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Hyperthermia in Humans Enhances Interferon-γ Synthesis and Alters the Peripheral Lymphocyte Population

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ABSTRACT

Induction of hyperthermia (39°C) in human volunteers by immersion in warm water (41–45°C) rapidly alters the cell populations in the peripheral blood. In addition to granulocytosis, there is an alteration of the normal ratios among T-lymphocyte subsets. Following *in vitro* mitogen stimulation, lymphocytes from hyperthermic individuals produce as much as 10-fold more interferon-γ (IFN-γ) than cells withdrawn at basal core temperatures from the same individuals. A temperature threshold of 39°C for this response suggests potential relevance to fever. No change was noted in the activity of the macrophage population. The possible involvement of interleukin-2 (IL-2) in this enhanced production is discussed. No changes were noted in the circulating levels of IFN-γ.

INTRODUCTION

In vertebrates, fever represents a complex adaptive response to infection. An elevation of the normal body temperature results in enhanced survival to microbial challenge.[1] Fever is associated with an increase in the number of circulating polymorphonuclear leukocytes,[2] increased mobilization of leukocytes,[3] elevated production of and responsiveness to leukocyte migration inhibitory factor,[4] and augmented antibody synthesis.[5,6]

Although interferon-γ (IFN-γ) confers an antiviral state on cells, as does IFN-α and IFN-β, it has additional immunomodulatory functions. These include macrophage activation,[7] induction of HLA antigens on the surface of responsive cells,[8-10] and activation of natural killer (NK) cells.[11] Additionally, IFN-γ is directly involved in the generation of cytotoxic T lymphocytes[12] and in the maturation of resting B lymphocytes to active plasma cells.[13] Thus, this lymphokine appears to occupy a pivotal point in both humoral and cell-mediated immune responses.

While most studies of enhanced immune responsiveness at febrile temperatures have been per-

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formed *in vitro*, we wished to examine possible *in vivo* mechanisms involved in lymphokine production. Thus, we designed an experiment that would allow investigation of such mechanisms, without the complexities concomitant with direct immune stimulation.

Preliminary experiments were performed by inducing hyperthermia in rhesus monkeys by placing them in a regulated climatic room at a temperature of 45°C. Within 90–120 min, the animals' rectal temperatures had increased 2°C. Mitogen-stimulated mononuclear cells isolated immediately after this elevation of core temperature showed a significant increase in IFN-γ activity relative to similarly treated samples isolated at normal resting temperatures.[14]

Here we demonstrate that a similar mechanism exists in humans potentially to augment IFN-γ synthesis. A temperature threshold of 38.5–39.0°C is required to elicit this response, which suggests a direct relationship with fever. Additionally, an analysis of the subsets of T and B lymphocytes by flow cytometry indicated a change in the T-subset populations, as well as an increase in NK cells. This is accompanied by an increase in IL-2 production, which may account for the enhanced IFN-γ synthesis.

MATERIALS AND METHODS

Human Subjects and Induction of Hyperthermia: Healthy volunteers, between the ages of 20 and 35 were used in this study. Core body temperature was measured rectally with a Digitec 5810 digital thermometer. A heparinized blood sample was obtained *via* venipuncture and stored on ice. The subject was then approximately 70% immersed in a warm water bath (40–45°C). Rectal temperature was measured at 30-min intervals. Subjects were withdrawn from the experiments when core body temperature was between 39 and 39.5°C.

Isolation of Mononuclear Cells: Heparinized blood samples were obtained *via* venous cannulation of the anticubital vein and stored on ice. The blood was diluted with three volumes of phosphate-buffered saline (PBS, pH 7.4) and the mononuclear fraction isolated by Ficoll-Hypaque density gradient centrifugation as described previously.[15] Cells were resuspended at 4×10^6 cells/ml in RPMI-1640 medium, supplemented with 10% fetal calf serum, 20 m*M* glutamine, 100 μg/ml streptomycin, and 50 units of Penicillin G.

Macrophage Separation: Macrophages were separated from the lymphocytes by adherence to plastic for 2 h at 37°C in 24-well plates. The nonadherent lymphocytes were isolated by vigorously washing the wells with PBS. Lymphocytes were then centrifuged, and the culture reconstituted at the original cell density of 1.5×10^6 cells/ml.

