in Douglas bag with a face mask, measured with a dry gas meter and an aliquot of sample was analyzed for O₂ and CO₂ with Scholander micrometer gas analyzer. Pulse rate was determined every 5 min before and during cold exposure by counting the radial pulse for 30 sec. Blood pressure was measured with a mercury sphygmomanometer every 5 min before and during exposure to cold. Skin temperatures were continuously and simultaneously recorded by a thermistor thermometer (TER-36, Takara Kogyo, Co., Ltd., Tokyo) at five different locations (forehead, chest, abdomen, thigh and calf) on the body. Rectal temperature was obtained by a thermistor thermometer probe inserted in the anus, and extending 10 cm beyond, and secured by tape. An average skin temperature was calculated by multiplying the temperature at five locations mentioned above as proposed by MORRISON (1965). Mean body temperature was calculated as the sum of 0.67 times the rectal temperature and 0.33 times the average skin temperature (BUSKIRK *et al.*, 1963). Body heat content was calculated as the product of mean body temperature times the specific heat of the tissue (0.83 kcal/g·°C) times the body weight in kg (BURTON and EDHOLM, 1955). Heat loss in the cold was expressed as the difference between the initial heat content and the heat content after cold exposure. A measurement of tissue body insulation (I_b) was derived from the equation

(CARLSON, 1954): $I_b = (T_r - \bar{T}_s)/0.76M$, where 0.76, correction constant for evaporate heat loss (assumed to be 24%); T_r , rectal temperature; $\bar{T}_s$, average skin temperature; and M , metabolism.

Immediately after initial measurements, the subjects were transferred into the cold room. In the cold, the subjects lay fully extended with legs spread apart and arms away from the body. The same measurements as in the controls were made periodically during cold exposure.

Shivering was estimated by the inspection every 1 min throughout cold exposure by the same observer in every experiment and recorded according to a 4-point scale (0-3), corresponding to none, mild, severe and violent shivering. Onset of shivering was observed by the observer and evaluated by the subjects.

Eight ml of blood sample was obtained from the antecubital vein simultaneously with the collection of the expired gas. Plasma concentration of FFA was determined by the method of ITAYA and UI (1965), plasma glucose by the anthrone reagent method (ROE, 1955) and plasma β -hydroxybutyrate by the enzymatic method of GIBBARD and WATKINS (1968). Plasma total protein content was determined with a protein refractometer (Hitachi, Ltd., Tokyo).

Results were expressed as means $\pm$ standard errors. The statistical significance of the results was tested by Student *t*-test. Linear regressions were determined by the method of least squares.

RESULTS

Changes in heat production after cold exposure

As shown in Table 3, exposure to cold produced a significant increase in the heat production in the control study. The heat production increased from 38.9 ± 2.44 kcal/m²·hr to 51.9 ± 2.24 (+33.4%, $p < 0.001$) 30 min and to 62.6 ± 4.10 (+60.9%, $p < 0.001$) 60 min after cold exposure. An administration of nicotinic acid brought about a significant reduction in the elevation of heat production 60 min after exposure to cold.

Table 3. The changes in the heat production and R.Q. in response to cold.

Time after cold exposure (min)	0	15		30		60	
			<i>p</i> vs. 0		<i>p</i> vs. 0		<i>p</i> vs. 0
Heat production (kcal/m ² ·hr)							
Male students							
Control study (10)	38.9 ± 2.44	46.2 ± 3.19	N.S.	51.9 ± 2.24	<0.001	62.6 ± 4.10	<0.001
NA-study (10)	40.0 ± 2.39	45.6 ± 3.88	N.S.	56.1 ± 7.16	N.S.	50.2 ± 3.21	<0.05
Control vs. NA	N.S.	N.S.		N.S.		<0.05	
R.Q.							
Control study (10)	0.84 ± 0.011	0.82 ± 0.018	N.S.	0.80 ± 0.012	<0.001	0.79 ± 0.013	<0.001
NA-study (10)	0.82 ± 0.017	0.84 ± 0.014	N.S.	0.85 ± 0.011	N.S.	0.84 ± 0.018	N.S.
Control vs. NA	N.S.	N.S.		<0.01		<0.05	

Each value represents the mean $\pm$ standard error. Number in the parenthesis indicates the number of subjects. NA: nicotinic acid. N.S.: not significant.

