Morphostasis of the adult gastrointestinal tract
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APPENDIX 1

"Feed a cold, starve a fever"?

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Appendix 1

An English old wives’ tale advises us to “feed a cold and starve a fever”. Here we report that the nutritional status modulates the Th1/Th2 balance of activated T cells in human volunteers. Food intake resulted in increased IFN-γ production, whereas food deprivation stimulated IL-4 release.

Despite the fact that popular wisdom holds that one should “feed a cold and starve a fever” it is, to the best of our knowledge, not known if nutrient availability acutely modulates the immune response. The adaptive immune response employs different strategies to ward off infection by pathogens. A subset of T lymphocytes, the CD4 expressing, T helper (Th) cells are important in directing this strategy. So-called Th1 cells stimulate primarily the cell-mediated immune response against intracellular invaders by activating macrophages and CD8+ cytotoxic T lymphocytes. Th2 cells favor the B cell dependent humoral immune response against extracellular organisms. Whereas interferon (IFN)-g is the hallmark Th1 cytokine, interleukin (IL)-4 is an important Th2 cytokine. We decided to study the Th1/Th2 balance in blood of healthy volunteers in response to food intake.

Six non-smoking healthy male volunteers (mean age 28, range 26-33, mean Body Mass Index 23.8, range 21.5-26.3) were studied on two occasions. The medical ethical committee of our hospital approved the study. After overnight starvation the participants received a liquid meal on one occasion (800 ml “nutridrink”, containing 1200 kcal, 40 g protein, 144 g carbohydrate, 88 g lipids of Nutricia, Zoetermeer, the Netherlands), and an equal volume of water on the second occasion. The water was to control for gastric distension. Heparinized blood was obtained at the start of the experiment at 9:00 am and every hour for six hours hereafter. Blood was diluted 1:1 in pyrogen-free medium (RPMI 1640, Bio Whittaker, Verviers, Belgium) and 1 ml aliquots were cultured in triplicate for 24 hr in the presence or absence of the T cell receptor activating antibodies anti (α)-CD3/α-CD28 (CLB, Amsterdam, The Netherlands, at concentrations of 1.5 mg/ml and 2 mg/ml respectively). IFN-γ and IL-4 were measured by ELISA according to the manufacturers protocol (kits from CLB). Different time points of the same volunteer were always measured in the same assay.

In unstimulated blood both IFN-γ and IL-4 were below the detection limit of the assay. Upon a 24 hour stimulation mean baseline levels (t=0) of IL-4 production were 61±22 pg/ml in controls and 62±43 pg/ml in volunteers about to receive nutridrink. Baseline levels of INF-γ were 76±55 ng/ml and 85±38 ng/ml respectively. Thus the baseline cytokine levels were comparable in both groups. These levels were altered in blood obtained at later time points, both in the calorie-fed group as well as in the control situation. Six hour after calorie ingestion, six out of six volunteers showed strongly increased IFN-γ production averaging 450% of the starting value (range: 117-867%). Fasting however, decreased IFN-γ production to an average 83% of the starting value (range: 47-115%), see figure 1. Both calorie intake and water ingestion increased IL-4 production. The increase was significantly
higher however in fasted volunteers, the most marked difference being noted five hours after meal intake. Whereas in fasted controls IL-4 levels reached an average 398% of the starting value (range: 67-1114%), after food intake IL-4 production reached only an average of 142% of the starting value (range: 80-243%), see figure 1. Hence food intake acutely increases the IFN-\(\gamma\), not the IL-4 lymphocyte response. Conversely, starvation increases the IL-4 and not the IFN-\(\gamma\) response in T lymphocytes.

Calorie ingestion apparently favors cell-mediated immunity (as evident by the dramatic upregulation of IFN-\(\gamma\) production),\(^2,^3\) whereas starvation skews the immune system toward a humoral immune response.\(^4,^5\) In our whole blood approach we did not correct for possible changes in white blood cell counts, it is possible that these are influenced by food intake. We feel however this is unlikely to have an effect on the Th1/Th2 ratio as observed in our study and such differences would be unlikely to explain our results. Although clearly further studies are needed for a better comprehension of the relation between food consumption and the immune response, our data support the notion that such a relation does exist. Our results also have the important implication that one should carefully standardize food intake when comparing cytokine production between different time points or people. Thus the English popular belief "feed a cold, starve a fever" may reflect the observation of a bona fide effect of the nutritional status on the regulation of the immune response.

![Figure 1](image_url)

**Figure 1.** Changes in IFN-\(\gamma\) and IL-4 production in response to meal intake (n=6, closed circles) and fasting (n=6, open circles) during six hour follow-up. % cytokine production of baseline. Baseline levels (t=0) of IL-4 production were 61±22 pg/ml in controls and 62±43 pg/ml in volunteers about to receive nutridrink. Baseline levels of INF-\(\gamma\) were 76±55 ng/ml and 85±38 ng/ml respectively. Statistical analysis was performed using a two-factor repeated-measurement design on absolute measurements relative to baseline.\(^6\) The food/time interaction was significant for both cytokines, p<0.001 for IFN-\(\gamma\), p<0.05 for IL-4.
References