Induction and Assay of IFN: IFN-γ was induced by incubation of mononuclear cells with phytohemagglutinin (PHA, Difco, Detroit, MI) at 33 μg/ml. Quantitation of IFN production was either by a cytopathic effect (CPE) protection assay using vesicular stomatitis virus (VSV) on Hep-2 and WISH cells, or by using a radioimmune assay (Boots-Celltech, Slough, UK).

Flow Cytometry: Flourescence-activated flow cytometric analysis was performed on a Coulter Epic 753 Cell Sorter. Washed mononuclear cells were resuspended at 10^6 cells/50 μl cold PBS. Ten microliters of commercially available flourescein isothiocyanate-conjugated antibodies to human lymphocyte or monocyte surface antigens was added. Tubes were agitated and incubated on ice for 30 min with occasional agitation. The labeled cells were then washed twice with cold PBS and fixed in 1 ml of cold 1% paraformaldehyde solution. Fixed cells were stored in the dark for up to 1 week. Specific monoclonal antibodies were purchased from Becton-Dickinson (Mountain View, CA).

Assay of IL-2 Activity: Serial twofold dilution of an IL-2 standard (Electronucleonics) or medium from 48 h PHA-stimulated mononuclear cell cultures was added to 96-well microtiter plates

containing the IL-2-dependent cell line CTLL-2. Target cells were plated at a concentration of 5×10^3 cells/well in a total volume of 200 μl. After 24 h of incubation at 37°C in a CO_2 incubator, each well was pulse-labeled with 0.5 μCi [^{3}H]thymidine for 6 h. Cells were harvested using a Cambridge Technology PHD Cell Harvester, and the DNA precipitated in 95% ethanol and incorporation counted on GF/A glass fiber filters.

RESULTS

The effect of in vivo *hyperthermia on IFN-γ synthesis*

Hyperthermia was previously shown to result in increased IFN-γ synthesis in mononuclear cell cultures.[14] If such a mechanism were related to the physiologic effects of fever, then a threshold temperature should exist for the occurrence of this response beyond the normal diurnal variations of body temperature. Hyperthermia was induced in male human volunteers by immersion in a warm water bath at 41–45°C. As shown in Fig. 1A, after a short lag period, the core body temperature of subjects increased linearly at a rate of approximately 0.5°C per 30 min. Venous cannulation allowed removal of peripheral blood samples at specific intervals. Figure 1B shows the levels of IFN-γ induced by PHA in mononuclear cell cultures isolated from individuals with the corresponding rectal temperatures. The mean values from four subjects represented in the figure are 380 U/ml IFN-γ at 37°C, 430 U/ml at 37.5°C, 800 U/ml at 38°C, 580 U/ml at 38.5°C, and 4,000 U/ml at 39°C. Therefore, the highest value obtained from hyperthermic individuals is a 10-fold elevation in IFN-γ compared to control levels. This difference is statistically significant ($p < 0.01$) by *t*-test analysis. The effect is not limited to PHA as the inducer of IFN-γ, as similar enhancing effects in hyperthermic samples were observed using staphylococcal enterotoxin B. Thus, there is a physiological response *in vivo* to febrile temperature which includes changes in the circulating lymphocyte pool that increase their potential to synthesize IFN-γ. No effect of hyperthermia was found on the circulating levels of IFN-α or IFN-γ.

The effect of pre- and post-hyperthermia macrophages on IFN-γ synthesis

While T lymphocytes are the source of IFN-γ, several previous studies have established that macrophages provide an accessory function to enhance IFN-γ production in mitogen-stimulated mononuclear cell cultures.[16] Depletion of macrophages from such cell cultures significantly reduced IFN-γ synthesis. We examined whether the posthyperthermic macrophage population of the peripheral blood had the capacity to augment the synthesis of IFN-γ by macrophage-depleted control (37°C) lymphocyte cultures. Washed Ficoll-separated mononuclear cells were incubated in wells of a 24-well plate for 2 h at 37°C to permit attachment of macrophages. The nonadherent lymphocyte fraction was then removed by repeated vigorous washing. Lymphocytes were then restored to the original concentration by centrifugation. Lymphocytes thus obtained from normothermic individuals were added to a monocyte population isolated from the same individual following the induction of hyperthermia, and subsequent IFN-γ production was measured after 72 h co-incubation. No increased IFN-γ release was detected when lymphocytes from hyperthermic individuals were added to control lymphocytes, or vice versa. Thus, the macrophage fraction does not appear to be responsible for the enhanced IFN-γ synthesis during the *in vitro* incubation period.