The values of R.Q. were calculated in order to assess the preferential substrates utilized during cold exposure (Table 3). The initial value of 0.84 ± 0.001 declined to 0.80 ± 0.012 ($p < 0.001$) 30 min and to 0.79 ± 0.013 ($p < 0.001$) 60 min after cold exposure in the control study. On the other hand, in the nicotinic acid study the values of respiratory quotient (R.Q.) remained at the initial level throughout cold exposure.

Shivering and its onset time

Figure 1 shows that there was only slight shivering in the control study. The average shivering score was 0.3 ± 0.03 units ($p < 0.01$) 30 min and 1.0 ± 0.11 ($p < 0.01$) 60 min after cold exposure, while, in the nicotinic acid study, the same cold exposure caused a marked increase in shivering. Shivering elevated to the extent of 2.5 ± 0.27 units ($p < 0.001$) 30 min and to 3.0 ± 0.41 ($p < 0.001$) 60 min following cold exposure. Significant greater increases have been observed in the extent of shivering 30 min ($p < 0.001$) and 60 min ($p < 0.001$) after cold exposure in the nicotinic acid study as compared with the corresponding values in the control study. Mean onset time of shivering after cold exposure was 18 ± 2.1 min in the control study and 4 ± 0.34 in the nicotinic acid study. These results indicate that shivering occurred more rapidly ($p < 0.001$) in the nicotinic acid study than in the control study.

Changes in blood constituents after cold exposure

The effect of cold exposure on blood substrates is summarized in Table 4. The plasma levels of FFA measured simultaneously with the heat production

Fig. 1. Changes in the shivering after cold exposure. ○, cold exposure (10°C); ●, cold exposure after an administration of nicotinic acid. Arrow indicates the onset of shivering. Vertical bar denotes standard error.

Table 5. The changes in the thermal responses to cold exposure.

Time after cold exposure (min)	0	15	30	60	p vs. 0	p vs. 0
Male students						
Control study (10)	37.2±0.35	37.3±0.45	37.4±0.29	37.4±0.35	N.S.	N.S.
NA-study (10)	37.2±0.35	37.1±0.40	37.1±0.31	37.0±0.36	N.S.	N.S.
Control vs. NA	N.S.	N.S.	N.S.	N.S.		
Rectal temperature (°C)						
Control study (10)	32.8±0.29	28.0±0.38	26.9±0.38	25.6±0.43	<0.001	<0.001
NA-study (10)	32.3±0.20	28.0±0.41	27.5±0.34	25.8±0.83	<0.001	<0.001
Control vs. NA	N.S.	N.S.	N.S.	N.S.		
Mean skin temperature (°C)						
Control study (10)	36.0±0.16	34.9±0.28	33.9±0.30	33.5±0.29	<0.001	<0.001
NA-study (10)	36.0±0.10	34.7±0.29	33.9±0.31	33.2±0.40	<0.001	<0.001
Control vs. NA	N.S.	N.S.	N.S.	N.S.		
Mean body temperature (°C)						
Control study (10)	1875±66.8	1820±71.2	1791±64.2	1771±62.8	N.S.	N.S.
NA-study (10)	1833±93.8	1789±60.3	1741±85.6	1706±83.2	N.S.	N.S.
Control vs. NA	N.S.	N.S.	N.S.	N.S.		
Heat content (kcal)						
Control study (10)	0	55±5.0	84±5.1	104±6.1		
NA-study (10)	0	44±6.7	92±8.5	127±20.5		
Control vs. NA		N.S.	N.S.	N.S.		
Heat debt (kcal)						
Control study (10)	0.154±0.0117	0.193±0.0065	0.267±0.0168	0.249±0.0231	<0.001	<0.001
NA-study (10)	0.155±0.0099	0.192±0.0071	0.270±0.0192	0.250±0.0185	<0.001	<0.001
Control vs. NA	N.S.	N.S.	N.S.	N.S.		
Body insulation (kcal/m ² ·hr·°C)						
Control study (10)	0	32±3.0	49±5.5	60±8.8		
NA-study (10)	0	26±4.6	53±6.0	74±12.5		
Control vs. NA		N.S.	N.S.	N.S.		
Body heat loss (kcal/m ²)						

