Suppressive effect of a selective increase in plasma linoleic acid concentration and intravascular lipolysis on peripheral T cell activation

Dear Sir:

With interest we read in the Journal the findings of a recent study by Larbi et al (1), in which the authors reported on the suppressive effects on T cell activation and function, together with changes in the membrane properties of these cells, that are brought about by the intravenous administration of a soybean oil–based lipid emulsion (Intralipid 20%; Baxter, Mississauga, Canada). The authors concluded that these results should have serious implications for nutritional therapy in patients at high risk of septic complications.

We have several concerns with regard to the latter statement. First, the investigation by Larbi et al was performed in healthy subjects, and, therefore, their results cannot be extrapolated to patients with an inflammatory condition. Second, several reviews focused on immune modulation by parenteral lipids in general (2) and by soybean oil–based emulsions in particular (3) concluded that no clear picture exists, because of the very disparate outcomes of the studies reviewed. For instance, our group has consistently found that Intralipid, an emulsion that is rich in long-chain triacylglycerols, does not affect human neutrophil and mononuclear cell functions, including oxygen radical production, adhesion, chemotaxis, pathogen killing, and cytokine production (4–8). In our recent report (1) of a reduction in circulating T cell activation by Larbi et al, these observations were made in cells obtained from healthy volunteers and in studies with both in vitro and in vivo designs. It is important that, in our hands, Intralipid did not alter membrane fluidity, as measured by the same technique that Larbi et al used, or signal transduction of leukocytes (9, 10). In contrast, the administration of an emulsion containing medium-chain triacylglycerols in these investigations resulted in cell activation, altered cytokine responses, increased membrane fluidity, and attenuation of calcium signaling in neutrophils and mononuclear cells (4–10). In our opinion, these conflicting outcomes show that, at present, we do not fully comprehend the nature of the interaction of immune cells and parenteral lipids and the circumstances influencing that interaction.

The author had no personal or financial conflict of interest with respect to the study of Larbi et al or the report on that study.

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Reply to GJ Wanten

Dear Sir:

We read with great interest the comments of GJ Wanten concerning our recent report (1) of a reduction in circulating T cell activation and proliferation, and cell activation and proliferation during enhanced intravascular lipolysis with Intralipid and heparin that resulted in a selective increase in plasma linoleate concentrations in healthy humans. We agree with Wanten that the results in healthy subjects cannot be directly extrapolated to the usual intensive-care-unit patients who have severe inflammatory conditions often associated with a severe catabolic state—a state that in itself may alter the immune response. As mentioned by Wanten, the data from the literature are conflicting with respect to the unfavorable effects of intravenous lipid emulsions on the immune function in humans. Although early studies did not find evidence of an immunosuppressive effect of total parenteral nutrition with Intralipid or other lipid emulsions in the critical or postoperative care setting (2–5), more recent randomized controlled trials found that the administration of an intravenous lipid emulsion with total parenteral nutrition was associated with less T cell proliferation, a higher rate of infection, more prolonged need for mechanical ventilation, and more prolonged stays in the intensive care unit or in the hospital (6, 7). Our findings (1) also confirmed those of several previous
studies that showed a reduced reactivity of human peripheral lymphocytes after either in vitro or in vivo exposure to Intralipid or another lipid emulsion composed of long-chain fatty acids (8–10). Thus, we believe that evidence of a role for long-chain fatty acids in the modulation of T cell function is accumulating. Whether this effect and the proposed mechanisms we showed in our study are relevant in pathophysiological states in humans clearly needs more investigation.

Our report did not address the potential role of a selective elevation of plasma linoleate concentrations on the function of circulating monocytes and neutrophils. Neutrophils and monocytes may behave very differently in response to fatty acids than do T lymphocytes. Thus, we agree with Wanten that the effect of long-chain fatty acids shown in one class of white blood cells cannot be extrapolated to other such classes and that more studies are needed to integrate the multiple potential effects of long-chain fatty acids on the immune system in healthy and pathophysiological states in humans.

The authors had no conflict of interest.

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Effect of nutritional manipulation on brain function: implications for future research

Dear Sir:

I am writing about the recently published review by McCann and Ames (1). This review addresses the behavioral effects of n-3 fatty acids in humans and animals. The authors are to be commended on their thoroughness in researching the extensive literature on this topic and in invoking the necessary methodologic considerations when evaluating the outcomes of studies conducted in both animals and humans. In their discussion of the various behavioral studies included in this review, they raise an important issue—that different neural systems might be affected differently by nutritional manipulations, and, thus, some outcomes might be more sensitive indicators than others with respect to the role of a particular nutrient. From my perspective as a behavioral scientist who works with rodents, I would like to expand on this observation and explore the implications for future research.

Although the terms cognitive and behavioral are often used freely in relation to nutritional interventions, what is meant by these terms is not always defined precisely. Thus, whereas both the human and animal literature encompass a diverse array of behavioral outcomes, there is often little discussion of exactly which specific psychological construct is being measured by each test and how this relates to overall cognitive function. This is despite an accumulation of evidence in both humans and animals during the past 15–20 y that supports the hypothesis that the brain comprises multiple memory systems, each anatomically and biochemically distinct and each processing information in a specialized way (2). On the basis of behavioral dissociations in studies using lesions in rats, 3 independent systems have been identified: 1) flexible use of knowledge involving the hippocampus, 2) habitual responses (reinforced stimulus-response associations) involving the dorsal striatum, and 3) emotional responses (Pavlovian stimulus—affect conditioning) involving the amygdala. In most situations, these systems operate in parallel, and, depending on the circumstances, interact either competitively or cooperatively. For example, depending on the protocol, different types of learning, either cognitive or stimulus-response, can occur in the place version of the Morris water maze. If the start position is varied over trials, the animal is required to use spatial information flexibly, whereas if the start position remains the same, the animal can use the response system, eg, swim 45 degrees left. What is important to note, however, is that when one system is damaged, performance will be impaired on tasks associated with the function of that particular system, but very often enhanced on the tasks associated with the other. For example, animals with hippocampal damage often perform better than do control animals on stimulus-response type learning tasks. Thus, it is entirely possible for an intervention that improves one type of memory to have deleterious effects on another type of memory or to have effects on other measures, such as arousal, that affect task performance.

In summary, the point being made herein is that broad terms such as cognition need to be carefully operationalized and then tested by...