Fluorescence-activated cell sorter analysis of lymphocyte subsets

Since this increased capacity for IFN-γ induction in response to temperature occurred relatively quickly, we analyzed whether changes in the peripheral blood population might be correlated with this effect. Examination of peripheral blood leukocytes from three subjects revealed that the induc-

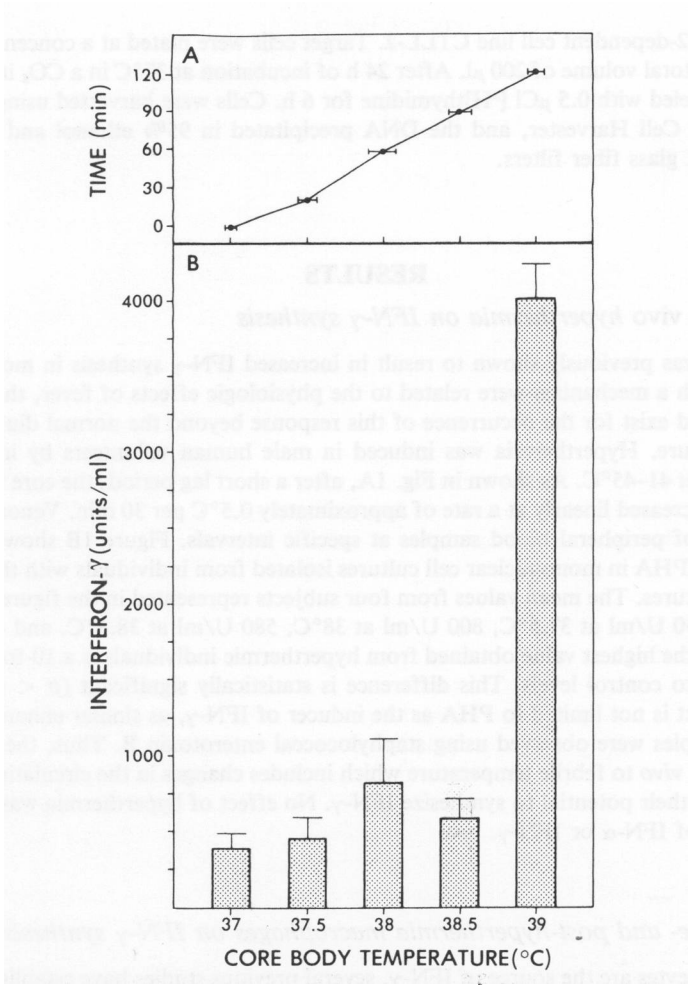

FIG. 1. Determination of an *in vivo* threshold temperature associated with augmented IFN-γ synthesis in leukocyte cultures. A. Increase in core body temperature with time. B. IFN-γ production from PHA-stimulated lymphocyte culture withdrawn from subjects at differing core body temperatures. Bar indicates standard deviation.

tion of febrile temperatures results in a rapid granulocytosis (Table 1). This agrees with previous findings of an elevated number of circulating polymorphonuclear cells during fever.[2] However, the total number of lymphocytes increased only slightly (9%) and the number of circulating monocytes and eosinophils remained essentially unchanged. Although the phenotype of the IFN-γ-producing cell remains obscure, several studies have shown that less than 1.0% of lymphocytes synthesize this lymphokine after mitogen stimulation.[17,18] The observed increase in IFN-γ synthesis then could be due to an influx of producer cells into the circulation. We investigated the effect of hyperthermia on several T-cell subsets to correlate any change that might occur in the lymphocyte population with the enhanced IFN-γ production.

Subsets of lymphocytes can be defined by the use of commercially available monoclonal antibodies directed against several well-characterized surface antigens. The Becton-Dickinson series of antibodies (leu 2, leu 3, leu 4, leu 7, leu 11, leu 12, and leu M3) were used to examine the lymphocyte fraction of blood withdrawn from individuals with normal or hyperthermic core body tempera-

TABLE 1. ANALYSIS OF LEUKOCYTE POPULATION OF PERIPHERAL BLOOD FROM CONTROL (T_{RE} = 37°C) OR HYPERTHERMIC (T_{RE} = 39°C) HUMANS

	Control (T_{re} = 37°C)	*Hyperthermia* (T_{re} = 39°C)	*Percent change*
Total WBC	6,200 ± 1,100	7,900 ± 1,400	+27.4%
Granulocytes	3,925 ± 455	5,435 ± 652	+39.5%
Eosinophils	186 ± 16	198 ± 22	+6.0%
Lymphocytes	1,890 ± 16	2,078 ± 275	+9.8%
Monocytes	205 ± 19	198 ± 20	−4.0%

Values represent the mean number of each cell type/mm³ ± S.D. (N = 3).

tures. Each antibody was used as a fluorescein-isothiocyanate (FITC) conjugate. Figure 2 presents a composite of the typical determinations from one subject.