Legends same as in Table 3.

elevated significantly from 576 ± 44.4 $\mu\text{Eq/liter}$ to 719 ± 49.4 (24.8%, $p < 0.05$) 30 min and to 816 ± 55.0 (41.7%, $p < 0.01$) 60 min after cold exposure in the control study. After an administration of nicotinic acid, the increment of plasma FFA due to cold was completely abolished. On the contrary, a pronounced fall from 645 ± 50.9 $\mu\text{Eq/liter}$ to 453 ± 69.1 (42.4%, $p < 0.05$) was observed 60 min after cold exposure. Ketone bodies, measured as β -hydroxybutyrate, increased from 0.042 ± 0.0071 mm/liter to 0.059 ± 0.0012 ($p < 0.05$) 60 min after cold exposure in the control study, while it decreased from 0.040 ± 0.0013 mm/liter to 0.021 ± 0.0011 ($p < 0.001$) 30 min and to 0.016 ± 0.0012 ($p < 0.001$) 60 min following cold exposure in the nicotinic acid study.

Variations of core and peripheral temperatures, heat content, heat debt, heat loss and body insulation in the cold

As shown in Table 5, small changes in the rectal temperature was observed during cold exposure, though it was not significantly different. Mean skin temperature fell sharply, up to 30 min, after cold exposure and thereafter decreased at a relatively slow rate up to 60 min. There was no significant difference in the rate of fall between the control and nicotinic acid studies. The pattern of fall in the mean body temperature was essentially the same as that observed in the mean skin temperature. There was a progressive and significant decline up to the end of cold exposure, but no significant difference in the extent of decrease between two studies. There was a small decline in the heat content, heat loss and a little change in the heat debt in both control and nicotinic acid studies, but their variations in response to cold were not significantly different between two studies. The marked elevation of the body insulation was observed during cold exposure, but there was no significant difference between two studies.

Table 6. The changes in pulse rate and blood pressure after cold exposure.

Time after cold exposure (min)		0	15	p vs. 0	30	p vs. 0	60	p vs. 0
Pulse rate (counts/min)								
Male students								
Control study	(10)	60 ± 5.0	59 ± 3.2	N.S.	57 ± 5.2	N.S.	60 ± 3.3	N.S.
NA-study	(10)	59 ± 3.0	59 ± 2.8	N.S.	61 ± 4.5	N.S.	62 ± 4.0	N.S.
Control vs. NA		N.S.	N.S.		N.S.		N.S.	
Blood pressure (systolic) (mmHg)								
Control study	(10)	112 ± 3.8	128 ± 5.3	< 0.05	127 ± 4.7	< 0.05	130 ± 7.1	< 0.05
NA-study	(10)	110 ± 3.5	131 ± 6.0	< 0.01	132 ± 5.8	< 0.01	131 ± 7.3	< 0.05
Control vs. NA		N.S.	N.S.		N.S.		N.S.	
Blood pressure (diastolic) (mmHg)								
Control study	(10)	76 ± 2.0	90 ± 6.0	< 0.05	92 ± 6.2	< 0.05	88 ± 3.8	< 0.05
NA-study	(10)	75 ± 2.2	94 ± 5.2	< 0.001	95 ± 6.0	< 0.001	92 ± 4.5	< 0.001
Control vs. NA		N.S.	N.S.		N.S.		N.S.	

Legends same as in Table 3.

Changes in pulse rate and blood pressure after cold exposure

As can be seen in Table 6, the pulse rate remained unchanged during cold exposure in two studies. Both systolic and diastolic blood pressures were similarly elevated during cold exposure in two studies (Table 6).

DISCUSSION

As can be seen in Table 3, acute cold exposure produced a marked elevation of heat production in the control study already 30 min after cold exposure, although there appeared only slight shivering during this early period of cold exposure. These findings suggest that there exists nonshivering thermogenesis in men. However, these results do not exclude the possibility that even when shivering is not evident, the elevated heat production might be attributable to the increase in muscular tension (SWIFT, 1932; BURTON and EDHOLM, 1955). Therefore, even if there exists a certain amount of nonshivering thermogenesis involved in the elevated heat production, participation of muscle activity could not be denied. If it is possible to reduce or eliminate nonshivering thermogenesis, shivering must become greater to compensate for the reduced nonshivering thermogenesis. In this context, it is of interest to refer to our previous report (DOI *et al.*, 1969) and the study by HAVEL *et al.* (1964). DOI *et al.* (1969) showed that an administration of nicotinic acid produced a significant decrease of plasma FFA levels accompanied by a decrease in basal metabolism. Furthermore, according to HAVEL *et al.* (1964), the calorogenic effect of norepinephrine was partially inhibited by prior injection of nicotinic acid in quantities sufficient to prevent fat mobilizing action of norepinephrine. These results would appear to indicate that nonshivering thermogenesis is mediated by an increased mobilization of FFA due to norepinephrine. As would be expected, an administration of nicotinic acid prior to cold exposure resulted in the significant reduction of plasma FFA level, less elevation of heat production and a greater increase in shivering (Tables 3, 4 and Fig. 1). It was also demonstrated that the occurrence of generalized shivering was observed earlier in the nicotinic acid study than in the control study. These results may be explained as follows: since nonshivering thermogenesis was reduced due to the decreased supply of FFA as a fuel substrate, the intensity of shivering became greater to compensate for the reduced nonshivering thermogenesis. In any case, the present study has demonstrated that nonshivering thermogenesis as a source of heat production develops in men in the cold and it is achieved by enhanced utilization of lipids as conjectured by the fact that nicotinic acid inhibits nonshivering thermogenesis as well as lipid mobilization. In fact, men living in Hokkaido were reported to exhibit higher levels of basal metabolism (OHNO and KUROSHIMA, 1973), plasma FFA and urinary excretion of nitrogen during the winter (KUROSHIMA *et al.*, 1973). Thus, nonshivering thermogenesis is considered to develop in men in the cold due to the modified metabolism of energy-yielding

substrates.

It is presently believed that the lipids are the most important fuel in the cold in men as well as animals (ITO *et al.*, 1969; MASORO, 1966). An immediate and marked increase occurs in the plasma FFA level as an invariable response to low environmental temperature. The elevation of plasma FFA levels indicate the occurrence of an augmented fat mobilization during cold exposure. This was also the case in the present study. In fact, the marked increase of plasma FFA levels was observed in the control study during cold exposure, as seen in Table 4. The increase in total plasma protein and hematocrit, and the decrease in plasma volume were well-known effects of cold exposure. The study by WILSON *et al.* (1969) showed that the increase in plasma FFA levels was not significant when FFA levels were corrected for cold hemoconcentration. In the present study, however, this hemoconcentration (5.4 to 8.8% in terms of hematocrit and 5.0 to 8.1% in terms of plasma total protein) could not account for the elevation of plasma concentration of FFA (24.8 to 41.7%) in response to cold exposure. When the values of heat production were plotted against the plasma FFA levels, a significant, positive correlation was obtained ($p < 0.01$), as illustrated in Fig. 2. These findings support the concept that the increase in heat production due to cold exposure is possibly associated with the elevation of the mobilization and oxidation of FFA. Moreover, the values of R.Q. declined significantly in accordance with the elevated heat production in the control study, while no change in R.Q. was observed in the nicotinic acid study. As shown in Figs. 3 and 4, there was a significant inverse correlation either between R.Q. and the plasma FFA levels ($p < 0.005$) or between R.Q. and heat production in the control study ($p < 0.001$). Consequently, it is very likely that a marked increase in heat production in men in the cold is as-