Hyperthermia resulted in an increase in leu 2-staining cells (T suppressor/cytotoxic lymphocytes) and a decrease in the percentage of T helper cells. The total number of T lymphocytes as determined by a pan T-cell antibody (leu 4) remained nearly constant. Unaffected by the induction of hyperthermia were B lymphocytes (leu 12⁺) and myeloid lineage cells (leu M3⁺). As noted in Table 2 there is as great deal of individual variation in the absolute percentage of T_H and T_S cells, although the direction of change is consistent. The changes in T_H and T_S cells, although the direction of change is consistent. The changes in T_H and T_S cells are significantly different ($p < 0.05$). Monoclonal antibodies associated with natural killer (NK) cell subsets (leu 7⁺, leu 11⁺) showed increased staining on cells from hyperthermic individuals. In addition, there was a characteristic shift toward greater average cellular fluorescence intensity with leu 11, which suggests an increase in the average cell-surface density of the leu 11 epitope in hyperthermic individuals. The values of leu 7 and leu 11 were significantly different at 37°C and 39°C by paired *t* test ($p < 0.05$).

Preliminary experiments indicate an increase in IL-2 levels in phytohemagglutinin (PHA)-stimulated lymphocytes in hyperthermic individuals.[19] The levels vary with an increase of 1.5- to 6-fold, depending on the subject. Thus, the enhanced IFN-γ induction could be the direct result of enhanced IL-2 production, which in turn may result from an increase in IL-1. This is currently being investigated.

DISCUSSION

This report demonstrates that the potential for IFN-γ synthesis can be enhanced dramatically in lymphocytes isolated from peripheral circulation as a result of elevated body temperature. The possibility that this response may be directly related to fever is strongly supported by the apparent temperature threshold required for its occurrence. Interestingly, the 2°C rise in body temperature utilized in this study and correlated with immune enhancement is similar to the finding of Vaughn and Kluger[21] that a rise of 1.50–2.25°C increased the survival of infected rabbits. In fact, fevers above or below this level were detrimental to survival. Therefore, a "therapeutic window" may exist for positive influences of febrile temperatures on host resistance and survival.

The changes in lymphocyte subset distribution described in this report may reflect the activity of hormones on these cells. The specific alterations that occurred due to hyperthermia were very similar to reports by others which concluded that epinephrine induced fluctuations of the normal T-cell subset ratios.[22,23] Increases in circulating catecholamines during natural fevers have been inferred.[24] Consequently, such hormone-induced changes in T-lymphocyte ratios may occur *in vivo* during the course of infection-induced fevers.