Fig. 2. Correlation between the heat production and plasma FFA levels.

Fig. 3. Correlation between R.Q. and plasma FFA levels. Legends same as in Fig. 2.

Fig. 4. Correlation between R.Q. and heat production. Legends same as in Fig. 2.

sociated with a greater utilization and mobilization of FFA.

Ketone bodies have been shown to be another substrate for heat production. Their functions are considered to be analogous to those of FFA and glucose (KREBS, 1961). Exposure to cold induced a significant increase of ketone body formation in men (ITO, 1974). This was the case in the present study. Elevation of plasma ketone body measured as β -hydroxybutyrate was observed 60 min after

cold exposure in the control study ($p < 0.05$) (Table 4). However, the extent of increase in ketone body levels was not so great as that in FFA. An enhanced peripheral utilization of plasma FFA and/or ketone bodies may be responsible for less increment of plasma ketone body than that of plasma FFA. On the other hand, the plasma ketone body level significantly decreased 30 min and 60 min after cold exposure (respectively, $p < 0.001$) from the initial level in the nicotinic acid study, possibly resulting from less mobilization of FFA. It has been shown by JEANRENAUD (1961) that the ketone body formation is proportional to the concentration of FFA in the plasma.

As described in RESULTS, the blood glucose level remained at the initial levels during cold exposure. Lower R.Q. and no changes in plasma glucose level after cold exposure indicate that blood glucose does not play a great role as an energy-yielding substrate in the cold at least in the present study and further that the stimulus for increased fat mobilization is mediated primarily by norepinephrine released by the sympathetic nerves rather than adrenal medulla (WILSON *et al.*, 1969).

Since it is known that nicotinic acid has a vasodilating effect (ABRAMSON *et al.*, 1940) besides the action of inhibiting the release of FFA, the effect of this drug on thermal response to cold should be taken into consideration. In fact, the subcutaneous flushing on the face and the extremities appeared 3 to 5 min after an administration of nicotinic acid at the room temperature of 25°C, continuing for 5 min and then faded gradually. However, in the cold environment nicotinic acid showed only faint sign of vasodilatation. It could be supposed that the enhanced vasoconstricting activity due to cold stress outbalanced the transient effect of vasodilatation due to nicotinic acid. This finding is reflected in the result that there was no significant difference in the mean skin temperature, although it tends to be higher in the nicotinic acid study, and hence in the body heat loss between control and nicotinic acid studies. In addition, there was no significant difference in the variations of rectal temperatures, in the rate of fall of mean body temperature, heat content, heat debt, and heat loss between two studies. Therefore, it is unlikely that nicotinic acid itself altered the heat loss mechanism during cold exposure in the present study.

It has been previously shown that thyroid hormones are also important in regulating nonshivering thermogenesis (CHAFFEE and ROBERTS, 1971). Recently, several investigators reported a high level of plasma thyroid hormones in the winter in men (RASTOGI and SAWHNEY, 1976; NAGATA *et al.*, 1976; SMALS *et al.*, 1977). Therefore, it is surmised that thyroid hormones are involved in the presence of nonshivering thermogenesis observed here in men living in the northern area. But this problem remains to be studied in future.

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