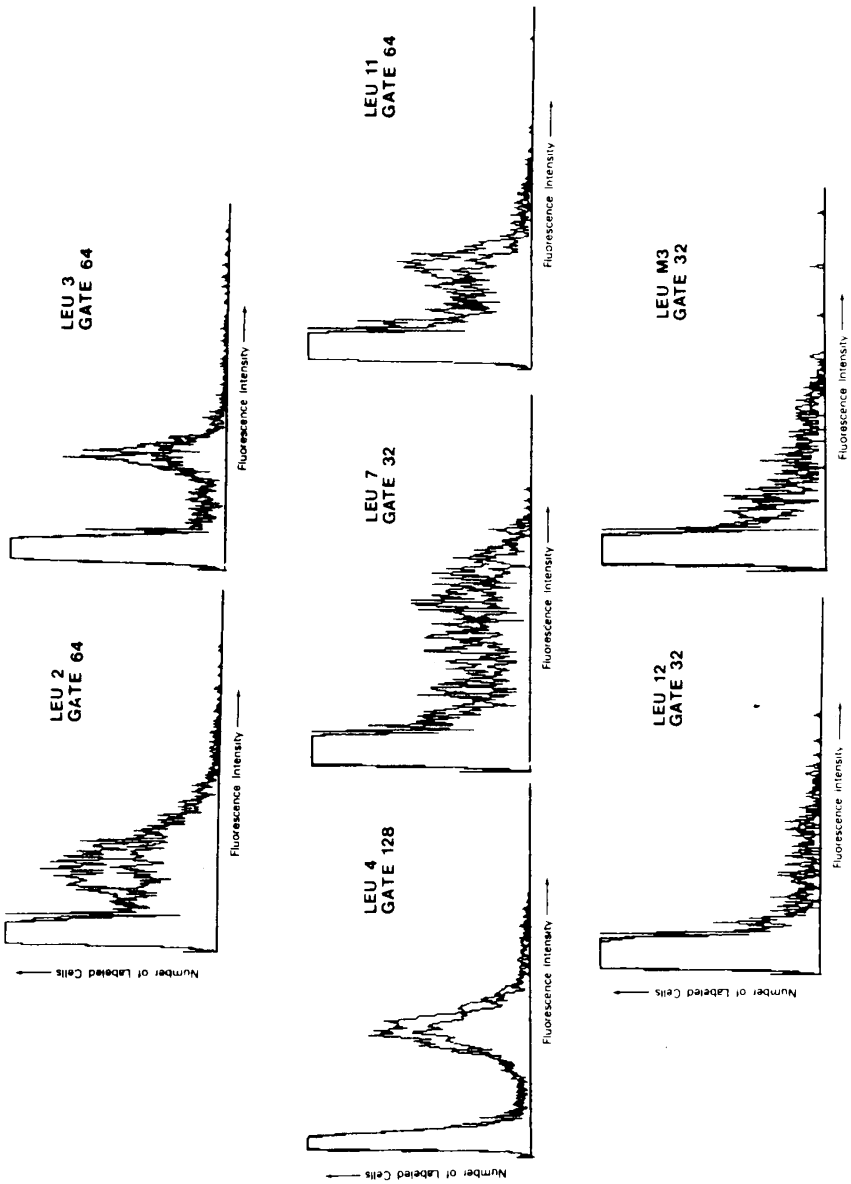

FIG. 2. Direct comparison of T-cell and B-cell subsets from an individual with normal (37°C) or hyperthermic (39°C) body temperature. The figure represents an overlay of separate histograms of labeled cells. Leu 2, upper curve 39°C, lower curve 37°C; leu 3, upper curve 37°C, lower curve 39°C; leu 4, upper curve 39°C, lower curve 37°C; leu 7, upper curve 39°C, lower curve 37°C; leu 11, upper curve 39°C, lower curve 37°C; and leu 12 and leu M3, where both curves are identical. Samples were of 10^4 cells/sample, the gate number given for each sample (32, 64, or 128).

TABLE 2. THE EFFECT OF *In Vivo* HYPERTHERMIA ON THE PERIPHERAL MONONUCLEAR CELL POPULATION FROM NINE INDIVIDUALS AS DETERMINED BY FLOW CYTOMETRY

	Percent positively labeled cells							
Antibody	*leu 2*		*leu 3*		*leu 7*		*leu 11*	
	37°	*39°*	*37°*	*39°*	*37°*	*39°*	*37°*	*39°*
Individual 1	17.1	18.5	17.2	16.5	37.0	45.9	21.5	30.1
Individual 2	21.9	30.0	46.6	33.0	14.8	18.7	24.7	25.3
Individual 3	20.2	41.9	44.1	19.4	–	–	–	–
Individual 4	30.9	39.0	37.9	28.7	–	–	–	–
Individual 5	14.6	16.4	34.8	34.8	18.7	19.4	15.6	21.4
Individual 6	31.1	39.2	38.1	29.0	–	–	–	–
Individual 7	6.6	9.2	20.4	18.1	20.5	21.4	15.1	30.1
Individual 8	10.7	14.7	28.8	13.5	4.9	5.4	15.4	19.2
Individual 9	29.9	32.8	14.1	7.2	11.1	17.3	21.9	25.2

The observed increase in IFN-γ may be a byproduct of a cascading mechanism in which interleukin-1 (IL-1) production is enhanced, stimulating the production of IL-2, which in turn would stimulate IFN-γ induction. Preliminary data indicate that IL-2 levels also increase in PHA-stimulated lymphocytes, and NK cell activity is enhanced by *in vivo* hyperthermia.[19] Thus, these factors may be involved in IFN-γ enhancement.

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